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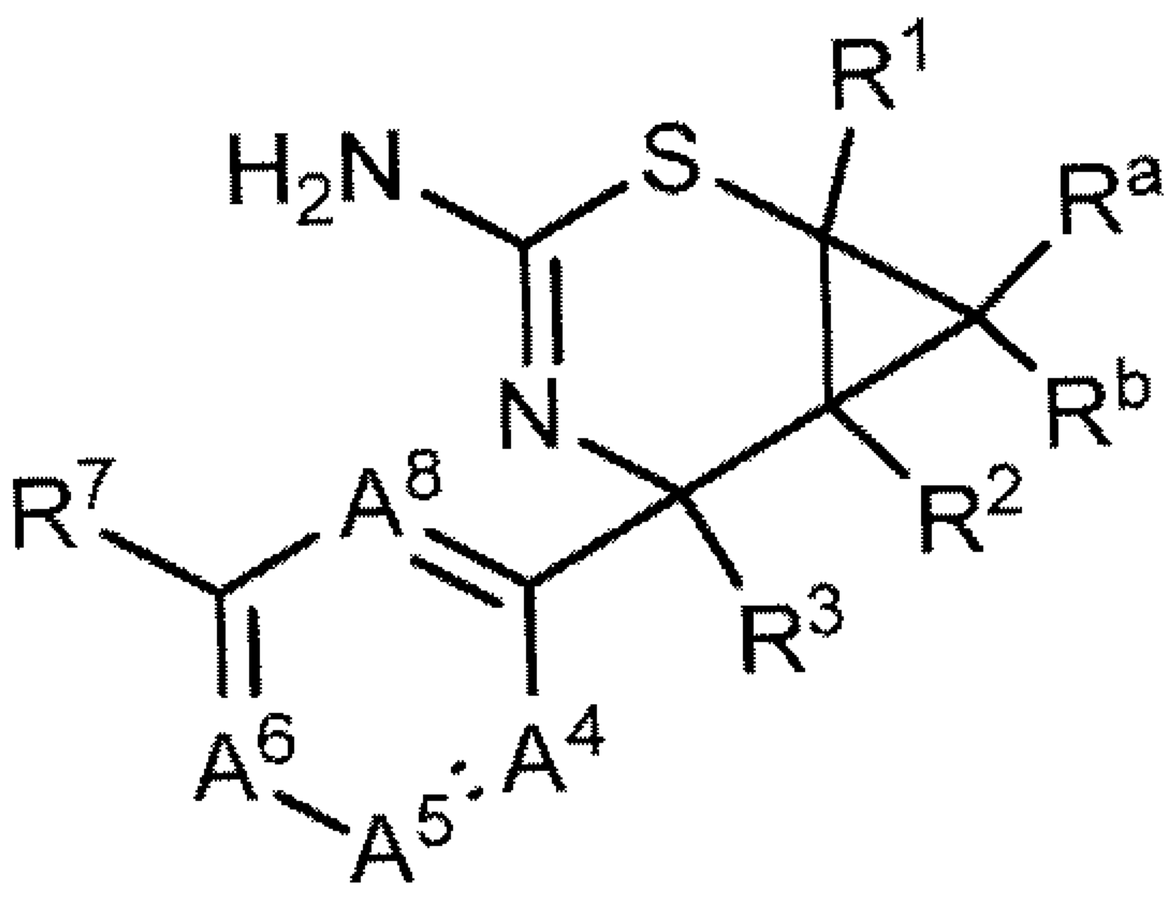
(71) Demandeur/Applicant:
AMGEN INC., US

(72) Inventeurs/Inventors:
ALLEN, JENNIFER R., US;
AMEGADZIE, ALBERT, US;
BOURBEAU, MATTHEW P., US;
BROWN, JAMES A., US;
CHEN, JIAN J., US;
CHENG, YUAN, US;
...

(74) Agent: SMART & BIGGAR

(54) Titre : COMPOSES THIAZIN-2-AMINE FUSIONNEE A UN GROUPEMENT CYCLOPROPYLE UTILISES EN TANT QU'INHIBITEURS DE LA BETA-SECRETASE ET LEURS PROCEDES D'UTILISATION

(54) Title: CYCLOPROPYL FUSED THIAZIN-2-AMINE COMPOUNDS AS BETA-SECRETASE INHIBITORS AND METHODS OF USE



(I)

(57) Abrégé/Abstract:
The present invention provides a new class of compounds useful for the modulation of beta-secretase enzyme (BACE) activity. The compounds have a general Formula (I): wherein variables A^4, A^5, A^6, A^8, and each of R^a, R^b, R^1, R^2, R^3 and R^7 of Formula (I), independently, are defined herein. The invention also provides pharmaceutical compositions comprising the compounds, and uses of the compounds and compositions for treatment of disorders and/or conditions related to A-beta plaque formation and 15 deposition, resulting from the biological activity of BACE. Such BACE mediated disorders include, for example, Alzheimers Disease, cognitive deficits, cognitive impairments, schizophrenia and other central nervous system conditions. The invention further provides compounds of Formulas (II) and (III), and sub-formula embodiments thereof, intermediates and methods for preparing compounds of the invention.

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(72) Inventeurs(suite)/Inventors(continued): FROHN, MICHAEL J., US; GUZMAN-PEREZ, ANGEL, US; HARRINGTON, PAUL E., US; LIU, LONGBIN, US; LIU, QINGYIAN, US; LOW, JONATHAN D., US; MA, VU VAN, US; MANNING, JAMES R., US; MINATTI, ANA ELENA, US; NGUYEN, THOMAS T., US; NISHIMURA, NOBUKO, US; NORMAN, MARK H., US; PETTUS, LIPING H., US; PICKRELL, ALEXANDER J., US; QIAN, WENYUAN, US; RUMFELT, SHANNON, US; RZASA, ROBERT M., US; SIEGMUND, AARON C., US; STEC, MARKIAN M., US; WHITE, RYAN D., US; XUE, QIUFEN, US

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(71) Applicant: **AMGEN INC.** [US/US]; One Amgen Center Drive, Thousand Oaks, California 91320-1799 (US).

(72) Inventors: **ALLEN, Jennifer R.**; 139 Via Aldea, Newbury Park, California 91320 (US). **AMEGADZIE, Albert**; 15242 Campus Park Drive, Apt. B, Moorpark, California 93021 (US). **BOURBEAU, Matthew P.**; 23510 Aetna Street, Woodland Hills, California 91367 (US). **BROWN, James A.**; 4438 Appleglen Court, Moorpark, California 93021 (US). **CHEN, Jian J.**; 5448 Castillo de Rosas, Camarillo, California 93012 (US). **CHENG, Yuan**; 5329 Via Jacinto, Newbury Park, California 91320 (US). **FROHN, Michael J.**; 2808 Cedar Wood Place, Thousand Oaks, California 91362 (US). **GUZMAN-PEREZ, Angel**; 20 Gilmore Road, Belmont, Massachusetts 02478 (US). **HARRINGTON, Paul E.**; 3824 Fountain Street, Camarillo, California 93012 (US). **LIU, Longbin**; 753 Rushing Creek Place, Thousand Oaks, California 91360 (US). **LIU, Qingyian**; 4631 Paseo Girasol, Camarillo, California 93012 (US). **LOW, Jonathan D.**; 19355 Sherman Way, Unit 39, Reseda, California 91335 (US). **MA, Vu Van**; 356 Countryside Road, Oak Park, California 91377 (US). **MANNING, James**; 201 Coffings Drive, Apt. #B403, Pleasant Hill, California 94523 (US). **MINATTI, Ana Elena**; 2219 3rd Street, Unit #6, Santa Monica, California 90405 (US). **NGUYEN, Thomas T.**; 468 Calle Veracruz, Newbury Park, California 91320 (US). **NISHMURA, Nobuko**; 24050 Arminta Street, West Hills, California 91304 (US). **NORMAN, Mark H.**; 130 Venus Street, Thousand Oaks, California 91360 (US). **PETTUS, Liping H.**; 3309 Big Cloud Circle, Thousand Oaks, California 91360 (US). **PICKRELL, Alexander J.**; 30948 Minute Man Way, Westlake Village, California 91361 (US). **QIAN, Wenyuan**; 4231 Via Azul, Thousand Oaks, California 91320 (US). **RUMFELT, Shannon**; 543 Lantana Street, #151, Camarillo, California 93101 (US). **RZASA, Robert M.**; One Amgen Center Drive, Thousand Oaks, California 91320 (US). **SIEGMUND, Aaron C.**; 5665 Pembroke Street, Ventura, California 93003 (US). **STEC, Markian M.**; One Amgen Center Drive, Thousand Oaks, California 91320 (US). **WHITE, Ryan**; 34 Willow Avenue, Unit #1, Somerville, Massachusetts 02144 (US). **XUE, Qiufen**; 5018 Via Mesita, Thousand Oaks, California 91320 (US).

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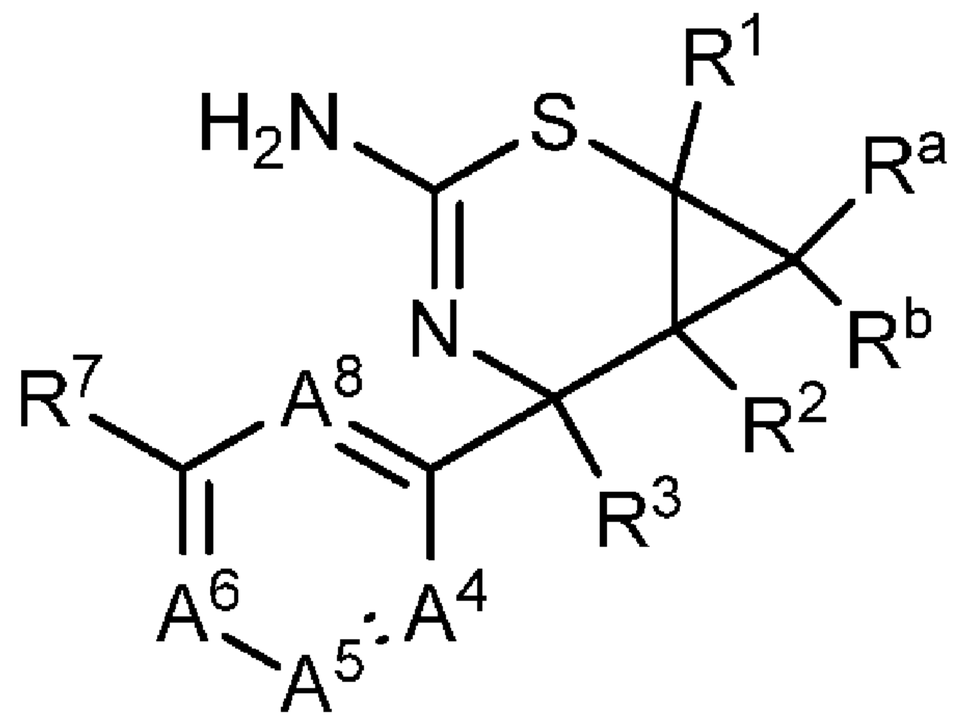
(54) Title: CYCLOPROPYL FUSED THIAZIN-2-AMINE COMPOUNDS AS BETA-SECRETASE INHIBITORS AND METHODS OF USE



(I)

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(74) **Agent**: **FRIEDRICHSEN, Bernard P.**; Amgen Inc., One Amgen Center Drive, M/S 28-2-C, Thousand Oaks, California 91320-1799 (US).

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CECI EST LE TOME 1 DE 2
CONTENANT LES PAGES 1 À 383

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THIS IS VOLUME 1 OF 2
CONTAINING PAGES 1 TO 383

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CYCLOPROPYL FUSED THIAZIN-2-AMINE COMPOUNDS AS BETA-SECRETASE INHIBITORS AND METHODS OF USE

RELATED APPLICATIONS

This application claims the benefit of and priority to U.S. Provisional Patent Application No. 62/035,269, filed on August 8, 2014,which specification is hereby incorporated herein by reference in its entirety and for all purposes as if specifically set forth herein.

FIELD OF THE INVENTION

The invention relates generally to pharmaceutically active compounds, pharmaceutical compositions and methods of use thereof, to treat beta-secretase mediated diseases and conditions, including, without limitation, Alzheimer's disease, plaque formation and associated central nervous system (CNS) disorders.

BACKGROUND OF THE INVENTION

Alzheimer's disease (AD) affects greater than 12 million aging people worldwide, and importantly, the number affected continues to grow. AD accounts for the majority of dementias clinically diagnosed after the age of 60. AD is generally characterized by the progressive decline of memory, reasoning, judgement and orientation. As the disease progresses, motor, sensory, and vocal abilities are affected until there is global impairment of multiple cognitive functions. The loss of cognitive function occurs gradually, typically leading to a diminished cognition of self, family and friends. Patients with severe cognitive impairment and/or diagnosed as end-stage AD are generally bedridden, incontinent, and dependent on custodial care. The AD patient eventually dies in about nine to ten years, on average, after initial diagnosis. Due to the incapacitating, generally humiliating and ultimately fatal effects of AD, there is a need to treat AD effectively upon diagnosis.

AD is characterized by two major physiological changes in the brain. The first change, beta amyloid plaque formation, supports the "amyloid cascade hypothesis" which conveys the thought that AD is caused by the formation of characteristic beta amyloid peptide (A-beta), or A-beta fragments thereof, deposits in the brain (commonly referred to as beta amyloid "plaques" or "plaque deposits") and in cerebral blood vessels (beta amyloid angiopathy). A wealth of evidence suggests that beta-amyloid and accompanying

amyloid plaque formation is central to the pathophysiology of AD and is likely to play an early role in this intractable neurodegenerative disorder. Vassar & Yan, *Lancet Neurology*, 13:319-329 (2014). The second change in AD is the formation of intraneuronal tangles, consisting of an aggregate form of the protein tau. Besides being found in patients with AD, intraneuronal tangles are also found in other dementia-inducing disorders. Joachim et al., *Alz. Dis. Assoc. Dis.*, 6:7-34 (1992).

Several lines of evidence indicate that progressive cerebral deposition of A-beta plays a seminal role in the pathogenisis of AD and can precede cognitive symptoms by years or even decades. Selkoe, *Neuron*, 6:487 (1991). Release of A-beta from neuronal cells grown in culture and the presence of A-beta in cerebrospinal fluid (CSF) of both normal individuals and AD patients has been demonstrated. Seubert et al., *Nature*, 359:325-327 (1992). Autopsies of AD patients have revealed large numbers of lesions comprising these 2 factors in areas of the human brain believed to be important for memory and cognition.

Smaller numbers of these lesions in a more restricted anatomical distribution are found in the brains of most aged humans who do not have clinical AD. Amyloid containing plaques and vascular amyloid angiopathy were also found in the brains of individuals with Down's Syndrome, Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-type (HCHWA-D), and other neurodegenerative disorders.

It has been hypothesized that A-beta formation is a causative precursor or factor in the development of AD. More specifically, deposition of A-beta in areas of the brain responsible for cognitive factors is believed to be a major factor in the development of AD. Beta amyloid plaques are primarily composed of amyloid beta peptide (A-beta peptide). A-beta peptide is derived from the proteolytic cleavage of a large transmembrane amyloid precursor protein (APP), and is a peptide comprised of about 39-42 amino acid residues. A-beta 42 (42 amino acids long) is thought to be the major component of these plaque deposits in the brains of Alzheimer's Disease patients. Citron, *Trends in Pharmacological Sciences*, 25(2):92-97 (2004).

Similar plaques appear in some variants of Lewy body dementia and in inclusion body myositis, a muscle disease. Aβ also forms aggregates coating cerebral blood vessels in cerebral amyloid angiopathy. These plaques are composed of a tangle of regularly ordered fibrillar aggregates called amyloid fibers, a protein fold shared by other peptides such as prions associated with protein misfolding diseases. Research on laboratory rats suggest that the dimeric, soluble form of the peptide is a causative agent in the

development of Alzheimer's and is the smallest synaptotoxic species of soluble amyloid beta oligomer. Shankar, G.M., *Nature Medicine* (June 22, 2008) online doi 10:1038 nm 1782.

Several aspartyl proteases, including beta-secretase and gamma-secretase, are thought to be involved in the processing or cleavage of APP, resulting in the formation of A-beta peptide. Beta secretase (BACE, also commonly referred to as memapsin) is thought to first cleave APP to generate two fragments: (1) a first N-terminus fragment (beta APP) and (2) a second C-99 fragment, which is subsequently cleaved by gamma secretase to generate the A-beta peptide. APP has also found to be cleaved by alpha-secretase to produce alpha-sAPP, a secreted form of APP that does not result in beta-amyloid plaque formation. This alternate pathway precludes the formation of A-beta peptide. A description of the proteolytic processing fragments of APP is found, for example, in U.S. Patent Nos. 5,441,870, 5,712,130 and 5,942,400.

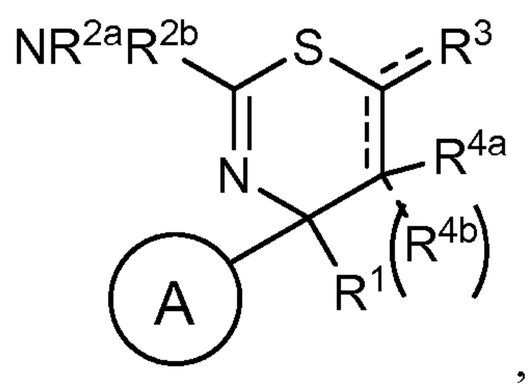
BACE is an aspartyl protease enzyme comprising 501 amino acids and responsible for processing APP at the beta-secretase specific cleavage site. BACE is present in two forms, BACE 1 and BACE 2, designated as such depending upon the specific cleavage site of APP. Beta secretase is described in Sinha et al., *Nature*, 402:537-554 (1999) (p510) and PCT application WO 2000/17369. It has been proposed that A-beta peptide accumulates as a result of APP processing by BACE. Moreover, in vivo processing of APP at the beta secretase cleavage site is thought to be a rate-limiting step in A-beta production. Sabbagh, M. et al., *Alz. Dis. Rev*. 3:1-19 (1997). Thus, inhibition of the BACE enzyme activity is desirable for the treatment of AD.

Studies have shown that the inhibition of BACE may be linked to the treatment of AD. The BACE enzyme is essential for the generation of beta-amyloid or A-beta. BACE knockout mice do not produce beta-amyloid and are free from Alzheimer's associated pathologies including neuronal loss and certain memory deficits. Cole, S.L., Vasser, R., *Molecular Degeneration* 2:22, 2007. When crossed with transgenic mice that over express APP, the progeny of BACE deficient mice show reduced amounts of A-beta in brain extracts as compares with control animals (Luo et al., *Nature Neuroscience*, 4:231-232 (2001)). The fact that BACE initiates the formation of beta-amyloid, and the observation that BACE levels are elevated in this disease provide direct and compelling reasons to develop therapies directed at BACE inhibition thus reducing beta-amyloid and its associated toxicities. To this end, inhibition of beta secretase activity and a

corresponding reduction of A-beta in the brain should provide a therapeutic method for treating AD and other beta amyloid or plaque related disorders.

Consequently, the approach of regulating or reducing the formation of A-beta peptide formation and deposition as a potential treatment for AD has received tremendous attention, support and commitment from both researchers and investors alike. A small molecule gamma-secretase inhibitor, LY450139 ("Semagacestat"), an A-beta lowering agent, advanced to phase III clinical trials for the treatment of Alzheimer's Disease. The pharmacokinetics of semagacestat in plasma, as well as the plasma and cerebral spinal fluid (CSF) A-Beta peptide levels as pharmacodynamic responses to semagacestat administration were evaluated in healthy human subjects in single and multiple doses, and pharmacokinetic and pharmacodynamic changes were also assessed in mild to moderate AD patients in two (2) clinical trials (*Expert Opin. Pharmacother*. (2009), 10 (10); *Clin. Neuropharmacol*. 2007; 30 (pgs 317-325); and *Neurology*, 2006, 66 (pgs 602-624)).

Additional approaches have been taken in attempts to treat AD and plaque-related disorders. One such approach to reduce the formation of plaque deposits in the brain involves the inhibition of and, therefore, the reduction of BACE activity. Vassar & Yan, *Lancet Neurology*, 13:319-329 (2014). For example, each of the following patent publications: WO14/098831, WO14/099794, WO14/099788, WO14/097038, WO14/093190, WO14/066132, WO14/65434, WO14/062553, WO14/062549, WO14/013076, WO13/182638, WO13/164730, WO13/030713, WO13/028670, WO13/004676, WO2012162334, WO12/162330, WO12/147762, WO2013139425, WO2012138734, US20120245157, US20120245154, US20120238557, US2009082560, US2010160290, US2010075957, WO2009151098, WO2011029803, WO2014045162, WO201105738, WO2009134617, WO201013794, WO201013302, US20110152253, US2009209755, EP 2703401 (equivalent of WO2012146762) and EP01942105 describe inhibitors of BACE, useful for treating AD and other beta-secretase mediated disorders. For Example, US20120245154 describes "Substituted Aminothiazine Derivative" as BACE inhibitors for the treatment of neurological disorders of the general formula:



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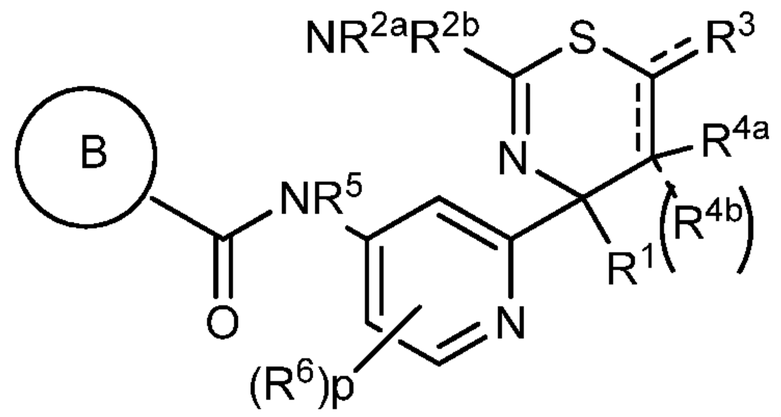
while EP2703401 describes "Pyridine Derivative and BACE1 Inhibitor Containing Same" and discloses compounds of the general formula:



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The lysosomal aspartic protease Cathepsin D (CatD) is ubiquitously expressed in eukaryotic organisms. CatD activity is essential to accomplish the acid-dependent extensive or partial proteolysis of protein substrates within endosomal and lysosomal compartments therein delivered via endocytosis, phagocytosis or autophagocytosis. CatD may also act at physiological pH on small-size substrates in the cytosol and in the extracellular milieu. Mouse and fruit fly CatD knock-out models have highlighted the multi-pathophysiological roles of CatD in tissue homeostasis and organ development.

Inhibition of protein Cathepsin D has been implicated in undesirable side effects. For instance, the inhibition of Cathepsin D is believed to be linked to adverse retinal development and retinal atrophy. Particularly, in mice it was found that cathepsin D is essential for the metabolic maintenance of retinal photoreceptor cells and that its deficiency induces apoptosis of the cells, while the loss of INL neurons is mediated by nitric oxide release from microglial cells. However, in the very same mice, it was also found that no atrophic change was detected in the retina of mice deficient in cathepsin B or L. *Mol. Cell. Neurosci*, 2003, Feb 22(2):146-161. Further, Animal models of cathepsin D (CatD) deficiency are characterized by a progressive and relentless neurodegenerative phenotype similar to that observed in Neuronal Ceroid Lipofuscinoses (NCL), a group of pediatric neurodegenerative diseases known collectively as Batten Disease. It has been shown that the targeted deletion of the pro-apoptotic molecule Bax prevents apoptotic markers but not neuronal cell death and neurodegeneration induced by CatD deficiency, which suggests that alterations in the macroautophagy-lysosomal degradation pathway can mediate neuronal cell death in NCL/Batten Disease in the absence of apoptosis. *Autophagy*, 2007, Sept-Oct;3(5):474-476. Finally, an adverse effect of the inhibition of Cat D is evident from the data presented in *PLoS One*, 2011; 6(7):e21908, published 7-1-2011. The authors of the PLoS One paper found that knock-down of cathepsin D affects the retinal pigment epithelium, impairs swim-bladder ontogenesis and causes premature

death in zebrafish. The main phenotypic alterations produced by CatD knock-down in zebrafish were: 1. abnormal development of the eye and of retinal pigment epithelium; 2. absence of the swim-bladder; 3. skin hyper-pigmentation; 4. reduced growth and premature death. Rescue experiments confirmed the involvement of CatD in the developmental processes leading to these phenotypic alterations.

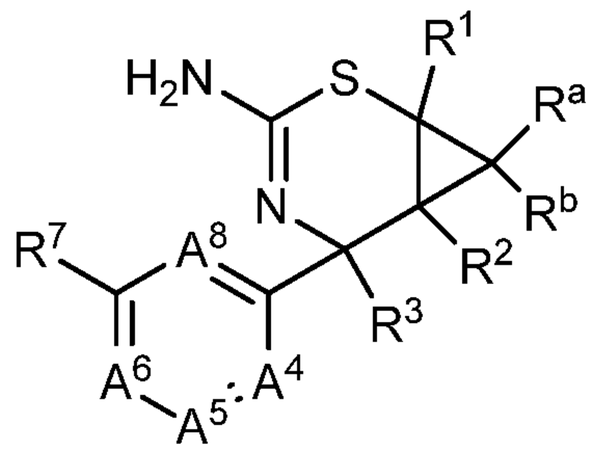
Moreover, such toxicity findings which, in view of the literature, may have played a role in the termination of a human Bace-mediated Alzheimer's Disease clinical trial. Eli Lilly terminated a phase I clinical trial of LY 2811376 after rat toxicology studies showed that a higher compound dose given for three months damaged the pigment epithelium of the rat's eye. The retinal layer had inclusions and extensive damage. The Ph I dosing trial was terminated and people brought in for eye assessments did not show any abnormalities. (Alzheimer's Research Forum News, 3-31-2011 reporting on Martin Citron's presentation at the AD/PD Conference 3-2011 in Barcelona, Spain)

Hence, it is desirable to provide compounds which modulate the activity of and are reasonably selective for BACE, while not suffering from undesirable side effects possibly due to intervention with or the reduction and/or direct or indirect inhibition of the expression and/or function of other proteins or biological pathways.

BRIEF DESCRIPTION OF THE INVENTION

The present invention provides a new class of compounds useful for the modulation of beta secretase activity, and as treatment of AD. Particularly, the compounds of the invention are useful for the regulation or reduction of the formation of A-beta peptide and, consequently, the regulation and/or reduction of formation of beta amyloid plaque both on the brain, as well as in the CNS. To this end, the compounds are useful for the treatment of AD and other beta secretase and/or plaque-related and/or mediated disorders. For example, the compounds are useful for the prophylaxis and/or treatment, acute and/or chronic, of AD and other diseases or conditions involving the deposition or accumulation of beta amyloid peptide, and formation of plaque, on the brain.

The compounds provided by the invention, including stereoisomers, tautomers, hydrates, solvates and pharmaceutically acceptable salts thereof, are generally defined by Formula I



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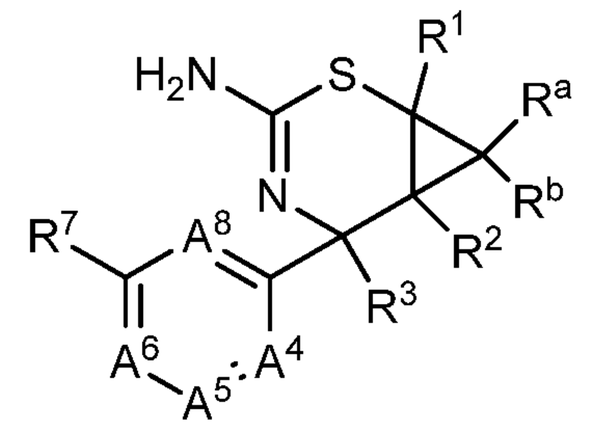
wherein each of A^4, A^5, A^6, A^8, R^a, R^b, R^1, R^2, R^3 and R^7 of Formula I are defined below. The invention also provides procedures for making compounds of Formula I, and sub-Formulas thereof, as well as intermediates useful in such procedures.

The invention further provides pharmaceutical compositions comprising compounds of the invention, and uses of these compositions in the treatment of beta secretase mediated diseases. For example, and in one embodiment, the invention provides a pharmaceutical composition comprising an effective dosage amount of a compound of Formula I in association with at least one pharmaceutically acceptable excipient.

The foregoing merely summarizes certain aspects of the invention and is not intended, nor should it be construed, as limiting the invention in any way. All patents and other publications recited herein are hereby incorporated by reference in their entirety.

DETAILED DESCRIPTION OF THE INVENTION

In embodiment 1 of the invention, there are provided compounds, including stereoisomers, tautomers, hydrates, solvates and pharmaceutically acceptable salts thereof, which are generally defined by Formula I:



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or a stereoisomer, tautomer, hydrate, solvate or pharmaceutically acceptable salt thereof, wherein

A^4 is CR^4 or N;

A^5 is CR^5 or N;

A^6 is CR^6 or N;

A^8 is CR^8 or N, provided that no more than two of A^4, A^5, A^6 and A^8 is N;

each of R^a and R^b, independently, is H, F, Cl, C_{1-6}-alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, CN, -CH_2OC_{1-6}-alkyl, -OC_{1-6}-alkyl, -$S(O)_oC_{1-6}$-alkyl, -NHC_{1-6}-alkyl or -$C(O)C_{1-6}$-alkyl, wherein each of the C_{1-6}-alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, and C_{1-6}-alkyl portion of -CH_2OC_{1-6}-alkyl, -OC_{1-6}-alkyl, -$S(O)_oC_{1-6}$-alkyl, -NHC_{1-6}-alkyl and -$C(O)C_{1-6}$-alkyl are optionally substituted with 1-4 substituents of F, oxo or OH;

each of R^1 and R^2, independently, is H, F, Cl, C_{1-6}-alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, CN, -CH_2OC_{1-6}-alkyl, -OC_{1-6}-alkyl, -$S(O)_oC_{1-6}$-alkyl, -NHC_{1-6}-alkyl, -$C(O)NH_2$, -$CH=CHC(O)NHC_{1-6}$-alkyl, -$CH=CHC(O)_2H$, -$CH=CHCH_2OH$, C_{1-6}-alkyl-$C(O)NHC_{1-6}$-alkyl, $C(O)C_{1-6}$-alkyl or -$C(O)C_{1-6}$-alkenyl, wherein each of the C_{1-6}-alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, and C_{1-6}-alkyl portion of -CH_2OC_{1-6}-alkyl, -OC_{1-6}-alkyl, -$S(O)_oC_{1-6}$-alkyl, -NHC_{1-6}-alkyl, $C(O)C_{1-6}$-alkyl, -$C(O)C_{1-6}$-alkenyl, -$CH=CHC(O)NHC_{1-6}$-alkyl and C_{1-6}-alkyl-$C(O)NHC_{1-6}$-alkyl, are optionally substituted with 1-4 substituents of F, CN, oxo or OH;

R^3 is C_{1-4}alkyl, CH_2OC_{1-4}alkyl, CH_2OH, C_{1-4}haloalkyl or cyclopropyl, wherein each of the C_{1-4}alkyl, CH_2OC_{1-4}alkyl, C_{1-4}haloalkyl and cyclopropyl is optionally substituted with 1-4 F atoms;

each of R^4, R^5, R^6 and R^8, independently, is H, halo, haloalkyl, haloalkoxyl, C_{1-4}-alkyl, CN, OH, OC_{1-4}-alkyl, $S(O)_oC_{1-4}$-alkyl, NHC_{1-4}-alkyl or $C(O)C_{1-4}$-alkyl;

R^7 is –NH-R^9 or -NH-C(=O)-R^9;

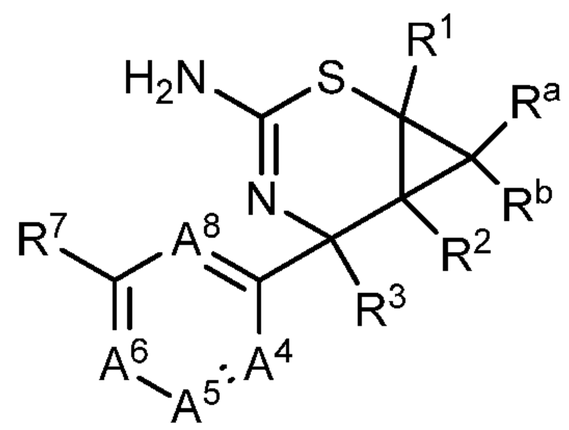
R^9 is a fully or partially unsaturated 3-, 4-, 5-, 6- or 7-membered monocyclic or 8-, 9- or 10-membered bicyclic ring formed of carbon atoms, said ring optionally including 1-4 heteroatoms if monocyclic or 1-5 heteroatoms if bicyclic, said heteroatoms selected from O, N or S, wherein the ring is optionally substituted, independently, with 1-5 substituents of R^{10};

each R^{10}, independently, is H, halo, haloalkyl, CN, OH, NO_2, NH_2, SF_5, acetyl, -$C(O)NHCH_3$, oxo, cyclopropylmethoxy, 2-propynyloxy, 2-butynyloxy, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkylamino-, C_{1-6}dialkylamino-, C_{1-6}alkoxyl, C_{1-6}thioalkoxyl, morpholinyl, pyrazolyl, isoxazolyl, dihydropyranyl, pyrrolyl, pyrrolidinyl, tetrahydropyrrolyl, piperazinyl, oxetan-3-yl, imidazo-pyridinyl or dioxolyl, wherein each of the cyclopropylmethoxy, 2-propynyloxy, 2-butynyloxy, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkylamino-, C_{1-6}dialkylamino-, C_{1-6}alkoxyl, C_{1-6}thioalkoxyl, morpholinyl, pyrazolyl, isoxazolyl, dihydropyranyl, pyrrolidinyl, oxetan-3-yl or dioxolyl,

is optionally substituted independently with 1-5 substituents of F, Cl, CN, NO_2, NH_2, OH, oxo, CF_3, CHF_2, CH_2F, methyl, methoxy, ethyl, ethoxy, CH_2CF_3, CH_2CHF_2, propyl, propoxy, isopropyl, isopropoxy, cyclopropyl, butyl, butoxyl, cyclobutyl, isobutoxy, *tert*-butoxy, isobutyl, sec-butyl, tert-butyl, cyclopentyl, cyclohexyl, C_{1-3}alkylamino-, C_{1-3}dialkylamino, C_{1-3}thioalkoxyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, thienyl, furyl, pyrrolyl, tetrahydropyranyl, tetrahydropyrrolyl or oxetan-3yl; and

the subscript o is selected from 0, 1, or 2.

In an alternative embodiment 1 of the invention, there are provided compounds, including stereoisomers, tautomers, hydrates, solvates and pharmaceutically acceptable salts thereof, which are generally defined by Formula I:



I

wherein

A^4 is CR^4 or N;

A^5 is CR^5 or N;

A^6 is CR^6 or N;

A^8 is CR^8 or N, provided that no more than two of A^4, A^5, A^6 and A^8 is N;

each of R^a and R^b, independently, is H, F, Cl, C_{1-6}-alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, CN, -CH_2OC_{1-6}-alkyl, -OC_{1-6}-alkyl, -$S(O)_oC_{1-6}$-alkyl, -NHC_{1-6}-alkyl or -$C(O)C_{1-6}$-alkyl, wherein each of the C_{1-6}-alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, and C_{1-6}-alkyl portion of -CH_2OC_{1-6}-alkyl, -OC_{1-6}-alkyl, -$S(O)_oC_{1-6}$-alkyl, -NHC_{1-6}-alkyl and -$C(O)C_{1-6}$-alkyl are optionally substituted with 1-4 substituents of F, oxo or OH;

R^1 and either R^a or R^b may optionally join to form a 5-membered saturated ring that includes one S heteroatom;

R^1 is H, F, Cl, C_{1-6}-alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, CN, -CH_2OC_{1-6}-alkyl, -OC_{1-6}-alkyl, -$S(O)_oC_{1-6}$-alkyl, -NHC_{1-6}-alkyl, -C_{1-6}-alkylNH_2, -C_{1-6}-alkylNHC_{1-6}-alkyl, -C_{1-6}-alkyl$NHC(O)OC_{1-6}$-alkyl, -C_{1-6}-alkyl$NHC(O)NHC_{1-6}$-alkyl, -C_{1-6}-alkyl$NHC(O)C_{1-6}$-alkyl, -$C(O)NH_2$, -CH=CHC(O)NH_2, -CH=CHC(O)NHC_{1-6}-alkyl, -CH=CHC(O)$N(C_{1-6}$-alkyl$)_2$, -CH=CHC(O)NHC_{1-6}-alkyl-OC_{1-6}-alkyl, -CH=CHC(O)-heterocyclyl, -

$CH=C(CH_3)C(O)$-heterocyclyl,-$CH=CHC(O)_2H$, -$CH=CHC(O)OC_{1-6}$-alkyl, -$CH=CHCH_2OH$, C_{1-6}-alkyl-$C(O)NHC_{1-6}$-alkyl, C_{1-6}-alkyl-$C(O)N(C_{1-6}$-$alkyl)_2$, -$C(O)C_{1-6}$-alkyl, -$C(O)C_{1-6}$-alkenyl, -C(O)OH, -$C(O)OC_1$-C_6alkyl, -$C(O)NHC_{1-6}$-alkyl ,-$C(O)N(C_{1-6}$-$alkyl)_2$, -$C(O)NHC_{3-6}$cycloalkyl, -$C(O)NHOC_{1-6}$-alkyl, -$C(O)N(C_{1-6}$-$alkyl)OC_{1-6}$-alkyl, -C(O)-heterocyclyl, -CH_2-heteroaryl, or heteroaryl, wherein the heterocyclyl groups of the -$CH=CHC(O)$-heterocyclyl, -$CH=C(CH_3)C(O)$-heterocyclyl, and -C(O)-heterocyclyl groups are fully or partially unsaturated 3-, 4-, 5-, 6- or 7-membered monocyclic rings that include 1 heteroatom selected from N, O, or S if the ring is a 3-membered ring, that include 1 or 2 heteroatoms independently selected from N, O, or S if the ring is a 4- or 5-membered ring, and include 1, 2, or 3 heteroatoms independently selected from N, O, or S if the ring is a 6- or 7-membered ring, wherein the heteroaryl groups of the -CH_2-heteroaryl and heteroaryl groups is a 5- or 6- membered ring that includes 1, 2, 3, or 4 heteroatoms selected from N, O, or S, wherein each of the C_{1-6}-alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, and C_{3-6}cycloalkyl portion of C_{1-6}-alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl ,-CH_2OC_{1-6}-alkyl, -OC_{1-6}-alkyl, -$S(O)_oC_{1-6}$-alkyl, -NHC_{1-6}-alkyl, $C(O)C_{1-6}$-alkyl, -$C(O)C_{1-6}$-alkenyl, -$C(O)NHC_{1-6}$-alkyl ,-$C(O)N(C_{1-6}$-$alkyl)_2$, -$C(O)NHC_{3-6}$cycloalkyl, -$CH=CHC(O)NHC_{1-6}$-alkyl and C_{1-6}-alkyl-$C(O)NHC_{1-6}$-alkyl groups are optionally substituted with 1-4 substituents of F, CN, methyl, oxo, or OH, and further wherein each of the heterocyclyl groups of the -$CH=CHC(O)$-heterocyclyl, -$CH=C(CH_3)C(O)$-heterocyclyl, and -C(O)heterocyclyl groups is optionally substituted with 1-4 substituents independently selected from F, methyl, OH, or OCH_3, and further wherein each of the heteroaryl groups of the -CH_2-heteroaryl and heteroaryl groups is optionally substituted with 1-3 substituents independently selected from halo, methyl, or OH;

R^2 is H, F, Cl, C_{1-6}-alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, CN, -CH_2OC_{1-6}-alkyl, -OC_{1-6}-alkyl, -$S(O)_oC_{1-6}$-alkyl, -NHC_{1-6}-alkyl, -$C(O)NH_2$, -$CH=CHC(O)NHC_{1-6}$-alkyl, -$CH=CHC(O)_2H$, -$CH=CHCH_2OH$, C_{1-6}-alkyl-$C(O)NHC_{1-6}$-alkyl, -$C(O)C_{1-6}$-alkyl or -$C(O)C_{1-6}$-alkenyl, wherein each of the C_{1-6}-alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, and C_{1-6}-alkyl portion of -CH_2OC_{1-6}-alkyl, -OC_{1-6}-alkyl, -$S(O)_oC_{1-6}$-alkyl, -NHC_{1-6}-alkyl, $C(O)C_{1-6}$-alkyl, -$C(O)C_{1-6}$-alkenyl, -$CH=CHC(O)NHC_{1-6}$-alkyl and C_{1-6}-alkyl-$C(O)NHC_{1-6}$-alkyl, are optionally substituted with 1-4 substituents of F, CN, oxo or OH;

R^3 is C_{1-4}alkyl, CH_2OC_{1-4}alkyl, CH_2OH, C_{1-4}haloalkyl or cyclopropyl, wherein each of the C_{1-4}alkyl, CH_2OC_{1-4}alkyl, C_{1-4}haloalkyl and cyclopropyl is optionally substituted with 1-4 F atoms;

each of R^4, R^5, R^6 and R^8, independently, is H, halo, haloalkyl, haloalkoxyl, C_{1-4}-alkyl, CN, OH, OC_{1-4}-alkyl, $S(O)_oC_{1-4}$-alkyl, NHC_{1-4}-alkyl,$C(O)C_{1-4}$-alkyl, $C(O)OC_{1-4}$-alkyl, or CH_2OH;

R^7 is –NH-R^9 or -NH-C(=O)-R^9;

R^9 is a fully or partially unsaturated 3-, 4-, 5-, 6- or 7-membered monocyclic or 8-, 9- or 10-membered bicyclic ring formed of carbon atoms, said ring optionally including 1-4 heteroatoms if monocyclic or 1-5 heteroatoms if bicyclic, said heteroatoms selected from O, N or S, wherein the ring is optionally substituted, independently, with 1-5 substituents of R^{10};

each R^{10}, independently, is H, halo, haloalkyl, CN, OH, NO_2, NH_2, SF_5, acetyl, -$C(O)NHC_{1-6}$-alkyl, -$OCH_2C(O)NHC_{1-6}$-alkyl, -$OCH_2C(O)N(C_{1-6}$-alkyl$)_2$, -OCH_2CH_2-pyrollidinonyl, oxo, cyclopropylmethoxy, 2-propynyloxy, 2-butynyloxy, 3-butynyloxy , 3-pentynyloxy, 2-pentyloxy, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkylamino-, C_{1-6}dialkylamino-, C_{1-6}alkoxyl, -OC_2-C_6alkenyl, C_{1-6}thioalkoxyl, -OCH_2C_{3-6}cycloaklyl, morpholinyl, pyrazolyl, isoxazolyl, dihydropyranyl, pyrrolyl, pyrrolidinyl, tetrahydropyrrolyl, piperazinyl, oxetan-3-yl, imidazo-pyridinyl, dioxolyl, -O-heterocyclyl, or –OCH_2-heteroaryl, wherein the heterocyclyl of the -O-heterocyclyl group is a 3-, 4-, 5-, 6- or 7-membered monocyclic saturated ring that includes 1 heteroatom selected from N, O, or S if the heterocyclyl ring is a 3-membered ring, that includes 1 or 2 heteroatoms independently selected from N, O, or S if the heterocyclyl ring is a 4- or 5-membered ring, and includse 1, 2, or 3 heteroatoms independently selected from N, O, or S if the heterocyclyl ring is a 6- or 7-membered ring wherein the heteroaryl group of the –OCH_2-heteroaryl group is a 5- or 6- membered ring that includes 1, 2, 3, or 4 heteroatoms selected from N, O, or S, and further wherein each of the cyclopropylmethoxy, 2-propynyloxy, 2-butynyloxy, 2-pentyloxy, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkylamino-, C_{1-6}dialkylamino-, C_{1-6}alkoxyl, C_{1-6}thioalkoxyl, , -OCH_2C_{3-6}cycloaklyl, morpholinyl, pyrazolyl, isoxazolyl, dihydropyranyl, pyrrolidinyl, oxetan-3-yl, dioxolyl, or –OCH_2-heteroaryl is optionally substituted independently with 1-5 substituents of F, Cl, Br, CN, NO_2, NH_2, OH, oxo, CF_3, CHF_2, CH_2F, methyl, methoxy, ethyl, ethoxy, CH_2CF_3, CH_2CHF_2, propyl, propoxy, isopropyl, isopropoxy, cyclopropyl, butyl, butoxyl, cyclobutyl, isobutoxy, *tert*-butoxy, isobutyl, sec-butyl, *tert*-butyl, cyclopentyl, cyclohexyl, phenyl, C_{1-3}alkylamino-, C_{1-3}dialkylamino, C_{1-3}thioalkoxyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, thienyl, furyl, pyrrolyl, tetrahydropyranyl, tetrahydropyrrolyl, oxetan-2-yl, or oxetan-3yl; and

the subscript o is selected from 0, 1, or 2.

In some embodiments of the alternative embodiment 1, the invention provides compounds according to alternative embodiment 1, or a stereoisomer or pharmaceutically acceptable salt thereof wherein R^1 is a -CH_2-heteroaryl or a heteroaryl and the heteroaryl groups of the -CH_2-heteroaryl and heteroaryl is selected from triazolyl, oxazolyl, or isoxazolyl optionally substituted with 1 or 2 methyl groups. In some such embodiments, R^{10} is a -OCH_2-heteroaryl and the heteroaryl group of the -OCH_2-heteroaryl is selected from an oxadiazolyl, thiadiazolyl, oxazolyl, thiazolyl, pyridinyl, or pyrimidinyl optionally substituted independently with 1 or 2 F, Cl, Br, or methyl groups.

In some embodiments of the alternative embodiment 1, the invention provides compounds according to alternative embodiment 1, or a stereoisomer or pharmaceutically acceptable salt thereof wherein, R^{10} is a -OCH_2-heteroaryl and the heteroaryl group of the -OCH_2-heteroaryl is selected from an oxadiazolyl, thiadiazolyl, oxazolyl, isoxazolyl, thiazolyl, pyridinyl, or pyrimidinyl optionally substituted independently with 1 or 2 F, Cl, Br, or methyl groups.

In embodiment 2, the invention provides compounds according to embodiment 1, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein each of R^1 and R^2, independently, is H, F, CH_3, CH_2OCH_3, CH_2F, CHF_2, CF_3, -$C(O)NH_2$, -$CH=CHC(O)NHC_{1\text{-}6}$alkyl, -$CH=CHC(O)_2H$, -$CH=CHCH_2OH$ or $C_{1\text{-}6}$-alkyl-$C(O)NHC_{1\text{-}6}$-alkyl.

In embodiment 3, the invention provides compounds according to any one of embodiments 1 and 2, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein each of R^a and R^b, independently, is H, F, CH_3, CH_2F, CHF_2 or CF_3.

In embodiment 4, the invention provides compounds according to any one of embodiments 1, 2 and 3, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein each of R^1 and R^2, independently, is H, F, CH_2OCH_3, or CF_3.

In embodiment 5, the invention provides compounds according to any one of embodiments 1-4, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein each of R^a and R^b, independently, is H or F.

In embodiment 6, the invention provides compounds according to any one of embodiments 1-5, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein each of H, F, CH_2OCH_3, or CF_3; and each of R^a and R^b, independently, is H or F.

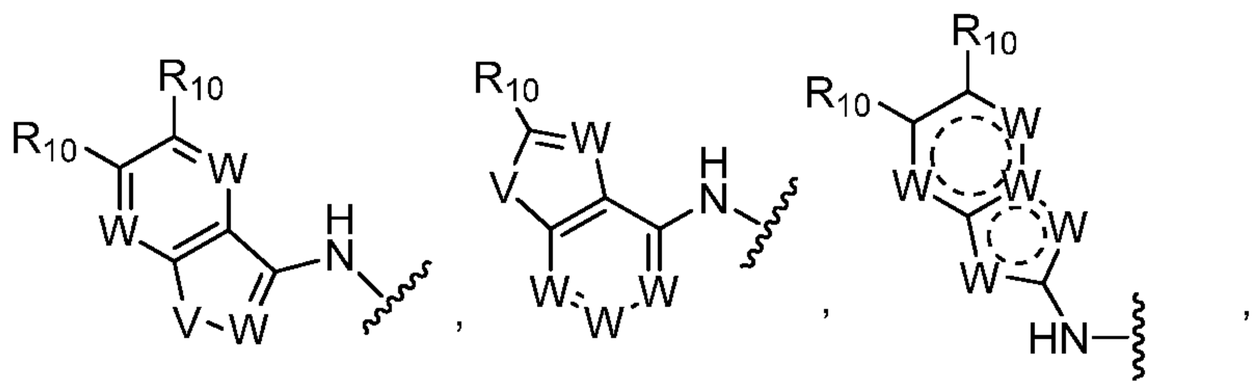
In embodiment 6a, the invention provides compounds according to any one of embodiments 1-5, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein each of H or CH_2OCH_3; and each of R^a and R^b, independently, is H.

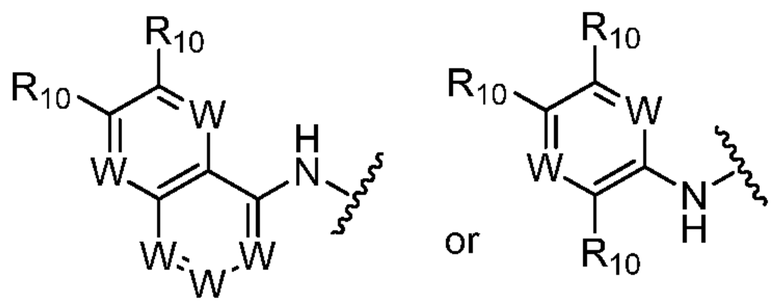
In embodiment 7, the invention provides compounds according to any one of embodiments 1-6, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein each of R^1, R^2, R^a and R^b, independently, is H.

In embodiment 8, the invention provides compounds according to any one of embodiments 1-7, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R^3 is CH_3, CF_3, CH_2F or CHF_2.

In embodiment 9, the invention provides compounds according to any one of embodiments 1-8, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R^7 is -NH-C(=O)-R^9;

or R^7 is





wherein V is NR^{10}, O or S; and

each W, independently, is CH, CF, CCl, CCH_3 or N.

In embodiment 10, the invention provides compounds according to any one of embodiments 1 and 9, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein

A^4 is CR^4 or N;

A^5 is CR^5 or N;

A^6 is CR^6 or N;

A^8 is CR^8 or N, provided that no more than one of A^4, A^5, A^6 and A^8 is N;

each of R^a and R^b, independently, is H, F, Cl, CF_3, OCF_3, methyl, ethyl, CN, OH, OCH_3, SCH_3, $NHCH_3$, $C(O)CH_3$ or CH_2OCHF_2;

each of R^1 and R^2, independently, is H, F, Cl, CF_3, OCF_3, methyl, ethyl, CN, OH, OCH_3, SCH_3, $NHCH_3$, $C(O)CH_3$, CH_2OCH_3 or CH_2OCHF_2;

R^3 is C_{1-4}alkyl, C_{1-4}haloalkyl, CH_2OH, CH_2OCHF_2 or cyclopropyl; and

each of R^4, R^5, R^6 and R^8, independently, is H, F, Cl, CF_2H, CH_2F, CF_3, OCF_3, methyl, ethyl, CN, OH, OCH_3, SCH_3, $NHCH_3$ or $C(O)CH_3$.

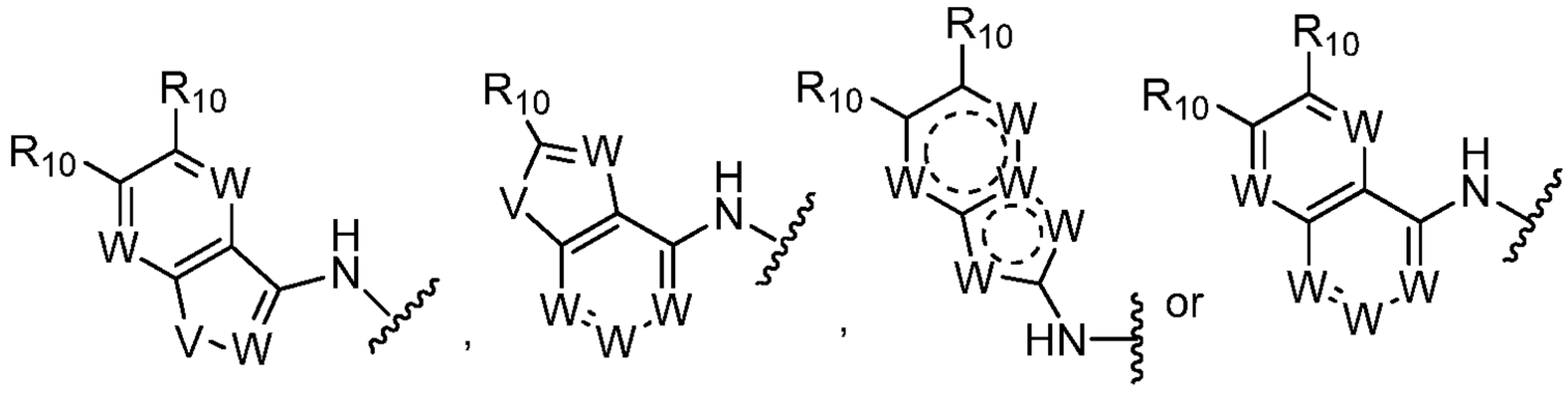
In embodiment 11, the invention provides compounds according to any one of embodiments 1-9, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein

each of R^1 and R^2, independently, is H, F, CH_2OCH_3 or CF_3;

each of R^a and R^b, independently, is H or F;

R^3 is CH_3, CF_3, CH_2F or CHF_2; and

R^7 is -NH-C(=O)-R^9 or

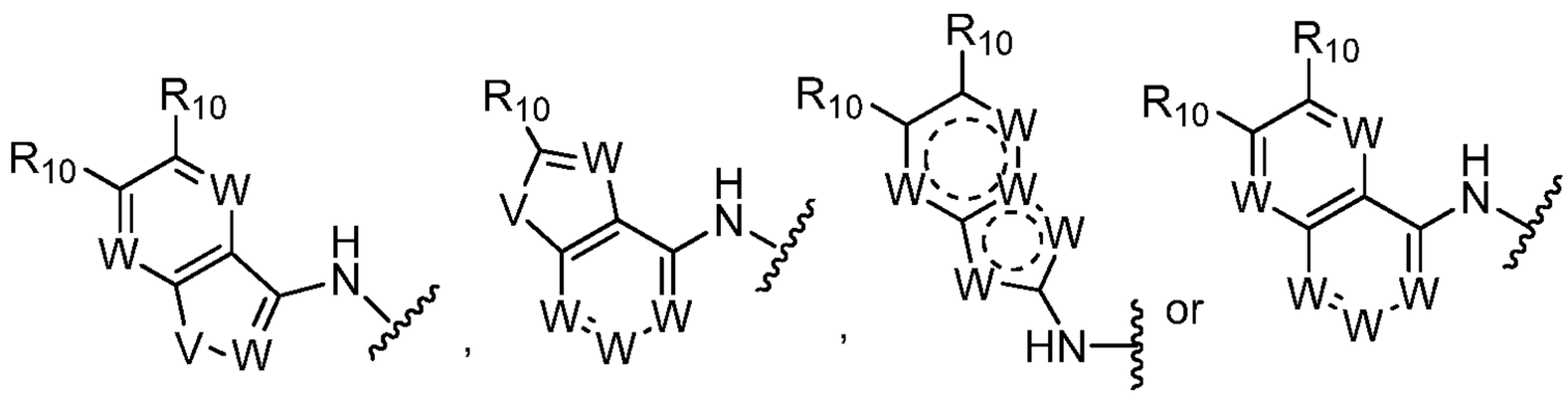


wherein V is NR^{10}, O or S; and

each W, independently, is CH, CF, CCl, CCH_3 or N.

In embodiment 12, the invention provides compounds according to any one of embodiments 1-11, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R^7 is -NH-C(=O)-R^9.

In embodiment 13, the invention provides compounds according to any one of embodiments 1-11, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R^7 is



wherein V is NR^{10}, O or S; and

each W, independently, is CH, CF, CCl, CCH_3 or N.

In embodiment 14, the invention provides compounds according to any one of embodiments 1-13, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein

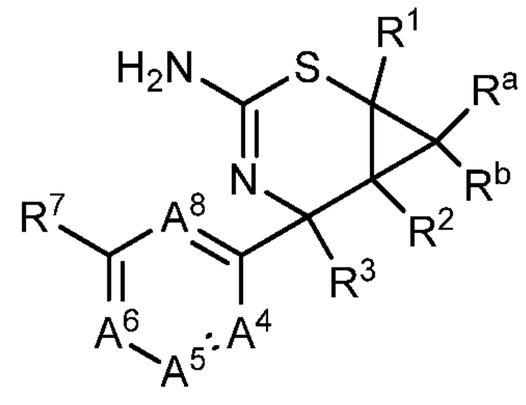
A^4 is CR^4;

A^5 is CR^5 or N;

A^6 is CR^6; and

A^8 is CR^8 or N, provided only one of A^5 and A^8 is N, and wherein each of R^4, R^5, R^6 and R^8, independently, is H, F, Cl, CF_3, CF_2H, CH_2F or CH_3.

In embodiment 15, the invention provides compounds, including stereoisomers, tautomers, hydrates, solvates and pharmaceutically acceptable salts thereof, which are generally defined by Formula I:



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or a stereoisomer, tautomer, hydrate, solvate or pharmaceutically acceptable salt thereof, wherein

A^4 is CH, CF or CCl;

A^5 is CH, CF, CCl, CCH_3 or N;

A^6 is CH or CF;

A^8 is CH, CF or N, provided that no more than one of A^5 and A^8 is N;

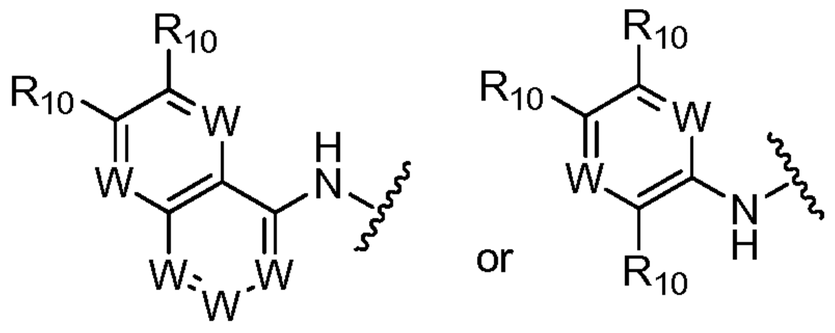
each of R^1 and R^2, independently, is H, F, CH_3, CH_2OCH_3, CH_2F, CHF_2 or CF_3;

each of R^a and R^b, independently, is H, F, CH_3, CH_2F, CHF_2 or CF_3;

R^3 is $C_{1\text{-}4}$alkyl, $CH_2OC_{1\text{-}4}$alkyl, CH_2OH, $C_{1\text{-}4}$haloalkyl or cyclopropyl, wherein each of the $C_{1\text{-}4}$alkyl, $CH_2OC_{1\text{-}4}$alkyl, $C_{1\text{-}4}$haloalkyl and cyclopropyl is optionally substituted with 1-4 F atoms;

R^7 is $-NH-R^9$ or $-NH-C(=O)-R^9$;

or R^7 is



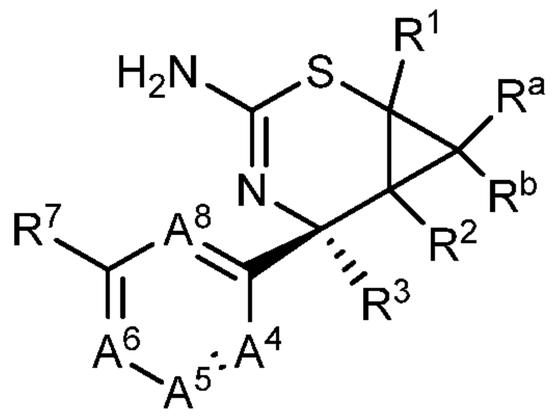
wherein V is NR^{10}, O or S; and

each W, independently, is CH, CF, CCl, CCH_3 or N;

R^9 is a ring selected from phenyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, pyrazolyl, pyrazolo[3,4-c]pyridinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl or thienyl, wherein the ring is optionally substituted with 1-5 substituents of R^{10}; and

each R^{10}, independently, is H, halo, haloalkyl, CN, OH, NO_2, NH_2, SF_5, acetyl, $-C(O)NHCH_3$, oxo, cyclopropylmethoxy, 2-propynyloxy, 2-butynyloxy, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkylamino-, C_{1-6}dialkylamino-, C_{1-6}alkoxyl, C_{1-6}thioalkoxyl, morpholinyl, pyrazolyl, isoxazolyl, dihydropyranyl, pyrrolyl, pyrrolidinyl, tetrahydropyrrolyl, piperazinyl, oxetan-3-yl, imidazo-pyridinyl or dioxolyl, wherein each of the cyclopropylmethoxy, 2-propynyloxy, 2-butynyloxy, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkylamino-, C_{1-6}dialkylamino-, C_{1-6}alkoxyl, C_{1-6}thioalkoxyl, morpholinyl, pyrazolyl, isoxazolyl, dihydropyranyl, pyrrolidinyl, oxetan-3-yl or dioxolyl, is optionally substituted independently with 1-5 substituents of F, Cl, CN, NO_2, NH_2, OH, oxo, CF_3, CHF_2, CH_2F, methyl, methoxy, ethyl, ethoxy, CH_2CF_3, CH_2CHF_2, propyl, propoxy, isopropyl, isopropoxy, cyclopropyl, butyl, butoxyl, cyclobutyl, isobutoxy, *tert*-butoxy, isobutyl, sec-butyl, *tert*-butyl, cyclopentyl, cyclohexyl, C_{1-3}alkylamino-, C_{1-3}dialkylamino, C_{1-3}thioalkoxyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, thienyl, furyl, pyrrolyl, tetrahydropyranyl, tetrahydropyrrolyl or oxetan-3yl.

In embodiment 16, the invention provides compounds, including stereoisomers, tautomers, hydrates, solvates and pharmaceutically acceptable salts thereof, which are generally defined by Formula II:



II

wherein

A^4 is CR^4 or N;

A^5 is CR^5 or N;

A^6 is CR^6 or N;

A^8 is CR^8 or N, provided that no more than two of A^4, A^5, A^6 and A^8 is N;

each of R^a and R^b, independently, is H, F, Cl, C_{1-6}-alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, CN, $-CH_2OC_{1-6}$-alkyl, $-OC_{1-6}$-alkyl, $-S(O)_oC_{1-6}$-alkyl, $-NHC_{1-6}$-alkyl or $-C(O)C_{1-6}$-alkyl, wherein each of the C_{1-6}-alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, and C_{1-6}-alkyl portion of $-CH_2OC_{1-6}$-alkyl, $-OC_{1-6}$-alkyl, $-S(O)_oC_{1-6}$-alkyl, $-NHC_{1-6}$-alkyl and $-C(O)C_{1-6}$-alkyl are optionally substituted with 1-4 substituents of F, oxo or OH;

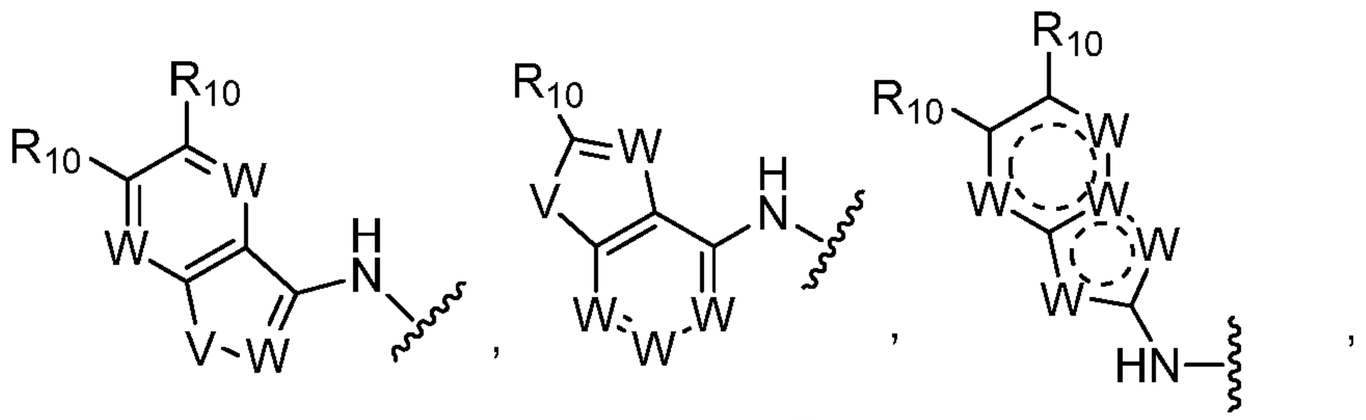
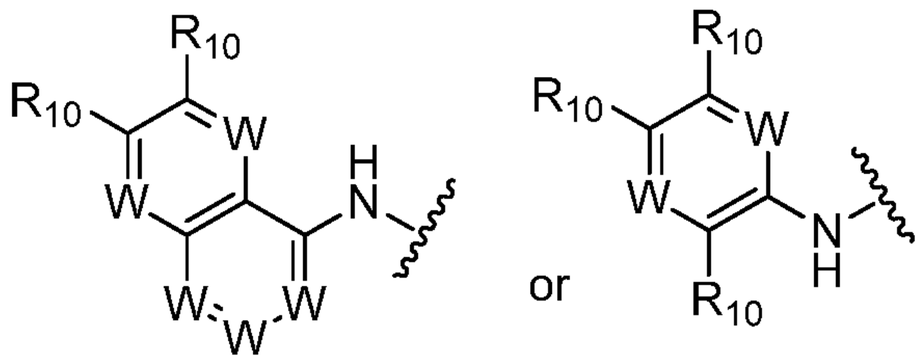
each of R^1 and R^2, independently, is H, F, Cl, C_{1-6}-alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, CN, $-CH_2OC_{1-6}$-alkyl, $-OC_{1-6}$-alkyl, $-S(O)_oC_{1-6}$-alkyl, $-NHC_{1-6}$-alkyl, $-C(O)NH_2$, $-CH=CHC(O)NHC_{1-6}$-alkyl, $-CH=CHC(O)_2H$, $-CH=CHCH_2OH$, C_{1-6}-alkyl-$C(O)NHC_{1-6}$-alkyl, $-C(O)C_{1-6}$-alkyl or $-C(O)C_{1-6}$-alkenyl, wherein each of the C_{1-6}-alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, and C_{1-6}-alkyl portion of $-CH_2OC_{1-6}$-alkyl, $-OC_{1-6}$-alkyl, $-S(O)_oC_{1-6}$-alkyl, $-NHC_{1-6}$-alkyl, $C(O)C_{1-6}$-alkyl, $-C(O)C_{1-6}$-alkenyl, $-CH=CHC(O)NHC_{1-6}$-alkyl and C_{1-6}-alkyl-$C(O)NHC_{1-6}$-alkyl, are optionally substituted with 1-4 substituents of F, CN, oxo or OH;

R^3 is C_{1-4}alkyl, CH_2OC_{1-4}alkyl, CH_2OH, C_{1-4}haloalkyl or cyclopropyl, wherein each of the C_{1-4}alkyl, CH_2OC_{1-4}alkyl, C_{1-4}haloalkyl and cyclopropyl is optionally substituted with 1-4 F atoms;

each of R^4, R^5, R^6 and R^8, independently, is H, halo, haloalkyl, haloalkoxyl, C_{1-4}-alkyl, CN, OH, OC_{1-4}-alkyl, $S(O)_oC_{1-4}$-alkyl, NHC_{1-4}-alkyl or $C(O)C_{1-4}$-alkyl;

R^7 is $-NH-C(=O)-R^9$;

or R^7 is

wherein V is NR^{10}, O or S; and

each W, independently, is CH, CF, CCl, CCH_3 or N;

R^9 is a fully or partially unsaturated 3-, 4-, 5-, 6- or 7-membered monocyclic or 8-, 9- or 10-membered bicyclic ring formed of carbon atoms, said ring optionally including 1-4 heteroatoms if monocyclic or 1-5 heteroatoms if bicyclic, said heteroatoms selected from O, N or S, wherein ring is optionally substituted, independently, with 1-5 substituents of R^{10};

each R^{10}, independently, is H, halo, haloalkyl, CN, OH, NO_2, NH_2, SF_5, acetyl, $-C(O)NHCH_3$, oxo, cyclopropylmethoxy, 2-propynyloxy, 2-butynyloxy, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkylamino-, C_{1-6}dialkylamino-, C_{1-6}alkoxyl, C_{1-6}thioalkoxyl, morpholinyl, pyrazolyl, isoxazolyl, dihydropyranyl, pyrrolyl, pyrrolidinyl, tetrahydropyrrolyl, piperazinyl, oxetan-3-yl, imidazo-pyridinyl or dioxolyl, wherein each of the cyclopropylmethoxy, 2-propynyloxy, 2-butynyloxy, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkylamino-, C_{1-6}dialkylamino-, C_{1-6}alkoxyl, C_{1-6}thioalkoxyl, morpholinyl, pyrazolyl, isoxazolyl, dihydropyranyl, pyrrolidinyl, oxetan-3-yl or dioxolyl, is optionally substituted independently with 1-5 substituents of F, Cl, CN, NO_2, NH_2, OH, oxo, CF_3, CHF_2, CH_2F, methyl, methoxy, ethyl, ethoxy, CH_2CF_3, CH_2CHF_2, propyl, propoxy, isopropyl, isopropoxy, cyclopropyl, butyl, butoxyl, cyclobutyl, isobutoxy, *tert*-butoxy, isobutyl, sec-butyl, *tert*-butyl, cyclopentyl, cyclohexyl, C_{1-3}alkylamino-, C_{1-3}dialkylamino, C_{1-3}thioalkoxyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, thienyl, furyl, pyrrolyl, tetrahydropyranyl, tetrahydropyrrolyl or oxetan-3yl; and

the subscript o is selected from 0, 1, or 2.

In embodiment 17, the invention provides compounds according any one of embodiments 1 and 16, or a stereoisomer, tautomer or pharmaceutically acceptable salt thereof, wherein

A^4 is CR^4 or N;

A^5 is CR^5 or N;

A^6 is CR^6 or N;

A^8 is CR^8 or N, provided no more than one of A^4, A^5, A^6 and A^8 is N;

each of R^a and R^b, independently, is H, F, CH_3, CH_2F, CHF_2 or CF_3;

each of R^1 and R^2, independently, is H, F, CH_3, CH_2OCH_3, CH_2F, CHF_2 or CF_3;

R^3 is C_{1-4}alkyl, C_{1-4}haloalkyl, CH_2OH, CH_2OCHF_2 or cyclopropyl; and

each of R^4, R^5, R^6 and R^8, independently, is H, F, Cl, CF_2H, CH_2F, CF_3, OCF_3, methyl, ethyl, CN, OH, OCH_3, SCH_3, $NHCH_3$ or $C(O)CH_3$.

In embodiment 18, the invention provides compounds according to any one of embodiments 1-6, 7 and 16-17, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein

A^4 is CR^4;

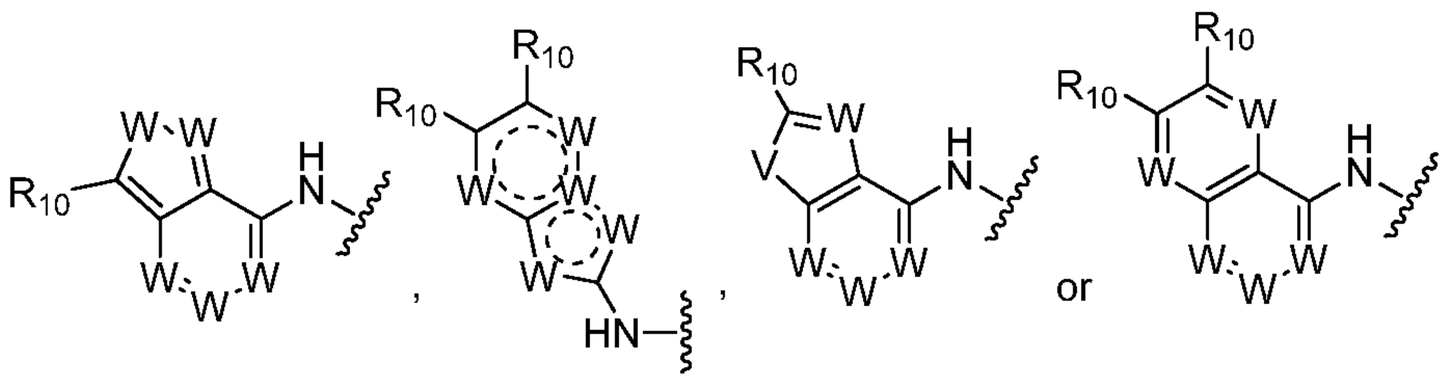
A^5 is CR^5;

A^6 is CR^6; and

A^8 is CR^8; wherein each of R^4, R^5, R^6 and R^8, independently, is H, F, Cl, CF_3, CF_2H, CH_2F or CH_3;

R^3 is CH_3, CF_3, CH_2F or CHF_2; and

R^7 is -NH-C(=O)-R^9 or



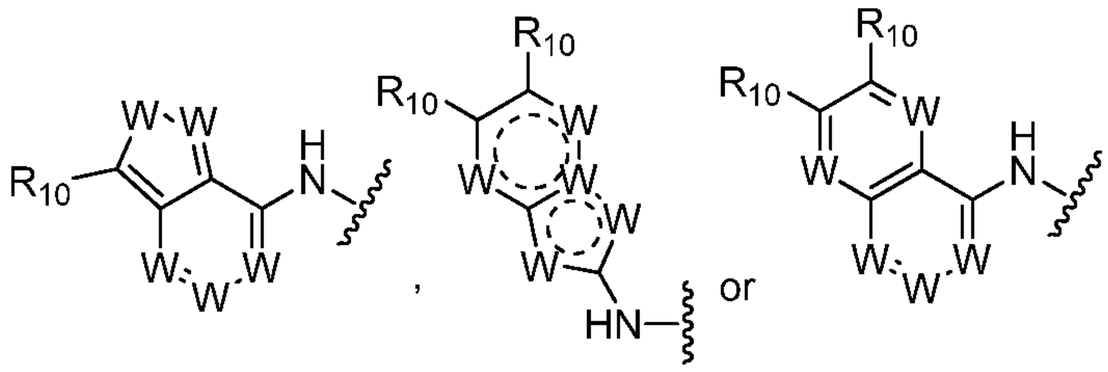
wherein V is NR^{10}, O or S; and

each W, independently, is CH, CF, CCl or N.

In embodiment 19, the invention provides compounds according to any one of embodiments 16-17, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R^7 is -NH-C(=O)-R^9.

In embodiment 20, the invention provides compounds according to any one of

embodiments 16-18, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R^7 is



wherein V is NR^{10}, O or S; and

each W, independently, is CH, CF, CCl, CCH_3 or N.

In embodiment 21, the invention provides compounds according to any one of embodiments 16-20, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein each of H, F, CH_2OCH_3 or CF_3; and each of R^a and R^b, independently, is H or F.

In embodiment 22, the invention provides compounds according to any one of embodiments 1-12, or a stereoisomer or pharmaceutically acceptable salt thereof, having a Formula I-A

I-A

wherein

A^4 is CR^4 or N;

A^5 is CR^5 or N;

A^6 is CR^6 or N;

A^8 is CR^8 or N, provided that no more than one of A^4, A^5, A^6 and A^8 is N;

each of R^a and R^b, independently, is H, F, Cl, C_{1-6}-alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, CN, $-CH_2OC_{1-6}$-alkyl, $-OC_{1-6}$-alkyl, $-S(O)_oC_{1-6}$-alkyl, $-NHC_{1-6}$-alkyl or $-C(O)C_{1-6}$-alkyl, wherein each of the C_{1-6}-alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, and C_{1-6}-alkyl portion of $-CH_2OC_{1-6}$-alkyl, $-OC_{1-6}$-alkyl, $-S(O)_oC_{1-6}$-alkyl, $-NHC_{1-6}$-alkyl and $-C(O)C_{1-6}$-alkyl are optionally substituted with 1-4 substituents of F, oxo or OH;

each of R^1 and R^2, independently, is H, F, Cl, C_{1-6}-alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, CN, $-CH_2OC_{1-6}$-alkyl, $-OC_{1-6}$-alkyl, $-S(O)_oC_{1-6}$-alkyl, $-NHC_{1-6}$-alkyl,

-C(O)NH_2, -CH=CHC(O)NHC_{1-6}-alkyl, -CH=CHC$(O)_2$H, -CH=CHCH_2OH, C_{1-6}-alkyl-C(O)NHC_{1-6}-alkyl, -C(O)C_{1-6}-alkyl or -C(O)C_{1-6}-alkenyl, wherein each of the C_{1-6}-alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, and C_{1-6}-alkyl portion of -CH_2OC_{1-6}-alkyl, -OC_{1-6}-alkyl, -$S(O)_oC_{1-6}$-alkyl, -NHC_{1-6}-alkyl, C(O)C_{1-6}-alkyl, -C(O)C_{1-6}-alkenyl, -CH=CHC(O)NHC_{1-6}-alkyl and C_{1-6}-alkyl-C(O)NHC_{1-6}-alkyl, are optionally substituted with 1-4 substituents of F, CN, oxo or OH;

R^3 is C_{1-4}alkyl, CH_2OC_{1-4}alkyl, CH_2OH, C_{1-4}haloalkyl or cyclopropyl, wherein each of the C_{1-4}alkyl, CH_2OC_{1-4}alkyl, C_{1-4}haloalkyl and cyclopropyl is optionally substituted with 1-4 F atoms;

each of R^4, R^5, R^6 and R^8, independently, is H, F, Cl or CH_3;

R^9 is a fully or partially unsaturated 3-, 4-, 5-, 6- or 7-membered monocyclic or 8-, 9- or 10-membered bicyclic ring formed of carbon atoms, said ring optionally including 1-4 heteroatoms if monocyclic or 1-5 heteroatoms if bicyclic, said heteroatoms selected from O, N or S, wherein the ring is optionally substituted, independently, with 1-5 substituents of R^{10};

each R^{10}, independently, is H, halo, haloalkyl, CN, OH, NO_2, NH_2, SF_5, acetyl, -C(O)NHCH_3, oxo, cyclopropylmethoxy, 2-propynyloxy, 2-butynyloxy, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkylamino-, C_{1-6}dialkylamino-, C_{1-6}alkoxyl, C_{1-6}thioalkoxyl, morpholinyl, pyrazolyl, isoxazolyl, dihydropyranyl, pyrrolyl, pyrrolidinyl, tetrahydropyrrolyl, piperazinyl, oxetan-3-yl, imidazo-pyridinyl or dioxolyl, wherein each of the cyclopropylmethoxy, 2-propynyloxy, 2-butynyloxy, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkylamino-, C_{1-6}dialkylamino-, C_{1-6}alkoxyl, C_{1-6}thioalkoxyl, morpholinyl, pyrazolyl, isoxazolyl, dihydropyranyl, pyrrolidinyl, oxetan-3-yl or dioxolyl, is optionally substituted independently with 1-5 substituents of F, Cl, CN, NO_2, NH_2, OH, oxo, CF_3, CHF_2, CH_2F, methyl, methoxy, ethyl, ethoxy, CH_2CF_3, CH_2CHF_2, propyl, propoxy, isopropyl, isopropoxy, cyclopropyl, butyl, butoxyl, cyclobutyl, isobutoxy, *tert*-butoxy, isobutyl, sec-butyl, *tert*-butyl, cyclopentyl, cyclohexyl, C_{1-3}alkylamino-, C_{1-3}dialkylamino, C_{1-3}thioalkoxyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, thienyl, furyl, pyrrolyl, tetrahydropyranyl, tetrahydropyrrolyl or oxetan-3yl; and

the subscript o is selected from 0, 1, or 2.

In embodiment 23, the invention provides compounds according to any one of embodiments 1-3, 8-20 and 22, or a stereoisomer, tautomer or pharmaceutically acceptable salt thereof, wherein

A^4 is CR^4;

A^5 is CR^5;

A^6 is CR^6;

A^8 is CR^8; wherein each of R^4, R^5, R^6 and R^8, independently, is H, F, Cl, CF_2H, CH_2F, CF_3, OCF_3, methyl, ethyl, CN, OH, OCH_3, SCH_3, $NHCH_3$ or $C(O)CH_3$;

each of R^a and R^b, independently, is H, F, CH_3, CH_2F, CHF_2 or CF_3;

each of R^1 and R^2, independently, is H, F, CH_3, CH_2OCH_3, CH_2F, CHF_2 or CF_3;

R^3 is CH_3, C_2H_5, CF_2H or CH_2F;

R^9 is a fully or partially unsaturated 3-, 4-, 5-, 6- or 7-membered monocyclic or 8-, 9- or 10-membered bicyclic ring formed of carbon atoms, said ring optionally including 1-4 heteroatoms if monocyclic or 1-5 heteroatoms if bicyclic, said heteroatoms selected from O, N or S, wherein the ring is optionally substituted, independently, with 1-5 substituents of R^{10}; and

each R^{10}, independently, is H, halo, haloalkyl, CN, OH, NO_2, NH_2, SF_5, acetyl, $-C(O)NHCH_3$, oxo, cyclopropylmethoxy, 2-propynyloxy, 2-butynyloxy, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkylamino-, C_{1-6}dialkylamino-, C_{1-6}alkoxyl, C_{1-6}thioalkoxyl, morpholinyl, pyrazolyl, isoxazolyl, dihydropyranyl, pyrrolyl, pyrrolidinyl, tetrahydropyrrolyl, piperazinyl, oxetan-3-yl, imidazo-pyridinyl or dioxolyl, wherein each of the cyclopropylmethoxy, 2-propynyloxy, 2-butynyloxy, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkylamino-, C_{1-6}dialkylamino-, C_{1-6}alkoxyl, C_{1-6}thioalkoxyl, morpholinyl, pyrazolyl, isoxazolyl, dihydropyranyl, pyrrolidinyl, oxetan-3-yl or dioxolyl, is optionally substituted independently with 1-5 substituents of F, Cl, CN, NO_2, NH_2, OH, oxo, CF_3, CHF_2, CH_2F, methyl, methoxy, ethyl, ethoxy, CH_2CF_3, CH_2CHF_2, propyl, propoxy, isopropyl, isopropoxy, cyclopropyl, butyl, butoxyl, cyclobutyl, isobutoxy, *tert*-butoxy, isobutyl, sec-butyl, *tert*-butyl, cyclopentyl, cyclohexyl, C_{1-3}alkylamino-, C_{1-3}dialkylamino, C_{1-3}thioalkoxyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, thienyl, furyl, pyrrolyl, tetrahydropyranyl, tetrahydropyrrolyl or oxetan-3yl.

In embodiment 24, the invention provides compounds according to any one of embodiments 1-19 and 22-23, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein

A^4 is CR^4 or N;

A^5 is CR^5 or N;

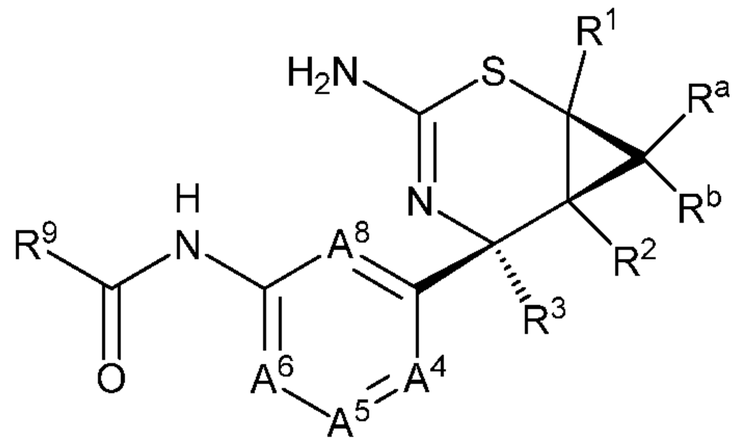
A^6 is CR^6 or N;

A^8 is CR^8 or N, wherein each of R^4, R^5, R^6 and R^8, independently, is H, F, Cl or CH_3, provided no more than one of A^4, A^5, A^6 and A^8 is N;

each of R^1, R^2, R^a and R^b, independently, is H; and

R^3 is CF_3, CH_3, CF_2H or CH_2F.

In embodiment 25, the invention provides compounds according to any one of embodiments 1-12, 16-19 and 22-24, or a stereoisomer or pharmaceutically acceptable salt thereof, having a Formula II-A



II-A

wherein

A^4 is CR^4, wherein R^4 is H, F or Cl;

A^5 is CR^5 or N, wherein R^5 is H, F, Cl or CH_3;

A^6 is CH;

A^8 is CR^8 or N, wherein R^8 is H or F,

provided that no more than one of A^5 and A^8 is N;

each of R^1 and R^2, independently, is H, F, CH_2OCH_3 or CF_3;

each of R^a and R^b, independently, is H or F;

R^3 is CH_3, CF_3, CH_2F or CHF_2;

R^9 is a fully unsaturated 5- or 6-membered monocyclic or 8-, 9- or 10-membered bicyclic ring formed of carbon atoms, said ring optionally including 1-4 heteroatoms if monocyclic or 1-5 heteroatoms if bicyclic, said heteroatoms selected from O, N or S, wherein the ring is optionally substituted, independently, with 1-5 substituents of R^{10}; and

each R^{10}, independently, is H, halo, haloalkyl, CN, OH, NO_2, NH_2, SF_5, acetyl, $-C(O)NHCH_3$, oxo, cyclopropylmethoxy, 2-propynyloxy, 2-butynyloxy, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkylamino-, C_{1-6}dialkylamino-, C_{1-6}alkoxyl, C_{1-6}thioalkoxyl, morpholinyl, pyrazolyl, isoxazolyl, dihydropyranyl, pyrrolyl, pyrrolidinyl, tetrahydropyrrolyl, piperazinyl, oxetan-3-yl, imidazo-pyridinyl or dioxolyl, wherein each of the cyclopropylmethoxy, 2-propynyloxy, 2-butynyloxy, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkylamino-, C_{1-6}dialkylamino-, C_{1-6}alkoxyl, C_{1-6}thioalkoxyl, morpholinyl, pyrazolyl, isoxazolyl, dihydropyranyl, pyrrolidinyl, oxetan-3-yl or dioxolyl, is optionally substituted independently with 1-5 substituents of F, Cl, CN, NO_2, NH_2, OH,

oxo, CF_3, CHF_2, CH_2F, methyl, methoxy, ethyl, ethoxy, CH_2CF_3, CH_2CHF_2, propyl, propoxy, isopropyl, isopropoxy, cyclopropyl, butyl, butoxyl, cyclobutyl, isobutoxy, *tert*-butoxy, isobutyl, sec-butyl, *tert*-butyl, cyclopentyl, cyclohexyl, C_{1-3}alkylamino-, C_{1-3}dialkylamino, C_{1-3}thioalkoxyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, thienyl, furyl, pyrrolyl, tetrahydropyranyl, tetrahydropyrrolyl or oxetan-3yl.

In embodiment 26, the invention provides compounds according to embodiment 25, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein each of R^a, R^b, R^1 and R^2, independently, is H.

In embodiment 27, the invention provides compounds according ng any one of embodiments 25 and 26, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R^3 is CH_3, CH_2F or CHF_2.

In embodiment 28, the invention provides compounds according to any one of embodiments 25-27, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R^3 is CH_2F or CHF_2.

In embodiment 29, the invention provides compounds according to any one of embodiments 25-28, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R^3 is CH_2F.

In embodiment 30, the invention provides compounds according to any one of embodiments 25-28, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R^3 is CHF_2.

In embodiment 31, the invention provides compounds according to any one of embodiments 25-30, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein A^4 is CF or CCl;

A^5 is CH, CF, CH_3 or N;

A^6 is CH; and

A^8 is CH.

In embodiment 32, the invention provides compounds according to any one of embodiments 25-31, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein A^4 is CF;

A^5 is CH, CF or N;

A^6 is CH; and

A^8 is CH.

In embodiment 33, the invention provides compounds according to any one of

embodiments 25-31, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein A^4 is CCl;

A^5 is CH or CF;

A^6 is CH; and

A^8 is CH.

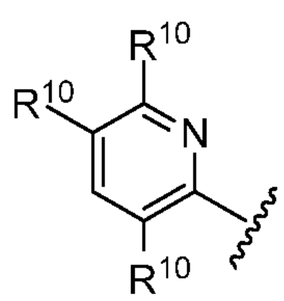
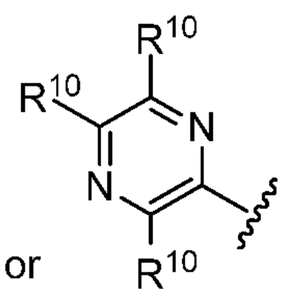
In embodiment 34, the invention provides compounds according to any one of embodiments 25-33, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein

R^9 is a ring selected from phenyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, pyrazolyl, pyrazolo[3,4-c]pyridinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl or thienyl, wherein the ring is optionally substituted with 1-5 substituents of R^{10}; and

each R^{10}, independently, is H, halo, haloalkyl, CN, OH, NO_2, NH_2, SF_5, acetyl, -C(O)NHCH$_3$, oxo, cyclopropylmethoxy, 2-propynyloxy, 2-butynyloxy, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkylamino-, C_{1-6}dialkylamino-, C_{1-6}alkoxyl, C_{1-6}thioalkoxyl, morpholinyl, pyrazolyl, isoxazolyl, dihydropyranyl, pyrrolyl, pyrrolidinyl, tetrahydropyrrolyl, piperazinyl, oxetan-3-yl, imidazo-pyridinyl or dioxolyl, wherein each of the cyclopropylmethoxy, 2-propynyloxy, 2-butynyloxy, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkylamino-, C_{1-6}dialkylamino-, C_{1-6}alkoxyl, C_{1-6}thioalkoxyl, morpholinyl, pyrazolyl, isoxazolyl, dihydropyranyl, pyrrolidinyl, oxetan-3-yl or dioxolyl, is optionally substituted independently with 1-5 substituents of F, Cl, CN, NO_2, NH_2, OH, oxo, CF_3, CHF_2, CH_2F, methyl, methoxy, ethyl, ethoxy, CH_2CF_3, CH_2CHF_2, propyl, propoxy, isopropyl, isopropoxy, cyclopropyl, butyl, butoxyl, cyclobutyl, isobutoxy, *tert*-butoxy, isobutyl, sec-butyl, *tert*-butyl, cyclopentyl, cyclohexyl, C_{1-3}alkylamino-, C_{1-3}dialkylamino, C_{1-3}thioalkoxyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, thienyl, furyl, pyrrolyl, tetrahydropyranyl, tetrahydropyrrolyl or oxetan-3yl.

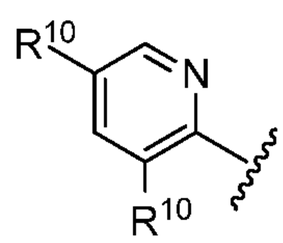
In embodiment 35, the invention provides compounds according to any one of embodiments 25-33, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R^9 is a ring selected from pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, pyrazolyl, pyrazolo[3,4-c]pyridinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl or thienyl, wherein the ring is optionally substituted with 1-5 substituents of R^{10}.

In embodiment 36, the invention provides compounds according to any one of embodiments 25-35 or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R^9 is



or ; and

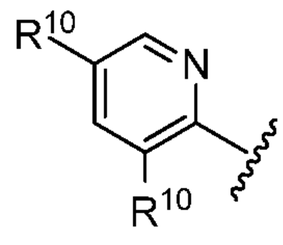
each R^{10}, independently, is H, F, Cl, Br, CF_3, CHF_2, CH_2F, CN, OH, -C(O)$NHCH_3$, cyclopropylmethoxy, 2-propynyloxy, 2-butynyloxy, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkoxyl or C_{1-6}thioalkoxyl, wherein each of the cyclopropylmethoxy, 2-propynyloxy, 2-butynyloxy, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkoxyl and C_{1-6}thioalkoxyl is optionally substituted independently with 1-5 substituents of F, Cl, CN, NO_2, NH_2, OH, oxo, CF_3, CHF_2, CH_2F, methyl, methoxy, ethyl, ethoxy, CH_2CF_3, CH_2CHF_2, propyl, propoxy, isopropyl, isopropoxy, cyclopropyl, butyl, butoxyl, cyclobutyl, isobutoxy, *tert*-butoxy, isobutyl, sec-butyl, *tert*-butyl, C_{1-3}alkylamino-, C_{1-3}dialkylamino, C_{1-3}thioalkoxyl, oxazolyl or thiazolyl.

In embodiment 37, the invention provides compounds according to any one of embodiments 25-36, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R^3 is CHF_2; and R^9 is


; and

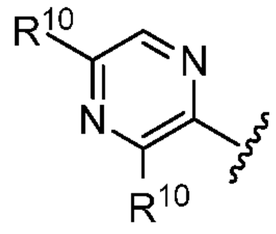
each R^{10}, independently, is H, F, Cl, Br, CH_3, CHF_2, CH_2F, CN, 2-propynyloxy, 2-butynyloxy or C_{1-2}alkoxyl, wherein the C_{1-2}alkoxyl is optionally substituted independently with 1-5 substituents of F, Cl, methyl, methoxy, ethyl, ethoxy, oxazolyl or thiazolyl.

In embodiment 38, the invention provides compounds according to any one of embodiments 25-36, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R^3 is CH_2F; and R^9 is


; and

each R^{10}, independently, is H, F, Cl, Br, CH_3, CHF_2, CH_2F, CN, 2-propynyloxy, 2-butynyloxy or C_{1-2}alkoxyl, wherein the C_{1-2}alkoxyl is optionally substituted independently with 1-5 substituents of F, Cl, methyl, methoxy, ethyl, ethoxy, oxazolyl or thiazolyl.

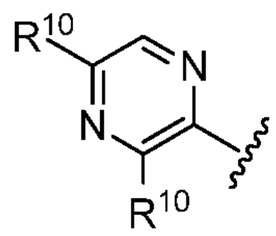
In embodiment 39, the invention provides compounds according to any one of embodiments 25-36, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R^3 is CHF_2; and R^9 is



; and

each R^{10}, independently, is H, F, Cl, Br, CH_3, CHF_2, CH_2F, CN, 2-propynyloxy, 2-butynyloxy or C_{1-2}alkoxyl, wherein the C_{1-2}alkoxyl is optionally substituted independently with 1-5 substituents of F, Cl, methyl, methoxy, ethyl, ethoxy, oxazolyl or thiazolyl.

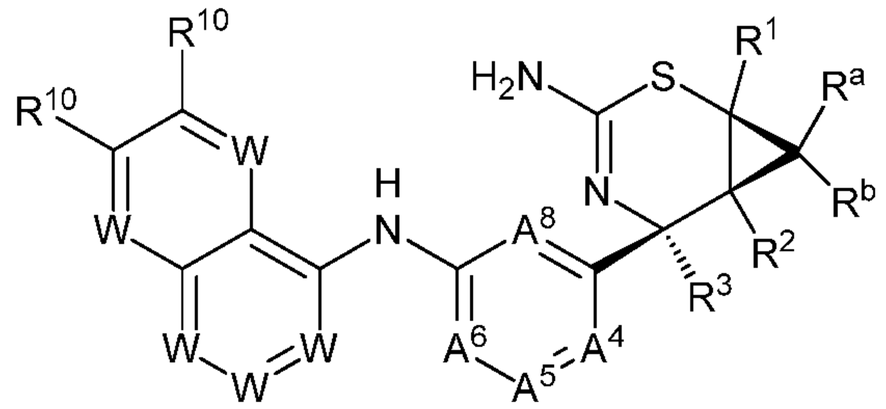
In embodiment 40, the invention provides compounds according to any one of embodiments 25-36, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R^3 is CH_2F; and R^9 is



; and

each R^{10}, independently, is H, F, Cl, Br, CH_3, CHF_2, CH_2F, CN, 2-propynyloxy, 2-butynyloxy or C_{1-2}alkoxyl, wherein the C_{1-2}alkoxyl is optionally substituted independently with 1-5 substituents of F, Cl, methyl, methoxy, ethyl, ethoxy, oxazolyl or thiazolyl.

In embodiment 41, the invention provides compounds according to any one of embodiments 1- 11, 13-18 and 20-21, or a stereoisomer, tautomer, hydrate, solvate or pharmaceutically acceptable salt thereof, having a Formula II-B:



II-B

wherein

A^4 is CR^4, wherein R^4 is H, F or Cl;

A^5 is CR^5 or N, wherein R^5 is H, F, Cl or CH_3;

A^6 is CH;

A^8 is CR^8 or N, wherein R^8 is H or F,

provided that no more than one of A^5 and A^8 is N;

each of R^1 and R^2, independently, is H, F, CH_2OCH_3 or CF_3;

each of R^a and R^b, independently, is H or F;

R^3 is CH_3, CF_3, CH_2F or CHF_2;

R^9 is a fully unsaturated 5- or 6-membered monocyclic or 8-, 9- or 10-membered bicyclic ring formed of carbon atoms, said ring optionally including 1-4 heteroatoms if monocyclic or 1-5 heteroatoms if bicyclic, said heteroatoms selected from O, N or S, wherein the ring is optionally substituted, independently, with 1-5 substituents of R^{10}; and

each R^{10}, independently, is H, halo, haloalkyl, CN, OH, NO_2, NH_2, SF_5, acetyl, $-C(O)NHCH_3$, oxo, cyclopropylmethoxy, 2-propynyloxy, 2-butynyloxy, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkylamino-, C_{1-6}dialkylamino-, C_{1-6}alkoxyl, C_{1-6}thioalkoxyl, morpholinyl, pyrazolyl, isoxazolyl, dihydropyranyl, pyrrolyl, pyrrolidinyl, tetrahydropyrrolyl, piperazinyl, oxetan-3-yl, imidazo-pyridinyl or dioxolyl, wherein each of the cyclopropylmethoxy, 2-propynyloxy, 2-butynyloxy, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkylamino-, C_{1-6}dialkylamino-, C_{1-6}alkoxyl, C_{1-6}thioalkoxyl, morpholinyl, pyrazolyl, isoxazolyl, dihydropyranyl, pyrrolidinyl, oxetan-3-yl or dioxolyl, is optionally substituted independently with 1-5 substituents of F, Cl, CN, NO_2, NH_2, OH, oxo, CF_3, CHF_2, CH_2F, methyl, methoxy, ethyl, ethoxy, CH_2CF_3, CH_2CHF_2, propyl, propoxy, isopropyl, isopropoxy, cyclopropyl, butyl, butoxyl, cyclobutyl, isobutoxy, *tert*-butoxy, isobutyl, sec-butyl, *tert*-butyl, cyclopentyl, cyclohexyl, C_{1-3}alkylamino-, C_{1-3}dialkylamino, C_{1-3}thioalkoxyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, thienyl, furyl, pyrrolyl, tetrahydropyranyl, tetrahydropyrrolyl or oxetan-3yl; and

each W, independently, is CH, CF, CCl, CCH_3 or N.

In embodiment 42, the invention provides compounds according according to embodiment 40, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein each of R^a, R^b, R^1 and R^2, independently, is H.

In embodiment 43, the invention provides compounds according to any one of embodiments 41 and 42, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R^3 is CH_3, CH_2F or CHF_2.

In embodiment 44, the invention provides compounds according to any one of embodiments 41-43, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R^3 is CH_2F or CHF_2.

In embodiment 45, the invention provides compounds according to any one of embodiments 41-44, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R^3 is CH_2F.

In embodiment 46, the invention provides compounds according to any one of embodiments 41-44, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R^3 is CHF_2.

In embodiment 47, the invention provides compounds according to any one of embodiments 41-46, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein A^4 is CF or CCl;

A^5 is CH, CF, CH_3 or N;

A^6 is CH; and

A^8 is CH.

In embodiment 48, the invention provides compounds according to any one of embodiments 41-47, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein A^4 is CF;

A^5 is CH, CF or N;

A^6 is CH; and

A^8 is CH.

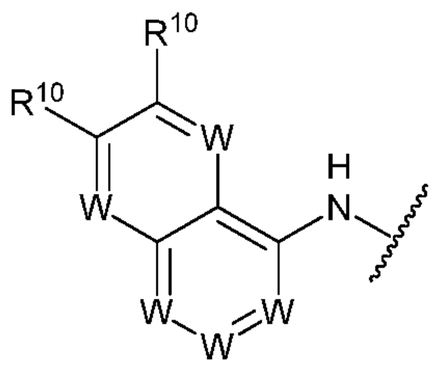
In embodiment 49, the invention provides compounds according to any one of embodiments 41-47, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein A^4 is CCl;

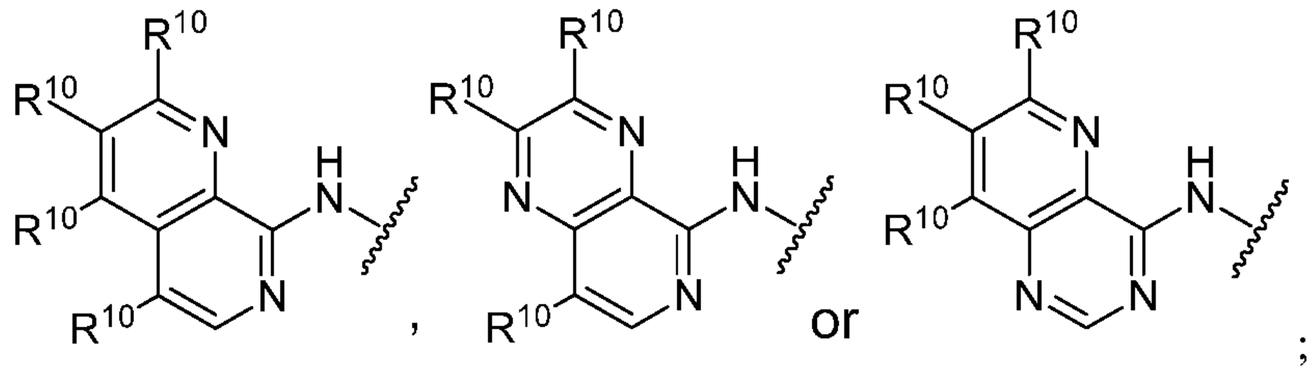
A^5 is CH or CF;

A^6 is CH; and

A^8 is CH.

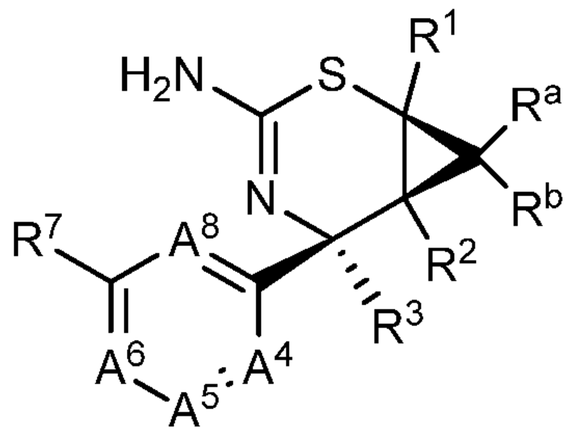
In embodiment 50, the invention provides compounds according to any one of embodiments 41-49 or a stereoisomer or pharmaceutically acceptable salt thereof, wherein


is


; and

each R^{10}, independently, is H, F, Cl, Br, CH_3, CHF_2, CH_2F, CN, 2-propynyloxy, 2-butynyloxy or C_{1-2}alkoxyl, wherein the C_{1-2}alkoxyl is optionally substituted independently with 1-5 substituents of F, Cl, methyl, methoxy, ethyl, ethoxy, oxazolyl or thiazolyl.

In embodiment 51, the invention provides compounds, including stereoisomers, tautomers, hydrates, solvates and pharmaceutically acceptable salts thereof, which are generally defined by Formula III:



III

wherein

A^4 is CR^4;

A^5 is CR^5 or N;

A^6 is CR^6;

A^8 is CR^8 or N, provided that no more than two of A^5 and A^8 is N;

each of R^a and R^b, independently, is H, F, CH_3, CH_2F, CHF_2 or CF_3;

each of R^1 and R^2, independently, is H, F, CH_3, CH_2OCH_3, CH_2F, CHF_2 or CF_3;

R^3 is CH_3, CF_3, CH_2F or CHF_2;

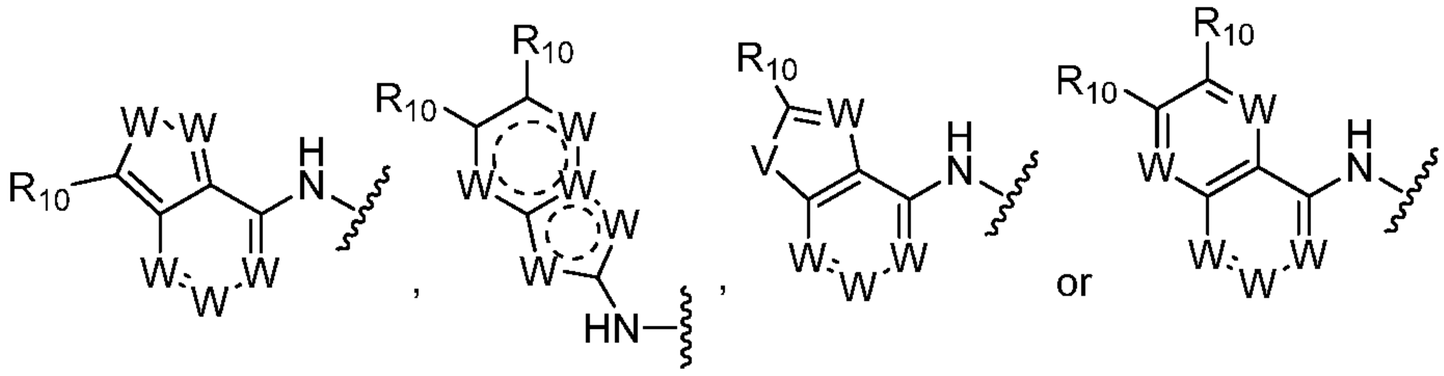
R^4 is F or Cl;

R^5 is H, F, Cl or CH_3;

each of R^6 and R^8, independently, is H or F;

R^7 is -NH-C(=O)-R^9, or

R^7 is



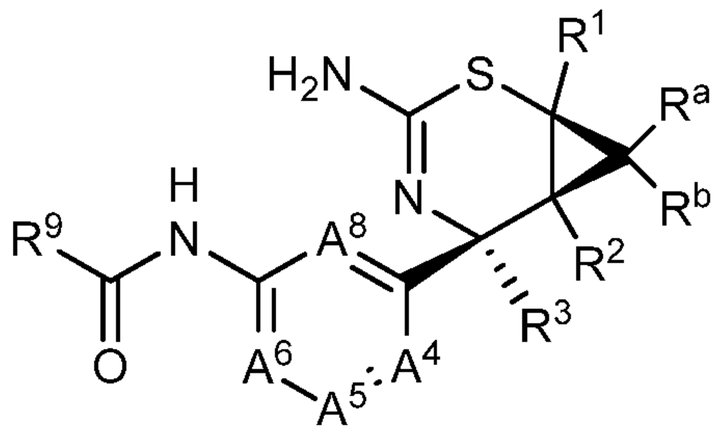
wherein V is NR^{10}, O or S; and

each W, independently, is CH, CF, CCl, CCH_3 or N;

R^9 is a ring selected from phenyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, pyrazolyl, pyrazolo[3,4-c]pyridinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl or thienyl, wherein the ring is optionally substituted with 1-5 substituents of R^{10}; and

each R^{10}, independently, is H, halo, haloalkyl, CN, OH, NO_2, NH_2, SF_5, acetyl, -C(O)$NHCH_3$, oxo, cyclopropylmethoxy, 2-propynyloxy, 2-butynyloxy, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkylamino-, C_{1-6}dialkylamino-, C_{1-6}alkoxyl, C_{1-6}thioalkoxyl, morpholinyl, pyrazolyl, isoxazolyl, dihydropyranyl, pyrrolyl, pyrrolidinyl, tetrahydropyrrolyl, piperazinyl, oxetan-3-yl, imidazo-pyridinyl or dioxolyl, wherein each of the cyclopropylmethoxy, 2-propynyloxy, 2-butynyloxy, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkylamino-, C_{1-6}dialkylamino-, C_{1-6}alkoxyl, C_{1-6}thioalkoxyl, morpholinyl, pyrazolyl, isoxazolyl, dihydropyranyl, pyrrolidinyl, oxetan-3-yl or dioxolyl, is optionally substituted independently with 1-5 substituents of F, Cl, CN, NO_2, NH_2, OH, oxo, CF_3, CHF_2, CH_2F, methyl, methoxy, ethyl, ethoxy, CH_2CF_3, CH_2CHF_2, propyl, propoxy, isopropyl, isopropoxy, cyclopropyl, butyl, butoxyl, cyclobutyl, isobutoxy, *tert*-butoxy, isobutyl, sec-butyl, *tert*-butyl, cyclopentyl, cyclohexyl, C_{1-3}alkylamino-, C_{1-3}dialkylamino, C_{1-3}thioalkoxyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, thienyl, furyl, pyrrolyl, tetrahydropyranyl, tetrahydropyrrolyl or oxetan-3yl.

In embodiment 52, the invention provides compounds including stereoisomers, tautomers, hydrates, solvates and pharmaceutically acceptable salts thereof, according to embodiment 51, which are generally defined by Formula III-A:



III-A

wherein

A^4 is CR^4, wherein R^4 is H, F or Cl;

A^5 is CR^5 or N, wherein R^5 is H, F, Cl or CH_3;

A^6 is CH;

A^8 is CR^8 or N, wherein R^8 is H or F, provided that no more than one of A^5 and A^8 is N;

each of R^a and R^b, independently, is H or F;

each of R^1 and R^2, independently, is H, CH_2OCH_3 or F;

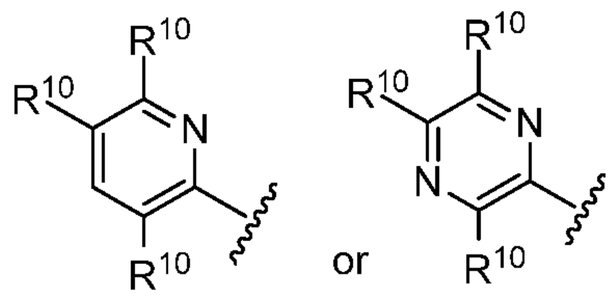
R^3 is CH_3, CH_2F or CHF_2;

R^9 is a ring selected from phenyl, pyridyl, pyrimidyl, pyrazinyl, pyrazolyl, pyrazolo[3,4-c]pyridinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl or thienyl, wherein the ring is optionally substituted with 1-5 substituents of R^{10}; and

each R^{10}, independently, is H, halo, haloalkyl, CN, OH, NO_2, NH_2, SF_5, acetyl, $-C(O)NHCH_3$, oxo, cyclopropylmethoxy, 2-propynyloxy, 2-butynyloxy, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkylamino-, C_{1-6}dialkylamino-, C_{1-6}alkoxyl, C_{1-6}thioalkoxyl, morpholinyl, pyrazolyl, isoxazolyl, dihydropyranyl, pyrrolyl, pyrrolidinyl, tetrahydropyrrolyl, piperazinyl, oxetan-3-yl, imidazo-pyridinyl or dioxolyl, wherein each of the cyclopropylmethoxy, 2-propynyloxy, 2-butynyloxy, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkylamino-, C_{1-6}dialkylamino-, C_{1-6}alkoxyl, C_{1-6}thioalkoxyl, morpholinyl, pyrazolyl, isoxazolyl, dihydropyranyl, pyrrolidinyl, oxetan-3-yl or dioxolyl, is optionally substituted independently with 1-5 substituents of F, Cl, CN, NO_2, NH_2, OH, oxo, CF_3, CHF_2, CH_2F, methyl, methoxy, ethyl, ethoxy, CH_2CF_3, CH_2CHF_2, propyl, propoxy, isopropyl, isopropoxy, cyclopropyl, butyl, butoxyl, cyclobutyl, isobutoxy, *tert*-butoxy, isobutyl, sec-butyl, *tert*-butyl, cyclopentyl, cyclohexyl, C_{1-3}alkylamino-, C_{1-3}dialkylamino, C_{1-3}thioalkoxyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, thienyl, furyl, pyrrolyl, tetrahydropyranyl, tetrahydropyrrolyl or oxetan-3yl.

In embodiment 53, the invention provides compounds according to any one of

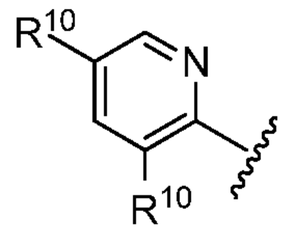
embodiments 51-52 or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R^9 is



; and

each R^{10}, independently, is H, F, Cl, Br, CF_3, CHF_2, CH_2F, CN, OH, -C(O)NHCH$_3$, cyclopropylmethoxy, 2-propynyloxy, 2-butynyloxy, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkoxyl or C_{1-6}thioalkoxyl, wherein each of the cyclopropylmethoxy, 2-propynyloxy, 2-butynyloxy, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkoxyl and C_{1-6}thioalkoxyl is optionally substituted independently with 1-5 substituents of F, Cl, CN, NO_2, NH_2, OH, oxo, CF_3, CHF_2, CH_2F, methyl, methoxy, ethyl, ethoxy, CH_2CF_3, CH_2CHF_2, propyl, propoxy, isopropyl, isopropoxy, cyclopropyl, butyl, butoxyl, cyclobutyl, isobutoxy, *tert*-butoxy, isobutyl, sec-butyl, *tert*-butyl, C_{1-3}alkylamino-, C_{1-3}dialkylamino, C_{1-3}thioalkoxyl, oxazolyl or thiazolyl.

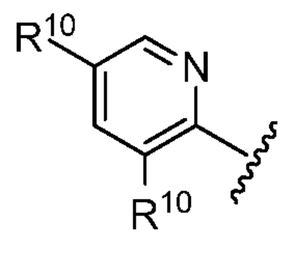
In embodiment 54, the invention provides compounds according to any one of embodiments 51-53, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R^3 is CHF_2; and R^9 is



; and

each R^{10}, independently, is H, F, Cl, Br, CH_3, CHF_2, CH_2F, CN, 2-propynyloxy, 2-butynyloxy or C_{1-2}alkoxyl, wherein the C_{1-2}alkoxyl is optionally substituted independently with 1-5 substituents of F, Cl, methyl, methoxy, ethyl, ethoxy, oxazolyl or thiazolyl.

In embodiment 55, the invention provides compounds according to any one of embodiments 51-53, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R^3 is CH_2F; and R^9 is

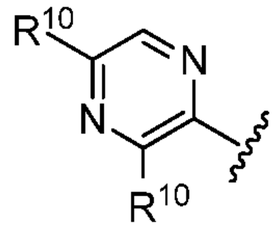


; and

each R^{10}, independently, is H, F, Cl, Br, CH_3, CHF_2, CH_2F, CN, 2-propynyloxy, 2-butynyloxy or C_{1-2}alkoxyl, wherein the C_{1-2}alkoxyl is optionally substituted

independently with 1-5 substituents of F, Cl, methyl, methoxy, ethyl, ethoxy, oxazolyl or thiazolyl.

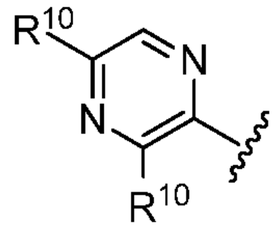
In embodiment 56, the invention provides compounds according to any one of embodiments 51-53 or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R^3 is CHF_2; and R^9 is



; and

each R^{10}, independently, is H, F, Cl, Br, CH_3, CHF_2, CH_2F, CN, 2-propynyloxy, 2-butynyloxy or C_{1-2}alkoxyl, wherein the C_{1-2}alkoxyl is optionally substituted independently with 1-5 substituents of F, Cl, methyl, methoxy, ethyl, ethoxy, oxazolyl or thiazolyl.

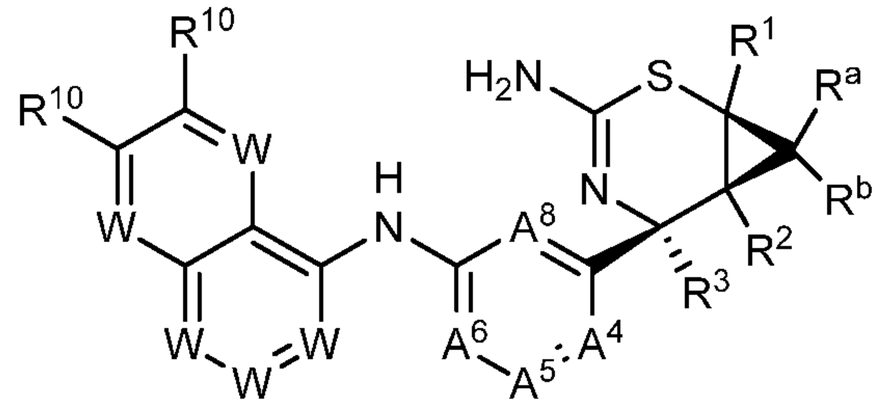
In embodiment 57, the invention provides compounds according to any one of embodiments 51-53, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R^3 is CH_2F; and R^9 is



; and

each R^{10}, independently, is H, F, Cl, Br, CH_3, CHF_2, CH_2F, CN, 2-propynyloxy, 2-butynyloxy or C_{1-2}alkoxyl, wherein the C_{1-2}alkoxyl is optionally substituted independently with 1-5 substituents of F, Cl, methyl, methoxy, ethyl, ethoxy, oxazolyl or thiazolyl.

In embodiment 58, the invention provides compounds, including stereoisomers, tautomers, hydrates, solvates and pharmaceutically acceptable salts thereof, which are generally defined by Formula III-B:



III-B

wherein

A^4 is CR^4, wherein R^4 is H, F or Cl;

A^5 is CR^5 or N, wherein R^5 is H, F, Cl or CH_3;

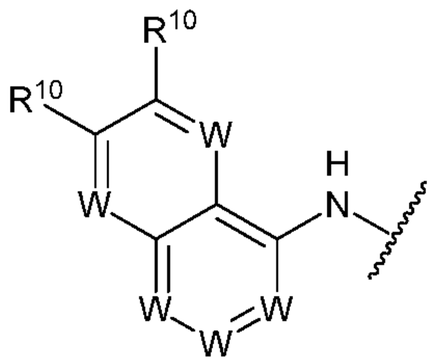
A^6 is CH;

A^8 is CR^8 or N, wherein R^8 is H or F, provided that no more than one of A^5 and A^8 is N;

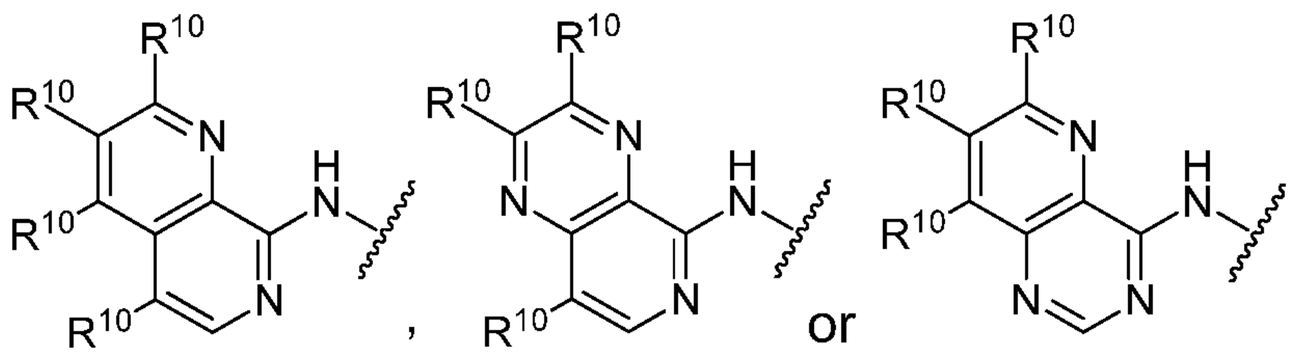
each of R^a and R^b, independently, is H or F;

each of R^1 and R^2, independently, is H, CH_2OCH_3 or F;

R^3 is CH_3, CH_2F or CHF_2;



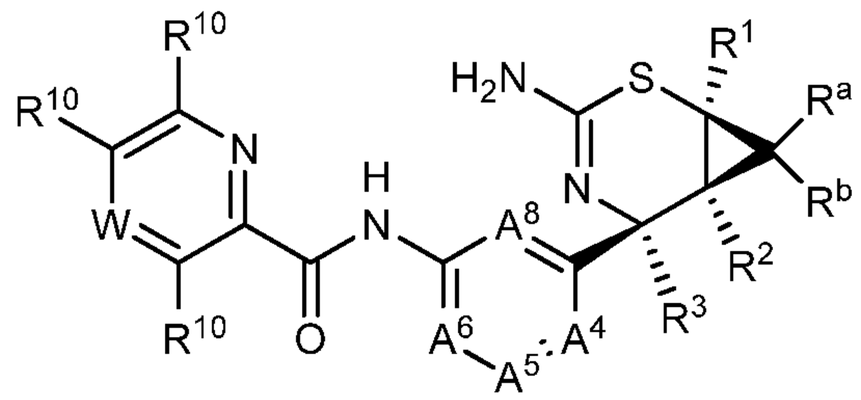
is



; and

each R^{10}, independently, is H, F, Cl, Br, CH_3, CHF_2, CH_2F, CN, 2-propynyloxy, 2-butynyloxy or C_{1-2}alkoxyl, wherein the C_{1-2}alkoxyl is optionally substituted independently with 1-5 substituents of F, Cl, methyl, methoxy, ethyl, ethoxy, oxazolyl or thiazolyl.

In embodiment 59, the invention provides compounds of formula III-A-1, or a pharmaceutically acceptable salt or tautomer thereof,



III-A-1

wherein, A^4 is CF;

A^5 is CH, CF, CCl, CCH_3 or N;

A^6 is CH;

A^8 is CH or N, provided that no more than one of A^5 and A^8 is N;

each of R^a and R^b, independently, is H;

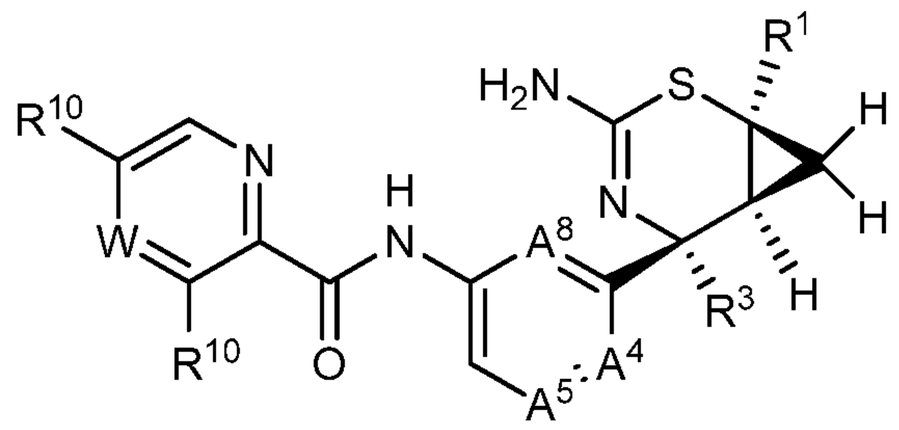
each of R^1 and R^2, independently, is H, CH_2OCH_3 or F;

R^3 is CH_3, CH_2F or CHF_2;

W is CR^{10} or N; and

each R^{10}, independently, is H, halo, haloalkyl, CN, OH, NO_2, NH_2, SF_5, acetyl, $-C(O)NHCH_3$, oxo, cyclopropylmethoxy, 2-propynyloxy, 2-butynyloxy, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkylamino-, C_{1-6}dialkylamino-, C_{1-6}alkoxyl, C_{1-6}thioalkoxyl, morpholinyl, pyrazolyl, isoxazolyl, dihydropyranyl, pyrrolyl, pyrrolidinyl, tetrahydropyrrolyl, piperazinyl, oxetan-3-yl, imidazo-pyridinyl or dioxolyl, wherein each of the cyclopropylmethoxy, 2-propynyloxy, 2-butynyloxy, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkylamino-, C_{1-6}dialkylamino-, C_{1-6}alkoxyl, C_{1-6}thioalkoxyl, morpholinyl, pyrazolyl, isoxazolyl, dihydropyranyl, pyrrolidinyl, oxetan-3-yl or dioxolyl, is optionally substituted independently with 1-5 substituents of F, Cl, CN, NO_2, NH_2, OH, oxo, CF_3, CHF_2, CH_2F, methyl, methoxy, ethyl, ethoxy, CH_2CF_3, CH_2CHF_2, propyl, propoxy, isopropyl, isopropoxy, cyclopropyl, butyl, butoxyl, cyclobutyl, isobutoxy, *tert*-butoxy, isobutyl, sec-butyl, *tert*-butyl, cyclopentyl, cyclohexyl, C_{1-3}alkylamino-, C_{1-3}dialkylamino, C_{1-3}thioalkoxyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, thienyl, furyl, pyrrolyl, tetrahydropyranyl, tetrahydropyrrolyl or oxetan-3yl.

In embodiment 60, the invention provides compounds of formula III-A-2, or a pharmaceutically acceptable salt or tautomer thereof,



III-A-2

wherein

A^4 is CF or CCl;

A^5 is CH, CF, CCl, CCH_3 or N;

A^8 is CH or N, provided no more than one of A^5 and A^8 is N;

R^1 is H, CH_2OCH_3 or F;

R^3 is CH_3, CH_2F or CHF_2;

W is CH or N; and

each R^{10}, independently, is H, F, Cl, Br, CH_3, CHF_2, CH_2F, CN, 2-propynyloxy, 2-butynyloxy or C_{1-2}alkoxyl, wherein the C_{1-2}alkoxyl is optionally substituted independently with 1-5 substituents of F, Cl, methyl, methoxy, ethyl, ethoxy, oxazolyl or thiazolyl.

In embodiment 61, the invention provides compounds according to any one of embodiments 59-60, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R^3 is CHF_2.

In embodiment 62, the invention provides compounds according to any one of embodiments 59-60, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R^3 is CH_2F.

In embodiment 63, the invention provides compounds according to any one of embodiments 59-62, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein W is CH.

In embodiment 64, the invention provides compounds according to any one of embodiments 59-62, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein W is N.

In embodiment 65, the invention provides compounds according to any one of embodiments 59-64, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein each R^{10}, independently, is H, F, Cl, Br, CH_3, CHF_2, CH_2F, CN, 2-propynyloxy, 2-butynyloxy or C_{1-2}alkoxyl, wherein the C_{1-2}alkoxyl is optionally substituted independently with 1-5 substituents of F, oxazolyl or thiazolyl.

In embodiment 66, the invention provides compounds according to any one of embodiments 59-65, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein each R^{10}, independently, is H, F, Cl, Br, CH_3, CHF_2, CH_2F, CN, 2-propynyloxy, 2-butynyloxy, $-OCHF_2$ or $-OCH_3$.

In embodiment 67, the invention provides compounds according to any one of embodiments 59-66, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein A^8 is CH.

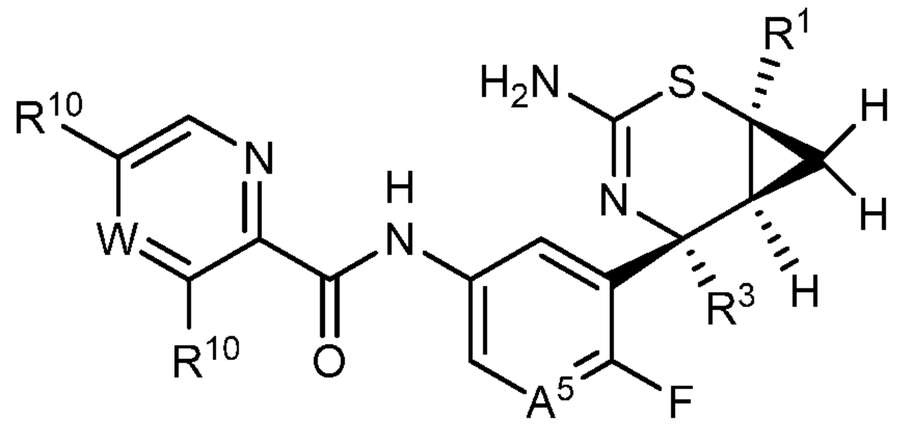
In embodiment 68, the invention provides compounds according to any one of embodiments 59-67, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein A^5 is CH, CF, CCl or CCH_3.

In embodiment 68, the invention provides compounds according to any one of

embodiments 59-67, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein A^5 is CH, CF or CCH_3.

In embodiment 68, the invention provides compounds according to any one of embodiments 59-67, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein A^5 is CH or N.

In embodiment 69, the invention provides compounds of formula III-A-3, or a pharmaceutically acceptable salt or tautomer thereof,



III-A-3

wherein

A^5 is CH, CF, CCl, CCH_3 or N;

R^3 is CH_3, CH_2F or CHF_2;

W is CH or N; and

each R^{10}, independently, is H, F, Cl, Br, CH_3, CHF_2, CH_2F, CN, 2-propynyloxy, 2-butynyloxy or C_{1-2}alkoxyl, wherein the C_{1-2}alkoxyl is optionally substituted independently with 1-5 substituents of F, Cl, methyl, methoxy, ethyl, ethoxy, oxazolyl or thiazolyl.

In embodiment 70, the invention provides compounds according to any one of embodiment 69, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R^3 is CHF_2.

In embodiment 71, the invention provides compounds according to any one of embodiment 69, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R^3 is CH_2F.

In embodiment 72, the invention provides compounds according to any one of embodiments 69-71, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein W is CH.

In embodiment 73, the invention provides compounds according to any one of embodiments 69-71, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein W is N.

In embodiment 74, the invention provides compounds according to any one of embodiments 69-74, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein each R^{10}, independently, is H, F, Cl, Br, CH_3, CHF_2, CH_2F, CN, 2-propynyloxy, 2-butynyloxy or C_{1-2}alkoxyl, wherein the C_{1-2}alkoxyl is optionally substituted independently with 1-5 substituents of F, oxazolyl or thiazolyl.

In embodiment 75, the invention provides compounds according to any one of embodiments 69-75, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein each R^{10}, independently, is H, F, Cl, Br, CH_3, CHF_2, CH_2F, CN, 2-propynyloxy, 2-butynyloxy, $-OCHF_2$ or $-OCH_3$.

In embodiment 77, the invention provides compounds according to any one of embodiments 69-76, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein A^5 is CH, CF, CCH_3 or N.

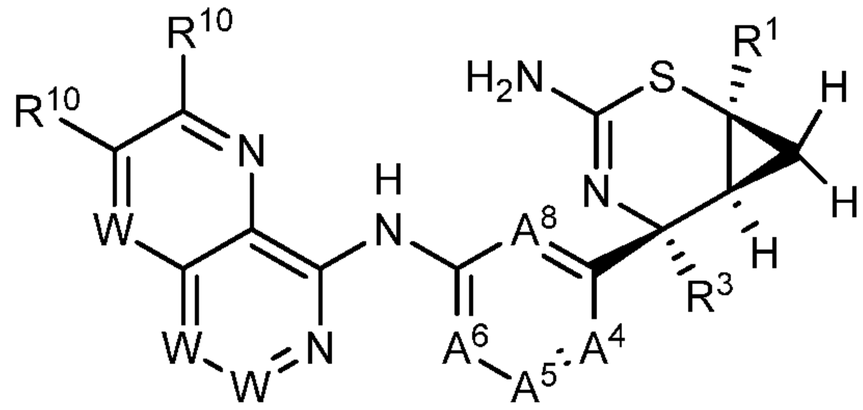
In embodiment 78, the invention provides compounds according to any one of embodiments 69-77, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein A^5 is CH, CF or N.

In embodiment 79, the invention provides compounds according to any one of embodiments 69-78, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein A^5 is CH or N.

In embodiment 80, the invention provides compounds according to any one of embodiments 69-79, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein A^5 is CH.

In embodiment 81, the invention provides compounds according to any one of embodiments 69-79, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein A^5 is N.

In embodiment 82, the invention provides compounds of formula III-B-1, or a pharmaceutically acceptable salt or tautomer thereof,



III-B-1

wherein

A^4 is CF;

A^5 is CH, CF, CCl, CCH_3 or N;

A^6 is CH;

A^8 is CH or N, provided that no more than one of A^5 and A^8 is N;

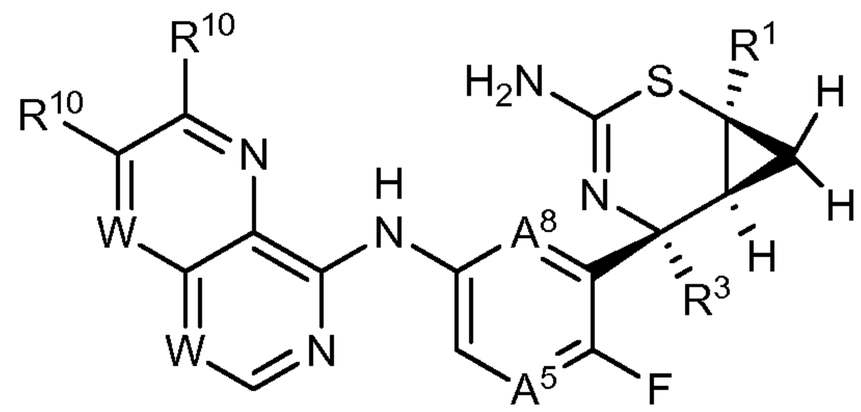
R^1 is H, CH_2OCH_3 or F;

R^3 is CH_3, CH_2F or CHF_2;

each W, independently, is CR^{10} or N, provided no more than 2 W's are N; and

each R^{10}, independently, is H, halo, haloalkyl, CN, OH, NO_2, NH_2, SF_5, acetyl, $-C(O)NHCH_3$, oxo, cyclopropylmethoxy, 2-propynyloxy, 2-butynyloxy, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkylamino-, C_{1-6}dialkylamino-, C_{1-6}alkoxyl, C_{1-6}thioalkoxyl, morpholinyl, pyrazolyl, isoxazolyl, dihydropyranyl, pyrrolyl, pyrrolidinyl, tetrahydropyrrolyl, piperazinyl, oxetan-3-yl, imidazo-pyridinyl or dioxolyl, wherein each of the cyclopropylmethoxy, 2-propynyloxy, 2-butynyloxy, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkylamino-, C_{1-6}dialkylamino-, C_{1-6}alkoxyl, C_{1-6}thioalkoxyl, morpholinyl, pyrazolyl, isoxazolyl, dihydropyranyl, pyrrolidinyl, oxetan-3-yl or dioxolyl, is optionally substituted independently with 1-5 substituents of F, Cl, CN, NO_2, NH_2, OH, oxo, CF_3, CHF_2, CH_2F, methyl, methoxy, ethyl, ethoxy, CH_2CF_3, CH_2CHF_2, propyl, propoxy, isopropyl, isopropoxy, cyclopropyl, butyl, butoxyl, cyclobutyl, isobutoxy, *tert*-butoxy, isobutyl, sec-butyl, *tert*-butyl, cyclopentyl, cyclohexyl, C_{1-3}alkylamino-, C_{1-3}dialkylamino, C_{1-3}thioalkoxyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, thienyl, furyl, pyrrolyl, tetrahydropyranyl, tetrahydropyrrolyl or oxetan-3yl.

In embodiment 83, the invention provides compounds of formula III-B-2, or a pharmaceutically acceptable salt or tautomer thereof,



III-B-2

wherein

A^5 is CH, CF, CCl, CCH_3 or N;

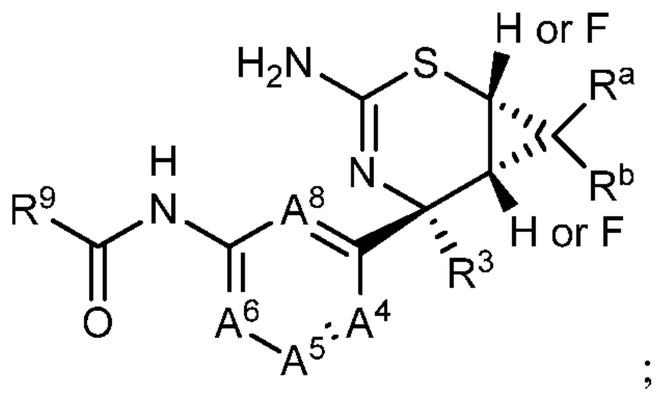
A^8 is CH or N, provided no more than one of A^5 and A^8 is N;

R^3 is CH_3, CH_2F or CHF_2;

each W, independently, is CR^{10} or N, provided no more than 1 W is N; and

each R^{10}, independently, is H, F, Cl, Br, CH_3, CHF_2, CH_2F, CN, 2-propynyloxy, 2-butynyloxy or C_{1-2}alkoxyl, wherein the C_{1-2}alkoxyl is optionally substituted independently with 1-5 substituents of F, Cl, methyl, methoxy, ethyl, ethoxy, oxazolyl or thiazolyl.

Similarly, the invention provides compounds of sub-formulas III-C, III-D, III-E and III-F, respectively, as described below,



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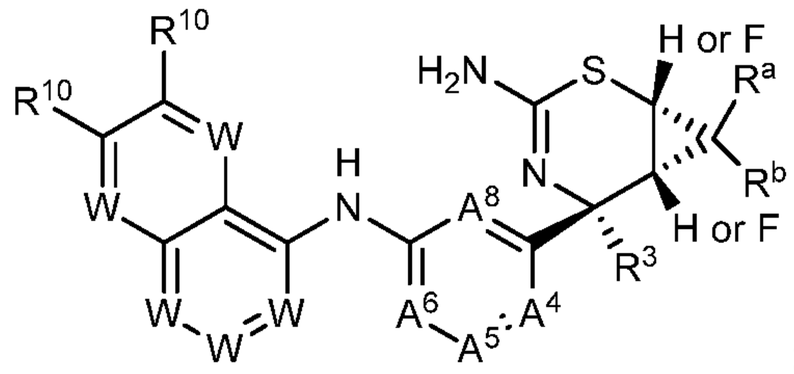
III-C



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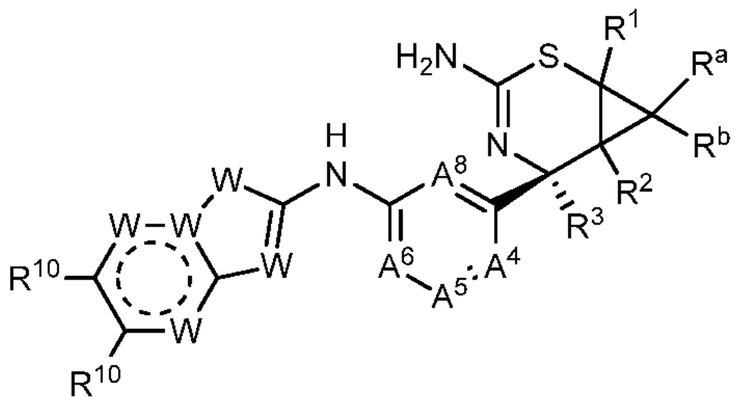
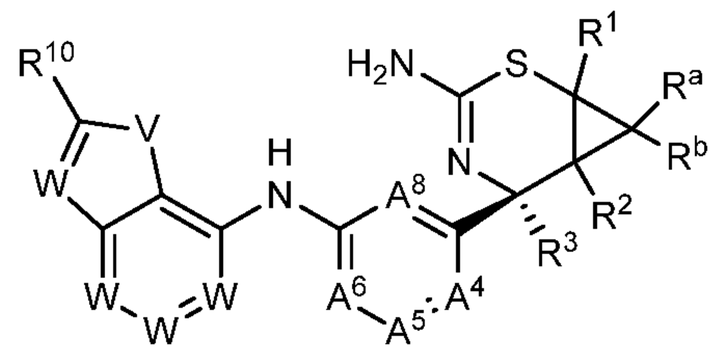
III-D



III-E

and



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III-F

in conjunction with any of the above or below embodiments, including those described in embodiments A, A-1 to A-4, B, B-1 to B-10, C, C-1 to C-10, D, D-1 to D-6, E, E-1 to E-5, F, F-1 to F-4, G, G-1 to G-4, H, H-1 to H-4, I, I-1 to I-9, J, J-1 to J-8, K, K-1 to K-2, L, M, N-1 to N-2, O-1 to O-2, P-1 to P-2, Q and Q-1 to Q-2 described herein.

The present invention contemplates that the various different embodiments of Formulas I, II and III, and sub-Formulas I-A, I-B, I-C and III-A throught III-F thereof, described herein, may comprise the following embodiments with respect to individual variables of A^4, A^5, A^6, A^8, R^1, R^2, R^3, R^7, V and W, where applicable, as described below. Hence, these embodiments with respect to individual variables A^4, A^5, A^6, A^8, R^1, R^2, R^3, R^7, V and W where applicable, may be applied "in conjunction with any of the other {above and below} embodiments" to create various embodiments of general Formulas I, II and III, and each sub-formula thereof, which are not literally or identically described herein. More specifically, the term "in conjunction with any of the above or below embodiments" includes embodiments A, A-1 to A-4, B, B-1 to B10, C, C-1 to C-

10, D, D-1 to D-6, E, E-1 to E-5, F, F-1 to F-4, G, G-1 to G-4, H, H-1 to H-4, I, I-1 to I-9, J, J-1 to J-8, K, K-1 to K-2, L, M, N-1 to N-2, O-1 to O-2, P-1 to P-2, Q and Q-1 to Q-2 described herein, as it applies to general Formulas I, II and III, and sub-formulas I-A, I-B and I-C and III-A through III-F, also described herein.

In another embodiment A, the invention includes compounds wherein each of R^a and R^b, independently, is H, F, Cl, C_{1-6}-alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, CN, $-CH_2OC_{1-6}$-alkyl, $-OC_{1-6}$-alkyl, $-S(O)_oC_{1-6}$-alkyl, $-NHC_{1-6}$-alkyl or $-C(O)C_{1-6}$-alkyl, wherein each of the C_{1-6}-alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, and C_{1-6}-alkyl portion of $-CH_2OC_{1-6}$-alkyl, $-OC_{1-6}$-alkyl, $-S(O)_oC_{1-6}$-alkyl, $-NHC_{1-6}$-alkyl and $-C(O)C_{1-6}$-alkyl are optionally substituted with 1-4 substituents of F, oxo or OH, in conjunction with any of the above or below embodiments.

In another embodiment A-1, the invention includes compounds wherein each of R^a and R^b, independently, is H, F, Cl, CF_3, OCF_3, methyl,ethyl, CN, OH, OCH_3, SCH_3, $NHCH_3$, $C(O)CH_3$ or CH_2OCHF_2, in conjunction with any of the above or below embodiments.

In another embodiment A-2, the invention includes compounds wherein each of R^a and R^b, independently, is H, F, CF_3, CH_3, CF_2H or CH_2F, in conjunction with any of the above or below embodiments.

In another embodiment A-3, the invention includes compounds wherein R^1 is H or F, in conjunction with any of the above or below embodiments.

In another embodiment A-4, the invention includes compounds wherein R^1 is H, in conjunction with any of the above or below embodiments.

In another embodiment B, the invention includes compounds wherein R^1 is each of R^1 and R^2, independently, is H, F, Cl, C_{1-6}-alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, CN, $-CH_2OC_{1-6}$-alkyl, $-OC_{1-6}$-alkyl, $-S(O)_oC_{1-6}$-alkyl, $-NHC_{1-6}$-alkyl, $-C(O)NH_2$, $-CH=CHC(O)NHC_{1-6}$-alkyl, $-CH=CHC(O)_2H$, $-CH=CHCH_2OH$, C_{1-6}-alkyl-$C(O)NHC_{1-6}$-alkyl, $-C(O)C_{1-6}$-alkyl or $-C(O)C_{1-6}$-alkenyl, wherein each of the C_{1-6}-alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, and C_{1-6}-alkyl portion of $-CH_2OC_{1-6}$-alkyl, $-OC_{1-6}$-alkyl, $-S(O)_oC_{1-6}$-alkyl, $-NHC_{1-6}$-alkyl, $C(O)C_{1-6}$-alkyl, $-C(O)C_{1-6}$-alkenyl, $-CH=CHC(O)NHC_{1-6}$-alkyl and C_{1-6}-alkyl-$C(O)NHC_{1-6}$-alkyl, are optionally substituted with 1-4 substituents of F, CN, oxo or OH, in conjunction with any of the above or below embodiments.

In another embodiment B-1, the invention includes compounds wherein R^1 is H, F, Cl, C_{1-6}-alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, CN, $-CH_2OC_{1-3}$-alkyl, $-OC_{1-3}$-alkyl and $-C(O)OC_{1-6}$-alkyl, wherein each of the C_{1-6}-alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl and C_{1-3}-alkyl

portion of -CH_2OC_{1-3}-alkyl, -$C(O)OC_{1-6}$-alkyl and -OC_{1-3}-alkyl are optionally substituted with 1-4 substituents of F and OH, in conjunction with any of the above or below embodiments.

In another embodiment B-2, the invention includes compounds wherein R^1 is H, F, CH_3, CH_2OCH_3, CH_2F, CHF_2, CF_3, -$C(O)NH_2$, -$CH=CHC(O)NHC_{1-6}$alkyl, -$CH=CHC(O)_2H$, -$CH=CHCH_2OH$ or C_{1-6}-alkyl-$C(O)NHC_{1-6}$-alkyl, in conjunction with any of the above or below embodiments.

In another embodiment B-3, the invention includes compounds wherein R^1 is H, F, CH_3, C_2H_5, CF_2H, CH_2F, or CH_2OCH_3, CH_2OCH_2F, CH_2OCF_2H or CH_2OCF_3, in conjunction with any of the above or below embodiments.

In another embodiment B-4, the invention includes compounds wherein R^1 is H, F, Cl, CF_3, CH_3, CF_2H or CH_2F, in conjunction with any of the above or below embodiments.

In another embodiment B-5, the invention includes compounds wherein R^1 is H, F, CF_3, CH_3, CF_2H or CH_2F, in conjunction with any of the above or below embodiments.

In another embodiment B-6, the invention includes compounds wherein R^1 is H, F, CH_2OCH_3 or CH_2OH, in conjunction with any of the above or below embodiments.

In another embodiment B-7, the invention includes compounds wherein R^1 is H or F, in conjunction with any of the above or below embodiments.

In another embodiment B-8, the invention includes compounds wherein R^1 is H, in conjunction with any of the above or below embodiments.

In another embodiment B-9, the invention includes compounds wherein R^1 is F, in conjunction with any of the above or below embodiments.

In another embodiment B-10, the invention includes compounds wherein R^1 is H, CH_2OCH_3 or CH_2OH, in conjunction with any of the above or below embodiments.

In another embodiment C, the invention includes compounds wherein R^2 is H, F, Cl, C_{1-6}-alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, CN, -CH_2OC_{1-6}-alkyl, -OC_{1-6}-alkyl, -$S(O)_oC_{1-6}$-alkyl, -NHC_{1-6}-alkyl or -$C(O)C_{1-6}$-alkyl, wherein each of the C_{1-6}-alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, and C_{1-6}-alkyl portion of -CH_2OC_{1-6}-alkyl, -OC_{1-6}-alkyl, -$S(O)_oC_{1-6}$-alkyl, -NHC_{1-6}-alkyl and -$C(O)C_{1-6}$-alkyl are optionally substituted with 1-4 substituents of F, oxo or OH, in conjunction with any of the above or below embodiments.

In another embodiment C-1, the invention includes compounds wherein R^2 is H, F, Cl, C_{2-4}alkenyl, C_{2-4}alkynyl, CN, -CH_2OC_{1-3}-alkyl, -OC_{1-3}-alkyl, wherein each of the C_{2-4}alkenyl, C_{2-4}alkynyl and C_{1-3}-alkyl portion of -CH_2OC_{1-3}-alkyl and -OC_{1-3}-alkyl are

optionally substituted with 1-4 substituents of F, in conjunction with any of the above or below embodiments.

In another embodiment C-2, the invention includes compounds wherein R^2 is H, F, Cl, CF_3, OCF_3, methyl,ethyl, CN, OH, OCH_3, SCH_3, $NHCH_3$, $C(O)CH_3$ or CH_2OCHF_2, in conjunction with any of the above or below embodiments.

In another embodiment C-3, the invention includes compounds wherein R^2 is H, F, CH_3, C_2H_5, CF_2H, CH_2F, CH_2OCH_2F, CH_2OCF_2H or CH_2OCF_3, in conjunction with any of the above or below embodiments.

In another embodiment C-4, the invention includes compounds wherein R^2 is H, F, Cl, CF_3, CH_3, CF_2H or CH_2F, in conjunction with any of the above or below embodiments.

In another embodiment C-5, the invention includes compounds wherein R^2 is H, F, CF_3, CH_3, CF_2H or CH_2F, in conjunction with any of the above or below embodiments.

In another embodiment C-6, the invention includes compounds wherein R^2 is H, F or CF_3, in conjunction with any of the above or below embodiments.

In another embodiment C-7, the invention includes compounds wherein R^2 is H or F, in conjunction with any of the above or below embodiments.

In another embodiment C-8, the invention includes compounds wherein R^2 is H, in conjunction with any of the above or below embodiments.

In another embodiment C-9, the invention includes compounds wherein R^2 is F, in conjunction with any of the above or below embodiments.

In another embodiment C-10, the invention includes compounds wherein R^2 is CF_3, in conjunction with any of the above or below embodiments.

In another embodiment D, the invention includes compounds wherein R^3 is C_{1-4}alkyl, CH_2OC_{1-4}alkyl, CH_2OH, C_{1-4}haloalkyl or cyclopropyl, wherein each of the C_{1-4}alkyl, CH_2OC_{1-4}alkyl, C_{1-4}haloalkyl and cyclopropyl is optionally substituted with 1-4 F atoms, in conjunction with any of the above or below embodiments.

In another embodiment D-1, the invention includes compounds wherein R^3 is C_{1-4}alkyl, C_{1-4}haloalkyl, CH_2OH, CH_2OCHF_2 or cyclopropyl, wherein each of the C_{1-4}alkyl, C_{1-4}haloalkyl and cyclopropyl is optionally substituted with 1-4 F atoms, in conjunction with any of the above or below embodiments.

In another embodiment D-2, the invention includes compounds wherein R^3 is

C_{1-4}alkyl, CH_2OH, CH_2OCH_2F, CH_2OCF_2H, or cyclopropyl, wherein each of the C_{1-4}alkyl and cyclopropyl is optionally substituted with 1-2 F atoms, in conjunction with any of the above or below embodiments.

In another embodiment D-3, the invention includes compounds wherein R^3 is CH_3, CF_3, CF_2H or CH_2F, in conjunction with any of the above or below embodiments.

In another embodiment D-4, the invention includes compounds wherein R^3 is CH_3, CF_2H or CH_2F, in conjunction with any of the above or below embodiments.

In another embodiment D-5, the invention includes compounds wherein R^3 is CH_3 or CH_2F, in conjunction with any of the above or below embodiments.

In another embodiment D-6, the invention includes compounds wherein R^3 is CH_2F, in conjunction with any of the above or below embodiments.

In another embodiment E, the invention includes compounds wherein A^4 is CR^4 wherein R^4 is H, halo, haloalkyl, haloalkoxyl, C_{1-4}-alkyl, CN, OH, OC_{1-4}-alkyl, $S(O)_oC_{1-4}$-alkyl, NHC_{1-4}-alkyl or $C(O)C_{1-4}$-alkyl, in conjunction with any of the above or below embodiments.

In another embodiment E-1, the invention includes compounds wherein A^4 is CR^4 wherein R^4 is H, F, Cl, CF_3, OCF_3, methyl, ethyl, CN, OH, OCH_3, SCH_3, $NHCH_3$ or $C(O)CH_3$, in conjunction with any of the above or below embodiments.

In another embodiment E-2, the invention includes compounds wherein A^4 is CR^4 wherein R^4 is H, F, CF_3, CF_2H, CH_2F or CH_3, in conjunction with any of the above or below embodiments.

In another embodiment E-3, the invention includes compounds wherein A^4 is CR^4 wherein R^4 is H or F, in conjunction with any of the above or below embodiments.

In another embodiment E-4, the invention includes compounds wherein A^4 is CR^4 wherein R^4 is F, in conjunction with any of the above or below embodiments.

In another embodiment E-5, the invention includes compounds wherein A^4 is N, in conjunction with any of the above or below embodiments.

In another embodiment F, the invention includes compounds wherein A^5 is CR^5 and R^5 is H, halo, haloalkyl, haloalkoxyl, C_{1-4}-alkyl, CN, OH, OC_{1-4}-alkyl, $S(O)_oC_{1-4}$-alkyl, NHC_{1-4}-alkyl or $C(O)C_{1-4}$-alkyl, in conjunction with any of the above or below embodiments.

In another embodiment F-1, the invention includes compounds wherein A^5 is CR^5 wherein R^5 is H, F, Cl, CF_3, OCF_3, methyl, ethyl, CN, OH, OCH_3, SCH_3, $NHCH_3$ or $C(O)CH_3$, in conjunction with any of the above or below embodiments.

In another embodiment F-2, the invention includes compounds wherein A^5 is CR^5 and R^5 is H, F, Cl, CF_3, CF_2H, CH_2F, CH_3 or N in conjunction with any of the above or below embodiments.

In another embodiment F-3, the invention includes compounds wherein A^5 is CR^5 and R^5 is H, F, Cl or CH_3, in conjunction with any of the above or below embodiments.

In another embodiment F-4, the invention includes compounds wherein A^5 is N, in conjunction with any of the above or below embodiments.

In another embodiment G, the invention includes compounds wherein A^6 is CR^6 wherein R^6 is H, halo, haloalkyl, haloalkoxyl, C_{1-4}-alkyl, CN, OH, OC_{1-4}-alkyl, $S(O)_oC_{1-4}$-alkyl, NHC_{1-4}-alkyl or $C(O)C_{1-4}$-alkyl, in conjunction with any of the above or below embodiments.

In another embodiment G-1, the invention includes compounds wherein A^6 is CR^6 wherein R^6 is H, F, Cl, CF_3, OCF_3, methyl, ethyl, CN, OH, OCH_3, SCH_3, $NHCH_3$ or $C(O)CH_3$, in conjunction with any of the above or below embodiments.

In another embodiment G-2, the invention includes compounds wherein A^6 is CR^6 wherein R^6 is H, F, CF_3, CF_2H, CH_2F or CH_3, in conjunction with any of the above or below embodiments.

In another embodiment G-3, the invention includes compounds wherein A^6 is CR^6 wherein R^6 is H or F, in conjunction with any of the above or below embodiments.

In another embodiment G-4, the invention includes compounds wherein A^6 is N, in conjunction with any of the above or below embodiments.

In another embodiment H, the invention includes compounds wherein A^8 is CR^8 wherein R^8 is H, halo, haloalkyl, haloalkoxyl, C_{1-4}-alkyl, CN, OH, OC_{1-4}-alkyl, $S(O)_oC_{1-4}$-alkyl, NHC_{1-4}-alkyl or $C(O)C_{1-4}$-alkyl, in conjunction with any of the above or below embodiments.

In another embodiment H-1, the invention includes compounds wherein A^8 is CR^8 wherein R^8 is H, F, Cl, CF_3, OCF_3, methyl, ethyl, CN, OH, OCH_3, SCH_3, $NHCH_3$ or $C(O)CH_3$, in conjunction with any of the above or below embodiments.

In another embodiment H-2, the invention includes compounds wherein A^8 is CR^8 wherein R^8 is H, F, CF_3, CF_2H, CH_2F or CH_3, in conjunction with any of the above or below embodiments.

In another embodiment H-3, the invention includes compounds wherein A^8 is CR^8 wherein R^8 is H or F, in conjunction with any of the above or below embodiments.

In another embodiment H-4, the invention includes compounds wherein A^8 is N, in conjunction with any of the above or below embodiments.

In another embodiment I, the invention includes compounds wherein no more than two of A^4, A^5, A^6 and A^8 is N, in conjunction with any of the above or below embodiments.

In another embodiment I-1, the invention includes compounds wherein no more than one of A^4, A^5, A^6 and A^8 is N, in conjunction with any of the above or below embodiments.

In another embodiment I-2, the invention includes compounds wherein A^4 is CR^4, A^5 is CR^5 or N, A^6 is CR^6 and A^8 is CR^8, in conjunction with any of the above or below embodiments.

In another embodiment, the invention includes compounds wherein A^4 is CR^4 or N, A^5 is CR^5, A^6 is CR^6 and A^8 is CR^8, in conjunction with any of the above or below embodiments.

In another embodiment I-3, the invention includes compounds wherein A^4 is N, A^5 is CR^5, A^6 is CR^6 and A^8 is CR^8, in conjunction with any of the above or below embodiments.

In another embodiment I-4, the invention includes compounds wherein A^4 is CR^4, A^5 is N, A^6 is CR^6, and A^8 is CR^8, in conjunction with any of the above or below embodiments.

In another embodiment I-5, the invention includes compounds wherein A^4 is CR^4, A^5 is CR^5, A^6 is N, and A^8 is CR^8, in conjunction with any of the above or below embodiments.

In another embodiment I-6, the invention includes compounds wherein A^4 is CR^5, A^5 is CR^5, A^6 is CR^6, and A^8 is N, in conjunction with any of the above or below embodiments.

In another embodiment I-7, the invention includes compounds of of Formulas I, II or III, wherein

A^4 is CR^4 or N;

A^5 is CR^5 or N;

A^6 is CR^6 or N;

A^8 is CR^8 or N, provided that no more than one of A^4, A^5, A^6 and A^8 is N;

each of R^a and R^b, independently, is H, F, Cl, CF_3, OCF_3, methyl,ethyl, CN, OH, OCH_3, SCH_3, $NHCH_3$, $C(O)CH_3$ or CH_2OCHF_2;

each of R^1 and R^2, independently, is H, F, Cl, CF_3, OCF_3, methyl,ethyl, CN, OH, OCH_3, SCH_3, $NHCH_3$, $C(O)CH_3$, $C(O)OC_{1-3}$alkyl , CH_2OCH_3 or CH_2OCHF_2;

R^3 is C_{1-4}alkyl, C_{1-4}haloalkyl, CH_2OH, CH_2OCHF_2 or cyclopropyl; and

each of R^4, R^5, R^6 and R^8, independently, is H, F, Cl, CF_2H, CH_2F, CF_3, OCF_3, methyl, ethyl, CN, OH, OCH_3, SCH_3, $NHCH_3$ or $C(O)CH_3$, in conjunction with any of the above or below embodiments.

In another embodiment I-8, the invention includes compounds of Formulas I, II or III, wherein

A^4 is CR^4;

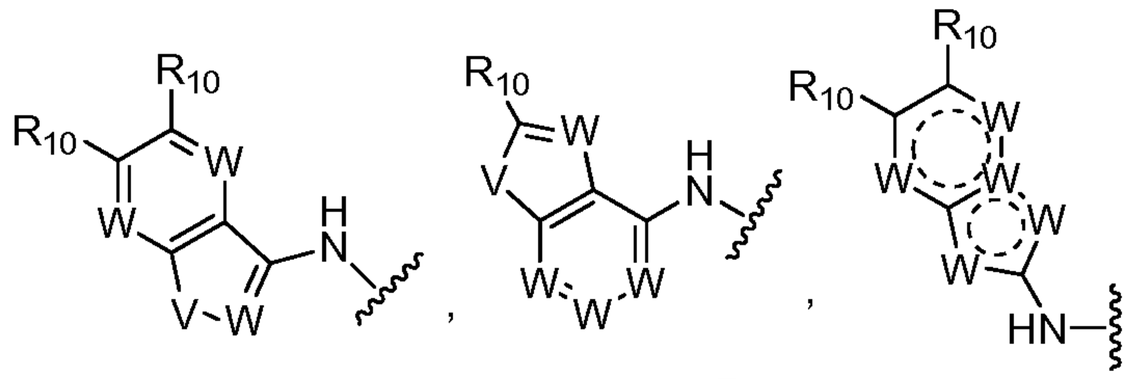
A^5 is CR^5;

A^6 is CR^6; and

A^8 is CR^8; wherein each of R^4, R^5, R^6 and R^8, independently, is H, F, CF_3, CF_2H, CH_2F or CH_3, in conjunction with any of the above or below embodiments.

In another embodiment I-9, the invention includes compounds of Formulas I, II or III, wherein A^4 is CH, CF or N, A^5 is CH, CF or N, A^6 is CH, CF or N, A^8 is CH, CF or N, one of A^4, A^5, A^6 and A^8 is N, in conjunction with any of the above or below embodiments.

In another embodiment J, the invention includes compounds of Formulas I, II or III, wherein R^7 is $-NH-R^9$ or $-NH-C(=O)-R^9$; or R^7 is



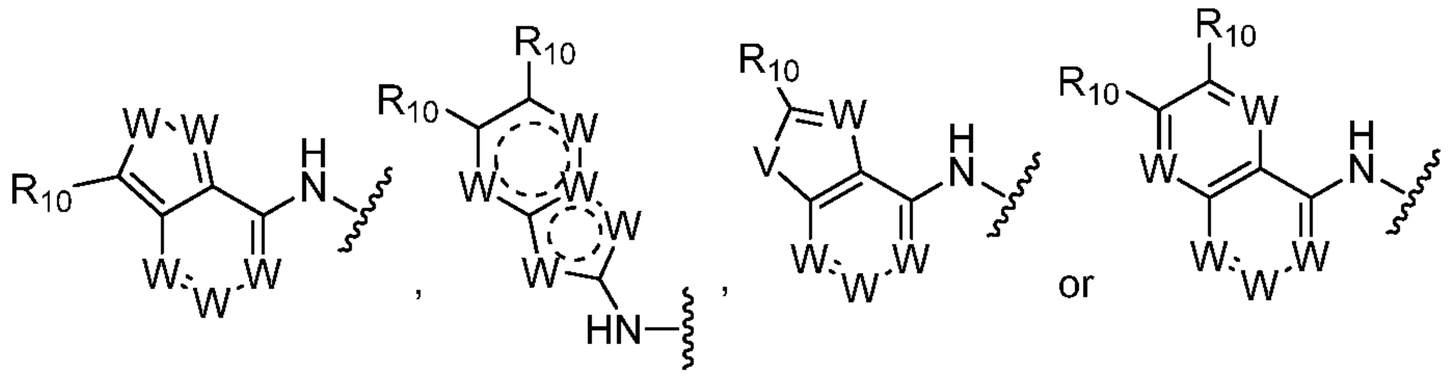
wherein V is NR^{10}, O or S;

each W, independently, is CH, CF, CCl, CCH_3 or N; and

each R^{10} is as defined herein, in conjunction with any of the above or below embodiments.

In another embodiment J-1, the invention includes compounds of Formulas I, II

or III, wherein R^7 is –NH-R^9, -NH-C(=O)-R^9 or

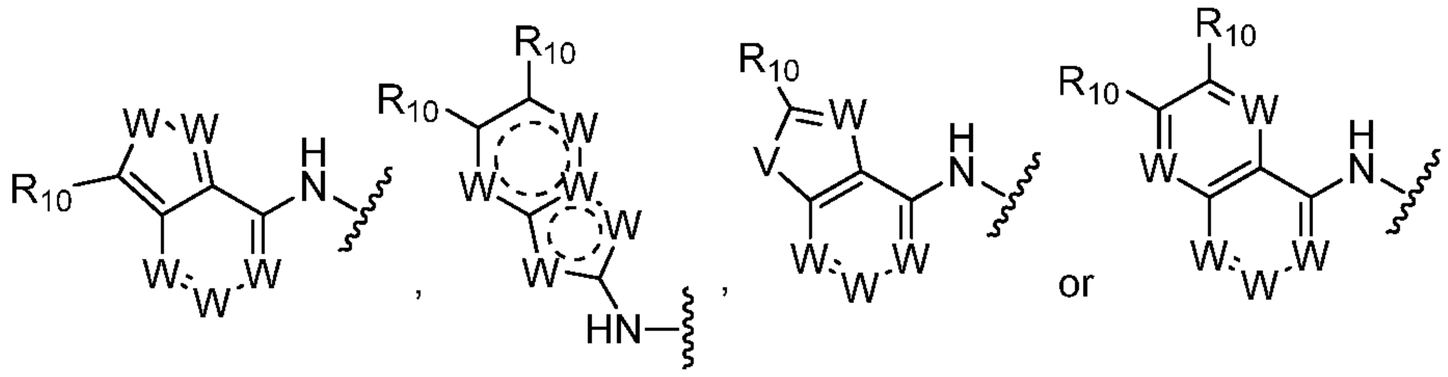


wherein V is NR^{10}, O or S; and

each W, independently, is CH, CF, CCl, CCH_3 or N; and

each R^{10} is as defined herein, in conjunction with any of the above or below embodiments.

In another embodiment J-2, the invention includes compounds of Formulas I, II or III, wherein R^7 is -NH-C(=O)-R^9 or



wherein V is NR^{10}, O or S; and

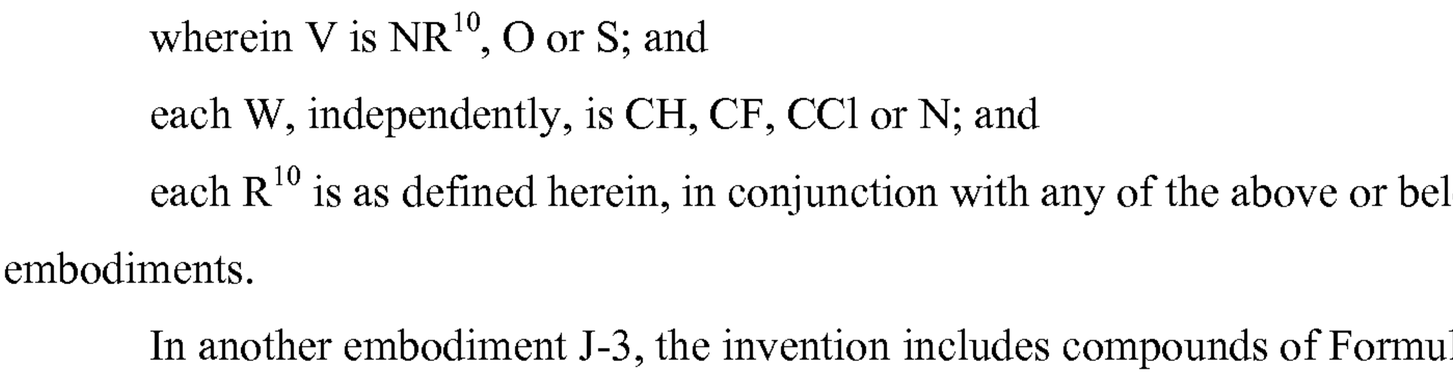
each W, independently, is CH, CF, CCl or N; and

each R^{10} is as defined herein, in conjunction with any of the above or below embodiments.

In another embodiment J-3, the invention includes compounds of Formulas I, II or III, wherein R^7 is -NH-C(=O)-R^9, in conjunction with any of the above or below embodiments.

In another embodiment J-4, the invention includes compounds of Formulas I, II or III, wherein R^7 is –NH-R^9, in conjunction with any of the above or below embodiments.

In another embodiment J-5, the invention includes compounds wherein R^7 is

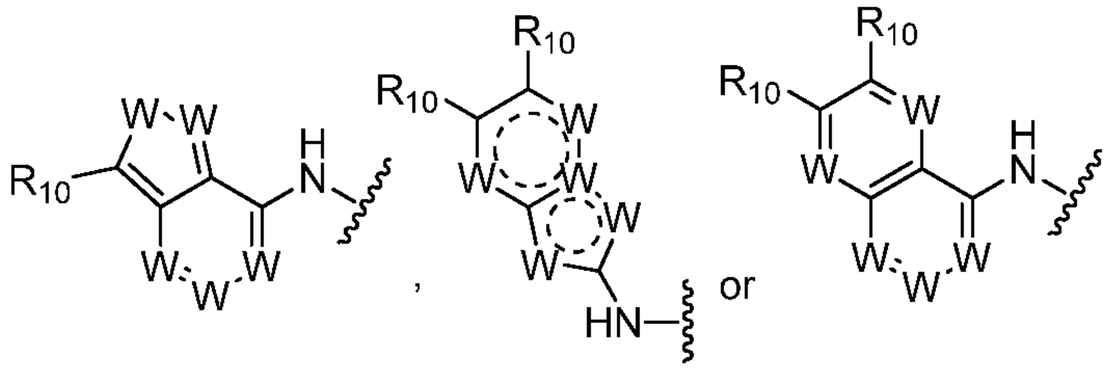


wherein V is NR^{10}, O or S; and

each W, independently, is CH, CF, CCl, CCH_3 or N, in conjunction with any of

the above or below embodiments.

In another embodiment J-6, the invention includes compounds wherein R^7 is



wherein V is NR^{10}, O or S; and

each W, independently, is CH, CF, CCl, CCH_3 or N, in conjunction with any of the above or below embodiments.

In another embodiment J-7, the invention includes compounds wherein R^7 is –NH-R^9, in conjunction with any of the above or below embodiments.

In another embodiment J-8, the invention includes compounds wherein R^7 is –NH-R^9 or -NH-C(=O)-R^9, wherein R^9 is a fully or partially unsaturated 3-, 4-, 5-, 6- or 7-membered monocyclic or 8-, 9- or 10-membered bicyclic ring formed of carbon atoms, said ring optionally including 1-4 heteroatoms if monocyclic or 1-5 heteroatoms if bicyclic, said heteroatoms selected from O, N or S, wherein the ring is optionally substituted, independently, with 1-5 substituents of R^{10}, in conjunction with any of the above or below embodiments.

In another embodiment K, the invention includes compounds wherein each R^9, independently, is a ring selected from phenyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, pyrazolyl, isoxazolyl, thiazolyl, naphthyl, quinolinyl, isoquinolinyl, quinazolinyl, naphthyridinyl, phthalazinyl, pyranyl, dihydropyranyl, tetrahydropyranyl, furanyl, dihydrofuranyl, tetrahydrofuranyl, thienyl, pyrrolyl, pyrrolidinyl, tetrahydropyrrolyl, piperidinyl, piperazinyl, morpholinyl, azetidinyl, 8-oxo-3-aza-bicyclo[3.2.1]oct-3-yl, aza-bicyclo[2.2.1]hept-5-yl, 2-oxo-7-aza-[3,5]-spironon-7-yl, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl, wherein the C_{1-6}-alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl and ring are optionally substituted, independently, with 1-5 substituents of R^{10}, in conjunction with any of the above or below embodiments.

In another embodiment K-1, the invention includes compounds wherein each R^9 is a ring selected from phenyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, pyrazolyl,

pyrazolo[3,4-c]pyridinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl or thienyl, wherein the ring is optionally substituted with 1-5 substituents of R^{10}, in conjunction with any of the above or below embodiments.

In another embodiment K-2, the invention includes compounds of Formulas I, II, and III, and any sub-formula thereof as described herein, wherein R^9 is a ring selected from the group consisting of phenyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, pyrazolyl, isoxazolyl, thiazolyl, thienyl, furanyl and pyrrolyl, wherein the ring is optionally substituted, independently, with 1-3 substituents of R^{10}, wherein each R^{10}, independently, is F, Cl, CN, NO_2, NH_2, OH, CF_3, CHF_2, CH_2F, CH_3, -OCH_3, C_2H_5, -OC_2H_5, -CH_2CF_3, -CH_2CHF_2, propyl, propoxy, isopropyl, isopropoxy, cyclopropyl, butyl, butoxyl, cyclobutyl, isobutoxy, *tert*-butoxy, isobutyl, sec-butyl, *tert*-butyl, cyclopropylmethoxy, 2-butynyloxy or oxetan-3yl, in conjunction with any of the above or below embodiments.

In another embodiment L, the present invention provides compounds, and solvates, tautomers, hydrates, stereoisomers and pharmaceutically acceptable salts thereof, as defined by Formulas I, I-A, I-B, I-C or II, wherein

A^4 is CR^4 or N;

A^5 is CR^5 or N;

A^6 is CR^6 or N;

A^8 is CR^8 or N, provided no more than one of A^4, A^5, A^6 and A^8 is N;

each of R^a and R^b, independently, is H, F, CH_3, CH_2F, CHF_2 or CF_3;

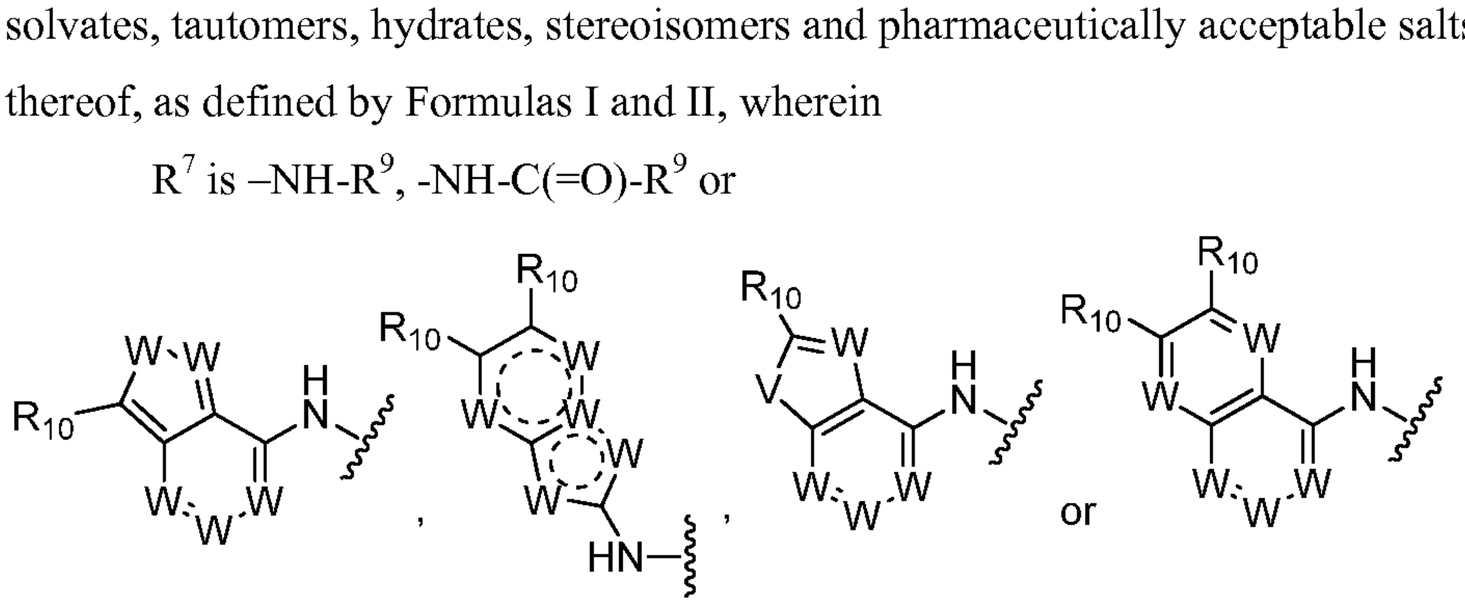
each of R^1 and R^2, independently, is H, F, CH_3, CH_2OCH_3, CH_2F, CHF_2 or CF_3;

R^3 is $C_{1\text{-}4}$alkyl, $C_{1\text{-}4}$haloalkyl, CH_2OH, CH_2OCHF_2 or cyclopropyl; and

each of R^4, R^5, R^6 and R^8, independently, is H, F, Cl, CF_2H, CH_2F, CF_3, OCF_3, methyl, ethyl, CN, OH, OCH_3, SCH_3, $NHCH_3$ or $C(O)CH_3$, in conjunction with any of the above or below embodiments.

In another embodiment M, the present invention provides compounds, and solvates, tautomers, hydrates, stereoisomers and pharmaceutically acceptable salts thereof, as defined by Formulas I and II, wherein

R^7 is –NH-R^9, -NH-C(=O)-R^9 or



wherein V is NR^{10}, O or S; and

each W, independently, is CH, CF, CCl, CCH_3 or N, in conjunction with any of the above or below embodiments.

In another embodiment N-1, the invention includes compounds of Formula I-A wherein A^4 is CR^4;

A^5 is CR^5 or N;

A^6 is CR^6;

A^8 is CR^8; wherein each of R^4, R^5, R^6 and R^8, independently, is H, F, Cl, CF_3, OCF_3, methyl, ethyl, CN, OH, OCH_3, SCH_3, $NHCH_3$ or $C(O)CH_3$;

each of R^a and R^b, independently, is H, F, CH_3, CH_2F, CHF_2 or CF_3;

R^1 is H, F, CH_3, CH_2OCH_3, CH_2F, CHF_2 or CF_3;

R^2 is H, F, CH_3, CH_2F, CHF_2 or CF_3;

R^3 is CH_3, C_2H_5, CF_2H or CH_2F;

R^9 is acetyl, C_{1-6}-alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl or a fully or partially unsaturated 3-, 4-, 5-, 6- or 7-membered monocyclic or 8-, 9- or 10-membered bicyclic ring formed of carbon atoms, said ring optionally including 1-4 heteroatoms if monocyclic or 1-5 heteroatoms if bicyclic, said heteroatoms selected from O, N or S, wherein the C_{1-6}-alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl and ring are optionally substituted, independently, with 1-5 substituents of R^{10}; and

each R^{10}, independently, is H, halo, haloalkyl, CN, OH, NO_2, NH_2, SF_5, acetyl, $-C(O)NHCH_3$, oxo, cyclopropylmethoxy, 2-propynyloxy, 2-butynyloxy, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkylamino-, C_{1-6}dialkylamino-, C_{1-6}alkoxyl, C_{1-6}thioalkoxyl, morpholinyl, pyrazolyl, isoxazolyl, dihydropyranyl, pyrrolyl, pyrrolidinyl, tetrahydropyrrolyl, piperazinyl, oxetan-3-yl, imidazo-pyridinyl or dioxolyl, wherein each of the cyclopropylmethoxy, 2-propynyloxy, 2-butynyloxy, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkylamino-, C_{1-6}dialkylamino-, C_{1-6}alkoxyl, C_{1-6}thioalkoxyl, morpholinyl, pyrazolyl, isoxazolyl, dihydropyranyl, pyrrolidinyl, oxetan-3-yl or dioxolyl, is optionally substituted independently with 1-5 substituents of F, Cl, CN, NO_2, NH_2, OH, oxo, CF_3, CHF_2, CH_2F, methyl, methoxy, ethyl, ethoxy, CH_2CF_3, CH_2CHF_2, propyl, propoxy, isopropyl, isopropoxy, cyclopropyl, butyl, butoxyl, cyclobutyl, isobutoxy, *tert*-butoxy, isobutyl, sec-butyl, *tert*-butyl, cyclopentyl, cyclohexyl, C_{1-3}alkylamino-, C_{1-3}dialkylamino, C_{1-3}thioalkoxyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, thienyl, furyl, pyrrolyl, tetrahydropyranyl, tetrahydropyrrolyl or oxetan-3yl.

In another embodiment N-2, the invention includes compounds of Formula I-A

wherein A^4 is CR^4;

A^5 is CR^5;

A^6 is CR^6;

A^8 is CR^8; wherein each of R^4, R^5, R^6 and R^8, independently, is H, F, CF_3, OCF_3, methyl, ethyl, CN or OCH_3;

each of R^a and R^b, independently, is H or F;

R^1 is H, F, CH_2OCH_3 or CF_3;

R^2 is H, F or CF_3;

R^3 is CF_3, CH_3, CF_2H or CH_2F;

R^9 is a ring selected from phenyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, pyrazolyl, isoxazolyl, thiazolyl, furanyl, thienyl and pyrrolyl, wherein the ring is optionally substituted, independently, with 1-3 substituents of R^{10}; and

each R^{10}, independently, is H, halo, haloalkyl, CN, OH, NO_2, NH_2, SF_5, acetyl, $-C(O)NHCH_3$, oxo, cyclopropylmethoxy, 2-propynyloxy, 2-butynyloxy, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkylamino-, C_{1-6}dialkylamino-, C_{1-6}alkoxyl, C_{1-6}thioalkoxyl, morpholinyl, pyrazolyl, isoxazolyl, dihydropyranyl, pyrrolyl, pyrrolidinyl, tetrahydropyrrolyl, piperazinyl, oxetan-3-yl, imidazo-pyridinyl or dioxolyl, wherein each of the cyclopropylmethoxy, 2-propynyloxy, 2-butynyloxy, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkylamino-, C_{1-6}dialkylamino-, C_{1-6}alkoxyl, C_{1-6}thioalkoxyl, morpholinyl, pyrazolyl, isoxazolyl, dihydropyranyl, pyrrolidinyl, oxetan-3-yl or dioxolyl, is optionally substituted independently with 1-5 substituents of F, Cl, CN, NO_2, NH_2, OH, oxo, CF_3, CHF_2, CH_2F, methyl, methoxy, ethyl, ethoxy, CH_2CF_3, CH_2CHF_2, propyl, propoxy, isopropyl, isopropoxy, cyclopropyl, butyl, butoxyl, cyclobutyl, isobutoxy, *tert*-butoxy, isobutyl, sec-butyl, *tert*-butyl, cyclopentyl, cyclohexyl, C_{1-3}alkylamino-, C_{1-3}dialkylamino, C_{1-3}thioalkoxyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, thienyl, furyl, pyrrolyl, tetrahydropyranyl, tetrahydropyrrolyl or oxetan-3yl.

In another embodiment O-1, the invention includes compounds of Formula I-B wherein A^4 is CR^4;

A^5 is CR^5;

A^6 is CR^6;

A^8 is CR^8; wherein each of R^4, R^5, R^6 and R^8, independently, is H, F, Cl, CF_3, OCF_3, methyl, ethyl, CN, OH, OCH_3, SCH_3, $NHCH_3$ or $C(O)CH_3$;

each of R^a and R^b, independently, is H, F, CH_3, CH_2F, CHF_2 or CF_3;

each of R^1 and R^2, independently, is H, F, CH_3, CH_2F, CHF_2 or CF_3; and

R^3 is CH_3, C_2H_5, CF_2H or CH_2F, in conjunction with any of the above or below embodiments with respect to Formula I-B.

In another embodiment O-2, the invention includes compounds of Formula I-B wherein A^4 is CR^4 or N;

A^5 is CR^5 or N;

A^6 is CR^6 or N;

A^8 is CR^8 or N, wherein each of R^4, R^5, R^6 and R^8, independently, is H or F and provided no more than one of A^4, A^5, A^6 and A^8 is N;

each of R^1 and R^2, independently, is H, F or CF_3;

each of R^a and R^b, independently, is H or F; and

R^3 is CF_3, CH_3, CF_2H or CH_2F, in conjunction with any of the above or below embodiments with respect to Formula I-B.

In another embodiment P-1, the invention includes compounds of Formula I-C wherein A^4 is CR^4;

A^5 is CR^5;

A^6 is CR^6;

A^8 is CR^8; wherein each of R^4, R^5, R^6 and R^8, independently, is H, F, Cl, CF_3, OCF_3, methyl, ethyl, CN, OH, OCH_3, SCH_3, $NHCH_3$ or $C(O)CH_3$;

each of R^a and R^b, independently, is H, F, CH_3, CH_2F, CHF_2 or CF_3;

each of R^1 and R^2, independently, is H, F, CH_3, CH_2F, CHF_2 or CF_3; and

R^3 is CH_3, C_2H_5, CF_2H or CH_2F, in conjunction with any of the above or below embodiments with respect to Formula I-C.

In another embodiment P-2, the invention includes compounds of Formula I-C wherein A^4 is CR^4 or N;

A^5 is CR^5 or N;

A^6 is CR^6 or N;

A^8 is CR^8 or N, wherein each of R^4, R^5, R^6 and R^8, independently, is H or F and provided no more than one of A^4, A^5, A^6 and A^8 is N;

each of R^1 and R^2, independently, is H, F or CF_3;

each of R^a and R^b, independently, is H or F; and

R^3 is CF_3, CH_3, CF_2H or CH_2F, in conjunction with any of the above or below embodiments with respect to Formula I-C.

In another embodiment, the invention provides one or more of the compounds, or a pharmaceutically acceptable salt thereof, of Formulas I, II and III, and sub-formulas thereof, as taught and described herein.

In another embodiment, the invention provides the compound of Formula I, II or III, or a stereoisomer or pharmaceutically acceptable salt thereof, selected from

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-cyano-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-cyano-3-methyl-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-methoxy-2-pyrazinecarboxamide; and

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-chloro-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-chloro-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-cyano-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-chloro-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-cyano-3-methyl-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

8-((3-((1S,5S,6S)-3-amino-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)amino)-1,7-naphthyridine-3-carbonitrile;

N-(3-((1S,5S,6S)-3-amino-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

8-((3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)amino)-1,7-naphthyridine-3-carbonitrile;

4-((3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)amino)pyrido[3,2-d]pyrimidine-7-carbonitrile;

8-((3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)amino)-1,7-naphthyridine-3-carbonitrile;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-7-chloropyrido[3,2-d]pyrimidin-4-amine;

4-((3-((1S,5S,6S)-3-amino-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)amino)pyrido[3,2-d]pyrimidine-7-carbonitrile;

8-((3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)amino)-1,7-naphthyridine-3-carbonitrile;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-7-chloropyrido[3,2-d]pyrimidin-4-amine;

4-((3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)amino)pyrido[3,2-d]pyrimidine-7-carbonitrile;

((1S,5S,6S)-3-amino-5-(5-((7-chloropyrido[3,2-d]pyrimidin-4-yl)amino)-2-fluorophenyl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)methanol;

4-((3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)amino)pyrido[3,2-d]pyrimidine-7-carbonitrile;

((1S,5S,6S)-3-amino-5-(fluoromethyl)-5-(2-fluoro-5-((3-(2-propyn-1-yloxy)-1,7-naphthyridin-8-yl)amino)phenyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)methanol;

8-((3-((1S,5S,6S)-3-amino-1-(hydroxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)amino)-1,7-naphthyridine-3-carbonitrile;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-2-(1,3-oxazol-2-ylmethoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

((1S,5S,6S)-3-amino-5-(2,3-difluoro-5-((2-(2-propyn-1-yloxy)pyrido[3,4-b] pyrazin-5-yl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)methanol;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-methyl-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide; or

4-((3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo [4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)amino)pyrido[3,2-d]pyrimidine-7-carbonitrile.

In another embodiment, the invention provides the compound of Formula I or a tautomer, stereoisomer, or pharmaceutically acceptable salt thereof selected from

N-(5-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoro-3-pyridinyl)-2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-amine;

N-(5-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoro-3-pyridinyl)-2-(1,3-oxazol-2-ylmethoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(5-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoro-3-pyridinyl)-3-methyl-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

8-((5-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoro-3-pyridinyl)amino)-1,7-naphthyridine-3-carbonitrile;

N-(5-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoro-3-pyridinyl)-7-(1,3-oxazol-2-ylmethoxy)pyrido[3,2-d]pyrimidin-4-amine;

N-(5-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoro-3-pyridinyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

N-(5-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoro-3-pyridinyl)-5-(1,3-oxazol-2-ylmethoxy)-2-pyrazinecarboxamide;

((1R,5S,6S)-3-amino-5-(2-fluoro-5-((7-(1,3-oxazol-2-ylmethoxy)pyrido[3,2-d]pyrimidin-4-yl)amino)-3-pyridinyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)acetonitrile;

N-(5-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoro-3-pyridinyl)-5-(2,2,3,3-tetrafluoropropoxy)-2-pyridinecarboxamide;

N-(5-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoro-3-pyridinyl)-5-(2,2,3,3-tetrafluoropropoxy)-2-pyrazinecarboxamide;

N-(5-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-methoxy-3-pyridinyl)-2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-amine;

N-(5-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-methoxy-3-pyridinyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

N-(5-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoro-3-pyridinyl)-2-((~2~H_5_)-2-butyn-1-yloxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-methyl-5-(2,2,2-trifluoroethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-methyl-5-(2,2,2-trifluoroethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-methyl-5-(((1S)-1-methyl-2-propyn-1-yl)oxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-methyl-5-(((1S)-1-methyl-2-propyn-1-yl)oxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-methyl-5-(2,2,2-trifluoroethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3-methyl-5-(((1S)-1-methyl-2-propyn-1-yl)oxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3-methyl-5-(2,2,2-trifluoroethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3-methyl-5-(((1S)-1-methyl-2-propyn-1-yl)oxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-methyl-5-(((1S)-1-methyl-2-propyn-1-yl)oxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3-methyl-5-(2,2,2-trifluoroethoxy)-2-pyrazinecarboxamide;

N-(5-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-methoxy-3-pyridinyl)-5-chloro-2-pyridinecarboxamide;

N-(5-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-methoxy-3-pyridinyl)-7-(2-propyn-1-yloxy)pyrido[3,2-d]pyrimidin-4-amine;

N-(5-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-methoxy-3-pyridinyl)-2-(1,3-oxazol-2-ylmethoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-(1,3-oxazol-4-ylmethoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-methoxy-1,7-naphthyridin-8-amine;

N-(3-((1R,5S,6S)-3-amino-5-methyl-1-(methylsulfonyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-(1,3-oxazol-2-ylmethoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-5-methyl-1-(1-pyrrolidinylcarbonyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-5-methyl-1-(1-pyrrolidinylcarbonyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-5-methyl-1-(1-pyrrolidinylcarbonyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(2,2,2-trifluoroethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1,5-bis(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-2-(2-methoxyethoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-7-fluoropyrido[3,2-d]pyrimidin-4-amine;

N-(5-((1S,5S,6S)-3-amino-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoro-3-pyridinyl)-5-chloro-2-pyridinecarboxamide;

5-((5-((1S,5S,6S)-3-amino-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoro-3-pyridinyl)amino)pyrido[3,4-b]pyrazin-2(1H)-one;

N-(5-((1S,5S,6S)-3-amino-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoro-3-pyridinyl)-2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-amine;

N-(5-((1S,5S,6S)-3-amino-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoro-3-pyridinyl)-2-(1,3-oxazol-2-ylmethoxy)pyrido[3,4-b]pyrazin-5-amine;

8-((5-((1S,5S,6S)-3-amino-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoro-3-pyridinyl)amino)-1,7-naphthyridine-3-carbonitrile;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3-methyl-5-(1,3-oxazol-2-ylmethoxy)-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-methyl-5-(1,3-oxazol-2-ylmethoxy)-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3-methyl-5-(1,3-oxazol-2-ylmethoxy)-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-methyl-5-(1,3-oxazol-2-ylmethoxy)-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-methyl-5-(1,3-oxazol-2-ylmethoxy)-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-methyl-5-(((1S)-1-methyl-2-propyn-1-yl)oxy)-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3-methyl-5-(((1S)-1-methyl-2-propyn-1-yl)oxy)-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3-methyl-5-(((1S)-1-methyl-2-propyn-1-yl)oxy)-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-methyl-5-(((1S)-1-methyl-2-propyn-1-yl)oxy)-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3-methyl-5-(((1S)-1-methyl-2-propyn-1-yl)oxy)-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3-methyl-5-(1,3-oxazol-2-ylmethoxy)-2-pyridinecarboxamide;

N-(5-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoro-3-pyridinyl)-2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-amine;

N-(5-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoro-3-pyridinyl)-2-(1,3-oxazol-2-ylmethoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(5-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoro-3-pyridinyl)-5-chloro-2-pyridinecarboxamide;

8-((5-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoro-3-pyridinyl)amino)-N-(1-methylethyl)-1,7-naphthyridine-3-carboxamide;

8-((5-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoro-3-pyridinyl)amino)-1,7-naphthyridine-3-carbonitrile;

4-((5-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoro-3-pyridinyl)amino)pyrido[3,2-d]pyrimidine-7-carbonitrile;

(1R)-1-((1S,5S,6S)-3-amino-5-(2-fluoro-5-((2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-yl)amino)-3-pyridinyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)-2,2,2-trifluoroethanol;

(1S)-1-((1S,5S,6S)-3-amino-5-(2-fluoro-5-((2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-yl)amino)-3-pyridinyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)-2,2,2-trifluoroethanol;

((1S,5S,6R)-3-amino-7,7-difluoro-5-(2-fluoro-5-((2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-yl)amino)-3-pyridinyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)methanol;

((1S,5S,6S)-3-amino-5-(2-fluoro-5-((2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-yl)amino)-3-pyridinyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)methanol;

((1S,5S,6R)-3-amino-7,7-difluoro-5-(2-fluoro-5-((2-(1,3-oxazol-2-ylmethoxy)pyrido[3,4-b]pyrazin-5-yl)amino)-3-pyridinyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)methanol;

((1S,5S,6R)-3-amino-7,7-difluoro-5-(2-fluoro-5-((7-(1,3-oxazol-2-ylmethoxy)pyrido[3,2-d]pyrimidin-4-yl)amino)-3-pyridinyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)methanol;

(1R)-1-((1S,5S,6S)-3-amino-5-(2-fluoro-5-((7-(2-propyn-1-yloxy)pyrido[3,2-d]pyrimidin-4-yl)amino)-3-pyridinyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)-2,2,2-trifluoroethanol;

(1S)-1-((1S,5S,6S)-3-amino-5-(2-fluoro-5-((7-(2-propyn-1-yloxy)pyrido[3,2-d]pyrimidin-4-yl)amino)-3-pyridinyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)-2,2,2-trifluoroethanol;

(1R)-1-((1S,5S,6S)-3-amino-5-(2-fluoro-5-((7-(1,3-oxazol-2-ylmethoxy)pyrido[3,2-d]pyrimidin-4-yl)amino)-3-pyridinyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)-2,2,2-trifluoroethanol;

(1S)-1-((1S,5S,6S)-3-amino-5-(2-fluoro-5-((7-(1,3-oxazol-2-ylmethoxy)pyrido[3,2-d]pyrimidin-4-yl)amino)-3-pyridinyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)-2,2,2-trifluoroethanol;

((1S,5S,6R)-3-amino-7,7-difluoro-5-(2-fluoro-5-((3-(1,3-oxazol-2-ylmethoxy)-1,7-naphthyridin-8-yl)amino)-3-pyridinyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)methanol;

((1S,5S,6S)-3-amino-5-(2-fluoro-5-((7-(2-propyn-1-yloxy)pyrido[3,2-d]pyrimidin-4-yl)amino)-3-pyridinyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)methanol;

(1R)-1-((1S,5S,6S)-3-amino-5-(2-fluoro-5-((2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-yl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)-2,2,2-trifluoroethanol;

(1S)-1-((1S,5S,6S)-3-amino-5-(2-fluoro-5-((2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-yl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)-2,2,2-trifluoroethanol;

N-(3-((1S,5S,6S)-3-amino-5-methyl-1-((1R)-2,2,2-trifluoro-1-hydroxyethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-5-methyl-1-((1S)-2,2,2-trifluoro-1-hydroxyethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-methyl-5-(2,2,2-trifluoroethoxy)-2-pyridinecarboxamide;

N-(5-((1S,5S,6S)-3-amino-5-methyl-1-((1R)-2,2,2-trifluoro-1-methoxyethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoro-3-pyridinyl)-2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-amine;

N-(5-((1S,5S,6S)-3-amino-5-methyl-1-((1S)-2,2,2-trifluoro-1-methoxyethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoro-3-pyridinyl)-2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-methyl-5-(2,2,2-trifluoroethoxy)-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-methyl-5-(2,2,2-trifluoroethoxy)-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3-methyl-5-(2,2,2-trifluoroethoxy)-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3-methyl-5-(2,2,2-trifluoroethoxy)-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-methyl-5-(2-propyn-1-yloxy)-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3-methyl-5-(2-propyn-1-yloxy)-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-methyl-5-(2-propyn-1-yloxy)-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-methyl-5-(2-propyn-1-yloxy)-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3-methyl-5-(2-propyn-1-yloxy)-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-methyl-5-((1S)-1-(1,3-oxazol-2-yl)ethoxy)-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-methyl-5-((1R)-1-(1,3-oxazol-2-yl)ethoxy)-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3-methyl-5-(2,2,2-trifluoroethoxy)-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3-methyl-5-(2-propyn-1-yloxy)-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-chloro-5-(2-propyn-1-yloxy)-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(2,2,2-trifluoroethoxy)-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-chloro-5-(2,2,2-trifluoroethoxy)-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(2,2,2-trifluoroethoxy)-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(2,2,2-trifluoroethoxy)-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(2,2,2-trifluoroethoxy)-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(2,2,2-trifluoroethoxy)-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(2,2,2-trifluoroethoxy)-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-5-methyl-1-(1-pyrrolidinylcarbonyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(2,2,2-trifluoroethoxy)-2-pyridinecarboxamide;

(1S,5S,6S)-3-amino-5-(2,3-difluoro-5-(((5-(2,2,2-trifluoroethoxy)-2-pyridinyl)carbonyl)amino)phenyl)-N,5-dimethyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-5-(2,3-difluoro-5-(((5-(2,2,2-trifluoroethoxy)-2-pyrazinyl)carbonyl)amino)phenyl)-N,5-dimethyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-5-(2,3-difluoro-5-(((3-methyl-5-(2,2,2-trifluoroethoxy)-2-pyridinyl)carbonyl)amino)phenyl)-N,5-dimethyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

4-((3-((1S,5S,6R)-3-amino-7,7-difluoro-1-(hydroxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)amino)pyrido[3,2-d]pyrimidine-7-carbonitrile;

N-(3-((1S,5S,6R)-3-amino-7,7-difluoro-1-(hydroxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide;

((1S,5S,6R)-3-amino-7,7-difluoro-5-(2-fluoro-5-((2-(1,3-oxazol-2-ylmethoxy)pyrido[3,4-b]pyrazin-5-yl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)methanol;

((1S,5S,6R)-3-amino-7,7-difluoro-5-(2-fluoro-5-((2-(1,3-oxazol-4-ylmethoxy)pyrido[3,4-b]pyrazin-5-yl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)methanol;

((1S,5S,6R)-3-amino-7,7-difluoro-5-(2-fluoro-5-((2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-yl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)methanol;

N-(3-((1S,5S,6R)-3-amino-7,7-difluoro-1-(hydroxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(2,2,3,3-tetrafluoropropoxy)-2-pyrazinecarboxamide;

4-((3-((1S,5S,6R)-3-amino-7,7-difluoro-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)amino)pyrido[3,2-d]pyrimidine-7-carbonitrile;

N-(3-((1S,5S,6R)-3-amino-7,7-difluoro-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide;

N-(3-((1S,5S,6R)-3-amino-7,7-difluoro-1-(1-hydroxy-1-methylethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide;

2-((1S,5S,6R)-3-amino-7,7-difluoro-5-(2-fluoro-5-((2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-yl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)-2-propanol;

(1R)-1-((1S,5S,6R)-3-amino-7,7-difluoro-5-(2-fluoro-5-((2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-yl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)ethanol;

(1S)-1-((1S,5S,6R)-3-amino-7,7-difluoro-5-(2-fluoro-5-((2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-yl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)ethanol;

N-(3-((1S,5S,6S)-3-amino-1-(ethoxymethyl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-cyano-3-methyl-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-(methoxymethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-cyano-3-methyl-2-pyridinecarboxamide;

8-((3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-(methoxymethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)amino)-1,7-naphthyridine-3-carbonitrile;

N-(3-((1R,5S,6S)-3-amino-1-(cyanomethyl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide;

8-((3-((1R,5S,6S)-3-amino-1-(cyanomethyl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)amino)-1,7-naphthyridine-3-carbonitrile;

((1R,5S,6S)-3-amino-5-(fluoromethyl)-5-(2-fluoro-5-((2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-yl)amino)phenyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)acetonitrile;

((1R,5S,6S)-3-amino-5-(fluoromethyl)-5-(2-fluoro-5-((2-(1,3-oxazol-2-ylmethoxy)pyrido[3,4-b]pyrazin-5-yl)amino)phenyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)acetonitrile;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-(1H-1,2,3-triazol-1-ylmethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(2-cyanoethyl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-((4-methyl-1H-1,2,3-triazol-1-yl)methyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-((5-methyl-1H-1,2,3-triazol-1-yl)methyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-(1,3-oxazol-5-ylmethoxy)-1,7-naphthyridin-8-amine;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-(1,3-oxazol-2-ylmethoxy)-1,7-naphthyridin-8-amine;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-(1,3-oxazol-4-ylmethoxy)-1,7-naphthyridin-8-amine;

((8-((3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)amino)-1,7-naphthyridin-3-yl)oxy)acetonitrile;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-(1,2,4-oxadiazol-3-ylmethoxy)-1,7-naphthyridin-8-amine;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-(2,2,3,3-tetrafluoropropoxy)-1,7-naphthyridin-8-amine;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(2,2,3,3-tetrafluoropropoxy)-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-(2-propyn-1-yloxy)-1,7-naphthyridin-8-amine;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(2,2,3,3-tetrafluoropropoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-((5-chloro-1,3-thiazol-2-yl)methoxy)-1,7-naphthyridin-8-amine;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-((4-bromo-1,3-thiazol-2-yl)methoxy)-1,7-naphthyridin-8-amine;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-(1,3-thiazol-2-ylmethoxy)-1,7-naphthyridin-8-amine;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(3,3,3-trifluoropropoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(2,2-difluoropropoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(3-fluoropropoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-((4,4,4-trifluoro-2-butyn-1-yl)oxy)-1,7-naphthyridin-8-amine;

N-(3-((1R,5S,6S)-3-amino-5-methyl-1-(methylsulfonyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-chloro-2-pyridinecarboxamide;

N-(3-((1R,5S,6S)-3-amino-5-methyl-1-(methylsulfonyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(2-propyn-1-yloxy)-2-pyridinecarboxamide;

N-(3-((1R,5S,6S)-3-amino-5-methyl-1-(methylsulfonyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

N-(3-((1R,5S,6S)-3-amino-5-methyl-1-(methylsulfonyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(1,3-oxazol-2-ylmethoxy)-2-pyridinecarboxamide;

N-(3-((1R,5S,6S)-3-amino-5-methyl-1-(methylsulfonyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(1,3-oxazol-2-ylmethoxy)-2-pyrazinecarboxamide;

N-(3-((1R,5S,6S)-3-amino-5-methyl-1-(methylsulfonyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-(1,3-oxazol-2-ylmethoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1R,5S,6R)-3-amino-7,7-difluoro-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-chloro-2-pyridinecarboxamide;

N-(3-((1S,5S,6R)-3-amino-7,7-difluoro-1-(hydroxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

((1S,5S,6R)-3-amino-7,7-difluoro-5-(2-fluoro-5-((7-(1,3-oxazol-2-ylmethoxy)pyrido[3,2-d]pyrimidin-4-yl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)methanol;

N-(3-((1S,5S,6R)-3-amino-7,7-difluoro-1-(hydroxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(2,2,3,3-tetrafluoropropoxy)-2-pyridinecarboxamide;

N-(3-((4S,4aR,7aS)-2-amino-4-(fluoromethyl)-4,4a,4b,5-tetrahydrothieno[3',4':2,3]cyclopropa[1,2-e][1,3]thiazin-4-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide;

N-(3-((4S,4aS,7aR)-2-amino-4-(fluoromethyl)-4,4a,4b,5-tetrahydrothieno[3',4':2,3]cyclopropa[1,2-e][1,3]thiazin-4-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide;

N-(3-((4S,4aS,7aR)-2-amino-4-(fluoromethyl)-4,4a,4b,5-tetrahydrothieno[3',4':2,3]cyclopropa[1,2-e][1,3]thiazin-4-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3-chloropyrido[2,3-d]pyridazin-8-amine;

ethyl (2E)-3-((1R,5S,6S)-3-amino-5-(5-(((5-chloro-2-pyridinyl)carbonyl)amino)-2-fluorophenyl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)-2-propenoate;

N-(3-((1R,5S,6S)-3-amino-5-(fluoromethyl)-1-((1E)-3-hydroxy-1-propen-1-yl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide;

(2E)-3-((1R,5S,6S)-3-amino-5-(5-(((5-chloro-2-pyridinyl)carbonyl)amino)-2-fluorophenyl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)-2-propenoic acid;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-(3-hydroxypropyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide;

N-(3-((1R,5S,6S)-3-amino-1-((1E)-3-amino-3-oxo-1-propen-1-yl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide;

N-(3-((1R,5S,6S)-3-amino-5-(fluoromethyl)-1-((1E)-3-(methylamino)-3-oxo-1-propen-1-yl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide;

N-(3-((1R,5S,6S)-3-amino-1-((1E)-3-(dimethylamino)-3-oxo-1-propen-1-yl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-7-(1,3-oxazol-2-ylmethoxy)pyrido[3,2-d]pyrimidin-4-amine;

N-(3-((1R,5S,6S)-3-amino-5-(fluoromethyl)-1-((1E)-3-(4-morpholinyl)-3-oxo-1-propen-1-yl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(3-(dimethylamino)-3-oxopropyl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide;

N-(3-((1R,5S,6S)-3-amino-5-(fluoromethyl)-1-((1E)-3-(3-methoxy-1-azetidinyl)-3-oxo-1-propen-1-yl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide;

N-(3-((1R,5S,6S)-3-amino-5-(fluoromethyl)-1-((1E)-3-((2-methoxyethyl)amino)-3-oxo-1-propen-1-yl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide;

(2E)-3-((1R,5S,6S)-3-amino-5-(fluoromethyl)-5-(2-fluoro-5-((2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-yl)amino)phenyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)-N,N-dimethyl-2-propenamide;

(2E)-3-((1R,5S,6S)-3-amino-5-(fluoromethyl)-5-(2-fluoro-5-((2-(1,3-oxazol-2-ylmethoxy)pyrido[3,4-b]pyrazin-5-yl)amino)phenyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)-N,N-dimethyl-2-propenamide;

(2E)-3-((1R,5S,6S)-3-amino-5-(fluoromethyl)-5-(2-fluoro-5-((3-(1,3-oxazol-2-ylmethoxy)-1,7-naphthyridin-8-yl)amino)phenyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)-N,N-dimethyl-2-propenamide;

(2E)-3-((1R,5S,6S)-3-amino-5-(5-((3-(2-butyn-1-yloxy)-1,7-naphthyridin-8-yl)amino)-2-fluorophenyl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)-N,N-dimethyl-2-propenamide;

N-(3-((1R,5S,6S)-3-amino-1-((1E)-3-(3,3-difluoro-1-azetidinyl)-3-oxo-1-propen-1-yl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide;

N-(3-((1R,5S,6S)-3-amino-1-((1E)-3-(3,3-difluoro-1-azetidinyl)-3-oxo-1-propen-1-yl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1R,5S,6S)-3-amino-1-((1E)-3-(dimethylamino)-3-oxo-1-propen-1-yl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

(2E)-3-((1R,5S,6S)-3-amino-5-(fluoromethyl)-5-(2-fluoro-5-((7-(1,3-oxazol-2-ylmethoxy)pyrido[3,2-d]pyrimidin-4-yl)amino)phenyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)-N,N-dimethyl-2-propenamide;

(2E)-3-((1R,5S,6S)-3-amino-5-(fluoromethyl)-5-(2-fluoro-5-((7-(2-propyn-1-yloxy)pyrido[3,2-d]pyrimidin-4-yl)amino)phenyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)-N,N-dimethyl-2-propenamide;

N-(3-((1R,5S,6S)-3-amino-5-(fluoromethyl)-1-((1Z)-2-methyl-3-(4-morpholinyl)-3-oxo-1-propen-1-yl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide;

N-(3-((1R,5S,6S)-3-amino-5-(fluoromethyl)-1-((1E)-2-methyl-3-(4-morpholinyl)-3-oxo-1-propen-1-yl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide;

(1S,5S,6S)-3-amino-5-(fluoromethyl)-5-(2-fluoro-5-((2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-yl)amino)phenyl)-N,N-dimethyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-(1,3-oxazol-5-yl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-(1,3-oxazol-5-yl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-(1,3-oxazol-5-yl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-7-(2-propyn-1-yloxy)pyrido[3,2-d]pyrimidin-4-amine;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-(1,3-oxazol-5-yl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(1,3-oxazol-2-ylmethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-(4-methyl-1,3-oxazol-5-yl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-(1,3-oxazol-5-yl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-(3-isoxazolyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-(4-methyl-1,3-oxazol-5-yl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-(4-methyl-1,3-oxazol-5-yl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-7-(2-propyn-1-yloxy)pyrido[3,2-d]pyrimidin-4-amine;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-(4-methyl-1,3-oxazol-5-yl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(2-propyn-1-yloxy)-2-pyridinecarboxamide;

(1S,5S,6S)-3-amino-5-(5-(((5-chloro-2-pyridinyl)carbonyl)amino)-2-fluorophenyl)-5-(fluoromethyl)-N,N-dimethyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-N-cyclopropyl-5-(2-fluoro-5-((7-(2-propyn-1-yloxy)pyrido[3,2-d]pyrimidin-4-yl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-5-(5-(((5-chloro-2-pyridinyl)carbonyl)amino)-2-fluorophenyl)-N-cyclopropyl-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-(3-isoxazolyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(2-propyn-1-yloxy)-2-pyridinecarboxamide;

(1S,5S,6S)-3-amino-N-cyclopropyl-5-(2-fluoro-5-((2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-yl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-N-cyclopropyl-5-(2-fluoro-5-(((5-(2-propyn-1-yloxy)-2-pyrazinyl)carbonyl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-N-cyclopropyl-5-(2-fluoro-5-((2-(1,3-oxazol-2-ylmethoxy)pyrido[3,4-b]pyrazin-5-yl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-N-tert-butyl-5-(5-(((5-chloro-2-pyridinyl)carbonyl)amino)-2-fluorophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-N-tert-butyl-5-(2-fluoro-5-(((5-(2-propyn-1-yloxy)-2-pyrazinyl)carbonyl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-N-cyclopropyl-5-(2-fluoro-5-(((5-(1,3-oxazol-2-ylmethoxy)-2-pyrazinyl)carbonyl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-N-cyclopropyl-5-(2-fluoro-5-(((5-(2,2,2-trifluoroethoxy)-2-pyrazinyl)carbonyl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

4-((3-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)amino)pyrido[3,2-d]pyrimidine-7-carbonitrile;

N-(3-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-(1,3-oxazol-2-ylmethoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-methyl-5-(1,3-oxazol-2-ylmethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-chloro-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-7-(1,3-oxazol-2-ylmethoxy)pyrido[3,2-d]pyrimidin-4-amine;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-7-(1,3-oxazol-2-ylmethoxy)pyrido[3,2-d]pyrimidin-4-amine;

N-(3-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(1,3-oxazol-2-ylmethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-7-(1,3-oxazol-2-ylmethoxy)pyrido[3,2-d]pyrimidin-4-amine;

N-(3-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-7-(2-propyn-1-yloxy)pyrido[3,2-d]pyrimidin-4-amine;

N-(3-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(2,2,2-trifluoroethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(2,2,2-trifluoroethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-2-(1,3-oxazol-2-ylmethoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-7-(2-propyn-1-yloxy)pyrido[3,2-d]pyrimidin-4-amine;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-7-(2-propyn-1-yloxy)pyrido[3,2-d]pyrimidin-4-amine;

N-(3-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-2-(1,3-oxazol-2-ylmethoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(2,2,2-trifluoroethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-2-(((1S)-1-methyl-2-propyn-1-yl)oxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-2-((5-methyl-1,2,4-oxadiazol-3-yl)methoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3-methyl-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3-methyl-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(2,2,2-trifluoroethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3-methyl-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3-methyl-5-(1,3-oxazol-2-ylmethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3-methyl-5-(1,3-oxazol-2-ylmethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3-methyl-5-(1,3-oxazol-2-ylmethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(1,1-dideuterium-prop-2-yn-1-yloxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(1,1-dideuterium-prop-2-yn-1-yloxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxy)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(1,1-dideuterium-prop-2-yn-1-yloxy)pyrazine-2-carboxamide;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-(1,3-oxazol-2-ylmethoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-(1,3-oxazol-4-ylmethoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(5-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoro-3-pyridinyl)-7-chloropyrido[3,2-d]pyrimidin-4-amine;

N-(5-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoro-3-pyridinyl)-3-methyl-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

4-((5-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoro-3-pyridinyl)amino)pyrido[3,2-d]pyrimidine-7-carbonitrile;

8-((5-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoro-3-pyridinyl)amino)-1,7-naphthyridine-3-carbonitrile;

N-(5-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoro-3-pyridinyl)-2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-amine;

N-(5-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoro-3-pyridinyl)-2-(1,3-oxazol-2-ylmethoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(5-((1S,5S,6S)-3-amino-5-methyl-1-(((~2~H_3_)methyloxy)methyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoro-3-pyridinyl)-3-methyl-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

N-(5-((1S,5S,6S)-3-amino-5-methyl-1-(((~2~H_3_)methyloxy)methyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoro-3-pyridinyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

N-(5-((1S,5S,6S)-3-amino-5-methyl-1-(((~2~H_3_)methyloxy)methyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoro-3-pyridinyl)-7-chloropyrido[3,2-d]pyrimidin-4-amine;

N-(5-((1S,5S,6S)-3-amino-5-methyl-1-(((~2~H_3_)methyloxy)methyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoro-3-pyridinyl)-2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-amine;

N-(5-((1S,5S,6S)-3-amino-5-methyl-1-(((~2~H_3_)methyloxy)methyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoro-3-pyridinyl)-2-((1,1-~2~H_2_)-2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-amine;

methyl (1S,5S,6S)-3-amino-5-(5-(((5-chloro-2-pyridinyl)carbonyl)amino)-2-fluoro-3-(methoxycarbonyl)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylate;

methyl (1S,5S,6S)-3-amino-5-(2-fluoro-3-(methoxycarbonyl)-5-((2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-yl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylate;

methyl 3-((1S,5S,6S)-3-amino-1-(hydroxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-2-fluoro-5-((2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-yl)amino)benzoate;

N-(3-((1S,5S,6S)-3-amino-1-(hydroxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluoro-5-(hydroxymethyl)phenyl)-5-chloro-2-pyridinecarboxamide;

N-(5-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoro-3-pyridinyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-methyl-5-(1,3-oxazol-2-ylmethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-methyl-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-methyl-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-methyl-5-(1,3-oxazol-2-ylmethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-methyl-5-((1S)-1-(1,3-oxazol-2-yl)ethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1,5-bis(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-2-(2-butyn-1-yloxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-(1,3-oxazol-2-ylmethoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-(1,3-oxazol-4-ylmethoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-(2-butyn-1-yloxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-(2-butyn-1-yloxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-((2-methyl-1,3-oxazol-4-yl)methoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-(3-fluoropropoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-(2,2-difluoropropoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-((3-fluoro-2-pyridinyl)methoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-((4-methyl-2-pyrimidinyl)methoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-(1,3-thiazol-4-ylmethoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-(1-methylethoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-((5-methyl-1,3,4-oxadiazol-2-yl)methoxy)pyrido[3,4-b]pyrazin-5-amine;

2-((5-((3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)amino)pyrido[3,4-b]pyrazin-2-yl)oxy)-N,N-dimethylacetamide;

N-(3-((1S,5S,6S)-3-amino-1,5-bis(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-2-(((1S)-1-methyl-2-propyn-1-yl)oxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1,5-bis(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-2-((3-methyl-1,2,4-oxadiazol-5-yl)methoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-(2-pyrimidinylmethoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-((3-methyl-1,2,4-oxadiazol-5-yl)methoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-((5-methyl-1,2,4-oxadiazol-3-yl)methoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-(2-pyrimidinylmethoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-((5-methyl-1,2,4-oxadiazol-3-yl)methoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-((2,5-dimethyl-1,3-oxazol-4-yl)methoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-((3-methyl-1,2,4-oxadiazol-5-yl)methoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-((5-methyl-1,3-oxazol-2-yl)methoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-((5-methyl-1,3,4-thiadiazol-2-yl)methoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-(((1S)-1-methyl-2-propyn-1-yl)oxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-((1R)-1-(1,3-oxazol-2-yl)ethoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-((1S)-1-(1,3-oxazol-2-yl)ethoxy)pyrido[3,4-b]pyrazin-5-amine;

1-(2-((5-((3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)amino)pyrido[3,4-b]pyrazin-2-yl)oxy)ethyl)-2-pyrrolidinone;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-((1S)-2-methoxy-1-methylethoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-methoxypyrido[3,4-b]pyrazin-5-amine;

5-((3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)amino)pyrido[3,4-b]pyrazin-2(1H)-one;

N-(3-((1S,5S,6S)-3-amino-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-7-methoxypyrido[3,2-d]pyrimidin-4-amine;

methyl (1S,5S,6S)-3-amino-5-(5-(((5-chloro-2-pyridinyl)carbonyl)amino)-2,3-difluorophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylate;

(1S,5S,6S)-3-amino-5-(5-(((5-chloro-2-pyridinyl)carbonyl)amino)-2,3-difluorophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylic acid;

N-(3-((1S,5S,6S)-3-amino-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-methoxypyrido[3,4-b]pyrazin-5-amine;

(1S,5S,6S)-3-amino-5-(5-((7-chloropyrido[3,2-d]pyrimidin-4-yl)amino)-2,3-difluorophenyl)-N-methoxy-N,5-dimethyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

1-((1S,5S,6S)-3-amino-5-(5-((7-chloropyrido[3,2-d]pyrimidin-4-yl)amino)-2,3-difluorophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)ethanone;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-(2-butyn-1-yloxy)-1,7-naphthyridin-8-amine;

4-((3-((1S,5S,6S)-1-acetyl-3-amino-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)amino)pyrido[3,2-d]pyrimidine-7-carbonitrile;

(1S,5S,6S)-3-amino-5-(5-(((5-chloro-2-pyridinyl)carbonyl)amino)-2,3-difluorophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

N-(3-((1S,5S,6S)-1-acetyl-3-amino-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-chloro-2-pyridinecarboxamide;

4-((3-((1S,5S,6S)-3-amino-1-(1-hydroxyethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)amino)pyrido[3,2-d]pyrimidine-7-carbonitrile;

4-((3-((1R,2S,6S)-4-amino-6-((R)-1-hydroxyethyl)-2-methyl-3-azabicyclo[4.1.0]hept-3-en-2-yl)-4,5-difluorophenyl)amino)pyrido[3,2-d]pyrimidine-7-carbonitrile;

4-((3-((1S,5S,6S)-3-amino-1-(1-hydroxy-1-methylethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)amino)pyrido[3,2-d]pyrimidine-7-carbonitrile;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(1,3-oxazol-2-ylmethoxy)-2-pyrazinecarboxamide;

(1S,5S,6S)-3-amino-5-(2,3-difluoro-5-((2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-yl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-5-(2,3-difluoro-5-((2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-yl)amino)phenyl)-N,N,5-trimethyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-5-(2,3-difluoro-5-(((5-(2-propyn-1-yloxy)-2-pyrazinyl)carbonyl)amino)phenyl)-N,N,5-trimethyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-5-(2,3-difluoro-5-(((5-(2-propyn-1-yloxy)-2-pyrazinyl)carbonyl)amino)phenyl)-N,5-dimethyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-5-(2,3-difluoro-5-((2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-yl)amino)phenyl)-N,5-dimethyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-5-(2,3-difluoro-5-((2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-yl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carbonitrile;

(1S,5S,6S)-3-amino-5-(2,3-difluoro-5-((7-(2-propyn-1-yloxy)pyrido[3,2-d]pyrimidin-4-yl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-5-(2,3-difluoro-5-((7-(1,3-oxazol-2-ylmethoxy)pyrido[3,2-d]pyrimidin-4-yl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-5-(2,3-difluoro-5-(((5-(2-propyn-1-yloxy)-2-pyrazinyl)carbonyl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-5-(5-((2-(2-butyn-1-yloxy)pyrido[3,4-b]pyrazin-5-yl)amino)-2,3-difluorophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-5-(2,3-difluoro-5-((7-(2-propyn-1-yloxy)pyrido[3,2-d]pyrimidin-4-yl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carbonitrile;

(1S,5S,6S)-3-amino-5-(2,3-difluoro-5-(((5-(2,2,3,3-tetrafluoropropoxy)-2-pyrazinyl)carbonyl)amino)phenyl)-N,N,5-trimethyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-5-(2,3-difluoro-5-((7-(1,3-oxazol-2-ylmethoxy)pyrido[3,2-d]pyrimidin-4-yl)amino)phenyl)-N,N,5-trimethyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

N-(3-((1S,5S,6S)-3-amino-1-cyano-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

(1S,5S,6S)-3-amino-5-(2,3-difluoro-5-((2-(((1S)-1-methyl-2-propyn-1-yl)oxy)pyrido[3,4-b]pyrazin-5-yl)amino)phenyl)-N,N,5-trimethyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-5-(2,3-difluoro-5-(((5-(2,2,2-trifluoroethoxy)-2-pyrazinyl)carbonyl)amino)phenyl)-N,N,5-trimethyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

N-(3-((1S,5S,6S)-3-amino-1-cyano-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

(1S,5S,6S)-3-amino-5-(2-fluoro-5-((7-(2-propyn-1-yloxy)pyrido[3,2-d]pyrimidin-4-yl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carbonitrile;

N-(3-((1S,5S,6S)-3-amino-1-cyano-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide;

(1S,5S,6S)-3-amino-5-(5-(((5-chloro-2-pyridinyl)carbonyl)amino)-2,3-difluorophenyl)-N,N,5-trimethyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-5-(2,3-difluoro-5-((2-(((1S)-1-methyl-2-propyn-1-yl)oxy)pyrido[3,4-b]pyrazin-5-yl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carbonitrile;

N-(3-((1S,5S,6S)-3-amino-1-cyano-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-chloro-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-5-methyl-1-(1-pyrrolidinylcarbonyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-7-(2-propyn-1-yloxy)pyrido[3,2-d]pyrimidin-4-amine;

N-(3-((1S,5S,6S)-3-amino-5-methyl-1-(1-pyrrolidinylcarbonyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-5-methyl-1-(1-pyrrolidinylcarbonyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-chloro-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-5-methyl-1-(1-pyrrolidinylcarbonyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-7-(1,3-oxazol-2-ylmethoxy)pyrido[3,2-d]pyrimidin-4-amine;

N-(3-((1S,5S,6S)-3-amino-5-methyl-1-(1-pyrrolidinylcarbonyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-(((1S)-1-methyl-2-propyn-1-yl)oxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-5-methyl-1-(1-pyrrolidinylcarbonyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-((1S)-1-(1,3-oxazol-2-yl)ethoxy)pyrido[3,4-b]pyrazin-5-amine;

(1S,5S,6S)-3-amino-5-(2,3-difluoro-5-((2-((1S)-1-(1,3-oxazol-2-yl)ethoxy)pyrido[3,4-b]pyrazin-5-yl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carbonitrile;

N-(3-((1S,5S,6S)-3-amino-1-cyano-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(2,2,2-trifluoroethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-7-(2-propyn-1-yloxy)pyrido[3,2-d]pyrimidin-4-amine;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-(methoxymethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-7-(2-propyn-1-yloxy)pyrido[3,2-d]pyrimidin-4-amine;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-7-(2-propyn-1-yloxy)pyrido[3,2-d]pyrimidin-4-amine;

N-(5-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoro-3-pyridinyl)-7-(2-propyn-1-yloxy)pyrido[3,2-d]pyrimidin-4-amine;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-7-(2-propyn-1-yloxy)pyrido[3,2-d]pyrimidin-4-amine;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-7-(2-methoxyethoxy)pyrido[3,2-d]pyrimidin-4-amine;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-(methoxymethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-7-(2-methoxyethoxy)pyrido[3,2-d]pyrimidin-4-amine;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-7-((2,5-dimethyl-1,3-oxazol-4-yl)methoxy)pyrido[3,2-d]pyrimidin-4-amine;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-fluoro-3-(1,3-oxazol-2-ylmethoxy)-1,7-naphthyridin-8-amine;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-fluoro-3-(1,3-oxazol-2-ylmethoxy)-1,7-naphthyridin-8-amine;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-fluoro-3-(2-propyn-1-yloxy)-1,7-naphthyridin-8-amine;

(2E)-3-((1R,5S,6S)-3-amino-5-(fluoromethyl)-5-(2-fluoro-5-((2-(2-pentyn-1-yloxy)pyrido[3,4-b]pyrazin-5-yl)amino)phenyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)-N,N-dimethyl-2-propenamide;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-((2,2,2-trifluoroethoxy)methyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-((2,2,2-trifluoroethoxy)methyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-((1-methylethoxy)methyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-(1H-1,2,3-triazol-4-yl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-(1H-1,2,3-triazol-4-yl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-2-(1,3-oxazol-2-ylmethoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-(1-propyn-1-yl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-2-(1,3-oxazol-2-ylmethoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-(1H-1,2,3-triazol-4-yl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-(1H-1,2,3-triazol-4-yl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-chloropicolinamide;

4-((3-((1R,5S,6S)-3-amino-7,7-difluoro-1-(hydroxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)amino)pyrido[3,2-d]pyrimidine-7-carbonitrile; or

N-(3-((4S,4aR,7aS)-2-amino-4-(fluoromethyl)-4a,4b,5,7-tetrahydro-4H-thieno[3',4':2,3]cyclopropa[1,2-e][1,3]thiazin-4-yl)-4-fluorophenyl)-5-chloropicolinamide.

In yet another embodiment, the invention provides the compound of Formula I or a tautomer, stereoisomer, or pharmaceutically acceptable salt thereof selected from

(1S,5S,6S)-3-amino-5-(2,3-difluoro-5-(((5-(2,2,3,3-tetrafluoropropoxy)-2-pyrazinyl)carbonyl)amino)phenyl)-N,5-dimethyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

N-(5-((1S,5S,6S)-3-amino-1-cyano-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-methoxy-3-pyridinyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(((1S)-1-methyl-2-propyn-1-yl)oxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(((1S)-1-methyl-2-propyn-1-yl)oxy)-2-pyrazinecarboxamide;

(1S,5S,6S)-3-amino-5-(2,3-difluoro-5-(((5-(((1S)-1-methyl-2-propyn-1-yl)oxy)-2-pyrazinyl)carbonyl)amino)phenyl)-N,5-dimethyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-((1R)-2,2,2-trifluoro-1-methylethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-((1S)-2,2,2-trifluoro-1-methylethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-5-methyl-1-((trideuteriummethyloxy)methyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-((1S)-2-methoxy-1-methylethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-((1S)-2-methoxy-1-methylethoxy)-2-pyrazinecarboxamide;

(1S,5S,6S)-3-amino-5-(2-fluoro-5-(((5-(2,2,2-trifluoroethoxy)-2-pyrazinyl)carbonyl)amino)phenyl)-5-methyl-N-(2,2,2-trifluoroethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-5-(2-fluoro-5-(((5-(2,2,2-trifluoroethoxy)-2-pyrazinyl)carbonyl)amino)phenyl)-N,5-dimethyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-N-((1S)-1,2-dimethylpropyl)-5-(2-fluoro-5-(((5-(2,2,2-trifluoroethoxy)-2-pyrazinyl)carbonyl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

methyl (1S,5S,6S)-3-amino-5-(2,3-difluoro-5-(((5-(2-propyn-1-yloxy)-2-pyrazinyl)carbonyl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylate;

(1S,5S,6S)-3-amino-5-(2-fluoro-5-(((5-(2,2,2-trifluoroethoxy)-2-pyrazinyl)carbonyl)amino)phenyl)-5-methyl-N-(1-methylethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-N-ethyl-5-(2-fluoro-5-(((5-(2,2,2-trifluoroethoxy)-2-pyrazinyl)carbonyl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-5-(2-fluoro-5-(((5-(((1S)-1-methyl-2-propyn-1-yl)oxy)-2-pyrazinyl)carbonyl)amino)phenyl)-N,5-dimethyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-5-(2-fluoro-5-((2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-yl)amino)phenyl)-N,5-dimethyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

tert-butyl (((1S,5S,6S)-3-amino-5-(2,3-difluoro-5-(((5-(2-propyn-1-yloxy)-2-pyrazinyl)carbonyl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)methyl)carbamate;

N-(3-((1S,5S,6S)-3-amino-1-(aminomethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

(1S,5S,6S)-3-amino-N-((1R)-2,2-difluorocyclopropyl)-5-(2-fluoro-5-(((5-(2,2,2-trifluoroethoxy)-2-pyrazinyl)carbonyl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-N-((1S)-2,2-difluorocyclopropyl)-5-(2-fluoro-5-(((5-(2,2,2-trifluoroethoxy)-2-pyrazinyl)carbonyl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-N-(2-fluoro-1,1-dimethylethyl)-5-(2-fluoro-5-(((5-(2,2,2-trifluoroethoxy)-2-pyrazinyl)carbonyl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-5-(2-fluoro-5-(((5-(2,2,2-trifluoroethoxy)-2-pyrazinyl)carbonyl)amino)phenyl)-N-methoxy-N,5-dimethyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-5-(5-(((5-chloro-2-pyridinyl)carbonyl)amino)-2-fluorophenyl)-N,5-dimethyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-N-tert-butyl-5-(5-(((5-cyano-2-pyridinyl)carbonyl)amino)-2-fluorophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-5-(2-fluoro-5-(((5-(2-propyn-1-yloxy)-2-pyrazinyl)carbonyl)amino)phenyl)-N,5-dimethyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(((1R)-1-methyl-2-propyn-1-yl)oxy)-2-pyrazinecarboxamide;

N-(5-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-methoxy-3-pyridinyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

N-(5-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-methoxy-3-pyridinyl)-5-chloro-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(((3R)-3-fluoro-1-pyrrolidinyl)carbonyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(2,2,2-trifluoroethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(((3S)-3-fluoro-1-pyrrolidinyl)carbonyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(2,2,2-trifluoroethoxy)-2-pyrazinecarboxamide;

(1S,5S,6S)-3-amino-N-cyclopropyl-5-(2-fluoro-5-(((5-(((1S)-1-methyl-2-propyn-1-yl)oxy)-2-pyrazinyl)carbonyl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-N-tert-butyl-5-(2-fluoro-5-(((5-(((1S)-1-methyl-2-propyn-1-yl)oxy)-2-pyrazinyl)carbonyl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-((1S)-2,2,2-trifluoro-1-methylethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-((1R)-2,2,2-trifluoro-1-methylethoxy)-2-pyrazinecarboxamide;

(1S,5S,6S)-3-amino-N-((1R)-1,2-dimethylpropyl)-5-(2-fluoro-5-(((5-(2,2,2-trifluoroethoxy)-2-pyrazinyl)carbonyl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

N-(3-((1S,5S,6S)-3-amino-5-methyl-1-(4-morpholinylcarbonyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(2,2,2-trifluoroethoxy)-2-pyrazinecarboxamide;

(1S,5S,6S)-3-amino-N-(2,2-difluoroethyl)-5-(2-fluoro-5-(((5-(2,2,2-trifluoroethoxy)-2-pyrazinyl)carbonyl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-5-(2-fluoro-5-(((5-(2,2,2-trifluoroethoxy)-2-pyrazinyl)carbonyl)amino)phenyl)-N,N,5-trimethyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-N-cyclopropyl-5-(2-fluoro-5-(((5-((1S)-2-methoxy-1-methylethoxy)-2-pyrazinyl)carbonyl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-N-tert-butyl-5-(2-fluoro-5-(((5-(2,2,2-trifluoroethoxy)-2-pyrazinyl)carbonyl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-N-tert-butyl-5-(2-fluoro-5-(((5-((1S)-2-methoxy-1-methylethoxy)-2-pyrazinyl)carbonyl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

N-(3-((1S,5S,6S)-3-amino-5-methyl-1-(4-morpholinylcarbonyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-5-methyl-1-(4-morpholinylcarbonyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

(1S,5S,6S)-3-amino-N-(2-fluoro-1,1-dimethylethyl)-5-(2-fluoro-5-(((5-(2-propyn-1-yloxy)-2-pyrazinyl)carbonyl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-chloro-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-((3-methyl-1,2,4-oxadiazol-5-yl)methoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(((1S)-1-methyl-2-propyn-1-yl)oxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-cyano-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-((1S)-2-methoxy-1-methylethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-cyano-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(((1S)-1-methyl-2-propyn-1-yl)oxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-cyano-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(2,2,2-trifluoroethoxy)-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-((5-methyl-1,2,4-oxadiazol-3-yl)methoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-((3-methyl-1,2,4-oxadiazol-5-yl)methoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-cyano-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-methyl-5-(2,2,2-trifluoroethoxy)-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-cyano-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-methyl-5-(2-propyn-1-yloxy)-2-pyridinecarboxamide;

(1S,5S,6S)-3-amino-N-ethyl-5-(2-fluoro-5-(((5-(2-propyn-1-yloxy)-2-pyrazinyl)carbonyl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-5-(5-(((5-cyano-2-pyridinyl)carbonyl)amino)-2-fluorophenyl)-N-(2-fluoro-1,1-dimethylethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-N-(2-fluoro-1,1-dimethylethyl)-5-(2-fluoro-5-(((5-(((1S)-1-methyl-2-propyn-1-yl)oxy)-2-pyrazinyl)carbonyl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(cyclobutylmethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(cyclopropylmethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(3-oxetanylmethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(((2R)-2-methoxypropyl)oxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(((2S)-2-methoxypropyl)oxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-((1S)-2-methoxy-1-methylethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(2,2-difluoroethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-((3,3-difluorocyclobutyl)methoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-oxo-4,5-dihydro-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(2-methylpropoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-((2R)-2-oxetanylmethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-((2S)-2-oxetanylmethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-((2-methyl-2-propen-1-yl)oxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-((3-methyl-5-isoxazolyl)methoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-((5-methyl-3-isoxazolyl)methoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(benzyloxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(1,3-thiazol-2-ylmethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(((1R)-2,2-difluorocyclopropyl)methoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(((1S)-2,2-difluorocyclopropyl)methoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(2-propen-1-yloxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-((5-methyl-1,3,4-oxadiazol-2-yl)methoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-ethoxy-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-((3-methyl-1,2,4-oxadiazol-5-yl)methoxy)-2-pyrazinecarboxamide;

(1S,5S,6S)-3-amino-N-(2-fluoroethyl)-5-(2-fluoro-5-(((5-(2,2,2-trifluoroethoxy)-2-pyrazinyl)carbonyl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-5-(2-fluoro-5-(((5-(2,2,2-trifluoroethoxy)-2-pyrazinyl)carbonyl)amino)phenyl)-5-methyl-N-(1-methylcyclopropyl)-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

N-(3-((1S,5S,6S)-1-((acetylamino)methyl)-3-amino-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluoro-5-methylphenyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluoro-5-methylphenyl)-5-((3-methyl-1,2,4-oxadiazol-5-yl)methoxy)-2-pyrazinecarboxamide;

(1S,5S,6S)-3-amino-N-((1R)-2,2-difluoro-1-methylethyl)-5-(2-fluoro-5-(((5-(2,2,2-trifluoroethoxy)-2-pyrazinyl)carbonyl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-N-((1S)-2,2-difluoro-1-methylethyl)-5-(2-fluoro-5-(((5-(2,2,2-trifluoroethoxy)-2-pyrazinyl)carbonyl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(ethoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(3-pentyn-1-yloxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(3-butyn-1-yloxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-((1-methylcyclopropyl)methoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-((3-methyl-3-oxetanyl)methoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(((1R)-1-methyl-2-propen-1-yl)oxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(((1S)-1-methyl-2-propen-1-yl)oxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(2-fluoroethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(cyclopropylmethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(cyclobutylmethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(3-oxetanylmethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(2-methylpropoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(2,2-difluoroethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-((2R)-2-oxetanylmethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-((2S)-2-oxetanylmethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(3-pentyn-1-yloxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(3-butyn-1-yloxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-((1-methylcyclopropyl)methoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-((3-methyl-3-oxetanyl)methoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(((1R)-1-methyl-2-propen-1-yl)oxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(((1S)-1-methyl-2-propen-1-yl)oxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(2-fluoroethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluoro-5-methylphenyl)-5-(2,2,2-trifluoroethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluoro-5-methylphenyl)-5-chloro-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(oxetan-3-yloxy)pyrazine-2-carboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(oxetan-3-yloxy)pyrazine-2-carboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(neopentyloxy)pyrazine-2-carboxamide;

N-(3-((1S,5S,6S)-1-acetyl-3-amino-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(prop-2-yn-1-yloxy)pyrazine-2-carboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluoro-5-methylphenyl)-5-(oxazol-2-ylmethoxy)pyrazine-2-carboxamide;

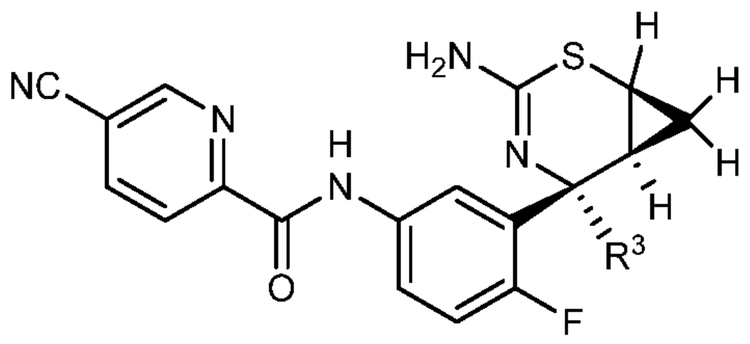
N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluoro-5-methylphenyl)-5-(prop-2-yn-1-yloxy)pyrazine-2-carboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluoro-5-methylphenyl)-5-(2,2,2-trifluoroethoxy)pyrazine-2-carboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluoro-5-methylphenyl)-5-(oxazol-2-ylmethoxy)pyrazine-2-carboxamide; or

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluoro-5-methylphenyl)-5-((3-methyl-1,2,4-oxadiazol-5-yl)methoxy)pyrazine-2-carboxamide.

Additional generic and specific compounds representative of the invention include: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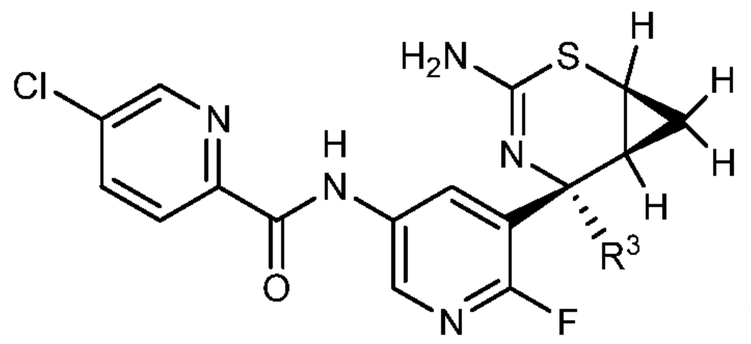
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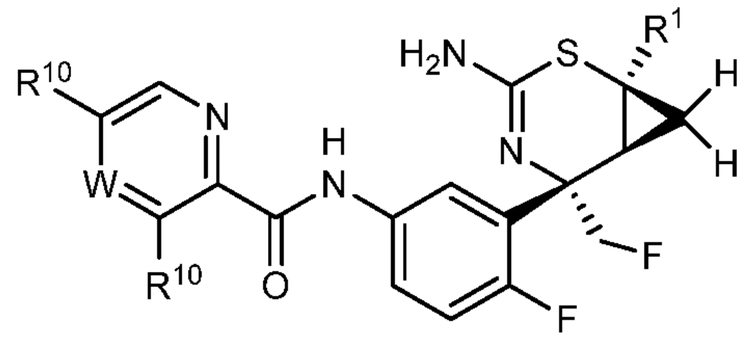
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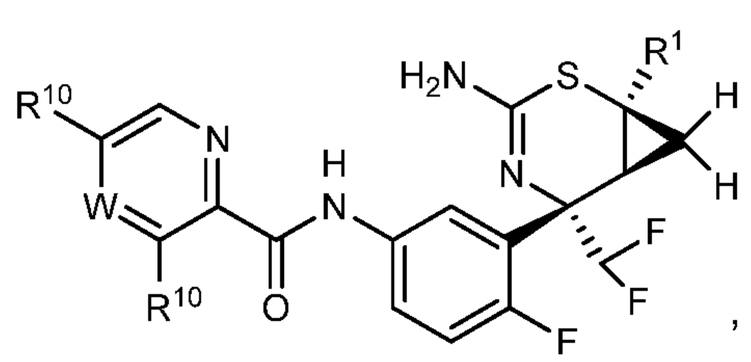
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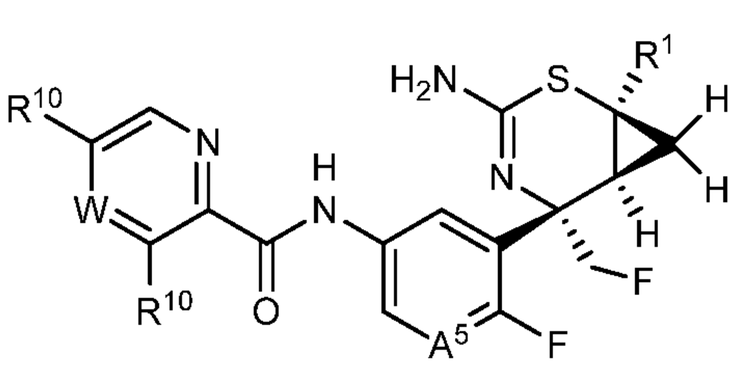
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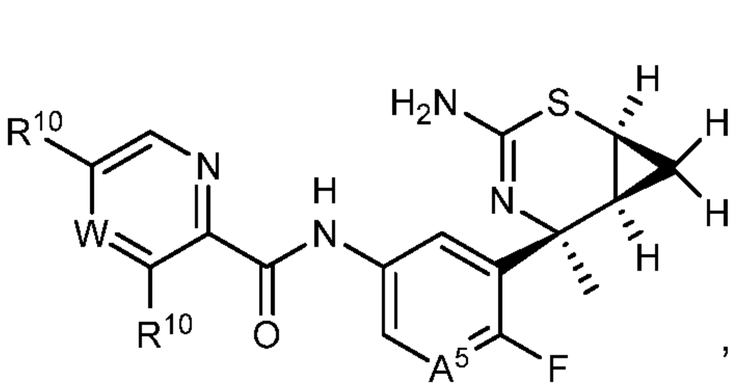
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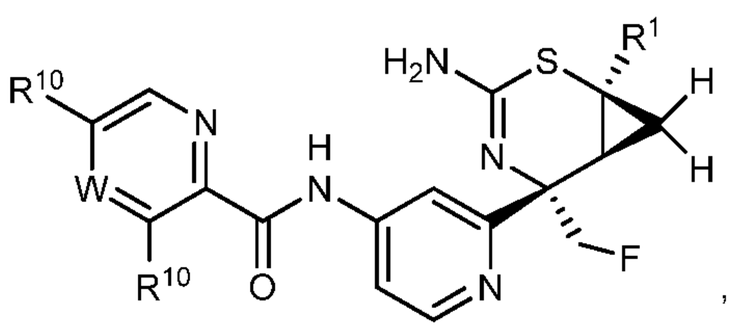
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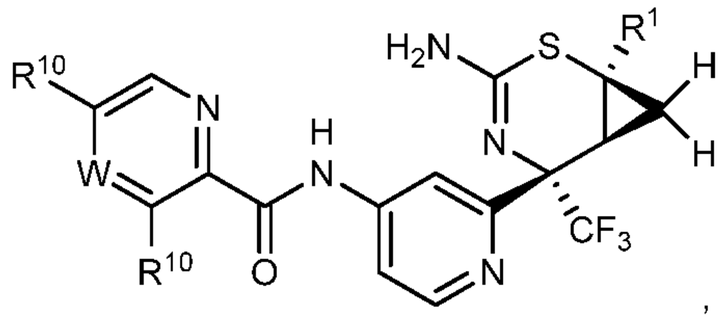
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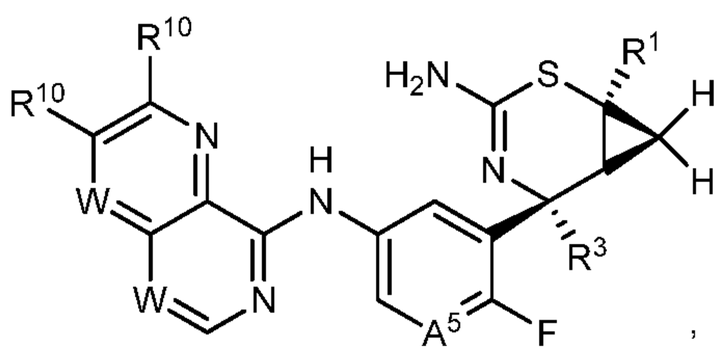
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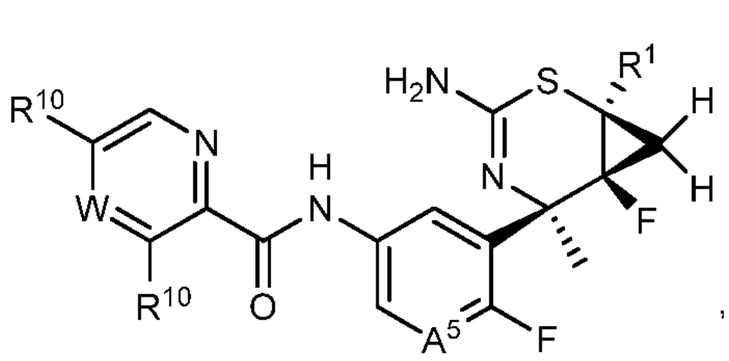
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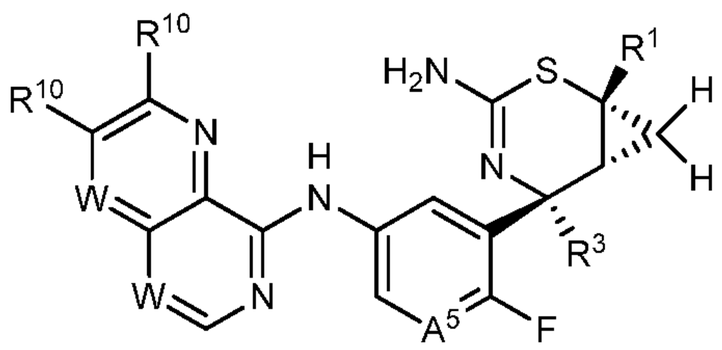
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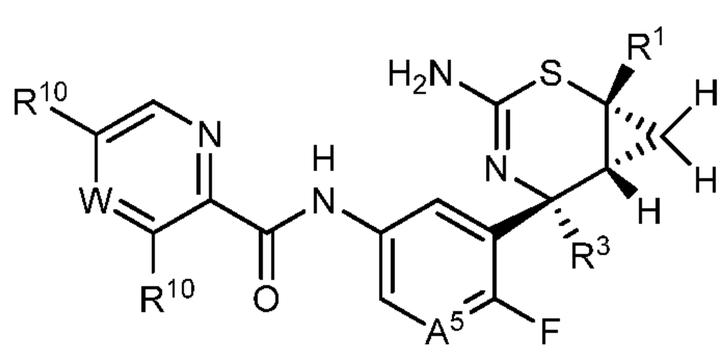
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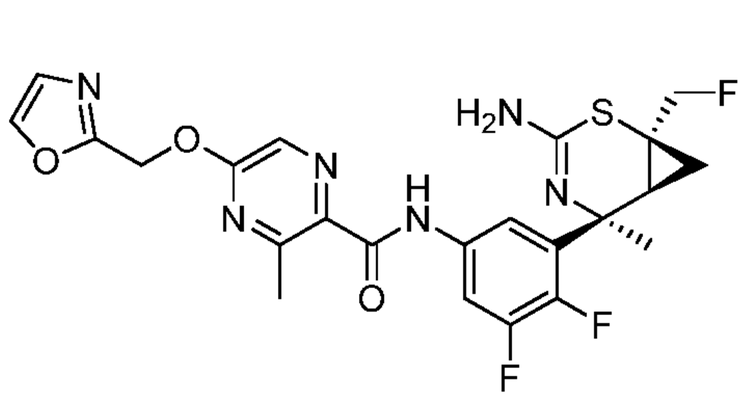
In an additional embodiment, the invention provides a compound, or a pharmaceutically acceptable salt or tautomer thereof, selected from: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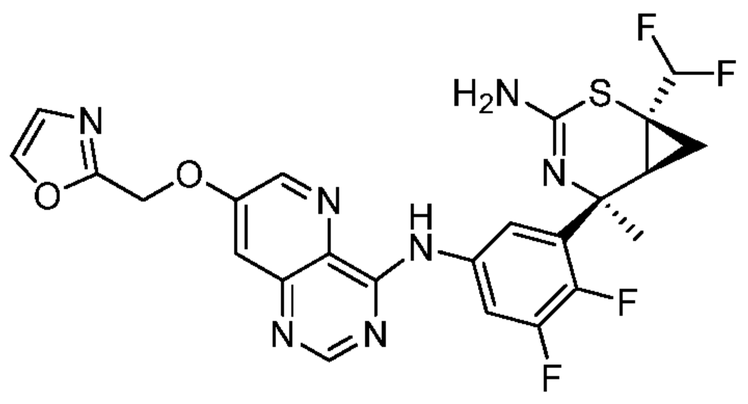
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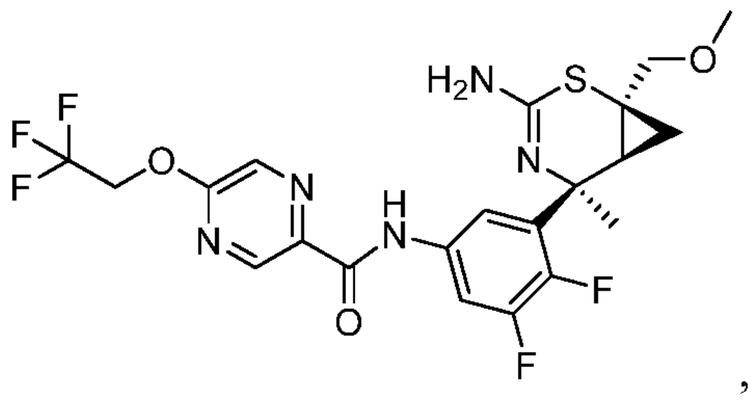
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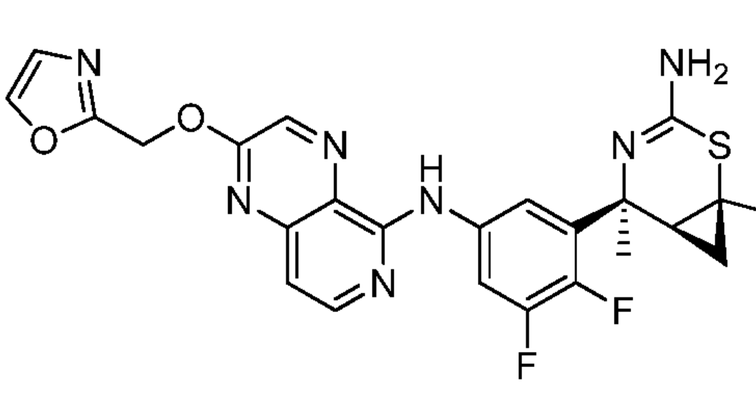
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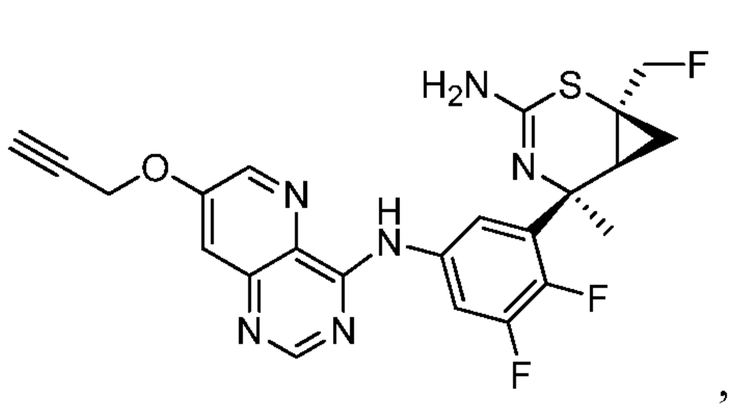
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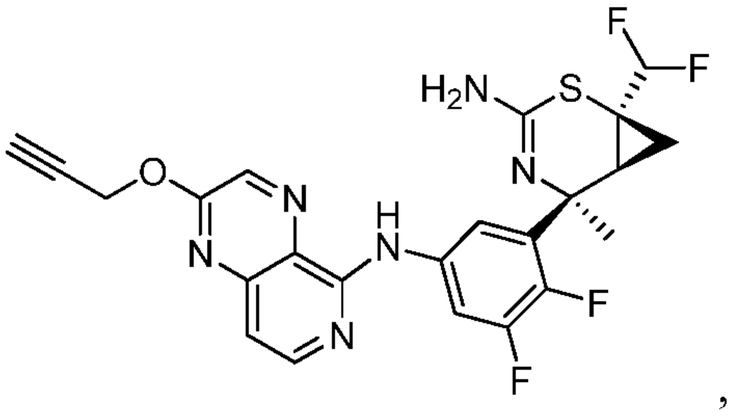
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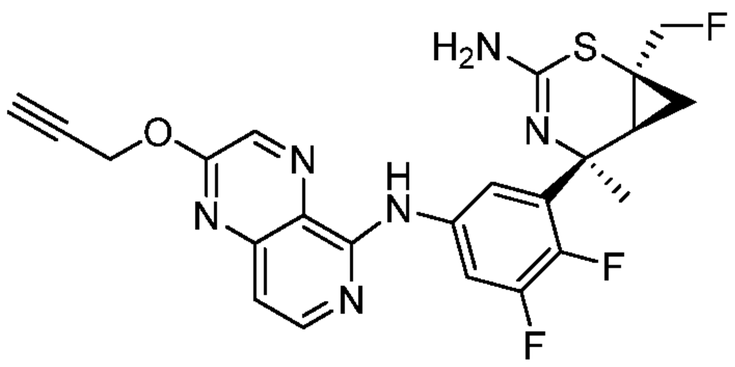
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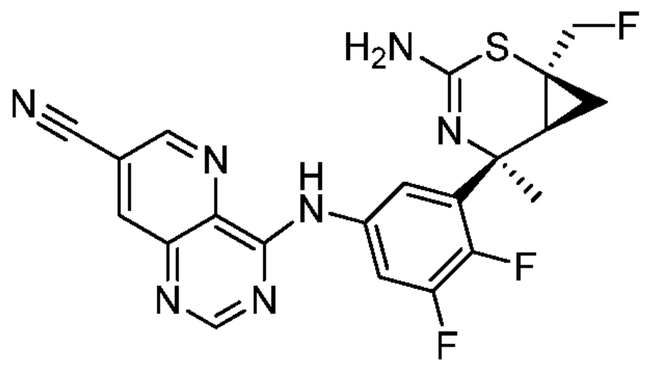
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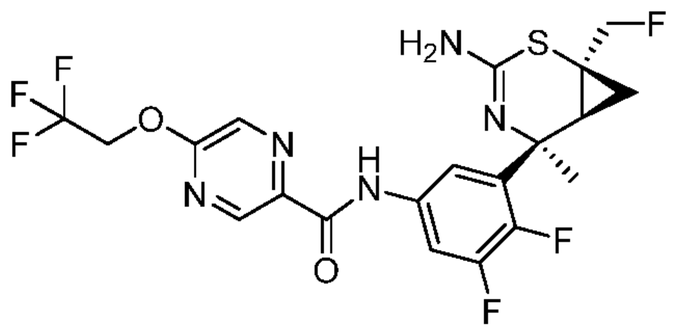
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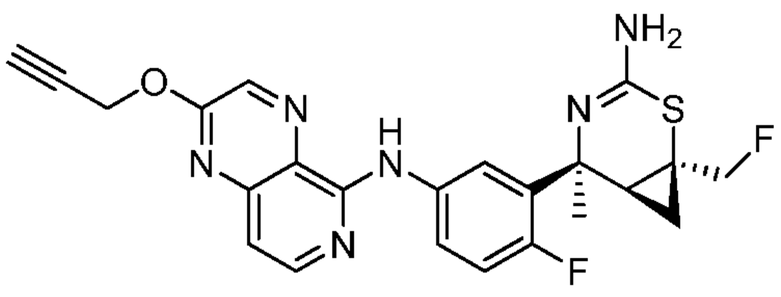
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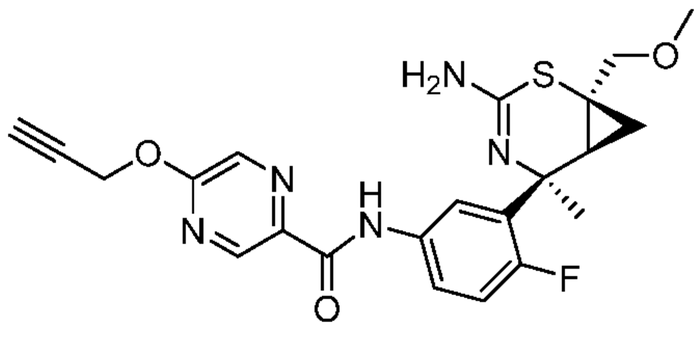
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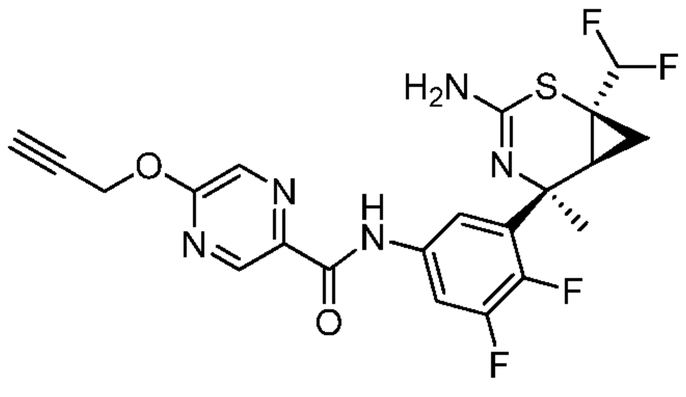
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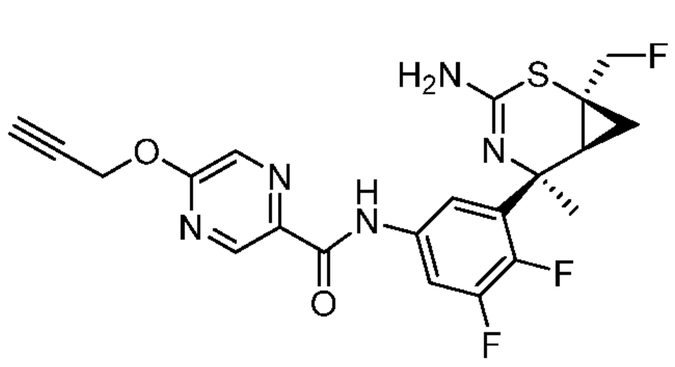
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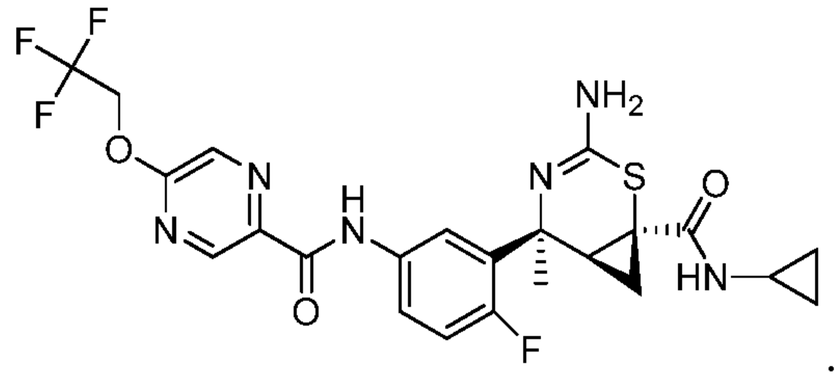
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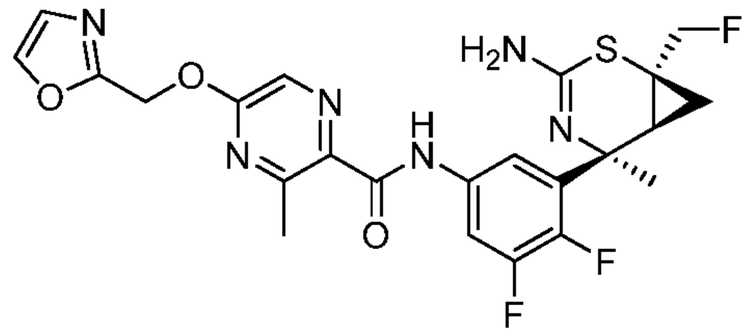
Thus, in one embodiment, the invention provides the compound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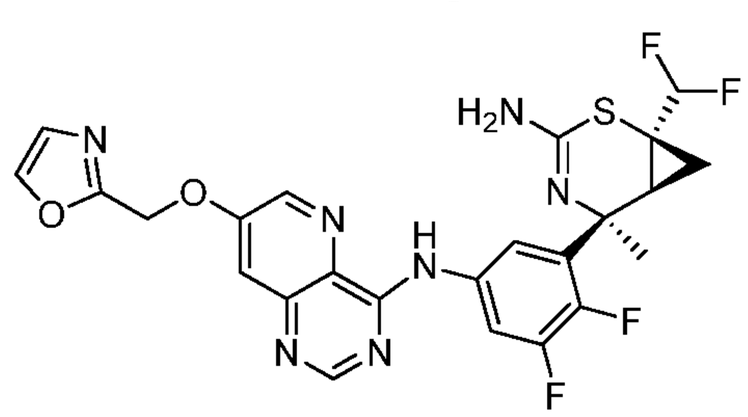
or a pharmaceutically acceptable salt or tautomer thereof.

Thus, in one embodiment, the invention provides the compound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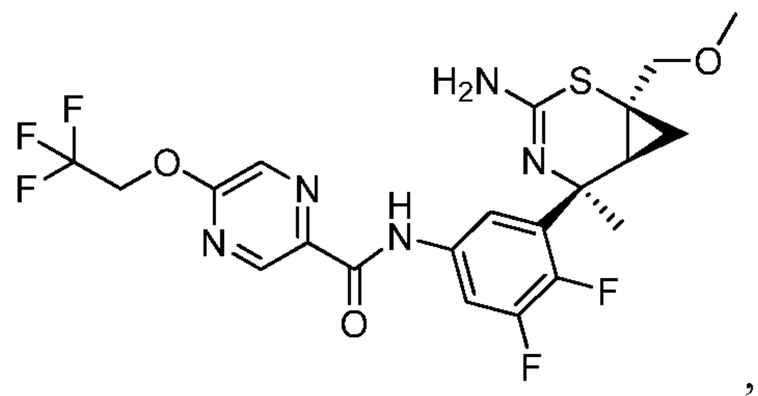
or a pharmaceutically acceptable salt or tautomer thereof.

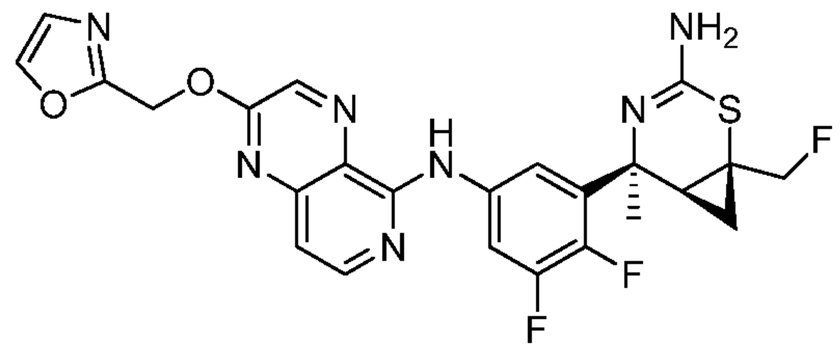
Thus, in one embodiment, the invention provides the compound



,

or a pharmaceutically acceptable salt or tautomer thereof.

Thus, in one embodiment, the invention provides the compound



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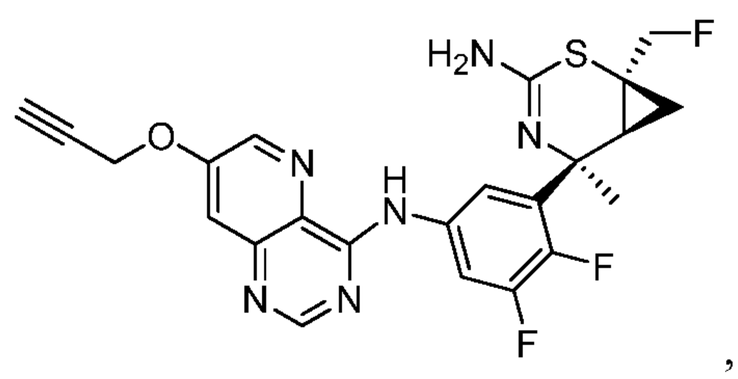
or a pharmaceutically acceptable salt or tautomer thereof.

Thus, in one embodiment, the invention provides the compound



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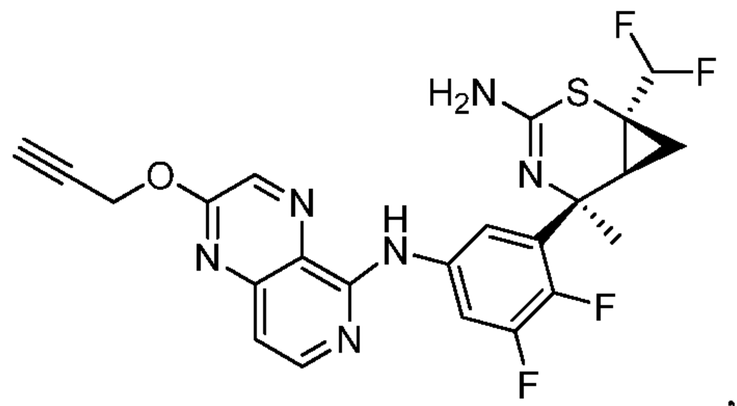
or a pharmaceutically acceptable salt or tautomer thereof.

Thus, in one embodiment, the invention provides the compound



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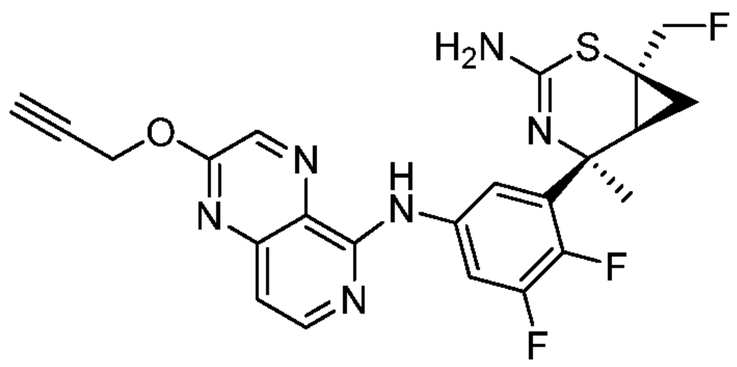
or a pharmaceutically acceptable salt or tautomer thereof.

Thus, in one embodiment, the invention provides the compound



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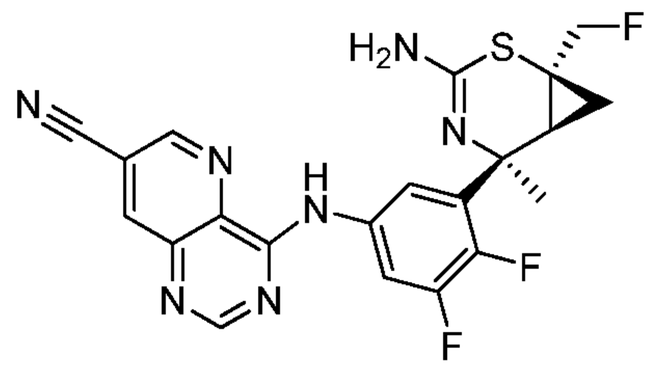
or a pharmaceutically acceptable salt or tautomer thereof.

Thus, in one embodiment, the invention provides the compound



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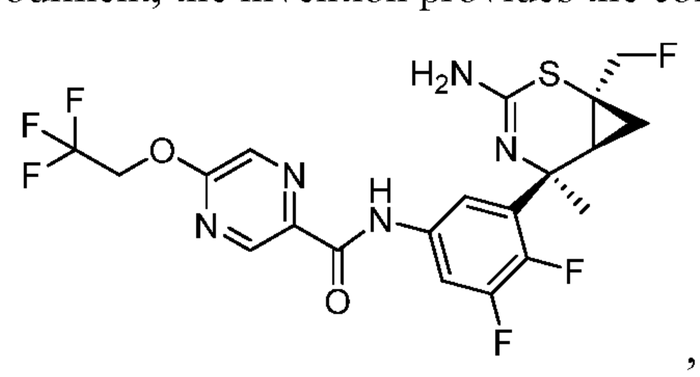
or a pharmaceutically acceptable salt or tautomer thereof.

Thus, in one embodiment, the invention provides the compound



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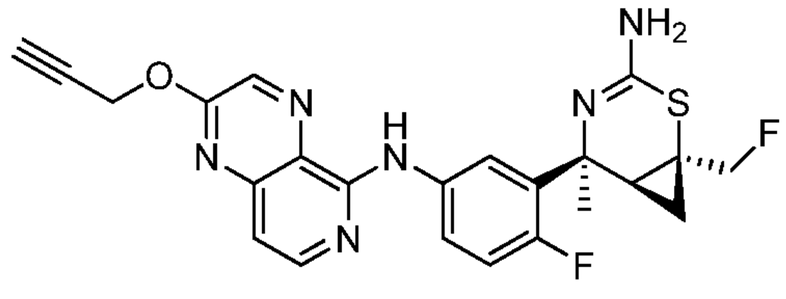
or a pharmaceutically acceptable salt or tautomer thereof.

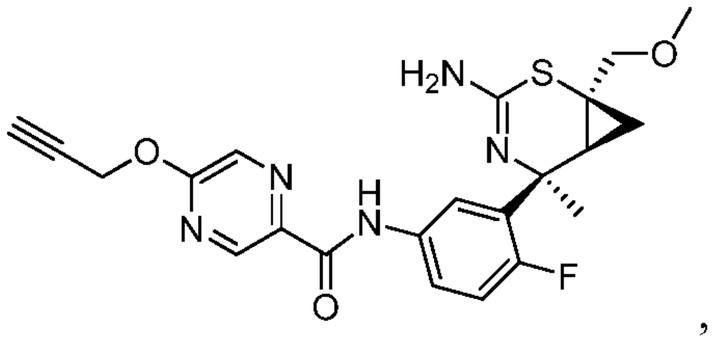
Thus, in one embodiment, the invention provides the compound



,

or a pharmaceutically acceptable salt or tautomer thereof.

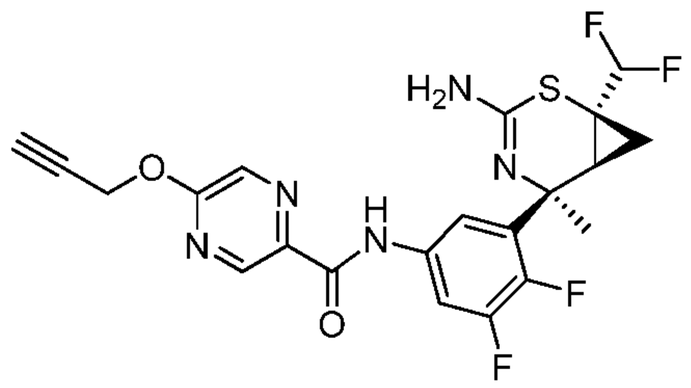
Thus, in one embodiment, the invention provides the compound



,

or a pharmaceutically acceptable salt or tautomer thereof.

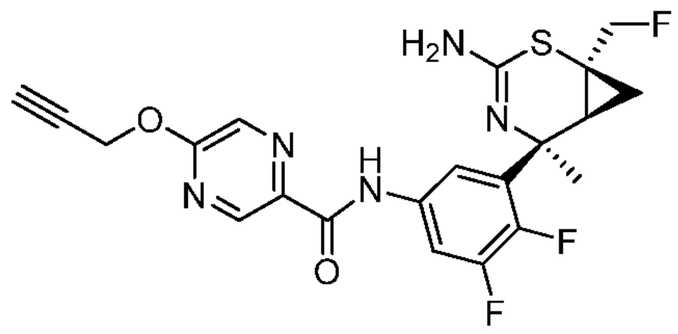
Thus, in one embodiment, the invention provides the compound



,

or a pharmaceutically acceptable salt or tautomer thereof.

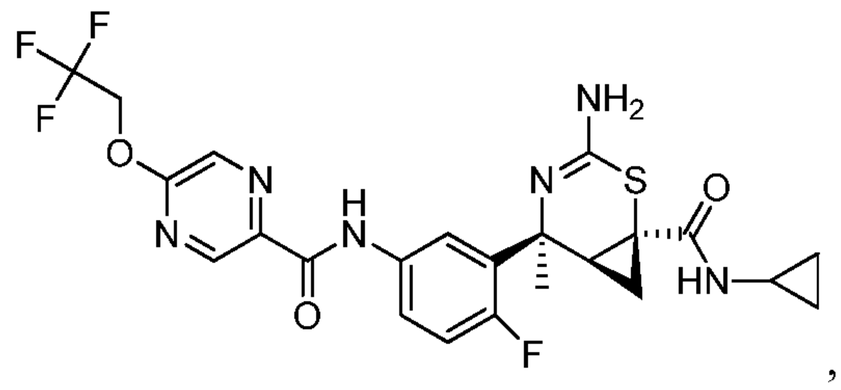
Thus, in one embodiment, the invention provides the compound



,

or a pharmaceutically acceptable salt or tautomer thereof.

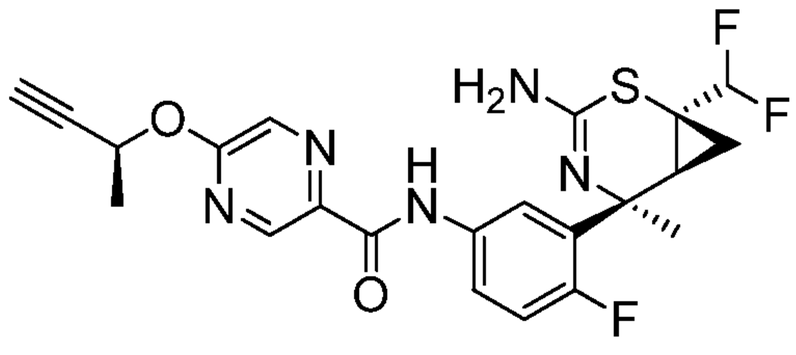
Thus, in one embodiment, the invention provides the compound



,

or a pharmaceutically acceptable salt or tautomer thereof.

In an additional embodiment, the invention provides a compound, or a pharmaceutically acceptable salt or tautomer thereof, selected from:



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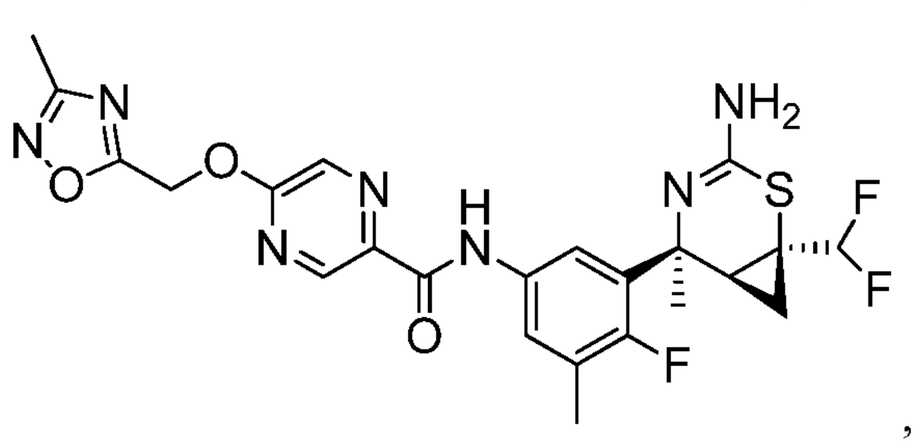

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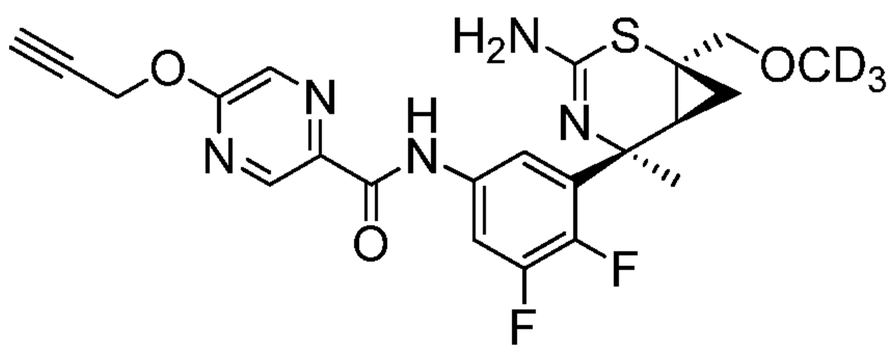

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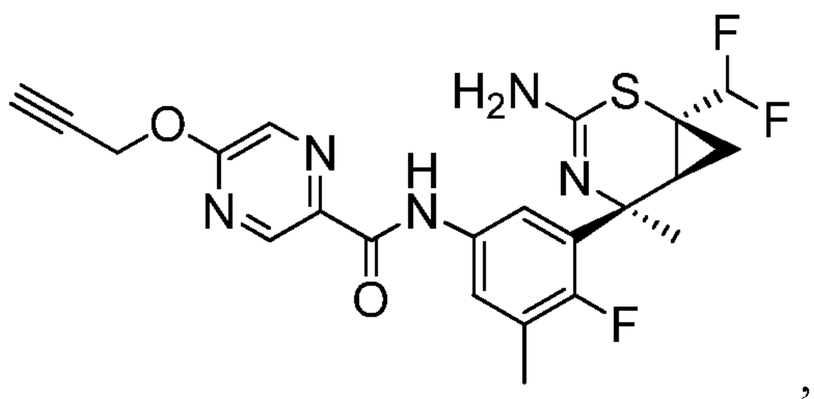

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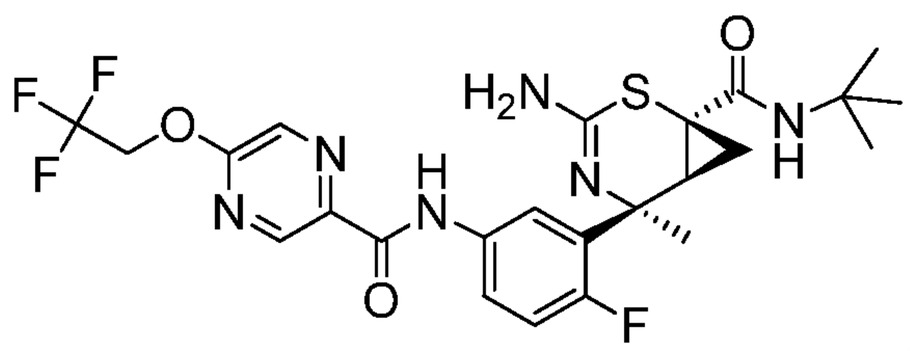

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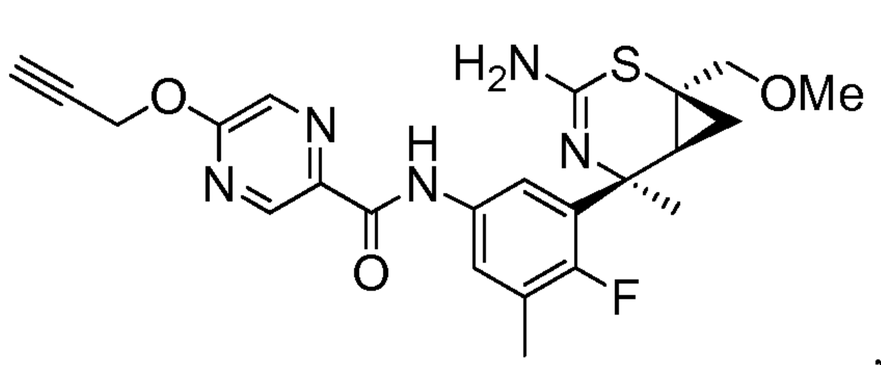

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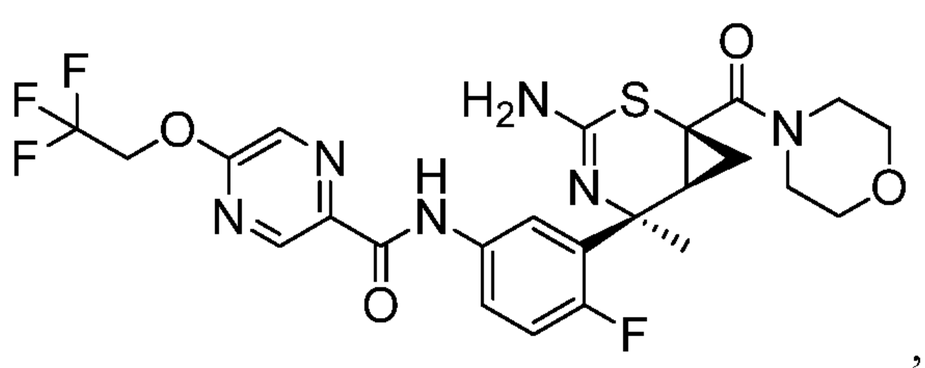

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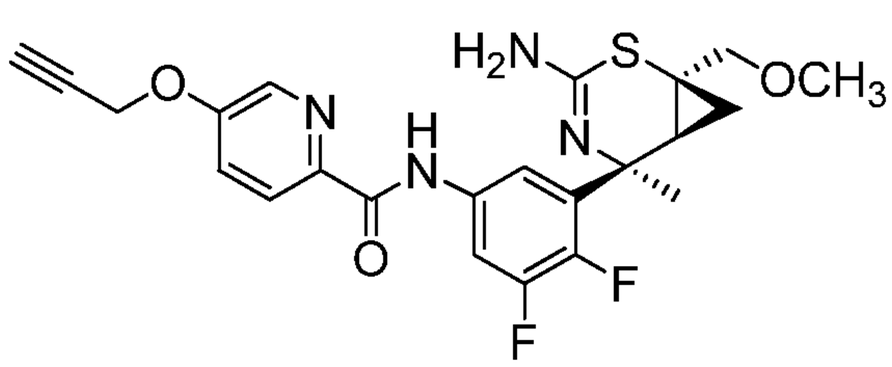
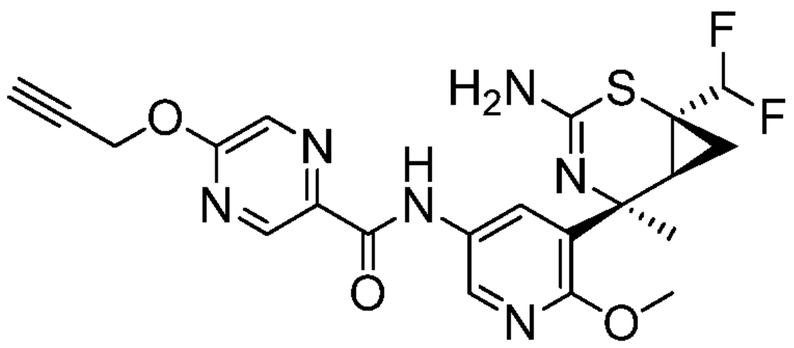
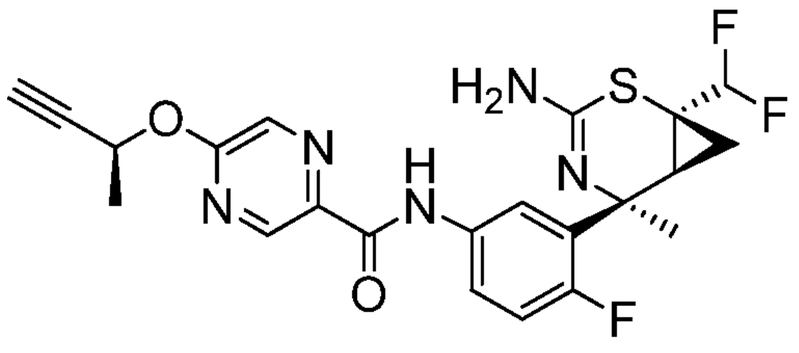


, or



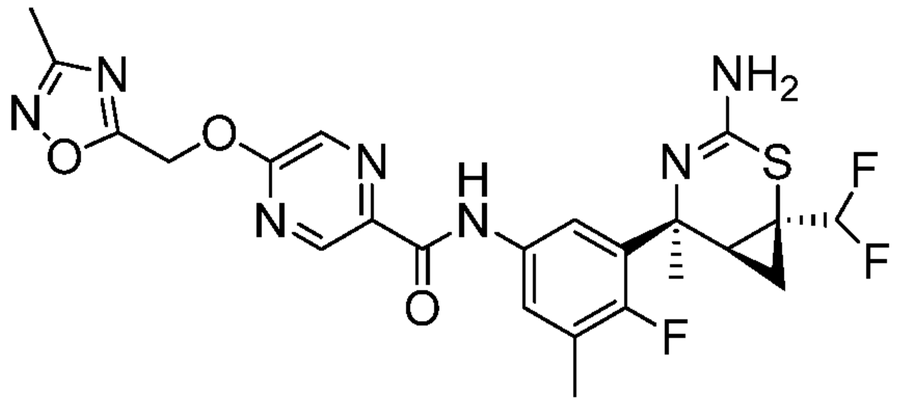
Thus, in one embodiment, the invention provides the compound



,

or a pharmaceutically acceptable salt or tautomer thereof.

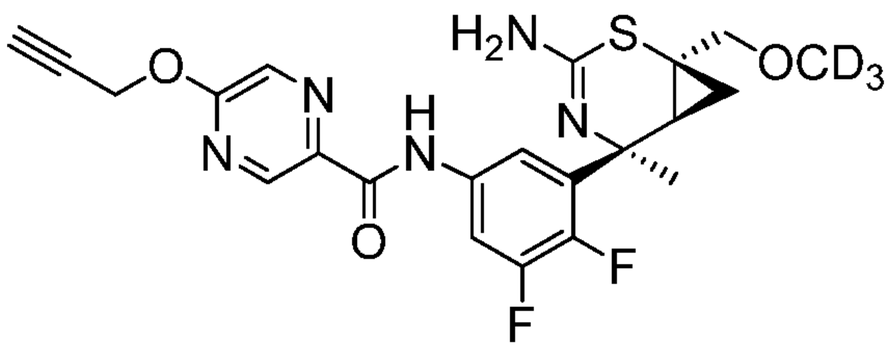
Thus, in one embodiment, the invention provides the compound



,

or a pharmaceutically acceptable salt or tautomer thereof.

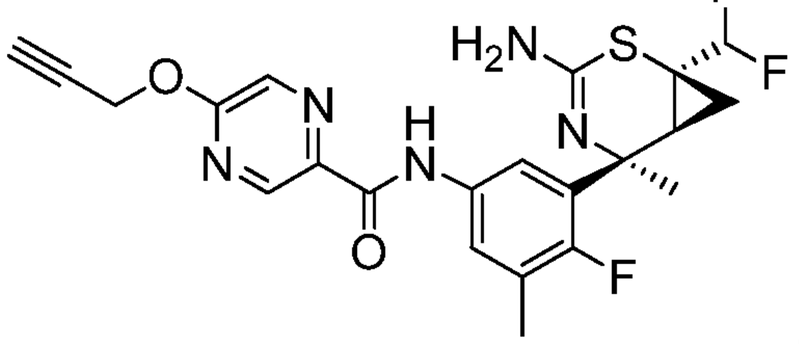
Thus, in one embodiment, the invention provides the compound



,

or a pharmaceutically acceptable salt or tautomer thereof.

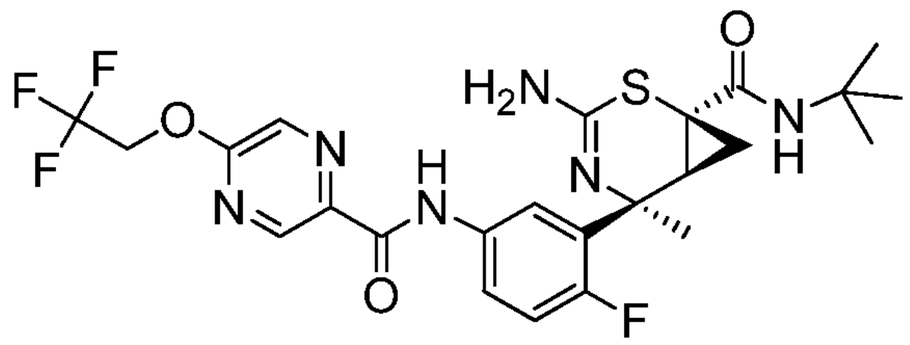
Thus, in one embodiment, the invention provides the compound



,

or a pharmaceutically acceptable salt or tautomer thereof.

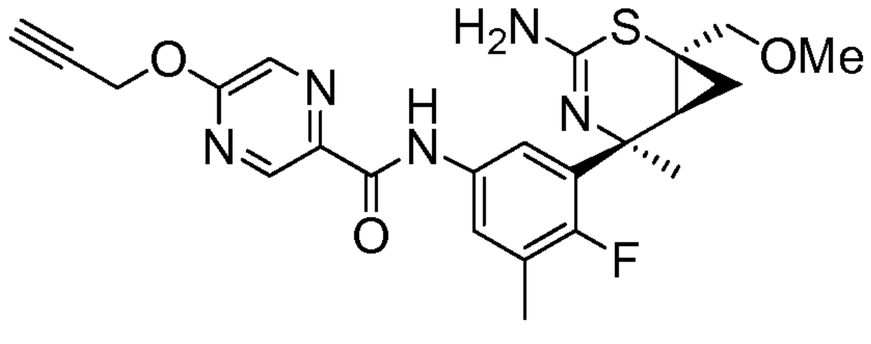
Thus, in one embodiment, the invention provides the compound



,

or a pharmaceutically acceptable salt or tautomer thereof.

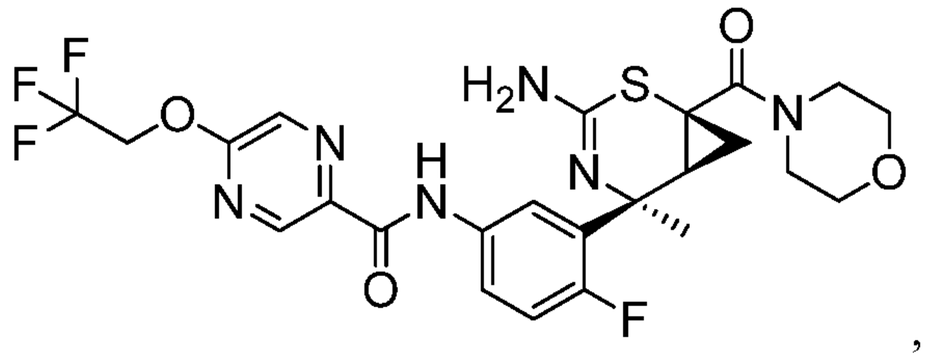
Thus, in one embodiment, the invention provides the compound



,

or a pharmaceutically acceptable salt or tautomer thereof.

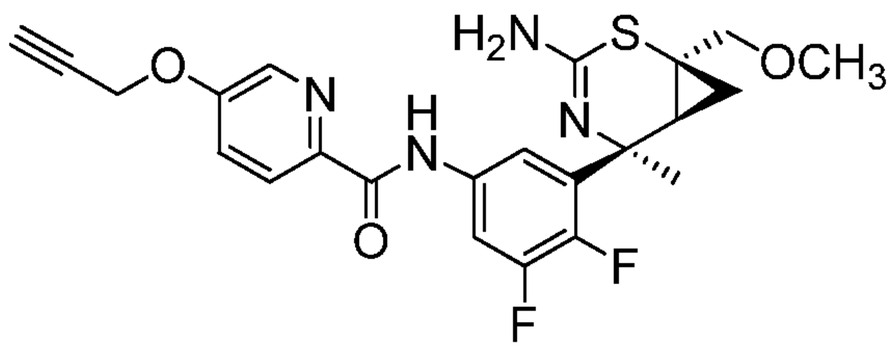
Thus, in one embodiment, the invention provides the compound



,

or a pharmaceutically acceptable salt or tautomer thereof.

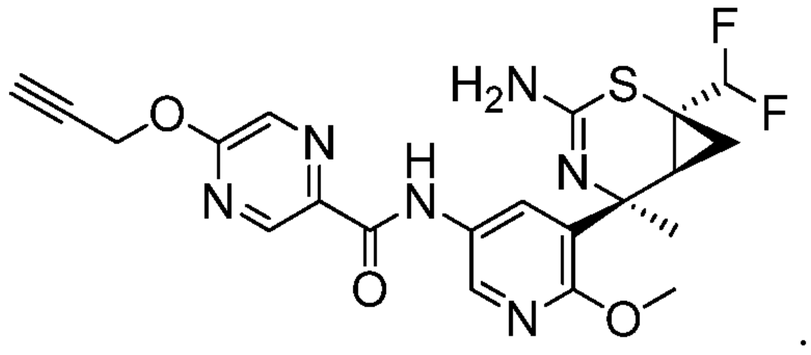
Thus, in one embodiment, the invention provides the compound



,

or a pharmaceutically acceptable salt or tautomer thereof.

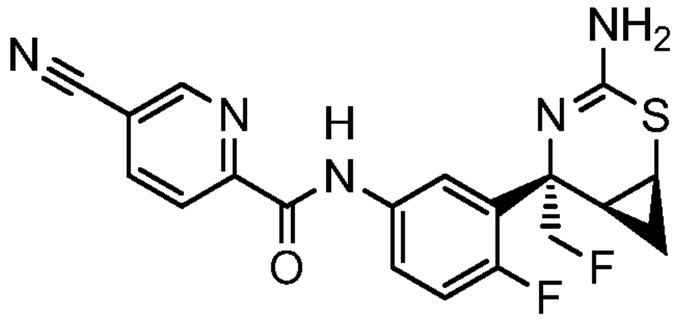
Thus, in one embodiment, the invention provides the compound



.

or a pharmaceutically acceptable salt or tautomer thereof.

In embodiment 84, the invention provides a compound, or a pharmaceutically acceptable salt or tautomer thereof, selected from: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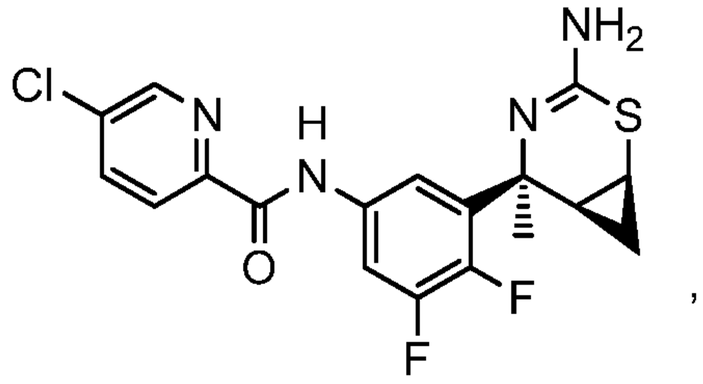
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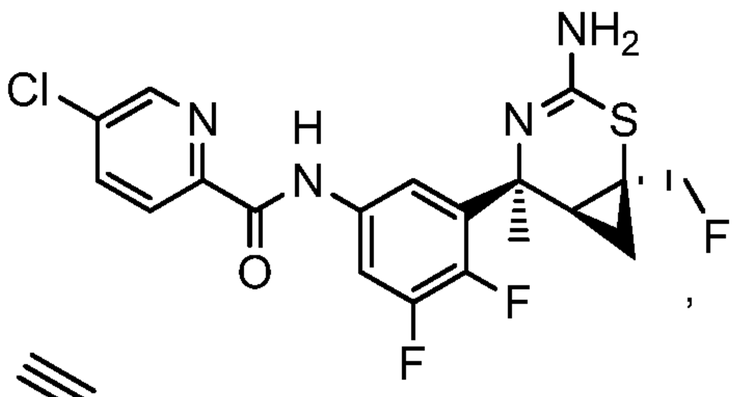
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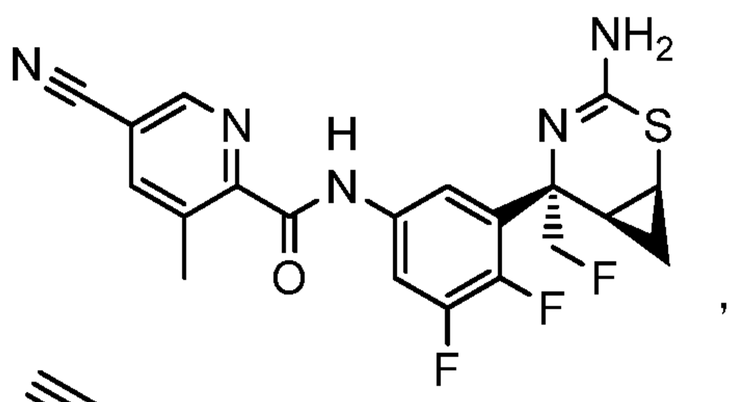
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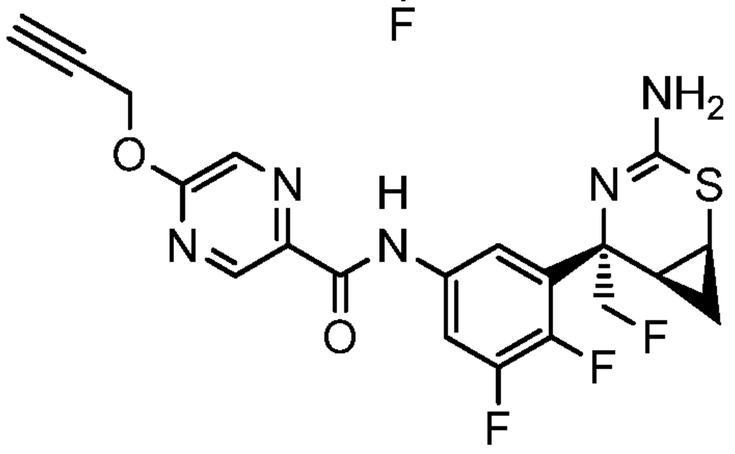
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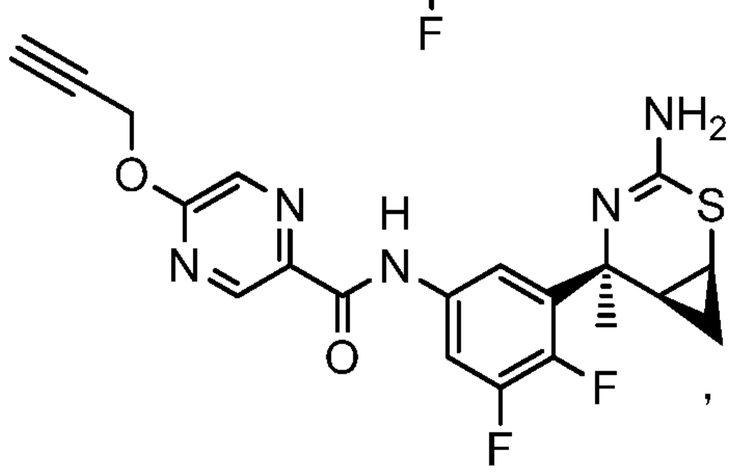
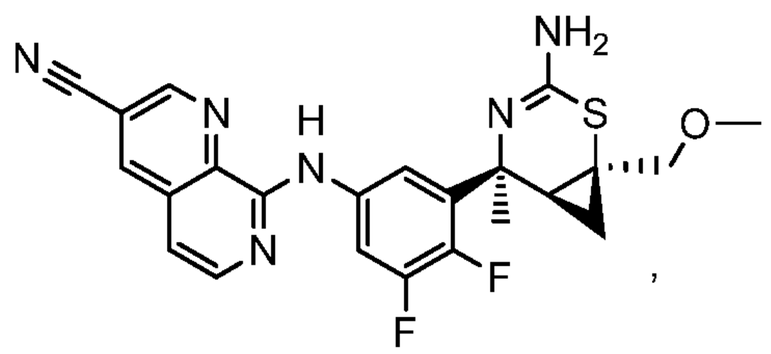

,

5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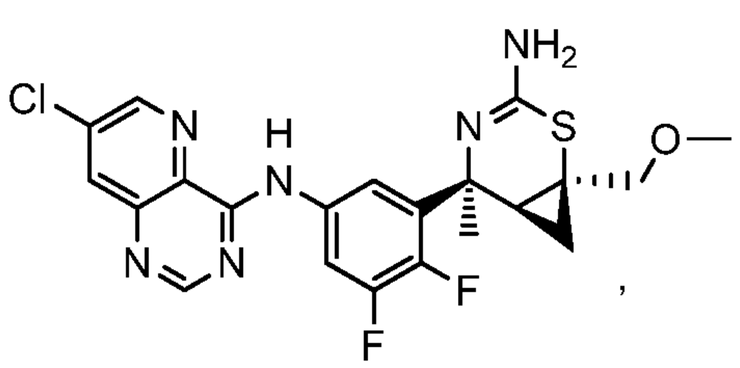
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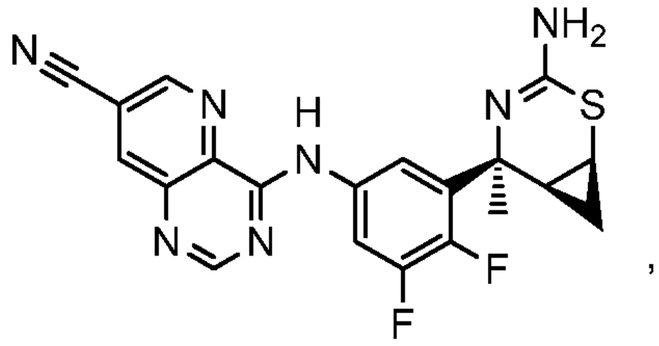
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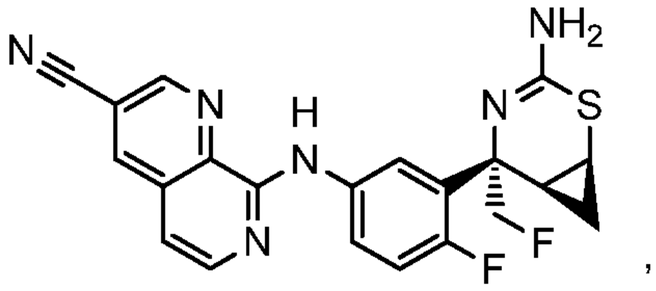
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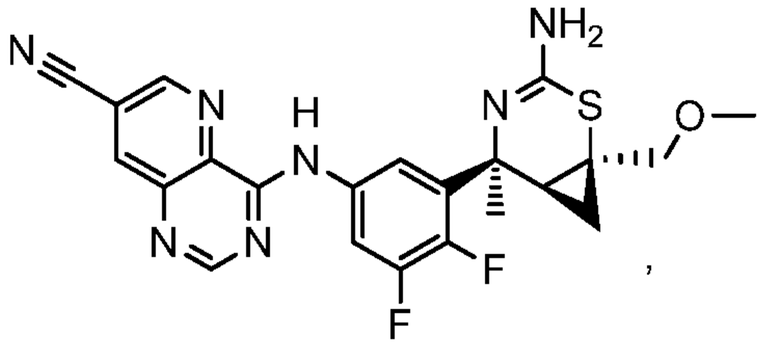
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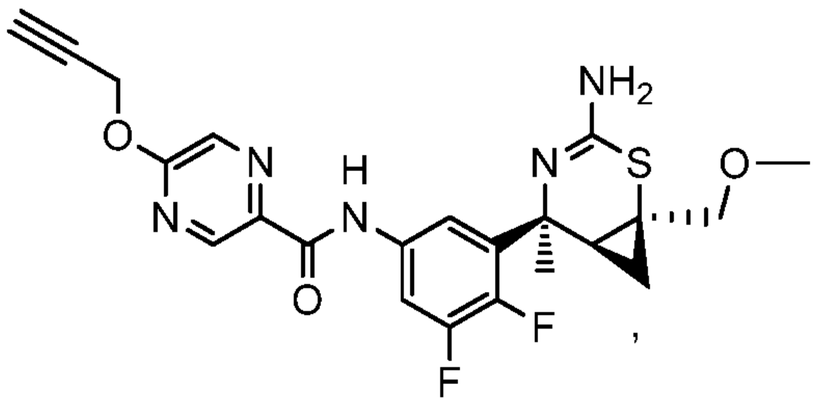
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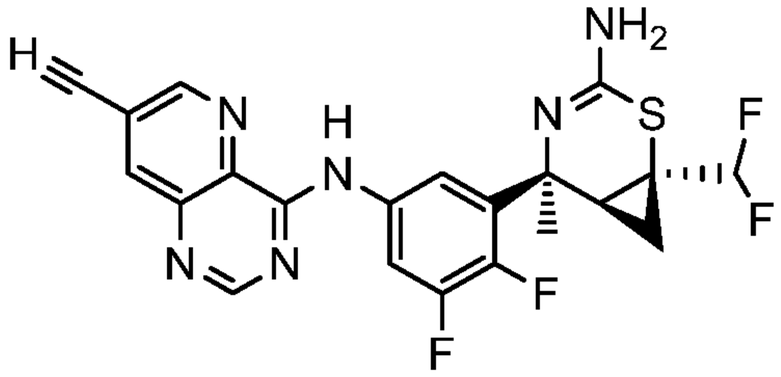
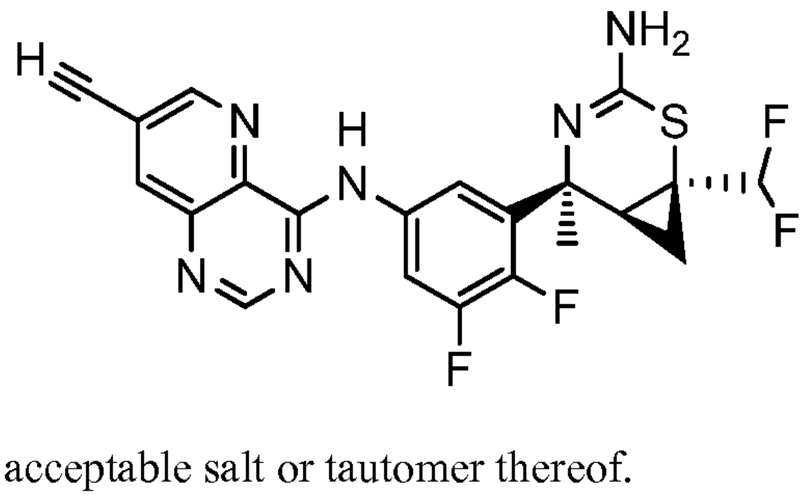

or .

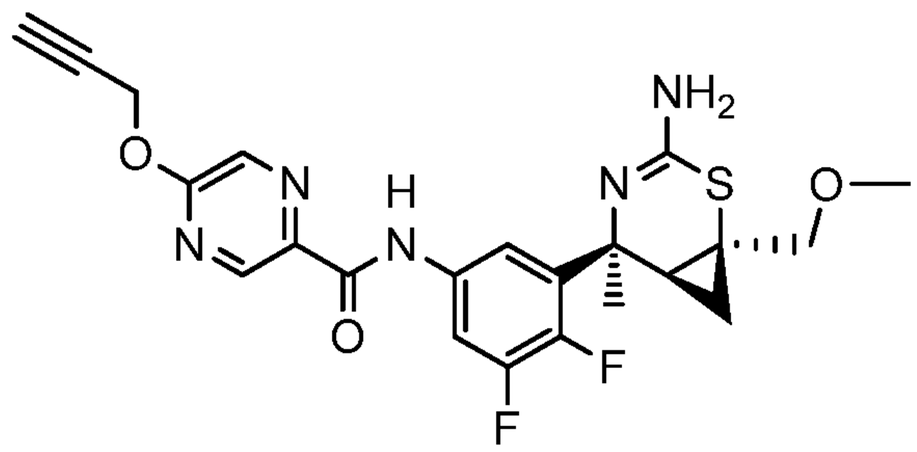
In embodiment 85, the invention provides each individual compound according to embodiments 82-84, or a pharmaceutically acceptable salt or tautomer thereof.

For instance, in embodiment 86, the invention provides the compound


,

or a pharmaceutically acceptable salt or tautomer thereof.

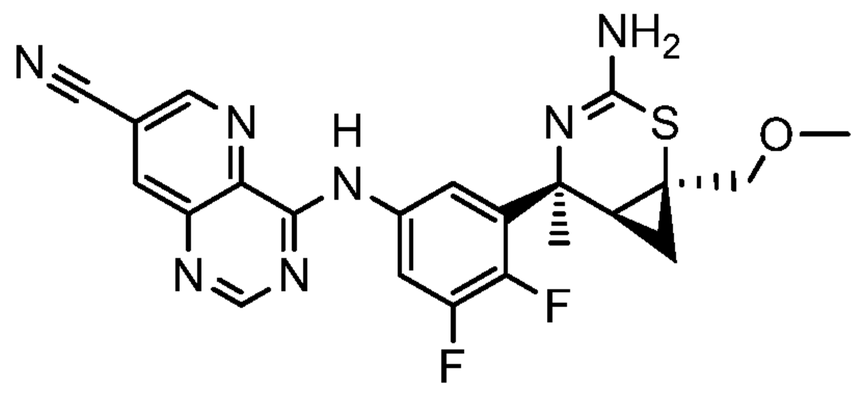
In embodiment 87, the invention provides the compound



,

or a pharmaceutically acceptable salt or tautomer thereof.

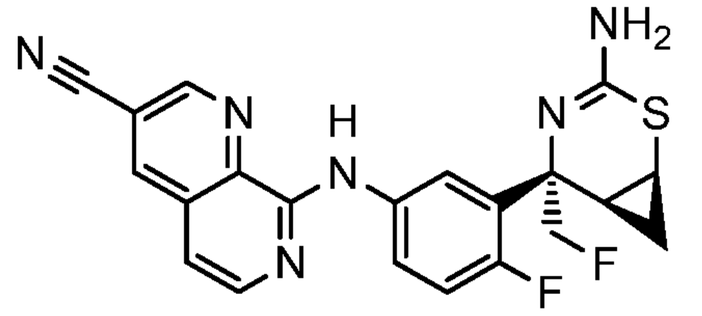
In embodiment 88, the invention provides the compound



,

or a pharmaceutically acceptable salt or tautomer thereof.

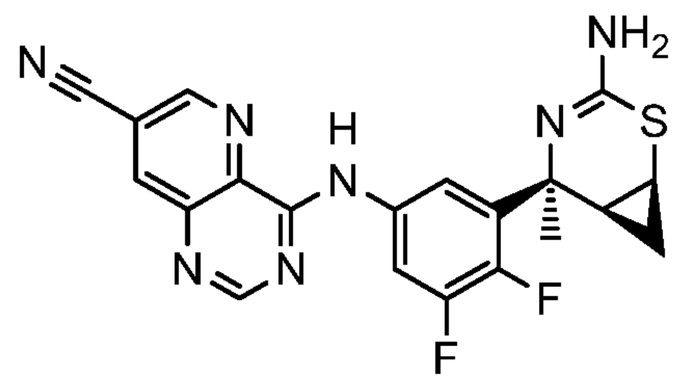
In embodiment 89, the invention provides the compound



,

or a pharmaceutically acceptable salt or tautomer thereof.

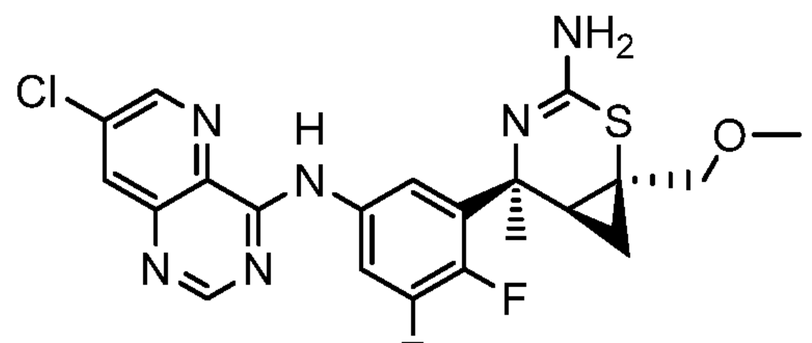
In embodiment 90, the invention provides the compound



,

or a pharmaceutically acceptable salt or tautomer thereof.

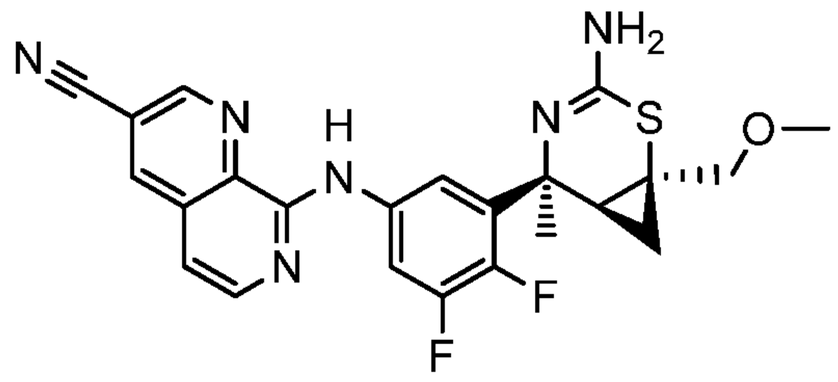
In embodiment 91, the invention provides the compound



,

or a pharmaceutically acceptable salt or tautomer thereof.

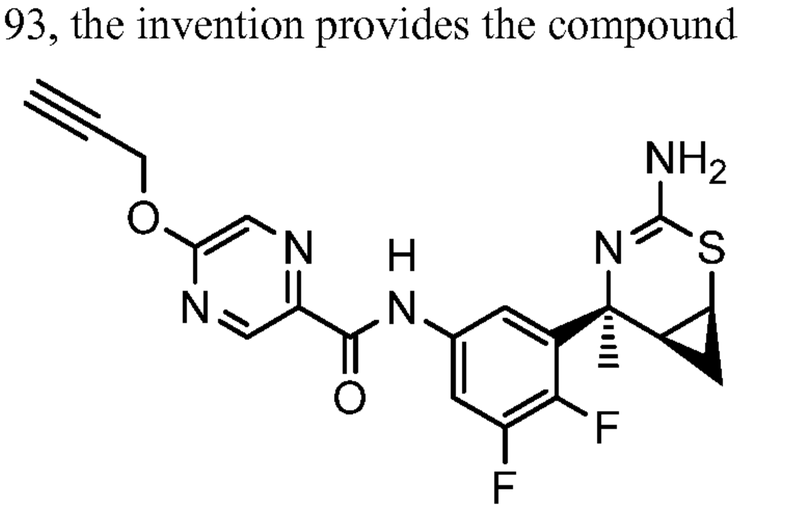
In embodiment 92, the invention provides the compound



,

or a pharmaceutically acceptable salt or tautomer thereof.

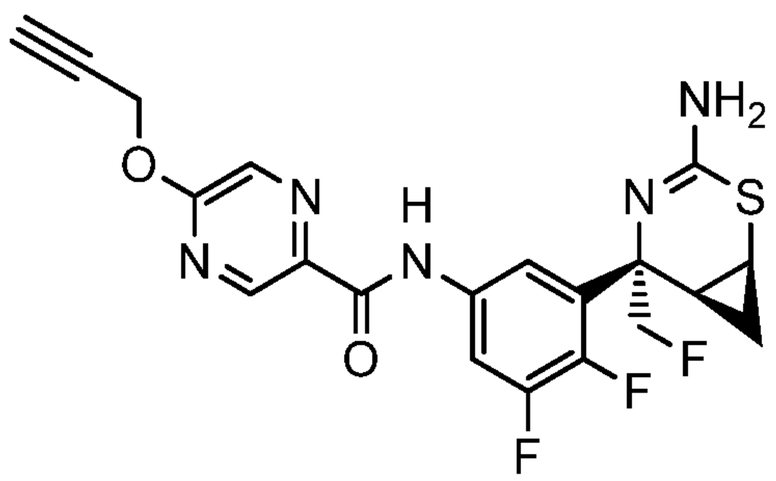
In embodiment 93, the invention provides the compound



,

or a pharmaceutically acceptable salt or tautomer thereof.

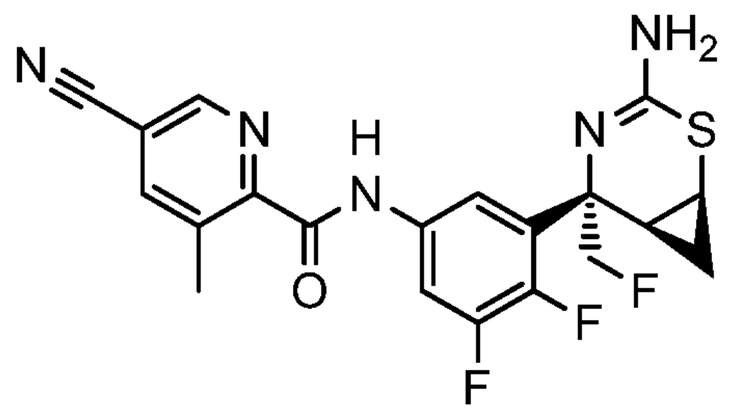
In embodiment 94, the invention provides the compound



,

or a pharmaceutically acceptable salt or tautomer thereof.

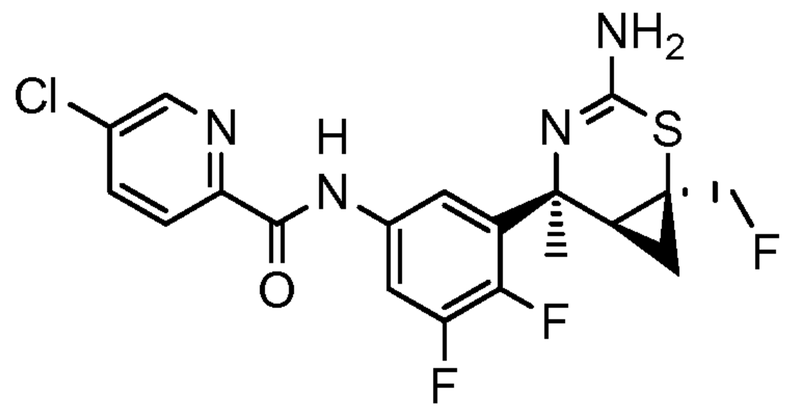
In embodiment 95, the invention provides the compound



,

or a pharmaceutically acceptable salt or tautomer thereof.

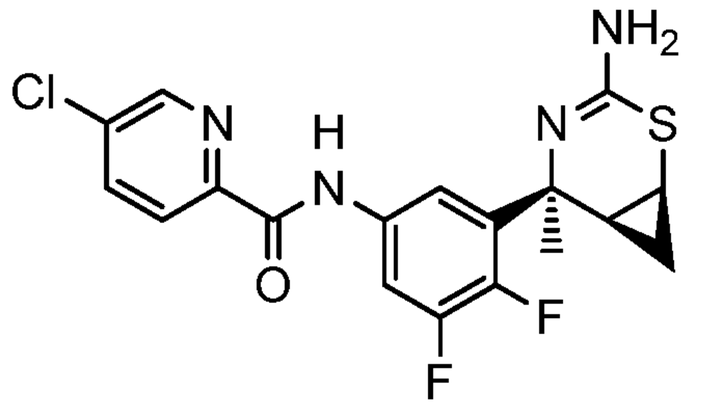
In embodiment 96, the invention provides the compound



,

or a pharmaceutically acceptable salt or tautomer thereof.

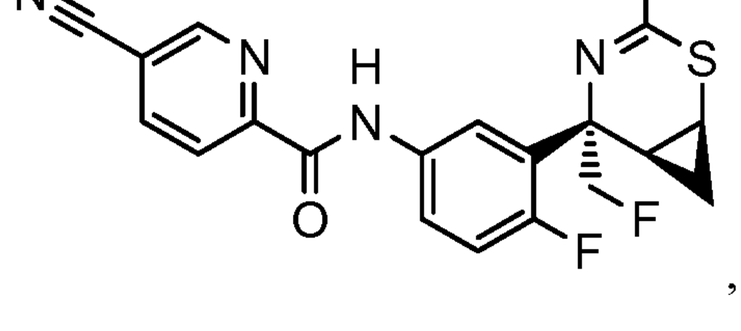
In embodiment 97, the invention provides the compound



,

or a pharmaceutically acceptable salt or tautomer thereof.

In embodiment 98, the invention provides the compound



,

or a pharmaceutically acceptable salt or tautomer thereof.

In the structures depicted hereinabove, an "-N" in the 1,3-oxazine head group is intended to be an $-NH_2$ (an amine groups); the "-N" in the amide linker is intended to be an $-NH$, and lines ending without an atom are understood by persons of ordinary skill in the art to be a $-CH_3$ group.

All of the possible embodiments described herein for various of the R groups of the compounds of Formula I may be applied, as appropriate, to compounds of Formulas II andIII, and any sub-formulas thereof.

In another embodiment, the invention provides each of the Examplary compounds, and stereoisomers, tautomers, solvates, pharmaceutically acceptable salts, derivatives or prodrugs thereof, and related intermediates, described herein.

In another embodiment, the invention provides the exemplified compounds described herein, and pharmaceutically acceptable salt forms of each thereof.

DEFINITIONS

The following definitions should assist in understanding the metes and bounds of the invention.

The term "comprising" is meant to be open ended, i.e., all encompassing and non-limiting. It may be used herein synonymously with “having.” Comprising is intended to include each and every indicated or recited component or element(s) while not excluding any other components or elements.

The compounds of the invention may contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (^{3}H), iodine-125 (^{125}I) or carbon-14 (^{14}C). Radiolabeled compounds are useful as therapeutic or prophylactic agents, research reagents, e.g., assay reagents, and diagnostic agents, e.g., in vivo imaging agents. All isotopic variations of the compounds of the invention, whether radioactive or not, are intended to be encompassed within the scope of the invention. For example, if a variable is said to be H, this means that variable may also be deuterium (D) or tritium (T). However, in certain deuterated compounds, if a structure is drawn showing D groups, then this site is enriched with respect to D.

The term "$C_{\alpha-\beta}$alkyl", when used either alone or within other terms such as "haloalkyl" and "alkylamino", embraces linear or branched radicals having α to β number of carbon atoms (such as C_1-C_{10}; C_1-C_6; or C_1-C_4). Unless otherwise specified, one or more carbon atoms of the “alkyl” radical may be substituted, such as with a cycloalkyl moiety. Examples of “alkyl” radicals include methyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, ethyl, cyclopropylethyl, cyclobutylethyl, cyclopentylethyl, n-propyl, isopropyl, n-butyl, cyclopropylbutyl, isobutyl, *sec*-butyl, *tert*-butyl, pentyl, isoamyl, hexyl and the like.

The term "$C_{\alpha-\beta}$alkenyl", when used alone or in combination, embraces linear or branched radicals having at least one carbon-carbon double bond in a moiety having a number of carbon atoms in the range from α and β. Included within alkenyl radicals are "lower alkenyl" radicals having two to about six carbon atoms and, for example, those radicals having two to about four carbon atoms. Examples of alkenyl radicals include, without limitation, ethenyl, propenyl, allyl, propenyl, butenyl and 4-methylbutenyl. The terms "alkenyl" and "lower alkenyl", embrace radicals having "cis" and "trans" orientations, or alternatively, "E" and "Z" orientations, as appreciated by those of ordinary skill in the art.

The term "$C_{\alpha-\beta}$alkynyl", when used alone or in combination, denotes linear or branched radicals having at least one carbon-carbon triple bond in a moiety having a number of carbon atoms in the range from α and β. Examples of alkynyl radicals include "lower alkynyl" radicals having two to about six carbon atoms and, for example, lower alkynyl radicals having two to about four carbon atoms. Examples of such radicals include, without limitation, ethynyl, propynyl (propargyl), butynyl, and the like.

The term "$C_{\alpha-\beta}$-alkyl", "$C_{\alpha-\beta}$-alkenyl" and "$C_{\alpha-\beta}$-alkynyl", when used with other terms such as "wherein 1, 2 or 3 carbon atoms of said $C_{\alpha-\beta}$-alkyl, $C_{\alpha-\beta}$-alkenyl or $C_{2\alpha-\beta}$-alkynyl is optionally replaced with a heteroatom selected from O, S, S(O), $S(O)_2$ and N" embraces linear or branched radicals wherein one or more of the carbon atoms may be replaced with a heteroatom. Examples of such "alkyl" radicals include –O-methyl, -O-ethyl, $-CH_2-O-CH_3$, $-CH_2CH_2-O-CH_3$, $-NH-CH_2$, $-CH_2CH_2-N(CH_3)-CH_3$, $-S-(CH_2)_3CH_2$, $-CH_2CH_2-S-CH_3$ and the like. Accordingly, such radicals also include radicals encompassed by $–OR^7$ where R^7 may be defined as a $C_{\alpha-\beta}$-alkyl. Examples of such "alkenyl" radicals include $-NH-CH_2CH=CH_2$, $-S-CH_2CH_2CH=CHCH_3$ and the like. Simlar examples exist for such "alkynyl" radicals, as appreciated by those skilled in the art.

The term "$C_{\alpha-\beta}$alkoxyl" or "$-OC_{\alpha-\beta}$alkyl" when used alone or in combination, embraces linear or branched oxygen-containing alkyl radicals each having α to β number of carbon atoms (such as C_1-C_{10}). The terms "alkoxy" and "alkoxyl", when used alone or in combination, embraces linear or branched oxygen-containing radicals each having alkyl and substituted alkyl portions of one or more carbon atoms. Examples of such radicals include methoxy, ethoxy, propoxy, butoxy, *tert*-butoxy and neopentoxy. Alkoxy radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or

bromo, to provide "haloalkoxy" radicals or with other substitution. Examples of such radicals include fluoromethoxy, chloromethoxy, trifluoromethoxy, trifluoroethoxy, fluoroethoxy and fluoropropoxy.

The term "aryl", when used alone or in combination, means a carbocyclic aromatic moiety containing one, two or even three rings wherein such rings may be attached together in a fused manner. Every ring of an "aryl" multi-ring system need not be aromatic, and the ring(s) fused to the aromatic ring may be partially or fully unsaturated and include one or more heteroatoms selected from nitrogen, oxygen and sulfur. Thus, the term "aryl" embraces aromatic radicals such as phenyl, naphthyl, indenyl, tetrahydronaphthyl, dihydrobenzafuranyl, anthracenyl, indanyl, benzodioxazinyl, and the like. The "aryl" group may be substituted, such as with 1 to 5 substituents including lower alkyl, hydroxyl, halo, haloalkyl, nitro, cyano, alkoxy and lower alkylamino, and the like. Phenyl substituted with $-O-CH_2-O-$ or $-O-CH_2-CH_2-O-$ forms an aryl benzodioxolyl substituent.

The term "$C_{\alpha-\beta}$-cycloalkyl", also referred to herein as "carbocyclic", when used alone or in combination, denotes a partially or fully saturated ring radical having a number of carbon atoms in the range from α and β. The "cycloalkyl" may contain one ("monocyclic"), two ("bicyclic") or even three ("tricyclic") rings wherein such rings may be attached together in a fused manner and each formed from carbon atoms. Examples of saturated carbocyclic radicals include saturated 3 to 6-membered monocyclic groups such as cyclopropane, cyclobutane, cyclopentane and cyclohexane. Cycloalkyls may be substituted as described herein.

The terms "ring" and "ring system" refer to a ring comprising the delineated number of atoms, the atoms being carbon or, where indicated, a heteroatom such as nitrogen, oxygen or sulfur. Where the number of atoms is not delineated, such as a "monocyclic ring system" or a "bicyclic ring system", the numbers of atoms are 3-8 for a monocyclic and 6-12 for a bicyclic ring. The ring itself, as well as any substitutents thereon, may be attached at any atom that allows a stable compound to be formed. The term "nonaromatic" ring or ring system refers to the fact that at least one, but not necessarily all, rings in a bicyclic or tricyclic ring system is nonaromatic.

The terms "partially or fully saturated or unsaturated" and "saturated or partially or fully unsaturated" with respect to each individual ring, refer to the ring either as fully aromatic (fully unsaturated), partially aromatic (or partially saturated) or fully saturated (containing no double or triple bonds therein). If not specified as such, then it is

contemplated that each ring (monocyclic) in a ring system (if bicyclic or tricyclic) may either be fully aromatic, partially aromatic or fully saturated, and optionally substituted with up to 5 substituents. This includes carbocyclics, heterocyclics, aryl and heteroaryl rings.

The term "halo", when used alone or in combination, means halogens such as fluorine, chlorine, bromine or iodine atoms.

The term "haloalkyl", when used alone or in combination, embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with halo as defined above. For example, this term includes monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals such as a perhaloalkyl. A monohaloalkyl radical, for example, may have either an iodo, bromo, chloro or fluoro atom within the radical. Dihalo and polyhaloalkyl radicals may have two or more of the same halo atoms or a combination of different halo radicals. Examples of haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl. "Perfluoroalkyl", as used herein, refers to alkyl radicals having all hydrogen atoms replaced with fluoro atoms. Examples include trifluoromethyl and pentafluoroethyl.

The term "heteroaryl", as used herein, either alone or in combination, means a fully unsaturated (aromatic) ring moiety formed from carbon atoms and having one or more heteroatoms selected from nitrogen, oxygen and sulfur. The ring moiety or ring system may contain one ("monocyclic"), two ("bicyclic") or even three ("tricyclic") rings wherein such rings are attached together in a fused manner. Every ring of a "heteroaryl" ring system need not be aromatic, and the ring(s) fused thereto (to the heteroaromatic ring) may be partially or fully saturated and optionally include one or more heteroatoms selected from nitrogen, oxygen and sulfur. The term "heteroaryl" does not include rings having ring members of -O-O-, -O-S- or -S-S-.

Examples of unsaturated heteroaryl radicals, include unsaturated 5- to 6-membered heteromonocyclyl groups containing 1 to 4 nitrogen atoms, including for example, pyrrolyl, imidazolyl, pyrazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl [e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl] and tetrazole; unsaturated 7- to 10- membered heterobicyclyl groups containing 1 to 4 nitrogen atoms, including for example, quinolinyl, isoquinolinyl, quinazolinyl, isoquinazolinyl, aza-quinazolinyl, and the like; unsaturated 5- to 6-membered

heteromonocyclic group containing an oxygen atom, for example, pyranyl, 2-furyl, 3-furyl, benzofuryl, etc.; unsaturated 5 to 6-membered heteromonocyclic group containing a sulfur atom, for example, 2-thienyl, 3-thienyl, benzothienyl, etc.; unsaturated 5- to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl [e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl]; unsaturated 5 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, isothiazolyl, thiadiazolyl [e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl].

The terms "heterocycle" or “heterocyclic”, when used alone or in combination, means a partially or fully saturated ring moiety containing one, two or even three rings wherein such rings may be attached together in a fused manner, formed from carbon atoms and including one or more heteroatoms selected from N, O or S. Examples of saturated heterocyclic radicals include saturated 3 to 6-membered heteromonocyclic groups containing 1 to 4 nitrogen atoms [e.g. pyrrolidinyl, imidazolidinyl, piperidinyl, pyrrolinyl, piperazinyl]; saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. morpholinyl]; saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., thiazolidinyl]. Examples of partially saturated heterocyclyl radicals include dihydrothienyl, dihydropyranyl, dihydrofuryl and dihydrothiazolyl.

The term “heterocycle” also embraces radicals where heterocyclic radicals are fused/condensed with aryl radicals: unsaturated condensed heterocyclic group containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl [e.g., tetrazolo [1,5-b]pyridazinyl]; unsaturated condensed heterocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. benzoxazolyl, benzoxadiazolyl]; unsaturated condensed heterocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., benzothiazolyl, benzothiadiazolyl]; and saturated, partially unsaturated and unsaturated condensed heterocyclic group containing 1 to 2 oxygen or sulfur atoms [e.g. benzofuryl, benzothienyl, 2,3-dihydro-benzo[1,4]dioxinyl and dihydrobenzofuryl]. Examples of heterocyclic radicals include five to ten membered fused or unfused radicals.

Examples of partially saturated and fully saturated heterocyclyls include, without limitation, pyrrolidinyl, imidazolidinyl, piperidinyl, pyrrolinyl, pyrazolidinyl, piperazinyl, morpholinyl, tetrahydropyranyl, thiazolidinyl, dihydrothienyl, 2,3-dihydro-benzo[1,4]dioxanyl, indolinyl, isoindolinyl, dihydrobenzothienyl, dihydrobenzofuryl,

isochromanyl, chromanyl, 1,2-dihydroquinolyl, 1,2,3,4-tetrahydro-isoquinolyl, 1,2,3,4-tetrahydro-quinolyl, 2,3,4,4a,9,9a-hexahydro-1H-3-aza-fluorenyl, 5,6,7-trihydro-1,2,4-triazolo[3,4-a]isoquinolyl, 3,4-dihydro-2H-benzo[1,4]oxazinyl, benzo[1,4]dioxanyl, 2,3-dihydro-1H-1λ'-benzo[d]isothiazol-6-yl, dihydropyranyl, dihydrofuryl and dihydrothiazolyl, and the like.

The term "a 3-8 membered monocyclic or 6-12 membered bicyclic ring system, said ring system formed of carbon atoms optionally including 1-3 heteroatoms if monocyclic or 1-6 heteroatoms if bicyclic, said heteroatoms selected from O, N, or S, wherein said ring system is optionally substituted" refers to a single ring of 3-, 4-, 5-, 6-, 7- or 8-atom memberd or a 6-, 7-, 8-, 9-, 10-, 11 or 12-atom membered bicyclic ring system comprising the delineated number of atoms, the atoms being carbon or, where indicated, a heteroatom such as nitrogen (N), oxygen (O) or sulfur (S). Where the number of atoms is not delineated, such as a "monocyclic ring system" or a "bicyclic ring system", the numbers of atoms are 3-8 for a monocyclic and 6-12 for a bicyclic ring. The ring or ring system may contain substitutents thereon, attached at any atom that allows a stable compound to be formed. A bicyclic ring is intended to include fused ring sytems as well as spiro-fused rings. This phrase encompasses carbocyclics, heterocyclics, aryl and heteroaryl rings.

The term "alkylamino" includes "N-alkylamino" where amino radicals are independently substituted with one alkyl radical. Preferred alkylamino radicals are "lower alkylamino" radicals having one to six carbon atoms. Even more preferred are lower alkylamino radicals having one to three carbon atoms. Examples of such lower alkylamino radicals include N-methylamino, and N-ethylamino, N-propylamino, N-isopropylamino and the like.

The term "dialkylamino" includes "N, N-dialkylamino" where amino radicals are independently substituted with two alkyl radicals. Preferred alkylamino radicals are "lower alkylamino" radicals having one to six carbon atoms. Even more preferred are lower alkylamino radicals having one to three carbon atoms. Examples of such lower alkylamino radicals include N,N-dimethylamino, N,N-diethylamino, and the like.

The term "carbonyl", whether used alone or with other terms, such as "aminocarbonyl", denotes -(C=O)-. "Carbonyl" is also used herein synonymously with the term "oxo".

The term "alkylthio" or "thioalkoxy" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent sulfur atom. An example of "alkylthio" or "thioalkoxy" is methylthio,(CH_3S-).

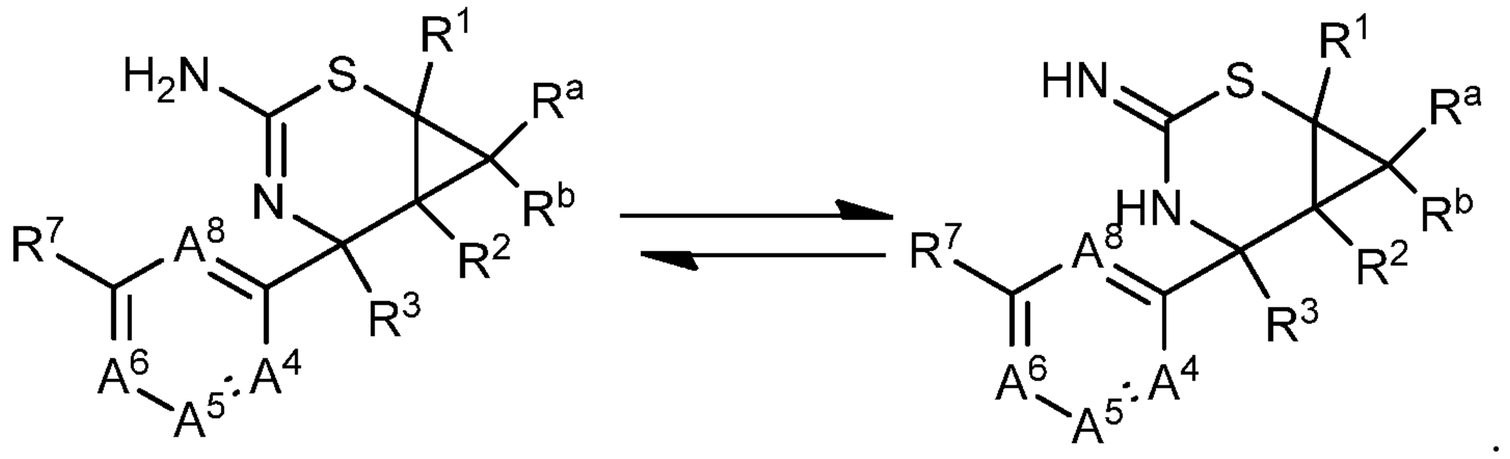
The term "Formula I" includes any sub formulas, such as Formulas II and III. Similar with Formulas II and III, in that they include sub-formulas where described.

As used herein and unless otherwise indicated, the term "stereoisomer" or "stereomerically pure" means one stereoisomer of a compound that is substantially free of other stereoisomers of that compound. For example, a stereomerically pure compound having one chiral center will be substantially free of the opposite enantiomer of the compound. A stereomerically pure compound having two chiral centers will be substantially free of other diastereomers of the compound. A typical stereomerically pure compound comprises greater than about 80% by weight of one stereoisomer of the compound and less than about 20% by weight of other stereoisomers of the compound, more preferably greater than about 90% by weight of one stereoisomer of the compound and less than about 10% by weight of the other stereoisomers of the compound, even more preferably greater than about 95% by weight of one stereoisomer of the compound and less than about 5% by weight of the other stereoisomers of the compound, and most preferably greater than about 97% by weight of one stereoisomer of the compound and less than about 3% by weight of the other stereoisomers of the compound. If the stereochemistry of a structure or a portion of a structure is not indicated with, for example, bold or dashed lines, the structure or portion of the structure is to be interpreted as encompassing all stereoisomers of it. A bond drawn with a wavy line indicates that both stereoisomers are encompassed.

Various compounds of the invention contain one or more chiral centers, and can exist as racemic mixtures of enantiomers, mixtures of diastereomers or enantiomerically or optically pure compounds. This invention encompasses the use of stereomerically pure forms of such compounds, as well as the use of mixtures of those forms. For example, mixtures comprising equal or unequal amounts of the enantiomers of a particular compound of the invention may be used in methods and compositions of the invention. These isomers may be asymmetrically synthesized or resolved using standard techniques such as chiral columns or chiral resolving agents. See, e.g., Jacques, J., et al., Enantiomers, Racemates and Resolutions (Wiley-Interscience, New York, 1981); Wilen, S. H., et al. (1997) Tetrahedron 33:2725; Eliel, E. L., Stereochemistry of Carbon Compounds (McGraw-Hill, NY, 1962); and Wilen, S. H., Tables of Resolving Agents

and Optical Resolutions p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN, 1972).

The present invention also includes tautomeric forms of compounds of the invention. For example, the invention comprises compounds of formula I as well as their tautomers, as shown:



Similarly, tautomers of compounds of Formulas II and III, and of compounds of sub-formulas of compounds of Formulas I, II and III, are also included in the invention.

The term "pharmaceutically-acceptable" when used with reference to a compound of Formulas I-III is intended to refer to a form of the compound that is safe for administration. For example, a salt form, a solvate, a hydrate, a prodrug or derivative form of a compound of Formulas I-III, which has been approved for mammalian use, via oral ingestion or other routes of administration, by a governing body or regulatory agency, such as the Food and Drug Administration (FDA) of the United States, is pharmaceutically acceptable.

Included in the compounds of Formulas I-III are the pharmaceutically acceptable salt forms of the free-base compounds. The term "pharmaceutically-acceptable salts" embraces salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. As appreciated by those of ordinary skill in the art, salts may be formed from ionic associations, charge-charge interactions, covalent bonding, complexation, coordination, etc. The nature of the salt is not critical, provided that it is pharmaceutically acceptable.

Suitable pharmaceutically acceptable acid addition salts of compounds of Formulas I-III may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, hydrofluoric, nitric, carbonic, sulfuric and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, arylaliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, examples of which include, without limitation, formic, acetic,

adipic, butyric, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, 4-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, ethanedisulfonic, benzenesulfonic, pantothenic, 2-hydroxyethanesulfonic, toluenesulfonic, sulfanilic, cyclohexylaminosulfonic, camphoric, camphorsulfonic, digluconic, cyclopentanepropionic, dodecylsulfonic, glucoheptanoic, glycerophosphonic, heptanoic, hexanoic, 2-hydroxy-ethanesulfonic, nicotinic, 2-naphthalenesulfonic, oxalic, palmoic, pectinic, persulfuric, 2-phenylpropionic, picric, pivalic propionic, succinic, thiocyanic, undecanoic, stearic, algenic, β-hydroxybutyric, salicylic, galactaric and galacturonic acid. Suitable pharmaceutically-acceptable base addition salts of compounds of Formulas I - III include metallic salts, such as salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc, or salts made from organic bases including, without limitation, primary, secondary and *tert*iary amines, substituted amines including cyclic amines, such as caffeine, arginine, diethylamine, N-ethyl piperidine, histidine, glucamine, isopropylamine, lysine, morpholine, N-ethyl morpholine, piperazine, piperidine, TEA, disopropylethylamine and trimethylamine. All of these salts may be prepared by conventional means from the corresponding compound of the invention by reacting, for example, the appropriate acid or base with the compound of Formulas I-III.

Also, the basic nitrogen-containing groups can be quaternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl, and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides, and others. Water or oil-soluble or dispersible products are thereby obtained.

Additional examples of such salts can be found in Berge et al., J. Pharm. Sci., 66:1 (1977). Conventional methods may be used to form the salts. For example, a phosphate salt of a compound of the invention may be made by combining the desired compound free base in a desired solvent, or combination of solvents, with phosphoric acid in a desired stoichiometric amount, at a desired temperature, typically under heat (depending upon the boiling point of the solvent). The salt can be precipitated upon cooling (slow or fast) and may crystallize (i.e., if crystalline in nature), as appreciated by those of ordinary skill in the art. Further, hemi-, mono-, di, tri- and poly-salt forms of the compounds of the present invention are also contemplated herein. Similarly, hemi-,

mono-, di, tri- and poly-hydrated forms of the compounds, salts and derivatives thereof, are also contemplated herein.

The term "pharmaceutically-acceptable derivative" as used herein, denotes a derivative which is pharmaceutically acceptable.

The compound(s) of Formulas I-III may be used to treat a subject by administering the compound(s) as a pharmaceutical composition. To this end, the compound(s) can be combined with one or more excipients, including without limitation, carriers, diluents or adjuvants to form a suitable composition, which is described in more detail herein.

The term “excipient”, as used herein, denotes any pharmaceutically acceptable additive, carrier, adjuvant, or other suitable ingredient, other than the active pharmaceutical ingredient (API), which is typically included for formulation and/or administration purposes. “Diluent” and “adjuvant” are defined hereinafter.

The terms “treat”, "treating," "treatment," and "therapy" as used herein refer to therapy, including without limitation, curative therapy, prophylactic therapy, and preventative therapy. Prophylactic treatment generally constitutes either preventing the onset of disorders altogether or delaying the onset of a pre-clinically evident stage of disorders in individuals.

The phrase "effective dosage amount" is intended to quantify the amount of each agent, which will achieve the goal of improvement in disorder severity and the frequency of incidence over treatment of each agent by itself, while avoiding adverse side effects typically associated with alternative therapies. Accordingly, this term is not limited to a single dose, but may comprise multiple dosages required to bring about a therapeutic or prophylactic response in the subject. For example, “effective dosage amount” is not limited to a single capsule or tablet, but may include more than one capsule or tablet, which is the dose prescribed by a qualified physician or medical care giver to the subject.

The term “leaving group” (also denoted as “LG”) generally refers to groups that are displaceable by a nucleophile. Such leaving groups are known in the art. Examples of leaving groups include, but are not limited to, halides (e.g., I, Br, F, Cl), sulfonates (e.g., mesylate, tosylate), sulfides (e.g., SCH_3), N-hydroxsuccinimide, N-hydroxybenzotriazole, and the like. Nucleophiles are species that are capable of attacking a molecule at the point of attachment of the leaving group causing displacement of the leaving group.

Nucleophiles are known in the art. Examples of nucleophilic groups include, but are not

limited to, amines, thiols, alcohols, Grignard reagents, anionic species (e.g., alkoxides, amides, carbanions) and the like.

GENERAL SYNTHETIC PROCEDURES

The present invention further comprises procedures for the preparation of compounds of Formulas I -III. The compounds of Formulas I-III can be synthesized according to the procedures described in the following Schemes 1, 2, 3a, 3b, 4 and 5, wherein the substituents are as defined for Formulas I-III above, except where further noted. The synthetic methods described below are merely exemplary, and the compounds of the invention may also be synthesized by alternate routes utilizing alternative synthetic strategies, as appreciated by persons of ordinary skill in the art.

The following list of abbreviations used throughout the specification represent the following and should assist in understanding the invention:

CAN	-	acetonitrile
Aq., aq.	-	aqueous
Ar	-	argon (gas)
Boc	-	*tert*-butoxycarbonyl
BOP	-	benzotriazol-1-yl-oxy Hexafluorophosphate
BuLi	-	Butyllithium
Cs_2CO_3	-	cesium carbonate
$CHCl_3$	-	chloroform
CH_2Cl_2, DCM	-	dichloromethane, methylene chloride
Cu(1)I	-	copper(1) iodide
COMU		(1-cyano-2-ethoxy-2-oxoethylidenaminooxy)dimethylaminomorpholinocarbenium hexafluorophosphate
DCC	-	dicyclohexylcarbodiimide
DEA	-	diethylamine
DIC	-	1,3-diisopropylcarbodiimide
DIEA, DIPEA	-	diisopropylethylamine
DME	-	dimethoxyethane
DMF	-	dimethylformamide
DMAP	-	4-dimethylaminopyridine

	DMSO	-	dimethylsulfoxide
	EDC, EDCI	-	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
	Et_2O	-	diethyl ether
	EtOAc	-	ethyl acetate
	EtOH		ethanol
	g, gm	-	gram
	h, hr	-	hour
	H_2	-	hydrogen (gas)
	H_2O	-	water
	HATU	-	O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluroniumhexafluorophosphate
	HBr	-	hydrobromic acid
	HCl	-	hydrochloric acid
	HMDS		hexamethyldisilazane or bis(trimethylsilyl)amine
	HOBt	-	1-hydroxybenzotriazole hydrate
	HOAc	-	acetic acid
	HPLC	-	high pressure liquid chromatography
	IPA, *i*PrOH	-	isopropyl alcohol
	K_2CO_3	-	potassium carbonate
	KI	-	potassium iodide
	LDA	-	Lithium diisopropylamide
	LG	-	leaving group
	LiHMDS		lithium bis(trimethylsilyl)amide
	LiOH	-	lithium hydroxide
	$MgSO_4$	-	magnesium sulfate
	MS	-	mass spectrum
	MeOH	-	methanol
	N_2	-	nitrogen (gas)
	$NaCNBH_3$	-	sodium cyanoborohydride
	Na_2CO_3	-	sodium carbonate
	$NaHCO_3$	-	sodium bicarbonate
	NaH	-	sodium hydride
	NaI	-	sodium iodide
	$NaBH_4$	-	sodium borohydride

	$NaOH$	-	sodium hydroxide
	Na_2SO_4	-	sodium sulfate
	NH_4Cl	-	ammonium chloride
	NH_4OH	-	ammonium hydroxide
	$P(t\text{-}Bu)_3$	-	tri(*tert*-butyl)phosphine
	Ph_3P or PPh_3	-	triphenylphosphine
	Pd/C	-	palladium on carbon
	$Pd(PPh_3)_4$	-	palladium(0)triphenylphosphine tetrakis
	$Pd(dppf)Cl_2$	-	palladium(1,1-bisdiphenylphosphinoferrocene) II chloride
	$Pd(PhCN)_2Cl_2$	-	palladium di-cyanophenyl dichloride
	$Pd(OAc)_2$	-	palladium acetate
	$Pd_2(dba)_3$	-	tris(dibenzylideneacetone) dipalladium
	PyBop	-	benzotriazol-1-yl-oxy-tripyrrolidino-phosphonium hexafluorophosphate
	RT, rt	-	room temperature
	RBF, rbf	-	round bottom flask
	SEM		[2-(trimethylsilyl)ethoxy]methyl acetal
	SFC	-	Supercritical fluid chromatography
	T3P		propylphosphonic anhydride
	TBAF	-	Tetrabutylammonium flouride
	TBTU	-	O-benzotriazol-1-yl-N,N,N,N'-tetramethyluronium tetrafluoroborate
	TEA, Et_3N	-	triethylamine
	TFA	-	trifluoroacetic acid
	THF	-	tetrahydrofuran
	TLC, tlc	-	thin layer chromatography
	TMSCl		trimethylsilyl chloride or chlorotrimethylsilane
	UV	-	ultraviolet light

General synthetic schemes and Examples

The general synthetic schemes, starting materials, synthetic intermediates and compounds (examples) representative of the invention, ie., compounds of Formulas I-III, should assist in a better understanding and appreciation of the scope of the present invention and of the various methods which may be used to synthesize compounds of Formulas I-III. It should be appreciated that the general methods above and specific examples below are illustrative only, for the purpose of assistance and of understanding the present invention, and should not be construed as limiting the scope of the present invention in any manner.

Chromatography:

Unless otherwise indicated, crude product-containing residues were purified by passing the crude material or concentrate through either a Biotage or Isco brand silica gel column (pre-packed or individually packed with SiO_2) and eluting the product off the column with a solvent gradient as indicated. For example a description of (330 g SiO_2, 0-40% EtOAc/Hexane) means the product was obtained by elution from the column packed with 330gms of silica, with a solvent gradient of 0% to 40% EtOAc in Hexanes.

Preparative HPLC Method:

Where so indicated, the compounds described herein were purified via reverse phase HPLC using one of the following instruments: Shimadzu, Varian, Gilson; utilizing one of the following two HPLC columns: (a) a Phenomenex Luna or (b) a Gemini column (5 micron or 10 micron, C18, 150x50 mm)

A typical run through the instrument included: eluting at 45 ml/min with a linear gradient of 10% (v/v) to 100% ACN (0.1% v/v TFA) in water (0.1% TFA) over 10 minutes; conditions can be varied to achieve optimal separations.

Proton NMR Spectra:

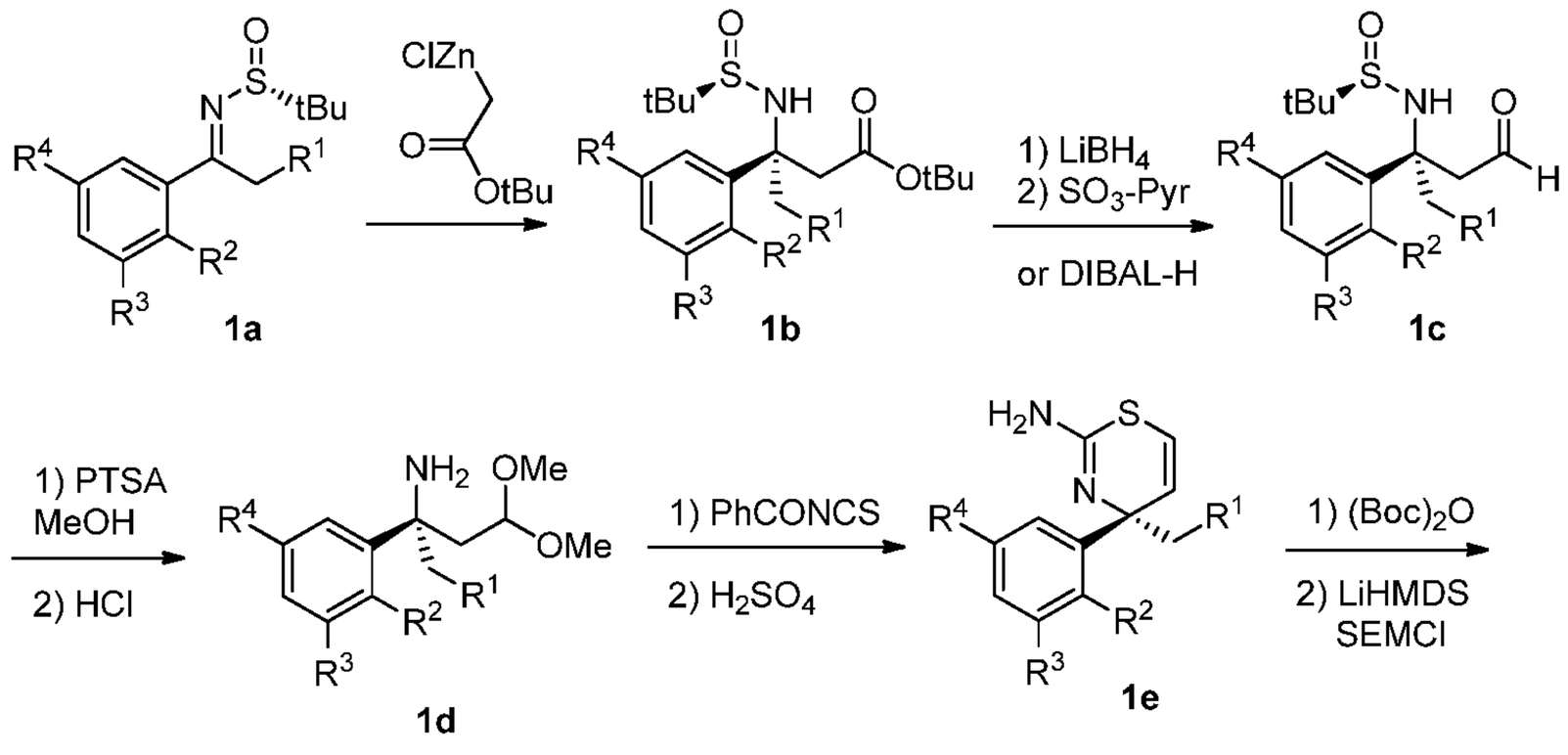
Unless otherwise indicated, all ^1H NMR spectra were run on a Bruker series 300 MHz instrument or a Bruker series 400 MHz instrument. Where so characterized, all observed protons are reported as parts-per-million (ppm) downfield from tetramethylsilane (TMS) or other internal reference in the appropriate solvent indicated.

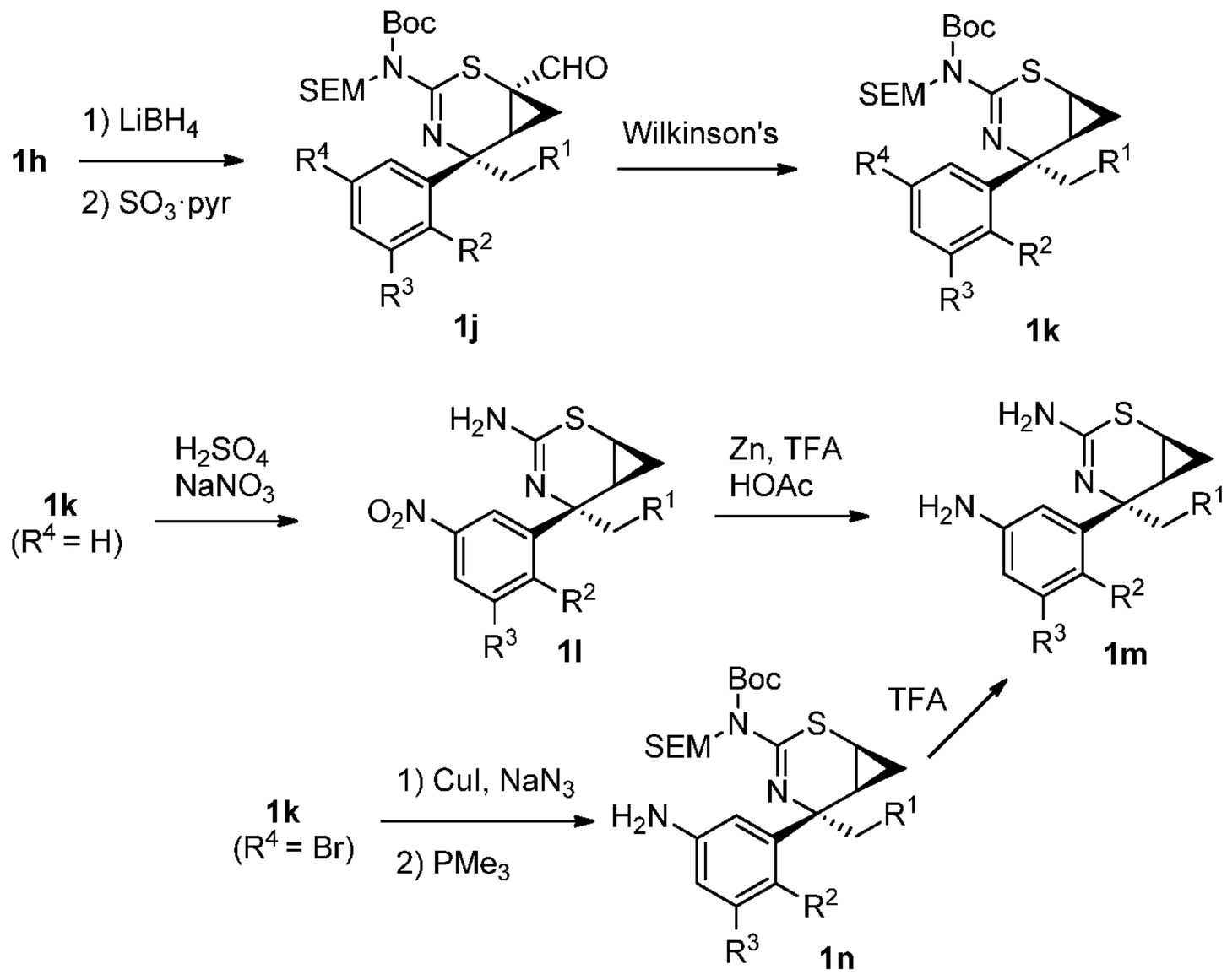
Mass Spectra (MS)

Unless otherwise indicated, all mass spectral data for starting materials, intermediates and/or exemplary compounds are reported as mass/charge (m/z), having an ($M+H^+$) molecular ion. The molecular ion reported was obtained by electrospray detection method (commonly referred to as an ESI MS) utilizing a PE SCIEX API 150EX MS instrument instrument or an Agilent 1100 series LC/MSD system. Compounds having an isotopic atom, such as bromine and the like, are generally reported according to the detected isotopic pattern, as appreciated by those skilled in the art.

The compounds disclosed and described herein have been named using either (1) the naming convention provided with Chem-Draw Ultra 11.0 software, available in Chem Office, or (2) by the ISIS database software (Advanced Chemistry Design Labs or ACD software).

General Synthetic Scheme 1


1) LiBH4
2) SO3-Pyr
or DIBAL-H
1) PTSA
MeOH
2) HCl
1) PhCONCS
2) H2SO4
1) (Boc)2O
2) LiHMDS
SEMCl
1) LDA, CO2
2) TMSCHN2
NaH
Me3SOI
1a
1b
1c
1d
1e
1f
1g
1h
1i



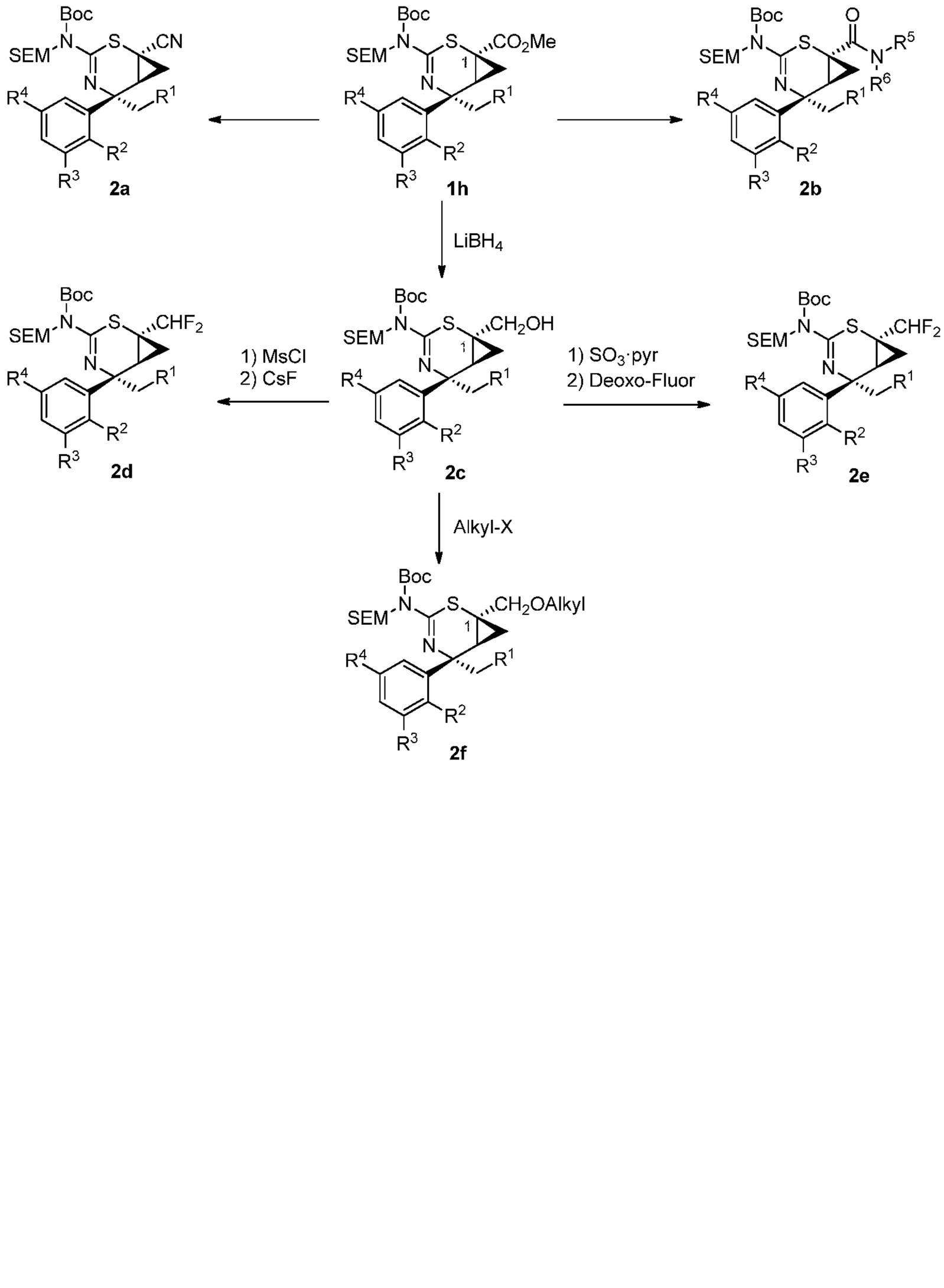
General Synthetic Scheme 1 describes an exemplary method for preparing the key intermediate, aniline **1m**. Beginning with Compound **1a**, ketimine was converted to the corresponding sulfinamide using (2-(*tert*-butoxy)-2-oxoethyl)zinc (II) chloride under suitable conditions. The ester of Compound **1b** was transformed to aldehyde by either a two-step procedure (treatment with $LiBH_4$ followed by SO_3-Pyridine) or reduction using DIBAL-H, to afford intermediate **1c**. The chiral auxiliary in **1c** was removed with PTSA / MeOH and the aldehyde converted to dimethyl acetal using HCl/MeOH to give **1d**. The treatment of **1d** with PhCONCS followed by heating in conc. sulfuric acid afforded thiazine **1e**. The amino group in **1e** was protected with Boc and SEM to give **1f**, which was converted to ester **1g** via a three-step procedure (lithiation, carboxylic acid formation and esterification). Cyclopropanation of **1g** gave a mixture 2 diastereomers, **1h** (major product) and **1i** (minor product), which could be separated via silica gel chromatography in most cases. Ester **1h** was converted to aldehyde **1j** (via treatment with $LiBH_4$ followed by SO_3-Pyridine), which was treated with chlorotris(triphenylphosphine)rhodium(I) (Wilkinson's) to afford intermediate **1k**.

Aniline **1m** was derived from **1k** (R^4 = H) via nitration followed by nitro group reduction. In other cases, aniline **1m** was obtained from **1k** (R^4 = Br) by a three-step

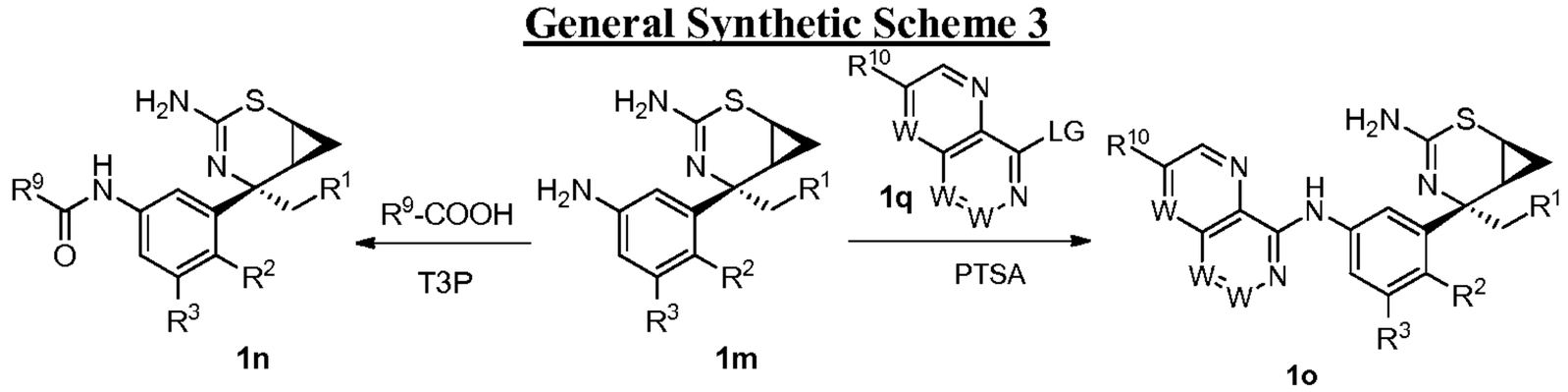
procedure: conversion of bromide to azide, azide reduction with trimethylphosphine followed by removal of protecting groups with TFA.

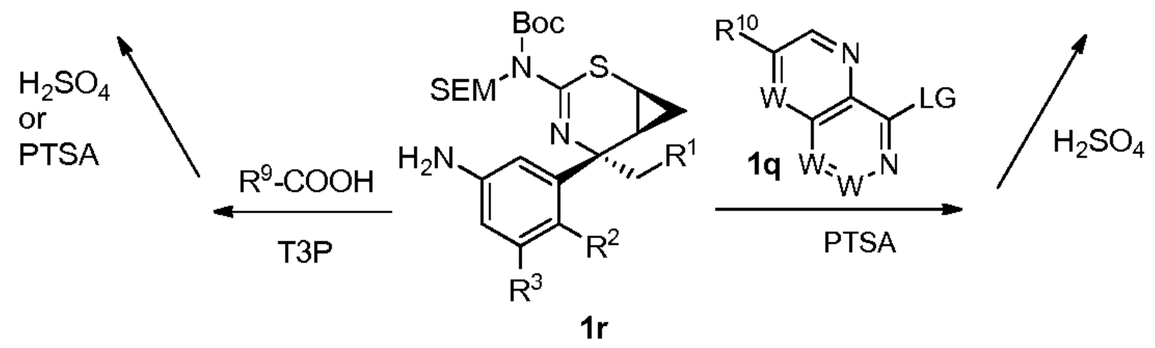
General Synthetic Scheme 2

General Synthetic Scheme 2 describes exemplary methods for preparing *c*Pr-thiazine that bears a substituent at the C-1 position. Saponification of **1h** gave an acid which could be derivatized to cyano (**2a**) or amide (**2b**). Reduction of **1h** gave alcohol **2c** which could be derivatized to CH_2F (**2d**) or CHF_2 (**2e**) or CH_2O-Alkyl (**2f**).



General Synthetic Scheme 3

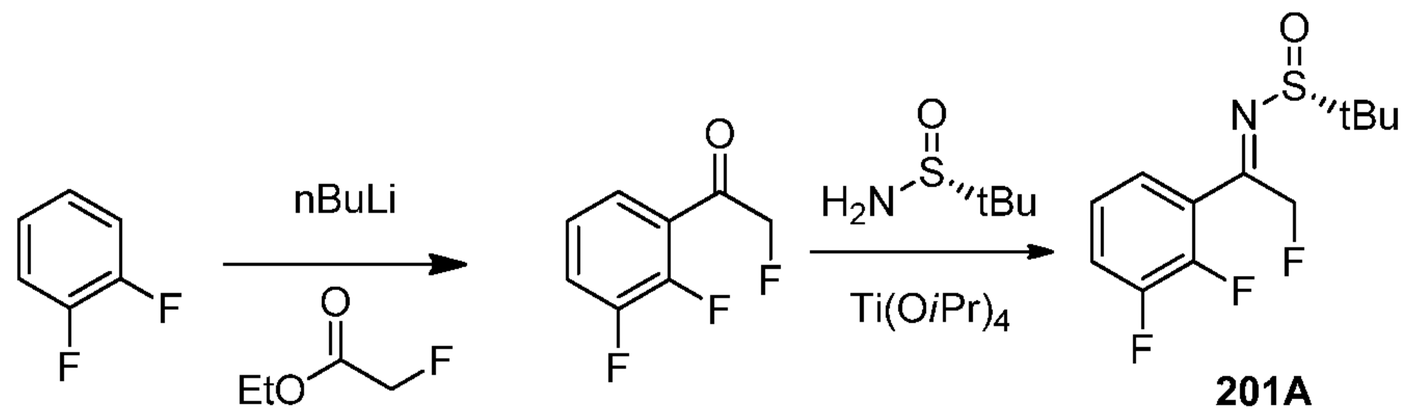




General Synthetic Scheme 3 describes exemplary methods for preparing the biological testing Compounds **1n** and **1o**. Aniline **1m** was coupled with a carboxylic acid in the presence of propylphosphonic anhydride (T3P) to afford amide **1n**. Displacement of the leaving group in **1q** with aniline **1m** in the presence of PTSA gave Compound **1o**. If aniline **1r** was used instead of aniline **1m**, an acid (such as H_2SO_4 or PTSA) could be used to remove the protecting groups (Boc and SEM) on the war head N-atom.

Syntheses of Intermediates

(R,Z)-N-(1-(2,3-Difluorophenyl)-2-fluoroethylidene)-2-methylpropane-2-sulfinamide (201A).

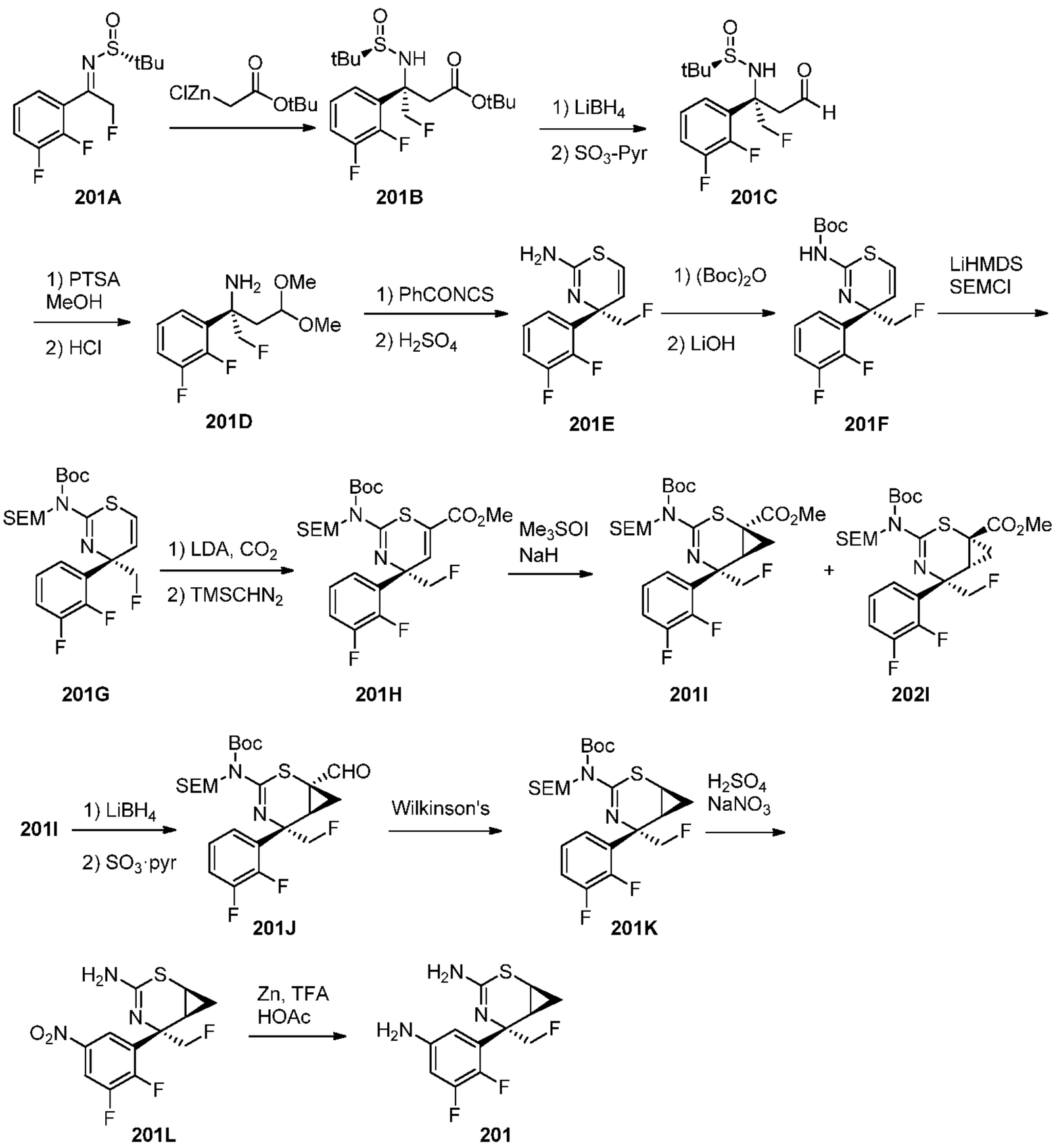


Preparation of 1-(2,3-difluorophenyl)-2-fluoroethanone. [Note: 3 x 10 g reactions were run separately. After quenched with saturated NH_4Cl, the reaction mixture were combined and then purified.] To a solution of 1,2-difluorobenzene (8.81 mL, 89 mmol) in THF (175 mL) at -78 °C was added dropwise *n*-BuLi (1.60 M in hexane, 61.50 mL, 98 mmol). After 2 h, ethyl fluoroacetate (8.64 mL, 89 mmol) was added dropwise. The reaction was stirred for 1 h at -78 °C and quenched with saturated NH_4Cl and then warmed to RT. The three batches were combined and extracted with EtOAc. The organic

extracts were washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated and purified by silica gel column (0-30% EtOAc/hexane) to afford 18.90 g of the desired product.

Preparation of Compound 201A. To a solution of 1-(2,3-difluorophenyl)-2-fluoroethanone (18.9 g, 109.0 mmol) in THF (400 mL) was added (*R*)-(+)-2-methyl-2-propanesulfinamide (26.3 g, 217.0 mmol) followed by tetraisopropoxytitanium (93.0 g, 326.0 mmol). The reaction was heated to reflux for 2 h. LCMS indicated complete consumption of the starting ketone. The mixture was allowed to cool to room temperature and then treated with brine (400 mL). The resulted suspension was stirred for 15 min and filtered through Celite® filter aid. The filter cake was washed with EtOAc. The filtrate was extracted with EtOAc (2 x). The organic extracts were washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated and purified by silica gel column (0-20% EtOAc/hexanes) to afford (R,E)-N-(1-(2,3-difluorophenyl)-2-fluoroethylidene)-2-methylpropane-2-sulfinamide (12.3 g, 44.4 mmol, 40.9% yield) as a yellow oil.

Preparation of (1S,5S,6S)-5-(5-Amino-2,3-difluorophenyl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (201).



Preparation of Compound 201B. 2-*Tert*-butoxy-2-oxoethylzinc chloride (0.5 M in THF, 24.2 mL, 12.1 mmol) was added dropwise over 5 min to a solution of (R,Z)-N-(1-(2,3-difluorophenyl)-2-fluoroethylidene)-2-methylpropane-2-sulfinamide (201A, 1.2 g, 4.33 mmol) in THF (15 mL) at 0°C. The solution was stirred at 0 °C for 5 min then RT for 2 h. The solution was then cooled back to 0 °C and treated dropwise with saturated aqueous ammonium chloride solution (7.5 mL), which resulted in a suspension. The suspension was filtered through Celite® filter aid and the filter cake was washed with EtOAc. The filtrate was concentrated *in vacuo* and the crude product was adsorbed onto a plug of silica gel and purified by silica gel chromatography, eluting with 0-50%

EtOAc/hexanes gradient, to provide (S)-*tert*-butyl 3-(2,3-difluorophenyl)-3-((R)-1,1-dimethylethylsulfinamido)-4-fluorobutanoate (**201B**, 1.55 g, 3.94 mmol, 91% yield) as an oil. LC/MS (ESI^-) *m/z* = 394.2 $(M+H)^+$. ^1H NMR (400 MHz, CHLOROFORM-*d*) δ 7.24 - 7.31 (m, 1 H) 7.08 - 7.21 (m, 2 H) 5.37 (s, 1 H) 5.17 (dd, *J*=47.14, 10.37 Hz, 1 H) 4.86 (dd, *J*=46.56, 10.17 Hz, 1 H) 3.20 (dd, *J*=16.24, 2.15 Hz, 1 H) 3.01 (d, *J*=15.85 Hz, 1 H) 1.37 - 1.41 (m, 9 H) 1.25 (s, 9 H).

Preparation of Compound 201C. Lithium borohydride (2.0 M solution in THF, 90.0 mL, 180.0 mmol) was added slowly over ~6 min to a stirred solution of (S)-*tert*-butyl 3-(2,3-difluorophenyl)-3-((R)-1,1-dimethylethylsulfinamido)-4-fluorobutanoate (201B, 35.4 g, 90.0 mmol) in THF (500 mL) in a 500 mL RBF equipped with a thermometer. Anhydrous MeOH (29.2 mL, 720 mmol) was then added over ~4 min via addition funnel. The internal temperature of the reaction rose to 41 °C and bubbling occurred. The reaction mixture was stirred for another 0.5 h, then cooled to 0 °C and quenched with saturated aqueous ammonium chloride solution. The mixture was extracted two times with EtOAc and the combined organic layers were washed with saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to provide (R)-N-((S)-2-(2,3-difluorophenyl)-1-fluoro-4-hydroxybutan-2-yl)-2-methylpropane-2-sulfinamide (**201C**, 27.8 g, 86 mmol, 96% crude yield) as a white solid that was used without further purification. LC/MS (ESI^-) *m/z* = 324.0 $(M+H)^+$.

N,N-Diisopropylethylamine (16.1 mL, 93 mmol) was added to a stirred solution of (R)-N-((S)-2-(2,3-difluorophenyl)-1-fluoro-4-hydroxybutan-2-yl)-2-methylpropane-2-sulfinamide (10.00 g, 30.9 mmol, crude from reaction above) in DCM (100 mL) and dimethyl sulfoxide (50.0 mL) at -10 °C. Sulfur trioxide pyridine complex (7.38 g, 46.4 mmol) was added in 4 portions over 8 min. The reaction mixture was stirred at -10 °C for another 8 min before being warmed to 0 °C and stirred for 3 h. Additional sulfur trioxide pyridine complex (0.74 g, 4.64 mmol) was added, and the reaction mixture was stirred at 0 °C for another 1 h. Additional sulfur trioxide pyridine complex (1.48 g, 9.28 mmol) was added, and the reaction mixture was stirred at 0 °C for another 1 h. Additional sulfur trioxide pyridine complex (2.96 g, 18.6 mmol) was added, and the reaction mixture was stirred at 0 °C for another 1 h. The reaction mixture was diluted with water and extracted with EtOAc. The organic layer was separated, washed with saturated aqueous ammonium chloride, washed with saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The resulting material

was azeotroped with toluene to remove residual pyridine to give (R)-N-((S)-2-(2,3-difluorophenyl)-1-fluoro-4-oxobutan-2-yl)-2-methylpropane-2-sulfinamide as an oil (201C, 11.9 g, 37.0 mmol). LC/MS (ESI^-) *m/z* = 322.1 $(M+H)^+$.

Preparation of Compound 201D. p-Toluenesulfonic acid monohydrate (0.35 g, 1.85 mmol) was added to a stirred solution of the crude (R)-N-((S)-2-(2,3-difluorophenyl)-1-fluoro-4-oxobutan-2-yl)-2-methylpropane-2-sulfinamide (201C, 11.9 g, 37.0) in MeOH (150 mL). The reaction mixture was heated to reflux for 3 h, then cooled to RT. HCl (4.0 M solution in 1,4-dioxane, 9.25 mL, 37.0 mmol) was added. The reaction mixture was stirred RT for 50 min, was partially concentrated *in vacuo*, and then was quenched with saturated aqueous sodium bicarbonate solution. The mixture was extracted with EtOAc (2 x), the combined organic extracts were washed with saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The resulting oil was purified via silica gel chromatography, eluting with 0-50% EtOAc/heptane gradient, to provide (S)-2-(2,3-difluorophenyl)-1-fluoro-4,4-dimethoxybutan-2-amine (**201D**, 6.25 g, 23.7 mmol, 64.1% yield for 2 steps) as a brown oil. LC/MS (ESI^-) *m/z* = 264.0 $(M+H)^+$. ^1H NMR (400 MHz, CHLOROFORM-*d*) δ 7.36 - 7.44 (m, 1 H) 7.07 - 7.19 (m, 2 H) 4.68 (dd, *J*=13.11, 8.80 Hz, 1 H) 4.56 (ddd, *J*=13.11, 8.80, 4.11 Hz, 1 H) 4.20 (dd, *J*=7.04, 4.30 Hz, 1 H) 3.21 (d, *J*=4.89 Hz, 6 H) 2.25 - 2.38 (m, 1 H) 1.93 - 2.22 (m, 3 H).

Preparation of Compound 201E. To a 1000 mL 3-neck RBF equipped with an internal temperature probe was added (S)-2-(2,3-difluorophenyl)-1-fluoro-4,4-dimethoxybutan-2-amine (**201D**, 24.7 g, 94.0 mmol) and DCM (300 mL). The mixture was cooled to 0 °C and benzoyl isothiocyanate (13.9 mL, 103 mmol) was added. After stirring at 0 °C for 15 min, the mixture was allowed to warm to RT and stirred for 2 h. The reaction was then concentrated *in vacuo* to give a brown oil. Sulfuric acid (150 mL) was added in 2 portions and then the mixture was stirred at 60 °C for 6 h. The solution was cooled in an ice bath and then poured into ice (2 x 2 L Erlenmeyer flasks, each with 700 mL ice in it) and these mixtures were carefully neutralized with aqueous sodium hydroxide solution (10 N) while keeping the mixtures near RT. The resulting solution was extracted with EtOAc, (3 x 250 mL for each 2 L Erlenmeyer flask) and the combined extracts were washed with water, saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and then adsorbed onto silica gel. Purification by silica gel chromatography, eluting with 5-55% EtOAc/heptane gradient provided (S)-4-(2,3-difluorophenyl)-4-(fluoromethyl)-4H-1,3-thiazin-2-amine (**201E**, 19.8 g, 76.0 mmol, 82%

yield) as a tan solid. LC/MS (ESI$^-$) *m/z* = 259.0 $(M+H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.29 - 7.39 (m, 1 H) 7.14 - 7.25 (m, 2 H) 6.60 - 6.73 (m, 3 H) 6.27 (dd, *J*=9.59, 5.48 Hz, 1 H) 4.35 - 4.78 (m, 2 H).

Preparation of Compound 201F. To a 2000 mL, 3-neck, RBF equipped with an internal temperature probe was added (S)-4-(2,3-difluorophenyl)-4-(fluoromethyl)-4H-1,3-thiazin-2-amine (**201E**, 19.7 g, 76 mmol) and THF (300 mL). di-*tert*-Butyl dicarbonate (21.6 g, 99 mmol) was then added in portions, then the mixture was heated at 50 °C for 15 h. Additional di-*tert*-butyl dicarbonate (3.2 g) was added, and the material was stirred for 2 h at 50 °C. The mixture was allowed to cool to RT and then was concentrated *in vacuo*. Purification by silica gel chromatography, eluting with 0-40% EtOAc/hexane gradient, provided (S)-*tert*-butyl (4-(2,3-difluorophenyl)-4-(fluoromethyl)-4H-1,3-thiazin-2-yl)carbamate (**201F**, 26.5 g, 73.8 mmol, 97% yield LC/MS (ESI$^-$) *m/z* = 359.3 $(M+H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.46 (br. s., 1 H) 7.18 - 7.42 (m, 3 H) 6.69 (d, *J*=9.78 Hz, 1 H) 6.18 (dd, *J*=9.00, 4.11 Hz, 1 H) 4.47 - 4.83 (m, 2 H) 1.44 (s, 9 H).

Preparation of Compound 201G. To a 1000 mL RBF equipped with an internal temperature probe was added (S)-*tert*-butyl (4-(2,3-difluorophenyl)-4-(fluoromethyl)-4H-1,3-thiazin-2-yl)carbamate (**201F**, 26.4 g, 73.7 mmol) and THF (220 mL). The mixture was cooled to -10 °C and lithium bis(trimethylsilyl)amide (1.0 M solution in THF, 81.0 mL, 81.0 mmol) was added over 5 min, keeping the internal temperature below -9 °C. After the addition was complete, the solution was stirred at -10 °C for 20 min and then 2-(trimethylsilyl)ethoxymethyl chloride (14.3 mL, 81.0 mmol) in 20 mL THF was added slowly, keeping the temperature below -9 °C. The solution was stirred for 5 min at -10 °C and then the cooling bath was removed and the solution was allowed to warm to RT. After 2 h, the solution was quenched with saturated aqueous ammonium chloride solution and the resulting mixture was extracted with EtOAc. The organic extracts were washed with saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and adsorbed onto silica. Purification by silica gel chromatography, eluting with 0 to 20% EtOAc/heptane gradient, provided (S)-*tert*-butyl (4-(2,3-difluorophenyl)-4-(fluoromethyl)-4H-1,3-thiazin-2-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (**201G**, 32.4 g, 66.3 mmol, 90% yield) as a colorless oil. LC/MS (ESI$^-$) *m/z* = 510.9 $(M+Na)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.41 (dd, *J*=9.88, 2.25 Hz, 1 H) 7.16 - 7.25 (m, 2 H) 6.83 (d, *J*=9.39 Hz, 1 H) 6.18 (dd, *J*=9.39, 4.11 Hz, 1 H) 5.19 (s, 2 H) 4.59 - 4.90 (m, 2 H) 3.57 (t, *J*=8.02 Hz, 2 H) 1.46 (s, 9 H) 0.78 - 0.90 (m, 2 H) -0.04 (s, 9 H).

Preparation of Compound 201H. Lithium diisopropylamide (2.0 M solution in THF/heptane/ethylbenzene) (2.58 mL, 5.16 mmol) was added dropwise to a -78 °C solution of (S)-*tert*-butyl (4-(2,3-difluorophenyl)-4-(fluoromethyl)-4H-1,3-thiazin-2-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (**201G**, 1.94 g, 3.97 mmol) in THF (18 mL). The mixture was stirred for 45 min before CO_2 gas was bubbled through the reaction at -78 °C. After 3 min, the cold bath was removed, the addition of CO_2 was stopped, and the mixture was warmed to RT. The reaction was then quenched with saturated aqueous ammonium chloride solution, and the product was extracted into EtOAc (3 x). The combined extracts were washed with aqueous HCl solution (1 M, 2 x), saturated aqueous sodium chloride solution (1 x), dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to give a yellow oil.

The oil was dissolved in (9:1) THF/MeOH (20 mL) and the mixture was cooled to 0 °C. (Trimethylsilyl)diazomethane (2.0 M in hexanes, 3.97 mL, 7.94 mmol) was added dropwise. This mixture was stirred for 30 min, at which time HOAc (0.92 mL, 32.9 mmol) was added dropwise. The mixture was stirred at that temperature until the solution became colorless. EtOAc and water were added, the layers were separated, and the aqueous layer was extracted with EtOAc (1 x). The combined extracts were washed with saturated aqueous sodium bicarbonate solution, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to give a yellow oil. The oil was purified by silica gel chromatography, eluting with 0 to 50% EtOAc/heptane gradient, to give (S)-methyl 2-((*tert*-butoxycarbonyl)((2-(trimethylsilyl)ethoxy)methyl)amino)-4-(2,3-difluorophenyl)-4-(fluoromethyl)-4H-1,3-thiazine-6-carboxylate (**201H**, 1.63 g, 3.0 mmol, 75% yield) as a colorless oil. LC/MS (ESI^-) *m/z* = 547.2 $(M+H)^+$. ^1H NMR (400 MHz, CHLOROFORM-*d*) δ 7.17 - 7.17 (m, 1 H) 6.98 - 7.25 (m, 3 H) 5.29 - 5.36 (m, 2 H) 4.90 (dd, *J*=46.95, 8.61 Hz, 1 H) 4.68 (dd, *J*=47.14, 9.00 Hz, 1 H) 3.84 (s, 3 H) 3.65 (t, *J*=8.22 Hz, 2 H) 1.54 (s, 9 H) 0.89 - 0.96 (m, 2 H) -0.01 (s, 9 H).

Preparation of Compound 201I and Compound 202I

Preparation of Corey-Chaykovsky reagent: Potassium *tert*-butoxide (3.42 g, 30.5 mmol) was added to a stirred suspension of trimethylsulfoxonium iodide (7.32 g, 33.3 mmol) in DMSO (27 mL) under an argon atmosphere at RT. The mixture was stirred for 1 h before being used as described below.

The ylide solution (13.5 mL, 15.3 mmol) was added to a stirred solution of (S)-methyl 2-((*tert*-butoxycarbonyl)((2-(trimethylsilyl)ethoxy)methyl)amino)-4-(2,3-difluorophenyl)-4-(fluoromethyl)-4H-1,3-thiazine-6-carboxylate (**201H**, 7.58 g, 13.87

mmol) in dimethyl sulfoxide (27 mL) under an argon atmosphere. The reaction mixture was stirred at RT for 1.5 h. An additional 2.0 mL of the ylide solution was added, and the reaction mixture was stirred for another 2.5 h. The reaction mixture was then quenched with saturated aqueous ammonium chloride solution and then extracted with EtOAc. The organic extracts were washed with water, saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to give an oil. The oil was purified via silica gel chromatography, eluting with 0 to 20% EtOAc/heptane gradient to provide (1S,5S,6S)-methyl 3-((*tert*-butoxycarbonyl)((2-(trimethylsilyl) ethoxy)methyl)amino)-5-(2,3-difluorophenyl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylate (201I, 5.60 g, 10.0 mmol, 72% yield) and (1R,5S,6R)-methyl 3-((*tert*-butoxycarbonyl)((2-(trimethylsilyl)ethoxy)methyl)amino)-5-(2,3-difluorophenyl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylate (202I, 0.95 g, 1.70 mmol, 12% yield).

201I: LC/MS (ESI$^-$) *m/z* = 561.2 $(M+H)^+$. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ 7.46 (t, *J*=7.14 Hz, 1 H) 7.08 - 7.20 (m, 2 H) 5.31 (d, *J*=10.37 Hz, 1 H) 5.08 (d, *J*=10.56 Hz, 1 H) 4.72 - 5.02 (m, 2 H) 3.81 (s, 3 H) 3.65 (t, *J*=8.22 Hz, 2 H) 2.68 (t, *J*=8.80 Hz, 1 H) 1.62 (dd, *J*=9.98, 5.28 Hz, 1 H) 1.51 - 1.56 (m, 9 H) 1.14 (dd, *J*=7.24, 5.48 Hz, 1 H) 0.87 - 0.99 (m, 2 H) 0.01 (s, 9 H).

202I: LC/MS (ESI$^-$) *m/z* = 561.2 $(M+H)^+$. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ 7.02 - 7.18 (m, 3 H) 5.24 (d, *J*=10.37 Hz, 1 H) 5.07 (d, *J*=10.37 Hz, 1 H) 4.92 (dd, *J*=46.95, 8.61Hz, 1 H) 4.71 (dd, *J*=46.95, 8.80 Hz, 1 H) 3.80 (s, 3 H) 3.58 (dd, *J*=9.00, 7.43 Hz, 2 H) 2.85 (dd, *J*=9.88, 7.34 Hz, 1 H) 1.73 (dd, *J*=9.78, 5.48 Hz, 1 H) 1.59 - 1.64 (m, 1 H) 1.51 (s, 9 H) 0.89 (dd, *J*=9.10, 7.34 Hz, 2 H) -0.01 - 0.02 (m, 9 H).

Preparation of Compound 201J. Lithium borohydride (2.0 M solution in THF, 9.9 mL, 19.8 mmol) was added slowly over ~3 min to a stirred solution of (1S,5S,6S)-methyl 3-((*tert*-butoxycarbonyl)((2-(trimethylsilyl)ethoxy)methyl)amino)-5-(2,3-difluorophenyl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylate (**201I**, 5.54 g, 9.9 mmol) in THF (60 mL) at RT under a nitrogen atmosphere. Anhydrous MeOH (3.20 mL, 79 mmol) was then added over ~1 min. The reaction mixture was stirred for 30 min, cooled to 0 °C, and then saturated aqueous sodium chloride. The mixture was extracted with EtOAc (2 x), then the combined extracts were washed with aqueous HCl solution (1 N), washed with saturated aqueous sodium bicarbonate solution, saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate,

filtered, and concentrated *in vacuo* to provide *tert*-butyl ((1S,5S,6S)-5-(2,3-difluorophenyl)-5-(fluoromethyl)-1-(hydroxymethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (5.93 g) as a colorless oil.

TEA (5.50 mL, 39.5 mmol) was added slowly via syringe to a stirred solution of *tert*-butyl ((1S,5S,6S)-5-(2,3-difluorophenyl)-5-(fluoromethyl)-1-(hydroxymethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (5.93 g, obtained from above reaction) in DCM (20 mL) and dimethyl sulfoxide (20 mL). Sulfur trioxide pyridine complex (3.15 g, 19.8 mmol) was added, and the reaction mixture was stirred at RT for 1 h. The reaction mixture was diluted with water and extracted with EtOAc. The organic extracts were combined and then washed with saturated aqueous ammonium chloride solution, water, saturated sodium chloride solution, then dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to give an oil. The resulting crude product was purified via silica gel chromatography, eluting with 0 to 30% EtOAc/heptane gradient to provide *tert*-butyl ((1S,5S,6S)-5-(2,3-difluorophenyl)-5-(fluoromethyl)-1-formyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (**201J**, 4.88 g, 9.2 mmol, 93% yield for 2 steps) LC/MS (ESI$^+$) *m/z* = 531.2 $(M+H)^+$. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ 9.16 (s, 1 H) 7.40 - 7.45 (m, 1 H) 7.08 - 7.21 (m, 2 H) 5.34 (d, *J*=10.37 Hz, 1 H) 5.14 (d, *J*=10.56 Hz, 1 H) 4.92 (dd, *J*=46.75, 8.61 Hz, 1 H) 4.72 (dd, *J*=46.75, 8.61 Hz, 1 H) 3.66 (t, *J*=8.31 Hz, 2 H) 2.57 (t, *J*=8.71 Hz, 1 H) 1.81 (dd, *J*=9.98, 5.67 Hz, 1 H) 1.52 - 1.57 (m, 9 H) 1.27 (dd, *J*=7.43, 5.67 Hz, 1 H) 0.83 - 1.05 (m, 2 H) -0.01 - 0.03 (m, 9 H).

Preparation of Compound 201K. Chlorotris(triphenylphosphine)rhodium(I) (4.26 g, 4.61 mmol) was added to a stirred solution of *tert*-butyl ((1S,5S,6S)-5-(2,3-difluorophenyl)-5-(fluoromethyl)-1-formyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (201J, 1.63 g, 3.07 mmol) in 1,2-dichloroethane (20 mL). The reaction mixture was heated to 80 °C and stirred for 6 h. The reaction mixture was concentrated *in vacuo* and the resulting reddish-brown sludge was triturated in heptane and then filtered through Celite® filter aid. The filter cake was washed multiple times with 9:1 EtOAc/heptane, then with DCM. The filtrate was concentrated *in vacuo*, slurried in DCM, and filtered. The yellow solid that was collected was discarded, and the filtrate was again concentrated *in vacuo* to give a brown oil. Heptane was added, the resulting suspension was filtered, and the collected solid was discarded. The filtrate was concentrated to give crude product, which was purified via silica gel chromatography, eluting with 0 to 20% EtOAc/heptane gradient to give *tert*-butyl

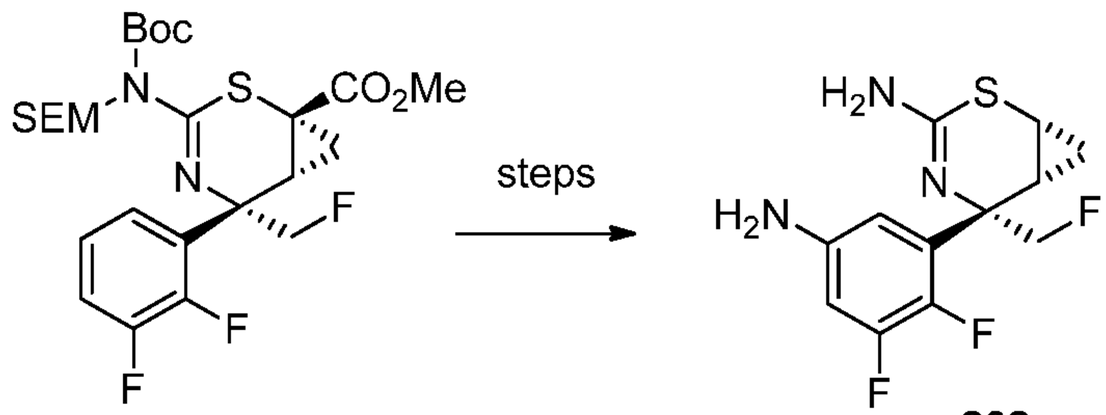
((1S,5S,6S)-5-(2,3-difluorophenyl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (201K, 1.54 g, 1.99 mmol, 65% yield) as a colorless oil. LC/MS (ESI^-) *m/z* = 503.1 $(M+H)^+$. ^1H NMR (400 MHz, CHLOROFORM-*d*) δ 7.43 (t, *J*=7.24 Hz, 1 H) 7.06 - 7.17 (m, 2 H) 5.30 (d, *J*=10.56 Hz, 1 H) 5.07 (d, *J*=10.56 Hz, 1 H) 4.73 - 5.02 (m, 2 H) 3.62 - 3.69 (m, 2 H) 2.24 - 2.31 (m, 1 H) 2.00 - 2.07 (m, 1 H) 1.53 (s, 9 H) 1.05 (ddd, *J*=9.15, 7.48, 5.87 Hz, 1 H) 0.94 (dd, *J*=9.10, 7.53 Hz, 2 H) 0.65 (q, *J*=5.87 Hz, 1 H) -0.02 - 0.03 (m, 9 H).

Preparation of Compound 201L. At RT, concentrated sulfuric acid (5 mL, 94 mmol) was added to *tert*-butyl ((1S,5S,6S)-5-(2,3-difluorophenyl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (201K, 1.00 g, 1.99 mmol). The mixture was stirred at RT for 15 min, then cooled to 0 °C. Sodium nitrate (0.24 g, 2.79 mmol) was added. The reaction mixture was warmed to RT and stirred for 1 h. The reaction mixture was poured into ice and diluted with DCM. K_3PO_4 (20 g) was added in portions over 15 min, and the mixture was then brought to pH 7-8 with aqueous NaOH solution (10 N). The resulting biphasic mixture was separated, and the aqueous layer was extracted DCM (2 x). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to give an oil. This oil was purified via silica gel chromatography, eluting with 0 to 50% EtOAc/heptane gradient to provide (1S,5S,6S)-5-(2,3-difluoro-5-nitrophenyl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (**201L**, 0.54 g, 1.67 mmol, 85% yield) as a light yellow solid. LC/MS (ESI^-) *m/z* = 318.0 $(M+H)^+$. ^1H NMR (400 MHz, CHLOROFORM-*d*) δ 8.51 - 8.56 (m, 1 H) 8.05 (ddd, *J*=9.05, 6.41, 2.93 Hz, 1 H) 4.73 (d, *J*=4.11 Hz, 4 H) 2.25 - 2.36 (m, 1 H) 1.92 - 2.06 (m, 1 H) 1.07 - 1.18 (m, 1 H) 0.66 (q, *J*=5.74 Hz, 1 H).

Preparation of Compound 201. Zinc (nanopowder, 1.73 g, 26.5 mmol) was added to a stirred mixture of (1S,5S,6S)-5-(2,3-difluoro-5-nitrophenyl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (**201L**, 1.68 g, 5.29 mmol) in HOAc (12 mL) and trifluroacetic acid (6 mL). The reaction mixture was stirred at RT for 45 min, then filtered through Celite® filter aid. The filtrate was diluted with EtOAc and treated with saturate sodium bicarbonate solution, and then the mixture was taken to pH ~7 w/ aqueous sodium NaOH (10 N). The organic layer was separated, and the aqueous layer was extracted once more with EtOAc. The combined organic extracts were washed with saturated sodium chloride solution, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The resulting crude product was purified via silica gel

chromatography, eluting with 0 to 10% MeOH/DCM gradient. The collected product was then dissolved in EtOAc and then washed two times with saturated sodium carbonate solution. The resulting organic solution was then washed with saturated sodium chloride solution, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to provide (1S,5S,6S)-5-(5-amino-2,3-difluorophenyl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (201, 1.29 g, 4.49 mmol, 85% yield) as a yellow solid. LC/MS (ESI$^-$) m/z = 288.0 $(M+H)^+$. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 6.66 (dt, *J*=4.84, 2.57 Hz, 1 H) 6.38 - 6.45 (m, 1 H) 4.78 (s, 4 H) 3.61 (br. s., 2 H) 2.26 - 2.34 (m, 1H) 1.78 - 1.89 (m, 1 H) 1.05 - 1.14 (m, 1 H) 0.53 (d, *J*=5.87 Hz, 1 H).

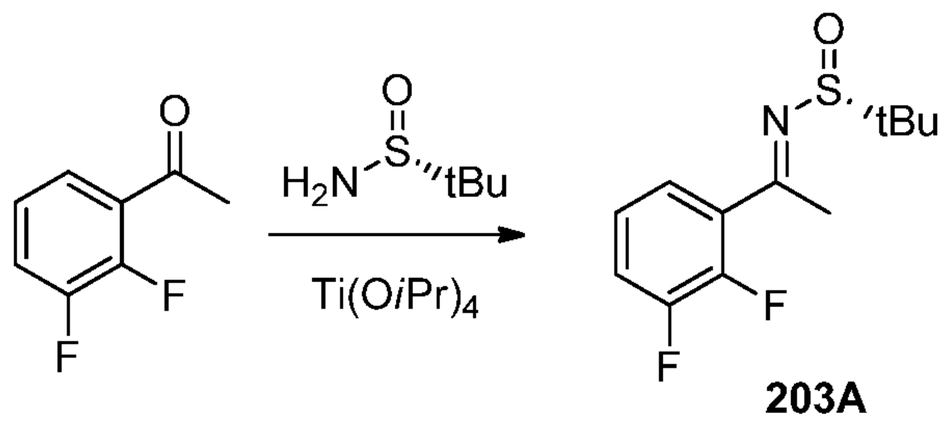
(1R,5S,6R)-5-(5-Amino-2,3-difluorophenyl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (202).



202I **202**

This compound was prepared from **202I** using the chemical procedures similar to that described for intermediate **201**. LC/MS (ESI$^-$) m/z = 288.0 $(M+H)^+$. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 6.38 - 6.49 (m, 2 H) 4.68 - 4.76 (m, 1 H) 4.50 - 4.66 (m, 1 H) 3.65 (br. s., 2 H) 2.05 - 2.18 (m, 1 H) 1.94 - 2.05 (m, 1 H) 1.02 - 1.11 (m, 2 H).

(R,E)-N-(1-(2,3-Difluorophenyl)ethylidene)-2-methylpropane-2-sulfinamide (203A).

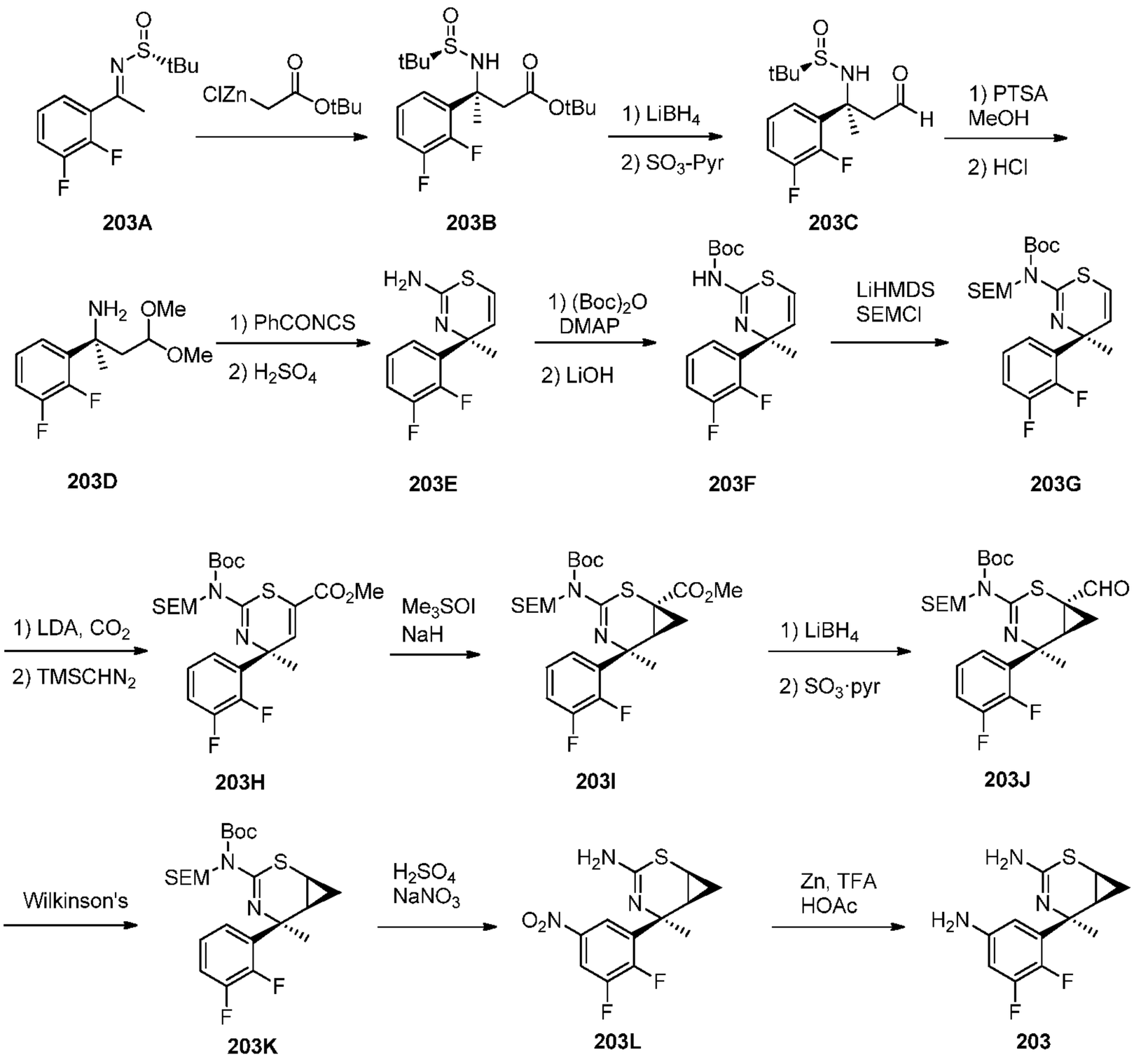


203A

To a solution of 2,3-difluoroacetophenone (25.0 g, 160 mmol) in THF (500 mL) was added (R)-(+)-2-methyl-2-propanesulfinamide (38.8 g, 320 mmol) followed by tetraisopropoxytitanium (142 mL, 480 mmol). The reaction was heated to reflux for 3 d. The mixture was allowed to cool to RT and then treated with brine (550 mL). The

resulted suspension was stirred for 15 min and filtered through a pad of Celite® filter aid. The filter cake was washed with EtOAc. The filtrate was extracted with EtOAc (2 x). The organic extracts were washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated and purified by silica gel column (10-35% EtOAc/hexanes) to afford (R,E)-N-(1-(2,3-difluorophenyl)ethylidene)-2-methylpropane-2-sulfinamide (**203A**, 35.6 g, 137 mmol, 86% yield) as yellow oil. MS *m/z*= 260.1 $[M+H]^+$.

(1S,5S,6S)-5-(5-Amino-2,3-difluorophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (203).



203A **203B** **203C** **203D** **203E** **203F** **203G** **203H** **203I** **203J** **203K** **203L** **203**

Preparation of Compound 203B. To a 3000 mL 3-neck RBF equipped with an addition funnel and internal temperature probe was added (R,E)-N-(1-(2,3-difluorophenyl)ethylidene)-2-methylpropane-2-sulfinamide (**203A**, 30 g, 116 mmol) and THF (450 mL). The mixture was cooled to 0 °C and 2-*tert*-butoxy-2-oxoethylzinc chloride (0.5 M in Et_2O, 463 mL, 231 mmol) was added dropwise over 2 h keeping the

internal temperature under 2 °C. The reaction mixture stayed homogeneous. After the addition was completed, the ice bath was allowed to melt (about 2-3 h) and warm to RT overnight. The reaction mixture was cooled with an ice bath and carefully quenched with the slow addition sat. NH_4Cl (200 mL). It was extracted with EtOAc (3 x 250 mL). The combined extracts were washed with brine (50 mL), dried (Na_2SO_4) and concentrated onto silica. Purification by silica gel chromatography (5-35% EtOAc/hexanes) afforded (S)-*tert*-butyl 3-(2,3-difluorophenyl)-3-((R)-1,1-dimethylethylsulfinamido)butanoate (**203B**, 30.2 g, 80 mmol, 69.5% yield) as a colorless oil. LC/MS (ESI^-) *m/z* = 376.1 $(M+H)^+$.

Preparation of Compound 203C. To a solution of (S)-*tert*-butyl 3-(2,3-difluorophenyl)-3-((R)-1,1-dimethylethylsulfinamido)butanoate (**203B**, 11.6 g, 31.0 mmol) in 150 mL of THF in a 500 mL 3-neck RBF equipped with an internal temperature probe at RT was added lithium borohydride (2.0 M solution in THF, 31.0 mL, 62.0 mmol) over 5 min. Anhydrous MeOH (10.0 mL, 248 mmol) was then added to the mixture slowly over 5 min. The internal temperature of the reaction rose to 37 °C, and gentle bubbling ensued. The mixture was stirred for 60 min. The reaction was chilled to 0 ^oC and slowly quenched with 80 mL of aq. NH_4Cl. The mixture was then extracted with 3 x 150 mL of EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give (R)-N-((S)-2-(2,3-difluorophenyl)-4-hydroxybutan-2-yl)-2-methylpropane-2-sulfinamide (9.7 g) as an off-white amorphous solid which was used without further purification. LC/MS (ESI^-) *m/z* = 306.2 $(M+H)^+$. N,N-diisopropylethylamine (21.6 mL, 124 mmol) was added dropwise via a syringe to a solution of (R)-N-((S)-2-(2,3-difluorophenyl)-4-hydroxybutan-2-yl)-2-methylpropane-2-sulfinamide (9.7 g crude from above reaction) in DCM (60 mL) and DMSO (30 mL) in 1000 mL RBF at -10 °C. Pyridine sulfur trioxide (7.9 g, 49.6 mmol) was added in three portions over 1 min. The mixture was stirred for 5 min, and then the cooling bath was replaced with an ice bath. The mixture was stirred for 5 h at ~ 0 °C. It was treated with water (50 mL) and extracted with 3 x 200 mL of DCM. The combined organic extracts were washed with saturated aqueous NH_4Cl (50 mL) followed by brine (25 mL), and dried over sodium sulfate. The solution was filtered and concentrated *in vacuo*to give the crude material. It was adsorbed onto a plug of silica gel and chromatographed through a Redi-Sep pre-packed silica gel column (220 g), eluting with a gradient of 1-5% MeOH in DCM, to provide (R)-N-((S)-2-(2,3-difluorophenyl)-4-oxobutan-2-yl)-2-methylpropane-

2-sulfinamide (**203C**, 9.6 g, 31.6 mmol, 102% yield) as an amorphous solid. LC/MS (ESI$^-$) *m/z* = 304.1 $(M+H)^+$.

Preparation of Compound 203D. To a 1000 mL RBF equipped with a reflux condenser was added (R)-N-((S)-2-(2,3-difluorophenyl)-4-oxobutan-2-yl)-2-methylpropane-2-sulfinamide (**203C**, 9.40 g, 31 mmol), MeOH (80 mL) and p-toluenesulfonic acid monohydrate (0.295 g, 1.550 mmol). The reaction mixture was stirred at 65 °C for 18 h. It was cooled to RT and treated with HCl (4.0 M solution in 1,4-dioxane, 8.14 mL, 32.6 mmol) dropwise. After the reaction mixture was stirred at RT for 3 h, it was concentrated *in-vacuo*, then diluted with 300 mL of chloroform and treated with 50 mL of sat. aq. $NaHCO_3$. The layers were separated and the aqueous layer was extracted with chloroform (2 x 100 mL). The combined organic extracts were washed with 10 mL of brine, dried over magnesium sulfate, filtered and concentrated *in-vacuo* to give light yellow oil. It was purified by silica gel chromatography (2 x 110 g Thomson column using a gradient of 1-8% MeOH in CH_2Cl_2) to provide (S)-2-(2,3-difluorophenyl)-4,4-dimethoxybutan-2-amine (**203D**, 6.05 g, 24.67 mmol, 80% yield) as a yellow oil. LC/MS (ESI$^-$) *m/z* = 246.2 $(M+H)^+$. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.30 (m, 1H), 7.07 (m, 2H), 4.10 (m, 1H), 3.21 (s, 3H), 3.18 (s, 3H), 2.25-2.44 (m, 1H), 2.08 (m, 1H), 1.93 (br., 2H), 1.54 (s, 3H). ^{19}F NMR (376 MHz, CHLOROFORM-d) δ -137.63 (d, *J*=20.16 Hz, 1F), -139.03 (d, *J*=19.51 Hz, 1F).

Preparation of Compound 203E. To a stirring solution of (S)-2-(2,3-difluorophenyl)-4,4-dimethoxybutan-2-amine (**203D**, 6.08 g, 24.79 mmol) in CH_2Cl_2 (50 mL) at 0 ºC under nitrogen was added a solution of benzoyl isothiocyanate (4.45 g, 27.3 mmol) in CH_2Cl_2 (12 mL) dropwise. It was stirred at 0 ºC for 20 min, and then treated with MeOH (1 mL). The solvents were removed under reduced pressure to afford a tan syrup. To the tan syrup at 0 ºC was added neat sulfuric acid (29.1 ml, 545 mmol). The warmed solution was stirred for 20 min then heated to 50 ºC for 22 h. The reaction was cooled to RT then poured onto 200 g of ice. To the slurry was added CH_2Cl_2 (200 mL), the biphasic solutions were chilled to 0 ºC with external wet ice bath, then basified to pH = 14 with very slow addition of 10 M NaOH. The organic layer was separated and the aqueous was extracted with 9:1 $CHCl_3$/IPA (2 x 50 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (160 g) using a gradient of 20-75% EtOAc in hexanes to afford (S)-4-(2,3-difluorophenyl)-4-methyl-4H-1,3-thiazin-2-amine (**203E**,

3.24 g, 13.48 mmol, 54% yield) as a brown amorphous solid. LC/MS (ESI^-) *m/z* = 241.1 $(M+H)^+$. ^1H NMR (400 MHz, CHLOROFORM-d) δ 7.19 (t, *J*=7.24 Hz, 1H), 6.98-7.09 (m, 2H), 6.26-6.32 (m, 2H), 5.00-4.00 (br., 2H), 1.74 (s, 3H). ^{19}F NMR (377 MHz, CHLOROFORM-d) δ -138.00 (d, *J*=20.27 Hz, 1F), -138.75 (d, *J*=20.27 Hz, 1F).

Preparation of Compound 203F. A solution of (S)-4-(2,3-difluorophenyl)-4-methyl-4H-1,3-thiazin-2-amine (**203E**, 3.06 g, 12.74 mmol) and 4-(dimethylamino) pyridine (0.039 g, 0.318 mmol) in THF (50 mL) at RT was treated with di-*tert*-butyl dicarbonate (6.11 g, 28.0 mmol) in THF (10 mL) slowly via a syringe. The solution was heated to 50 ºC in an oil bath for 1 h. The LCMS suggested full conversion to the di-Boc. The reaction mixture was cooled to 12 ºC and treated with water (10 mL), lithium hydroxide monohydrate (1.603 g, 38.2 mmol), and MeOH (10 mL). The reaction was heated to 50 ºC for 30 min. The LCMS suggested 100% conversion to the mono-Boc. The reaction was then partitioned between EtOAc (150 mL) and water (20 mL). Some white solid precipitated from the mixture. It was filtered through a fritted funnel. The solid was discarded (LCMS indicated no desired product). The filtrate was transferred to a separatory funnel. The aqueous was discarded. The organic layer was washed with 5 mL of brine, dried over sodium sulfate and concentrated. The residue was purified on a silica gel column (15-45% EtOAc in hexanes) to give (S)-*tert*-butyl (4-(2,3-difluorophenyl)-4-methyl-4H-1,3-thiazin-2-yl)carbamate (**203F**, 4.28 g, 12.57 mmol, 99% yield) as a viscous brown oil. LC/MS (ESI^-) *m/z* = 341.1 $(M+H)^+$. ^1H NMR (400 MHz, CHLOROFORM-d) δ 10.5 (br., 1H), 7.01-7.16 (m, 3H), 6.14-6.29 (m, 2H), 1.79 (br., 3H), 1.52 (s, 9H).

Preparation of Compound 203G. To a stirring solution of (S)-*tert*-butyl (4-(2,3-difluorophenyl)-4-methyl-4H-1,3-thiazin-2-yl)carbamate (**203F**, 4.20 g, 12.34 mmol) in THF (50 mL) at -12 ºC (wet ice/ acetone) under nitrogen was added lithium bis(trimethylsilyl)amide (1.0 M solution in THF, 16.04 mL, 16.04 mmol) at a rate not to exceed an internal temp of -5 ºC. After 15 min at -7 ºC, to the reaction mixture was added a solution of 2-(trimethylsilyl)ethoxymethyl chloride (2.84 mL, 16.04 mmol) in THF (10 mL) at a rate that did not exceed an internal temp of -2 ºC. After 15 min the cooling bath was removed and the reaction mixture became a clear solution. The reaction was run for 18 h at RT. The reaction was quenched with sat NH_4Cl (20 mL) and extracted with EtOAc (2 x 100 mL). The organic solution was washed with brine (10 mL), dried over $MgSO_4$, concentrated under reduced pressure. The residue was purified

by silica gel chromatography (5% EtOAc/Hextanes) to afford (S)-*tert*-butyl (4-(2,3-difluorophenyl)-4-methyl-4H-1,3-thiazin-2-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (**203G**, 5.3 g, 11.26 mmol, 91% yield) as viscous yellow oil. LC/MS (ESI^-) *m/z* = 471.1 $(M+H)^+$. ^1H NMR (400 MHz, CHLOROFORM-d) δ 7.23 (m, 1H), 7.08 (m, 2H), 6.33 (d, *J*=9.19 Hz, 1H), 6.08 (dd, *J*=3.42, 9.29 Hz, 1H), 5.32 (d, *J*=10.37 Hz, 1H), 5.23 (d, *J*=10.56 Hz, 1H), 3.67 (m, 2H), 1.73 (s, 3H), 1.54 (s, 9H), 0.94 (m, 2H), 0.00 (s, 9H). ^{19}F NMR (377 MHz, CHLOROFORM-d) δ -138.14 (d, *J*=20.27 Hz, 1F), -138.73 (d, *J*=20.27 Hz, 1F).

Preparation of Compound 203H. To a stirring solution of (S)-*tert*-butyl (4-(2,3-difluorophenyl)-4-methyl-4H-1,3-thiazin-2-yl)((2-(trimethylsilyl)ethoxy)methyl) carbamate (**203G**, 10.6 g, 22.5 mmol) in THF (100 mL) at -70 ºC was added lithium diisopropylamide (2.0 M in heptane/THF/ethylbenzene, 13.51 mL, 27.0 mmol) at a rate that did not exceed -68 ºC. The dark solution was stirred for 20 min at -72 ºC. The reaction was then exposed to a gentle stream of carbon dioxide from a lecture bottle in the head space of the stirring solution (not submerged). The internal temp slowly climbed to -60 ºC. After 7 min the carbon dioxide stream was removed and internal temp was -65 ºC. The reaction was then slowly quenched with sat. NH_4Cl (10 mL). Once the suspension reached 5 ºC, 1 M KH_2PO_4 (100 mL) was added. After the bubbling subsided, the reaction was partitioned between EtOAc (400 mL) and 1 M KH_2PO_4 (100 mL). The organic layer was separated, washed with brine (2 x 100 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the acid as colorless oil. The oil was dissolved in THF (100 mL) and MeOH (10 mL), chilled to 16 ºC under nitrogen and (trimethylsilyl)diazomethane (2 M in hexanes, 28.2 mL, 56.3 mmol) added at a rate not to exceed 22 ºC. The reaction was stirred for 30 min then quenched with glacial HOAc (10 mL) with reaction at 6 ºC. The quench is exothermic with temp surging to 19 ºC and gas evolution evident. The reaction was then partitioned between 1:1 EtOAc/heptane (500 mL) and 1 M KH_2PO_4 (100 mL). The organic layer was further washed with both 5% $NaHCO_3$ (100 mL) and brine (50 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (330 g) eluting with a gradient of 0-10% EtOAc/heptane to afford (S)-methyl 2-((*tert*-butoxycarbonyl)((2-(trimethylsilyl)ethoxy)methyl)amino)-4-(2,3-difluorophenyl)-4-methyl-4H-1,3-thiazine-6-carboxylate (**203H**, 10.9 g, 20.62 mmol, 92% yield) as a colorless oil. LC/MS (ESI^-)

m/z = 529.1 $(M+H)^+$. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.27 - 7.33 (m, 1 H), 7.01 - 7.13 (m, 3 H), 5.30 (dd, *J*=10.37, 6.06 Hz, 1 H), 5.18 - 5.23 (m, 1 H), 3.82 (s, 3 H), 3.62 - 3.68 (m, 2 H), 1.76 (s, 3 H), 1.52 - 1.55 (m, 9 H), 0.86 - 0.95 (m, 2 H), -0.01 (m, 9 H).

Preparation of Compound 203I. Corey-Chaykovsky Reagent [0.2 M in DMSO] was prepared in this fashion: To a stirring solution of trimethylsulfoxonium iodide (8.39 g, 38.1 mmol) in dimethyl sulfoxide (200 mL) at 20 ºC was added potassium *tert*-butoxide (4.28 g, 38.1 mmol) in one portion. The internal temperature increased to 22 ºC. The solution was stirred for 1 h.

To a stirring solution of (S)-methyl 2-((*tert*-butoxycarbonyl)((2-(trimethylsilyl)ethoxy)methyl)amino)-4-(2,3-difluorophenyl)-4-methyl-4H-1,3-thiazine-6-carboxylate (**203H**, 15.5 g, 29.3 mmol) in THF (200 mL) at 20 ºC under nitrogen was added freshly prepared Corey-Chaykovsky Reagent [0.2 M in DMSO] dropwise via addition funnel over a 10 min period. The reaction remained in the 21-23 ºC temperature range. After stirring at RT for 30 min, the reaction mixture was quenched with sat. NH_4Cl (50 mL) dropwise and diluted with water (400 mL). The reaction mixture was extracted with 3:1 heptane/EtOAc (600 mL). The aqueous was further extracted with 1:1 heptane/EtOAc (10 mL). The organics were washed with water (200 mL) then brine (50 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (330 g) loading material on with heptane and eluting products with 0-10% EtOAc/heptane gradient to afford (1S,5S,6S)-methyl 3-((*tert*-butoxycarbonyl)((2-(trimethylsilyl)ethoxy)methyl)amino)-5-(2,3-difluorophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylate (**203I**, 12.7 g, 23.40 mmol, 80% yield) as colorless oil. LC/MS (ESI^-) *m/z* = 543.1 $(M+H)^+$. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.37 (t, *J*=6.75 Hz, 1 H) 7.01 - 7.12 (m, 2 H) 5.26 (d, *J*=10.56 Hz, 1 H) 5.01 (d, *J*=10.56 Hz, 1 H) 3.78 (s, 3 H) 3.59 - 3.69 (m, 2 H) 2.61 (dd, *J*=8.71, 7.92 Hz, 1 H) 1.76 (s, 3 H) 1.50 - 1.55 (m, 9 H) 1.46 - 1.50 (m, 1 H) 1.21 (dd, *J*=7.43, 5.28 Hz, 1 H) 0.90 - 0.96 (m, 2 H) -0.03 - 0.00 (m, 9 H).

Preparation of Compound 203J. At RT, a solution of (1S,5S,6S)-methyl 3-((*tert*-butoxycarbonyl)((2-(trimethylsilyl)ethoxy)methyl)amino)-5-(2,3-difluorophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylate (**203I**, 4.1 g, 7.55 mmol) in 60 mL of THF was treated with lithium borohydride (2 M solution in THF) (7.55 mL, 15.11 mmol) followed by MeOH (2.45 mL, 60.4 mmol). The mixture was stirred for 1 h at RT

then cooled with an ice bath, and quenched with the dropwise addition of 10 mL of aq. NH_4Cl. The resulting biphasic mixture was extracted with (3 x 50 mL) of EtOAc. The organic extracts were washed sequentially with 10 mL of ice cold 1 N HCl, 5 mL of 1 N NaOH and 5 mL of brine, and dried over $MgSO_4$. It was filtered and concentrated under reduced pressure to provide *tert*-butyl ((1S,5S,6S)-5-(2,3-difluorophenyl)-1-(hydroxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (3.68 g, 7.15 mmol, 95% yield) as a clear viscous oil which was used without further purification. LC/MS (ESI^-) *m/z* = 515.2 $(M+H)^+$. At RT, the above obtained crude *tert*-butyl ((1S,5S,6S)-5-(2,3-difluorophenyl)-1-(hydroxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (3.36 g, 6.53 mmol) was taken up in 25 mL of DCM and 8.3 mL of DMSO. The solution was treated with Hunig's base (4.54 mL, 26.1 mmol) followed by pyridine-sulfur trioxide complex (2.078 g, 13.06 mmol). After 15 h, the mixture was diluted with 100 mL of DCM and washed with (2 x 15 mL) of sat. NH4Cl followed by 10 mL of brine, then dried over $MgSO_4$. Filtration and concentration under reduced pressure afforded a yellow oil which was purified on a silica gel column (10-35% EtOAc in Hexanes) to provide *tert*-butyl ((1S,5S,6S)-5-(2,3-difluorophenyl)-1-formyl-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (**203J**, 2.79 g, 5.44 mmol, 83% yield) as a yellow oil. LC/MS (ESI^-) *m/z* = 513.2 $(M+H)^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.91 (br., 1H), 7.45 (m, 2H), 7.27 (m, 1H), 5.19 (d, *J*=10.56 Hz, 1H), 5.00 (d, *J*=10.76 Hz, 1H), 3.58-3.65 (m, 2H), 2.82 (m, 1H), 1.87 (dd, *J*=5.87, 9.78 Hz, 1H), 1.71 (s, 3H), 1.50 (s, 9H), 1.25-1.40 (m, 2H), 0.90 (m, 1H), 0.02 (s, 9H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -139.15 (d, *J*=21.40 Hz, 1F), -139.46 (d, *J*=21.46 Hz, 1F).

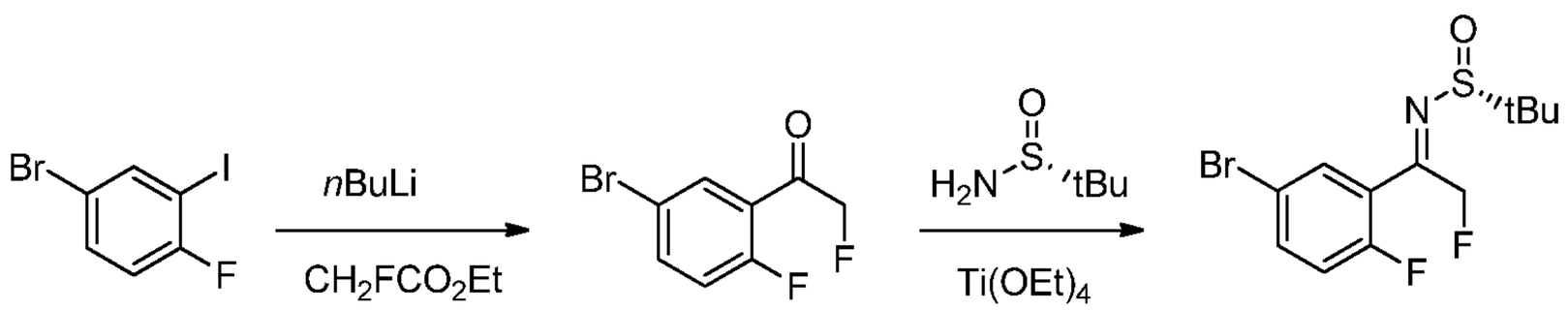
Preparation of Compound 203K. To a stirring solution of *tert*-butyl ((1S,5S,6S)-5-(2,3-difluorophenyl)-1-formyl-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (**203J**, 2.0 g, 3.90 mmol) in 1,2-dichloroethane (23.05 mL) at 20 ºC under nitrogen was added chlorotris(triphenylphosphine)rhodium(i) (Wilkinson's reagent, 5.41 g, 5.85 mmol) then heated to vigorous reflux under nitrogen. After 3 h the LCMS suggested 80% conversion. To the reaction mixture was added more Wilkinson's reagent (2.5 g) and returned to reflux for 1 h. It was cooled to RT and the solvents were removed under reduced pressure. The residue was triturated in 6:1 heptane/EtOAc (75 mL) by stirring for 20 h. The solid was further triturated in 6:1 heptane/EtOAc (2 x 50 mL) with the aid of

sonication each time capturing the solid through a bed of Celite® filter aid. The resulting filtrate was concentrated under reduced pressure. The resulting oil/solid was further triturated in 6:1 heptane/EtOAc (2 x 50 mL) with the aid of sonication each time capturing the solid through a bed of Celite® filter aid. The resulting filtrate was concentrated under reduced pressure, loaded onto silica with heptane, then purified by silica gel chromatography (80 g) eluting with a gradient of 0-10% EtOAc/heptane to afford *tert*-butyl ((1S,5S,6S)-5-(2,3-difluorophenyl)-1-formyl-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (**203K**, 2.0 g, 3.90 mmol) as colorless oil. LC/MS (ESI^-) *m/z* = 485.1 $(M+H)^+$. ^1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.32 - 7.40 (m, 1 H), 6.99 - 7.10 (m, 2 H), 5.26 (d, *J*=10.56 Hz, 1 H), 5.01 (d, *J*=10.37 Hz, 1 H), 3.60 - 3.70 (m, 2 H), 2.19 (td, *J*=8.36, 4.99 Hz, 1 H), 1.94 - 2.05 (m, 1 H), 1.78 (s, 3 H), 1.51 (s, 9 H), 0.90 - 0.98 (m, 2 H), 0.83 - 0.90 (m, 1 H), 0.70 (q, *J*=5.74 Hz, 1 H), 0.00 (s, 9 H).

Preparation of Compound 203L. At 0 °C, to *tert*-butyl ((1S,5S,6S)-5-(2,3-difluorophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl) carbamate (**203K**, 1.29 g, 2.66 mmol) was added H_2SO_4 (6.38 mL, 120 mmol). After 15 min, the ice bath was removed and syrup stirred for 30 min at 20 °C. The reaction was cooled to 0 °C and sodium nitrate (0.317 g, 3.73 mmol) was added. The reaction was stirred for 30 min at 0 °C. The ice bath was removed and reaction stirred at 20 °C for 15 min. The mixture was added to ice (100 g) via a pipet. The acidic solution was cooled with an ice bath and deluted with CH_2Cl_2 (50 mL). To the rapidly stirred mixture was added potassium phosphate tribasic (16.95 g, 80 mmol) over 20 min, and the mixture was then brought to pH ~8 with 1 M NaOH. The organic layer was separated, and the aqueous layer was extracted with DCM (2 x 50 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated under reduced pressure. The residue was purified via silica gel flash column chromatography eluting with a gradient of 0-25% EtOAc in heptane to afford (1S,5S,6S)-5-(2,3-difluoro-5-nitrophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0] hept-3-en-3-amine (**203L**, 0.45 g, 1.504 mmol, 56.5% yield) as tan oil. LC/MS (ESI^-) *m/z* = 300.0 $(M+H)^+$. ^1H NMR (400 MHz, CHLOROFORM-d) δ 8.44-8.50 (m, 1H), 7.98 (ddd, *J*=2.93, 6.31, 9.15 Hz, 1H), 4.04-4.95 (m, 2H), 2.24 (dt, *J*=5.28, 8.31 Hz, 1H), 1.84-1.99 (m, 1H), 1.77 (s, 3H), 0.85-0.97 (m, 1H), 0.64 (q, *J*=5.74 Hz, 1H).

Preparation of Compound 203. To a stirring solution of (1S,5S,6S)-5-(2,3-difluoro-5-nitrophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (**203L**, 0.46 g, 1.54 mmol) in glacial HOAc (5 mL) and TFA (5 mL) at 20 ºC was added zinc (nanopowder, 0.6 g, 9.22 mmol) in small portions. After 90 min, the reaction was concentrated under reduced pressure to a thick oil/suspension. The residue was partitioned between 9:1 $CHCl_3$/IPA (50 mL) and 10% NH_4OH (50 mL). The separated aqueous layer was further extracted with 9:1 $CHCl_3$/IPA (20 mL). The combined organics were washed with sat. NaCl (20 mL), dried over $MgSO_4$, concentrated under reduced pressure. The remaining solid was purified by silica gel chromatography (12 g) eluting with a gradient of 1-6% of 2 M NH_3 in MeOH in DCM to afford (1S,5S,6S)-5-(5-amino-2,3-difluorophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (**203**) (0.33 g, 1.22 mmol, 80% yield) as tan foam. LC/MS (ESI^-) *m/z* = 270.0 $(M+H)^+$. ^1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 6.69 (dt, *J*=4.99, 2.59 Hz, 1 H), 6.32 - 6.40 (m, 1 H), 3.81 - 4.58 (br., 2 H), 3.58 (br. s., 2 H), 2.18 (td, *J*=8.22, 5.09 Hz, 1 H), 1.80 - 1.91 (m, 1 H), 1.70 - 1.75 (m, 3 H), 0.88 - 0.97 (m, 1 H), 0.59 (q, *J*=5.67 Hz, 1 H).

(R,Z)-N-(1-(5-Bromo-2-fluorophenyl)-2-fluoroethylidene)-2-methylpropane-2-sulfinamide (204A).



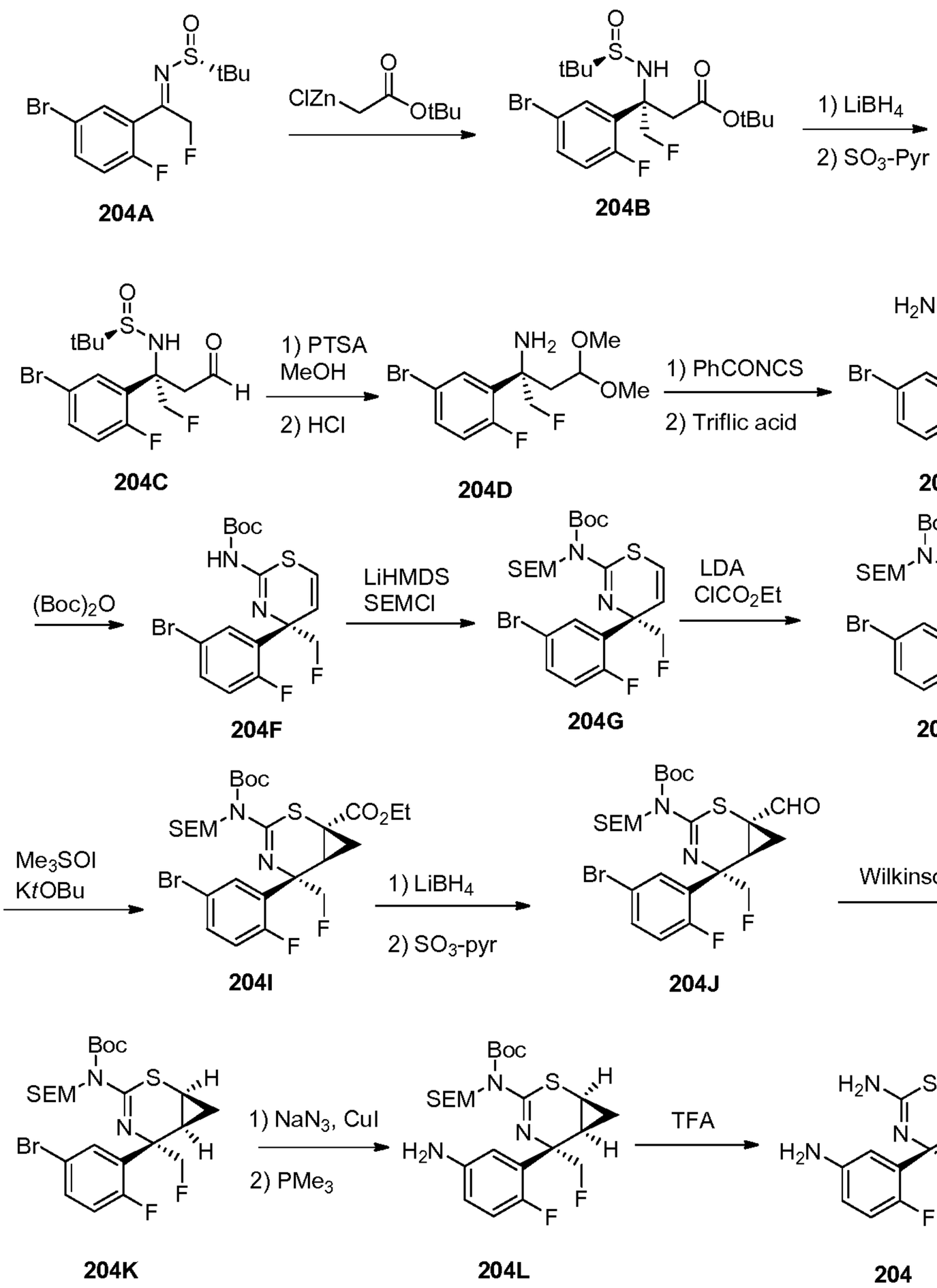
204A

Preparation of 1-(5-bromo-2-fluorophenyl)-2-fluoroethanone. A solution of 4-bromo-1-fluoro-2-iodobenzene (5.0g, 116 mmol, Aldrich) in THF (60 mL) under nitrogen atmosphere was cooled to -78 °C. A solution of *n*-BuLi (2.5 M in hexanes; 7.31 mL, 18.28 mmol, Aldrich) was added dropwise and the reaction was stirred at -78 °C for 1 h. Ethyl monofluoroacetate (2.1 g, 19.94 mmol, Aldrich) was added drop wise and the reaction was stirred at -78 °C for 1 h. The reaction was quenched with aqueous saturated ammonium chloride solution and allowed to warm to RT. The reaction was diluted with water and EtOAc. The organic layer was separated, washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The material was purified via silica gel flash chromatography using a gradient of 0-20% EtOAc in Hexanes to

afford the title compound as an off white solid (2.45 g, 10.42 mmol, 63% yield). MS *m/z* = 234.9 M^+.

Preparation of (R)-N-(1-(5-bromo-2-fluorophenyl)-2-fluoroethylidene)-2-methylpropane-2-sulfinamide (204A). To a solution of 1-(5-bromo-2-fluorophenyl)-2-fluoroethanone (14 g, 59.6 mmol) and (R)-2-methylpropane-2-sulfinamide (14.44 g, 119 mmol, AK Scientific) in THF (120 ml) was added tetraethoxytitanium (27.2 g, 119 mmol, Aldrich). The reaction was stirred at RT for 16 h. The reaction mixture was poured slowly into vigorously stirring water (700 mL) and the resulting suspension was stirred for 20 min. EtOAc (400 mL) was added and the suspension was stirred for an additional 20 min. The suspension was filtered through Celite® filter aid and the filter cake was washed with additional EtOAc. The organic layer was separated, washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The material was purified via silica gel flash chromatography using a gradient of 0-25% EtOAc in Hexanes to afford the title compound as a yellow oil (**204A**, 15.35g, 45.4 mmol, 76% yield). MS *m/z*= 338.0 M^+.

(1S,5S,6S)-5-(5-Amino-2-fluorophenyl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (204).



Preparation of Compound 204B. To a 2000 mL 3-neck RBF equipped with an addition funnel and internal temperature probe was added (R,Z)-N-(1-(5-bromo-2-fluorophenyl)-2-fluoroethylidene)-2-methylpropane-2-sulfinamide (**204A**, 21.35 g, 63.1 mmol) and THF (200 mL). The mixture was cooled to 0 °C and 2-*tert*-butoxy-2-oxoethylzinc chloride (0.5 M in Et_2O, 253 mL, 126 mmol) was added dropwise over 75 min keeping the internal temperature under 5 °C. After the addition was completed, the ice bath was removed and the reaction mixture was stirred at RT for 80 min. The reaction

mixture was carefully quenched with the slow addition of half-sat. NH_4Cl (100 mL) followed by water (200 mL). The layers were separated and the aqueous phase was extracted with EtOAc (200 mL). The combined organic extracts were washed with brine (300 mL), dried (Na_2SO_4) and concentrated. Purification by silica gel chromatography (5-50% EtOAc/hexanes) afforded (S)-*tert*-butyl 3-(5-bromo-2-fluorophenyl)-3-((R)-1,1-dimethylethylsulfinamido)-4-fluorobutanoate (**204B**, 22.33 g, 49.1 mmol, 78% yield) as a pale-yellow oil, which solidified upon standing. LC/MS (ESI$^-$) *m/z* = 475.8 $(M+Na)^+$.

Preparation of Compound 204C. To a solution of (S)-*tert*-butyl 3-(5-bromo-2-fluorophenyl)-3-((R)-1,1-dimethylethylsulfinamido)-4-fluorobutanoate (**204B**, 22.3 g, 49.1 mmol) in THF (250 mL) in a 1000 mL 3-neck round-bottomed flask equipped with an internal temperature probe at RT was added lithium borohydride (2.0 M solution in THF, 50.0 mL, 100 mmol) over 45 min. Anhydrous MeOH (16.0 mL, 395 mmol) was then added to the mixture slowly over 55 min keeping the internal temperature under 35 °C. The mixture was stirred for 30 min. The reaction was slowly quenched with 100 mL of sat. aq. NH_4Cl. The mixture was stirred at RT for 15 min then partitioned between water (100 mL) and EtOAc (100 mL). The aqueous phase was extracted with EtOAc (100 mL). The combined organic extracts were washed with brine (300 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by silica gel chromatography (30-80% EtOAc/hexanes) afforded ((R)-N-((S)-2-(5-bromo-2-fluorophenyl)-1-fluoro-4-hydroxybutan-2-yl)-2-methylpropane-2-sulfinamide (15.34 g, 39.9 mmol, 81%) as a white foam. LC/MS (ESI$^-$) *m/z* = 383.8 $(M+H)^+$. This material was dissolved in DCM (140 mL) and DMSO (70 mL) in a 1000 mL 3-neck RBF equipped with an internal temperature probe. The mixture was cooled in an ice/acetone bath to -10 °C. N,N-diisopropylethylamine (21 mL, 121 mmol) was added dropwise via a syringe followed by portion-wise addition of pyridine sulfur trioxide (9.51 g, 59.7 mmol) keeping the internal temperature below -5 °C. The mixture was stirred for 5 min, and then the cooling bath was replaced with an ice bath. The mixture was stirred for 1 h at ~0 °C. The mixture was poured into water (500 mL) and EtOAc (300 mL) was added. The layers were separated and the aqueous phase was extracted with EtOAc (3 x 150 mL). The combined organic extracts were washed with saturated aqueous ammonium chloride (2 x 500 mL), water (500 mL) and brine (500 mL). The organic was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the crude material. Purification by silica gel chromatography (20-80% EtOAc/hexanes) afforded (R)-N-((S)-2-(5-bromo-2-fluorophenyl)-1-fluoro-4-oxobutan-2-yl)-2-methylpropane-2-sulfinamide (**204C**, 11.36 g,

29.7 mmol, 74.6% yield) as a clear paste. LC/MS (ESI^-) *m/z* = 381.8 $(M+H)^+$. ^1H NMR (300 MHz, CHLOROFORM-d) δ 9.76 (s, 1H), 7.65 (d, *J*=7.02 Hz, 1H), 7.39-7.53 (m, 1H), 6.96 (dd, *J*=8.92, 11.98 Hz, 1H), 4.70-5.18 (m, 3H), 3.31-3.55 (m, 2H), 1.23-1.29 (m, 9H). ^{19}F NMR (282 MHz, CHLOROFORM-d) δ -111.72 (s, 1F), -217.48 (s, 1F).

Preparation of Compound 204D. The mixture of (R)-N-((S)-2-(5-bromo-2-fluorophenyl)-1-fluoro-4-oxobutan-2-yl)-2-methylpropane-2-sulfinamide (2.44 g, 6.38 mmol) and 4-methylbenzene sulfonic acid hydrate (0.085 g, 0.447 mmol) in MeOH (50 mL) was heated at 80 ^oC in 2h. After 2h, the reaction was cooled to RT. To this mixture, stirred in an ice bath, was added HCl (1.6 mL of 4 M in dioxane solution, 6.38 mmol). After the addition, the mixture was stirred at RT overnight. The mixture was concentrated to dryness, saturated aqueous Na_2CO_3 was added, extracted with EtOAc (3x). The extracts were dried over $MgSO_4$, concentrated to give (S)-2-(5-bromo-2-fluorophenyl)-1-fluoro-4,4-dimethoxybutan-2-amine (**204D**, 2.06 g, 100%) which was used in the next step without further purification. LC/MS (ESI^-) *m/z* = 324.0 $(M+H)^+$.

Preparation of Compound 204E. To a stirred solution of (S)-2-(5-bromo-2-fluorophenyl)-1-fluoro-4,4-dimethoxybutan-2-amine (**204D**, 25.4 g, 78 mmol) in DCM (150 mL) at 0 ^oC was added a solution of benzoyl isothiocyanate (14.07 g, 86 mmol) in DCM (100 mL) . After the addition, the ice bath was removed and stirred at RT in 2 h. The mixture was concentrated to dryness to give a brown oil which was treated with triflic acid (5.65 mL, 63.6 mmol). The mixture was heated to 50 ^oC for 3 h, then 70 ^oC for 2 h. The reaction mixture was cooled, poured onto ice in a beaker, basified with 10 N NaOH until pH = 9. It was extracted with DCM (3 x). The extracts were dried over Na_2SO_4, concentrated and purified by silica gel chromatography (0-50% EtOAc/Hexanes) to give (S)-4-(5-bromo-2-fluorophenyl)-4-(fluoromethyl)-4H-1,3-thiazin-2-amine (**204E**, 1.59 g, 78%). ^1H NMR (CHLOROFORM-d) δ: 7.58 (dd, J=6.8, 2.5 Hz, 1H), 7.37 (ddd, J=8.6, 4.3, 2.6 Hz, 1H), 6.92 (dd, J=11.2, 8.7 Hz, 1H), 6.47 (d, J=9.6 Hz, 1H), 6.32 (dd, J=9.6, 5.3 Hz, 1H), 4.90 (br. s., 2H), 4.81 (d, J=8.0 Hz,), 0.5H), 4.70 (d, J=8.0 Hz, 0.5H), 4.63 (d, J=8.6 Hz, 0.5H), 4.52 (d, J=8.6 Hz, 0.5H). LC/MS (ESI^-) *m/z* = 319.0 $(M+H)^+$.

Preparation of Compound 204F. A mixture of (S)-4-(5-bromo-2-fluorophenyl)-4-(fluoromethyl)-4H-1,3-thiazin-2-amine (**204E**, 4.81 g, 15.07 mmol) and di-*tert*-butyl dicarbonate (6.58 g, 30.1 mmol) was heated neat at 50 ^oC for 24 h. The reaction mixture was cooled to RT and purified by silica gel chromatography (0-20% EtOAc/Hexanes) to give (S)-*tert*-butyl (4-(5-bromo-2-fluorophenyl)-4-(fluoromethyl)-

4H-1,3-thiazin-2-yl)carbamate (**204F**, 6.32 g, 100%). LC/MS (ESI$^-$) *m/z* = 362.9.0 $(M+H)^+$.

Preparation of Compound 204G. To a stirred solution of (S)-*tert*-butyl (4-(5-bromo-2-fluorophenyl)-4-(fluoromethyl)-4H-1,3-thiazin-2-yl)carbamate (**204F**, 4 g, 9.54 mmol) in THF (20 mL) at -10 ^oC was added a solution of lithium bis(trimethylsilyl)amide (11.45 mL of 1 M solution in THF, 11.45 mmol) dropwise. The mixture was stirred at this temperature for 1 h, then a solution of 2-(trimethylsilyl)ethoxymethyl chloride (1.88 mL, 9.54 mmol) in THF (10 mL) was added. The reaction mixture was gradually warmed to RT and stirred for 16 h. It was treated with saturated aqueous NH_4Cl and extracted with hexanes. The combined extracts were dried over Na_2SO_4, concentrated, then purified by silica gel chromatography (0-20% EtOAc/Hexanes) to give (S)-*tert*-butyl (4-(5-bromo-2-fluorophenyl)-4-(fluoromethyl)-4H-1,3-thiazin-2-yl)((2-(trimethylsilyl)ethoxy)methyl) carbamate (**204G**, 4.77 g, 91%). ^1H NMR (DMSO-d_6) δ: 7.54-7.72 (m, 2H), 7.28 (dd, J=11.6, 8.5 Hz, 1H), 6.85 (d, J=9.4 Hz, 1H), 6.17 (dd, J=9.6, 4.3 Hz, 1H), 5.16-5.31 (m, 2H), 4.56-4.96 (m, 2H), 3.63 (dd, J=8.6, 7.4 Hz, 2H), 1.50 (s, 9H),0.69-1.03 (m, 2H), 0.03 (s, 9H). LC/MS (ESI$^-$) *m/z* = 573.0 $(M+Na)^+$.

Preparation of Compound 204H. To a stirred solution of (S)-*tert*-butyl (4-(5-bromo-2-fluorophenyl)-4-(fluoromethyl)-4H-1,3-thiazin-2-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (3.27 g, 5.71 mmol) in THF (30 mL) at -78 ^oC was added LDA (3.71 mL of 1 M in THF solution, 7.43 mmol) dropwise. After the addition, the mixture was stirred at -78 ^oC for 45 min, and then ethyl chloroformate (6.58 mL, 68.6 mmol) was added in single portion. It was stirred at -78 ^oC for 10 min then quenched with saturated NH_4Cl, and extracted with EtOAc (3x). The organic extracts were dried over Na_2SO_4, concentrated and purified by silica gel chromatography (0-20% EtOAc/Hexanes to give (S)-ethyl 4-(5-bromo-2-fluorophenyl)-2-((*tert*-butoxycarbonyl)((2-(trimethylsilyl)ethoxy)methyl)amino)-4-(fluoromethyl)-4H-1,3-thiazine-6-carboxylate (**204H**, 1.75 g, 49.3%). 1H NMR (CHLOROFORM-d) δ: 7.57-7.69 (m, 1H), 7.65 (dd, J=6.8, 2.3 Hz, 1H), 7.19 (d, J=4.3 Hz, 1H), 6.97 (dd, J=11.0, 8.8 Hz, 1H), 5.35-5.44 (m, 1H), 5.24-5.33 (m, 1H), 4.78-4.99 (m, 1H), 4.55-4.75 (m, 1H), 4.30 (q, J=7.1 Hz, 2H), 3.63-3.73 (m, 2H), 1.52-1.60 (m, 9H), 1.34 (t, J=7.0 Hz, 3H), 0.87-1.04 (m, 2H), 0.03 (s, 9H). LC/MS (ESI$^-$) *m/z* = 643.1 $(M+Na)^+$.

Preparation of Compound 204I. To a stirred suspension of trimethylsulfoxonium iodide (13.60 g, 61.8 mmol) in DMSO (30 mL) was added potassium *tert*-butoxide (6.35 g, 56.6 mmol) in single portion. After the addition, the

mixture was stirred for 1 h. The resulting mixture was added to a stirred solution of (S)-ethyl 4-(5-bromo-2-fluorophenyl)-2-((*tert*-butoxycarbonyl)((2-(trimethylsilyl)ethoxy)methyl)amino)-4-(fluoromethyl)-4H-1,3-thiazine-6-carboxylate (**204H**, 16 g, 25.7 mmol) in DMSO (70 mL). The reaction mixture was stirred at RT for 1 h, the treated with saturated aqueous NH_4Cl, and extracted with EtOAc (3x). The extracts were dried over Na_2SO_4, concentrated and purified by silica gel chromatography (0-20% EtOAc/Hexanes) to give (1S,5S,6S)-ethyl 5-(5-bromo-2-fluorophenyl)-3-((*tert*-butoxycarbonyl)((2-(trimethylsilyl)ethoxy)methyl)amino)-5-(f (1S,5S,6S)-ethyl 5-(5-bromo-2-fluorophenyl)-3-((*tert*-butoxycarbonyl)((2-(trimethylsilyl)ethoxy)methyl) amino)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylateluoromethyl) -2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylate (**204I**, 3.94 g, 24%). ^{1}H NMR (CHLOROFORM-d) δ: 7.84 (dd, J=6.8, 2.5 Hz, 1H), 7.41 (ddd, J=8.6, 4.3, 2.6 Hz, 1H), 6.98 (dd, J=11.5, 8.6 Hz, 1H), 5.29 (d, J=10.4 Hz, 1H), 5.04 (d, J=10.4 Hz, 1H), 4.59-4.99 (m, 2H), 4.24 (q, J=7.2 Hz, 2H), 3.67 (td, J=8.4, 1.5 Hz, 2H), 2.63 (ddd, J=9.9, 7.7, 1.8 Hz, 1H), 1.56 (d, J=4.9 Hz, 1H), 1.54 (s, 9H), 1.31 (t, J=7.1 Hz, 3H), 1.07 (dd, J=7.5, 5.2 Hz, 1H), 0.97 (dd, J=9.2, 7.4 Hz, 2H), -0.01-0.02 (s, 9H). LC/MS (ESI$^-$) *m/z* = 657.2 $(M+Na)^+$.

Preparation of Compound 204J. To a stirred solution of (1S,5S,6S)-ethyl 5-(5-bromo-2-fluorophenyl)-3-((*tert*-butoxycarbonyl)((2-(trimethylsilyl)ethoxy)methyl)amino)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylate (**204I**, 3.94 g, 6.20 mmol) in THF (40 mL) at RT was added lithium borohydride (6.20 mL of 1 M in THF solution, 12.40 mmol) dropwise. After the addition, MeOH (2.0 mL, 49.6 mmol) was added dropwise, and mixture stirred for 2 h. It was cooled in an ice bath and quenched with saturated aqueous NH_4Cl, extracted with EtOAc (3x). The extracts were dried over Na_2SO_4, concentrated to give *tert*-butyl ((1S,5S,6S)-5-(5-bromo-2-fluorophenyl)-5-(fluoromethyl)-1-(hydroxymethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy) methyl)carbamate as a colorless oil (3.64 g, 99%). ^{1}H NMR (CHLOROFORM-d) δ: 7.77 (dd, J=6.8, 2.5 Hz, 1H), 7.39 (ddd, J=8.7, 4.2, 2.6 Hz, 1H), 6.96 (dd, J=11.6, 8.7 Hz, 1H), 5.32 (d, J=10.6 Hz, 1H), 5.07 (d, J=10.6 Hz, 1H), 4.62-5.00 (m, 2H), 3.84 (dd, J=11.9, 4.3 Hz, 1H), 3.67 (dd, J=8.8, 7.8 Hz, 2H), 3.50-3.56 (m, 1H), 2.04 (t, J=6.0 Hz, 1H), 1.91 (ddd, J=9.5, 6.9, 2.2 Hz, 1H), 1.52 (s, 9H), 0.93-1.06 (m, 3H), 0.73 (t, J=6.3 Hz, 1H), -0.02-0.04 (s, 9H). LC/MS (ESI$^-$) *m/z* = 617.2 $(M+Na)^+$.

TEA (3.41 mL, 24.46 mmol) was added dropwise via syringe to a solution *tert*-butyl ((1S,5S,6S)-5-(5-bromo-2-fluorophenyl)-5-(fluoromethyl)-1-(hydroxymethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy) methyl)carbamate (3.62 g, 6.12 mmol) in DCM (20 mL) and DMSO (20 mL) in 100 mL RBF. Pyridine sulfur trioxide (4.33 g, 12.23 mmol) was added and the mixture was stirred for 2 h. Water was added and the mixture was extracted with DCM (3x). The combined organic extracts were washed with saturated aqueous ammonium chloride, water, saturated aqueous sodium chloride, and dried over sodium sulfate. The solution was filtered and concentrated *in vacuo* to give *tert*-butyl ((1S,5S,6S)-5-(5-bromo-2-fluorophenyl)-5-(fluoromethyl)-1-formyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (**204J**, 3.62 g, 100%). ^{1}H NMR (CHLOROFORM-d) δ: 9.15 (s, 1H), 7.83 (dd, J=6.8, 2.5 Hz, 1H), 7.44 (ddd, J=8.7, 4.3, 2.5 Hz, 1H), 7.00 (dd, J=11.5, 8.8 Hz, 1H), 5.33 (d, J=10.4 Hz, 1H), 5.11 (d, J=10.4 Hz, 1H), 4.59-4.97 (m, 2H), 3.67 (dd, J=9.0, 7.6 Hz, 2H), 2.40-2.59 (m, 1H), 1.77 (dd, J=10.0, 5.7 Hz, 1H), 1.50-1.58 (s, 9H), 1.16-1.34 (m, 1H), 0.98 (dd, J=9.2, 7.4 Hz, 2H), -0.03-0.04 (s, 9H). LC/MS (ESI$^-$) *m/z* = 615.0 $(M+Na)^+$.

Preparation of Compound 204K. A mixture of *tert*-butyl ((1S,5S,6S)-5-(5-bromo-2-fluorophenyl)-5-(fluoromethyl)-1-formyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (3.22 g, 5.44 mmol) and chlorotris(triphenylphosphine) rhodium(i) (3.53 g, 3.81 mmol) in DCE (20 mL) was heated at 85 °C for 4 h. The mixture was cooled, concentrated to dryness, triturated in 40% EtOAc/Hexanes. The orange solid was filtered off, washed with 40% EtOAc/Hexanes. The filtrate was concentrated and purified by silica gel chromatography (0-20% EtOAc/Hexanes) to give *tert*-butyl ((1S,5S,6S)-5-(5-bromo-2-fluorophenyl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (**204K**, 1.75 g, 57%). ^{1}H NMR (CHLOROFORM-d) δ: 7.81 (dd, J=7.0, 2.5 Hz, 1H), 7.39 (ddd, J=8.6, 4.2, 2.6 Hz, 1H), 6.96 (dd, J=11.6, 8.7 Hz, 1H), 5.29 (d, J=10.4 Hz, 1H), 5.04 (d, J=10.4 Hz, 1H), 4.69-4.98 (m, 2H), 3.62-3.70 (m, 2H), 2.25 (ddd, J=8.9, 7.7, 5.3 Hz, 1H), 2.00 (tdd, J=9.2, 6.6, 2.7 Hz, 1H), 1.52 (s, 9H), 0.94-1.05 (m, 2H), 0.88 (t, J=6.8 Hz, 1H), 0.60 (q, J=5.9 Hz, 1H), 0.00 (s, 9H). LC/MS (ESI$^-$) *m/z* = 585.0 $(M+Na)^+$.

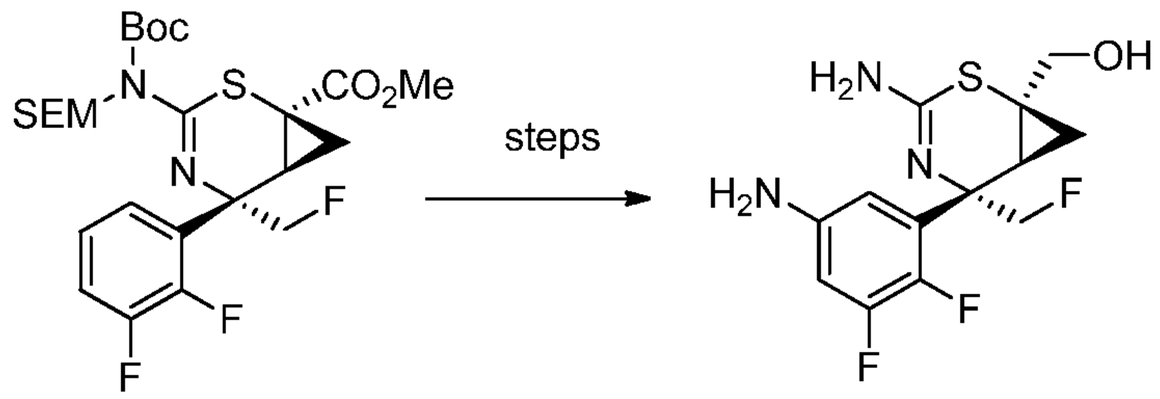
Preparation of Compound 204L. A mixture of *tert*-butyl ((1S,5S,6S)-5-(5-bromo-2-fluorophenyl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy) methyl)carbamate (3.31 g, 5.87 mmol), sodium (R)-2-((S)-1,2-

dihydroxyethyl)-4-hydroxy-5-oxo-2,5-dihydrofuran-3-olate (0.291 g, 1.468 mmol), copper(I) iodide (0.280 g, 1.468 mmol), sodium azide (1.145 g, 17.62 mmol), and (1R,2R)-N1,N2-dimethylcyclohexane-1,2-diamine (0.232 mL, 1.468 mmol) in EtOH/H_2O (5:1, 60 mL) was heated at 85 ^oC for 2 h. The reaction mixture was cooled, diluted with EtOAc, washed with 10:1 saturated NH_4Cl/NH_4OH, brine, dried over Na_2SO_4, and concentrated to give an oil.

A solution of the oil in 9:1 of THF/H_2O (50 mL) was added trimethylphosphine (6.46 mL of 1 M in THF, 6.46 mmol). After stirring for 30 min, it was diluted with EtOAc, washed with H_2O, dried over Na_2SO_4, and concentrated to give *tert*-butyl ((1S,5S,6S)-5-(5-amino-2-fluorophenyl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (**204L**, 2.85 g, 97%) as light brown oil. ^1H NMR (CHLOROFORM-d) δ: 6.96 (dd, J=6.5, 2.9 Hz, 1H), 6.85 (dd, J=11.9, 8.6 Hz, 1H), 6.55 (dt, J=8.5, 3.4 Hz, 1H), 5.29 (d, J=10.6 Hz, 1H), 5.05 (d, J=10.6 Hz, 1H), 4.85-5.02 (m, 1H), 4.66-4.84 (m, 1H), 3.62-3.69 (m, 2H), 2.20-2.29 (m, 1H), 1.99 (tdd, J=9.2, 6.7, 2.3 Hz, 1H), 1.51 (s, 9H), 0.97-1.04 (m, 1H), 0.90-0.97 (m, 2H), 0.58 (q, J=5.7 Hz, 1H), -0.02-0.02 (s, 9H). LC/MS (ESI^-) *m/z* = 500.1 $(M+H)^+$.

Preparation of Compound 204. To a stirred solution of *tert*-butyl ((1S,5S,6S)-5-(5-amino-2-fluorophenyl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy) methyl)carbamate (**204L**, 2.85 g, 5.70 mmol) in DCM (20 mL) was added TFA (4.39 mL, 57.0 mmol). The mixture was stirred at RT for 5 h then concentrated to dryness. The residue was treated with H_2O and basified with saturated aqueous $NaHCO_3$. The solid was collected, washed with H_2O, dried and purified by silica gel chromatography (0-40% acetone/DCM) to give (1S,5S,6S)-5-(5-amino-2-fluorophenyl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (**204**, 1.2 g, 78%). LC/MS (ESI^-) *m/z* = 270.1 $(M+H)^+$. ^1H NMR (300 MHz, CHLOROFORM-d) δ 6.78-7.03 (m, 2H), 6.55 (td, *J*=3.45, 8.44 Hz, 1H), 4.01-5.31 (m, 4H), 3.08-3.97 (m, 2H), 2.29 (ddd, *J*=5.04, 7.53, 8.92 Hz, 1H), 1.87 (ddt, *J*=1.75, 6.87, 9.06 Hz, 1H), 1.08 (ddd, *J*=5.85, 7.38, 9.28 Hz, 1H), 0.50 (q, *J*=5.70 Hz, 1H).

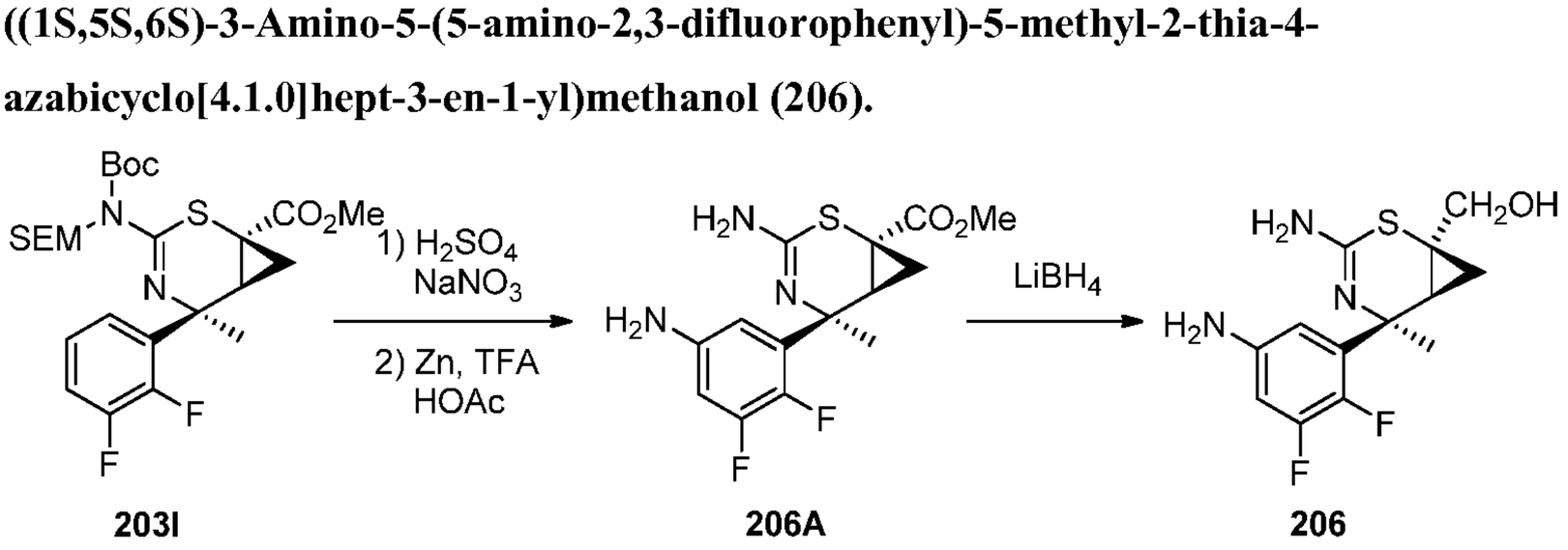
(1S,5S,6S)-Methyl 3-amino-5-(5-amino-2,3-difluorophenyl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylate (205).



201I **205**

The title Compound was prepared from 201I using the chemical procedures similar to that described for intermediate **206** (see below). LC/MS (ESI^-) *m/z* = 318.0 $(M+H)^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 6.59 - 6.65 (m, 1 H) 6.39 (ddd, *J*=12.57, 6.41, 2.74 Hz, 1 H) 6.16 (s, 2 H) 5.15 (s, 2 H) 5.03 (t, *J*=5.97 Hz, 1 H) 4.52 - 4.71 (m, 2 H) 3.52 (dd, *J*=11.64, 6.16 Hz, 1 H) 3.39 (dd, *J*=11.74, 5.67 Hz, 1 H) 1.51 - 1.60 (m, 1 H) 0.98 (dd, *J*=9.39, 5.09 Hz, 1 H) 0.44 (t, *J*=5.67 Hz, 1 H).

((1S,5S,6S)-3-Amino-5-(5-amino-2,3-difluorophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)methanol (206).



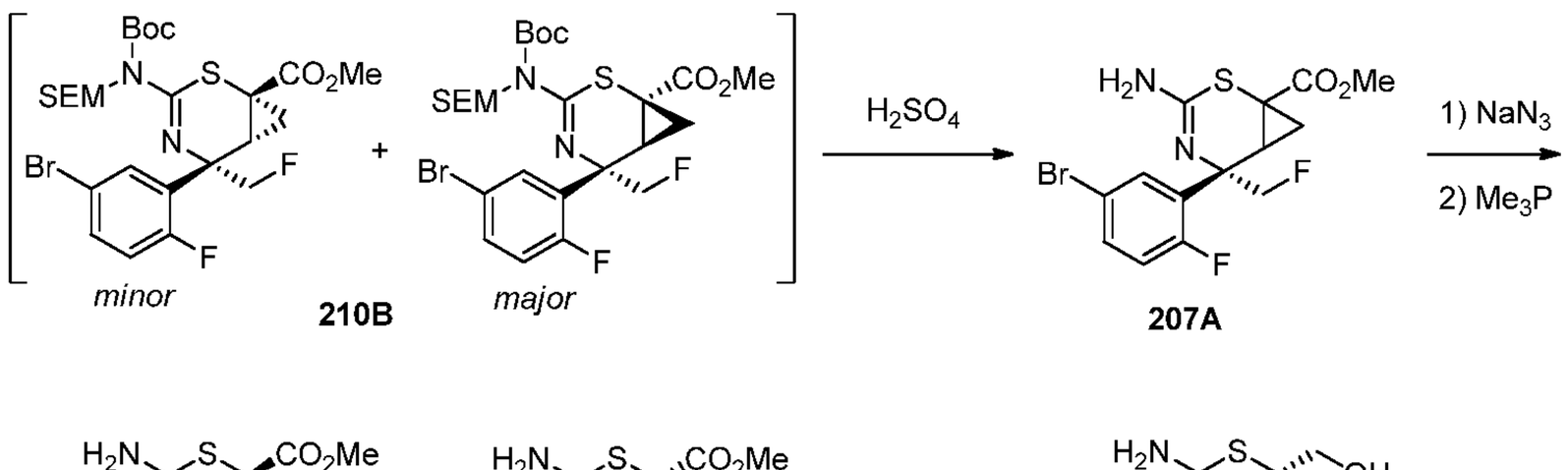
203I **206A** **206**

Preparation of Compound 206A. At RT, (1S,5S,6S)-methyl 3-((*tert*-butoxycarbonyl)((2-(trimethylsilyl)ethoxy) methyl)amino)-5-(2,3-difluorophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylate (**203I**, 2.00 g, 3.69 mmol) was treated with 4 mL of sulfuric acid and stirred for 10 min, then chilled to 0 °C. Sodium nitrate (0.41 g, 4.79 mmol) was added to the mixture. The mixture was stirred for 1 h. Additional sodium nitrate (0.41 g, 4.79 mmol) was added, and the mixture was warmed to RT. After 1 h, additional 3 mL of sulfuric acid was added (to try and solublized the starting material). The reaction was cooled to 0 °C to suppress an exotherm. After 30 min, the reaction mixture was poured into ~100 mL of wet ice. 50 mL of DCM was added. Potassium phosphate tribasic (29.70 g, 140 mmol) was added to the mixture over ~20 min. Aq 10 N NaOH was then added until the pH reached ~8. The mixture was

extracted three times with 100 mL of 9:1 chloroform:IPA. The combined organic extracts were dried over $MgSO_4$. Filtration and concentration under reduced pressure afforded (1S,5S,6S)-methyl 3-amino-5-(2,3-difluoro-5-nitrophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylate (LC/MS (ESI^-) *m/z* = 358.1 $(M+H)^+$) as a sticky brown solid. The solid was taken up in 4 mL of HOAc and 2 mL of TFA. Zinc (nanopowder, 1.20 g, 18.43 mmol) was added to the mixture. The mixture was stirred for 30 min, and then concentrated under reduced pressure. The residue was taken up in 50 mL of 9:1 chloroform:IPA and basified to pH~8.0 with 1.0 N aq NaOH. ~10 mL of NH_4OH was then added. The mixture was partitioned and the aqueous portion was extracted three times with 100 mL of 9:1 chloroform:IPA. The combined organic extracts were dried over $MgSO_4$. Filtration and concentration under reduced pressure, followed by flash chromatography on silica gel (40 g Grace column, eluted with 40-90% EtOAc in DCM) afforded (1S,5S,6S)-methyl 3-amino-5-(2,3-difluoro-5-nitrophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylate (**206A**, 0.63 g, 52% yield) as a yellow solid. *m/z* (ESI, +ve ion) 328.1 $(M+1)^+$. ^1H NMR (400 MHz, CHLOROFORM-d) δ 6.74 (d, *J*=5.35 Hz, 1H), 6.39 (m, 1H), 3.78 (s, 3H), 3.59 (br. s., 2H), 2.52 (m, 1H), 1.69 (s, 3H), 1.56 (br., 2 H), 1.54 (m, 1H), 1.11 (dd, *J*=5.18, 7.53 Hz, 1H).

Preparation of Compound 206. At RT, (1S,5S,6S)-methyl 3-amino-5-(5-amino-2,3-difluorophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylate (**206A**, 0.63 g, 1.92 mmol) was taken up in 10 mL of THF and treated with lithium borohydride (2.0 M solution in THF, 4.81 ml, 9.62 mmol) followed by MeOH (1.56 mL, 38.5 mmol). The mixture was stirred for 15 h. The reaction was cooled to 0 °C and quenched by dropwise addition of 30 mL of sat aq NH_4Cl. The mixture was extracted twice with 20 mL of EtOAc and the combined organic extracts were washed with 20 mL of brine and dried over $MgSO_4$. Filtration and concentration under reduced pressure afforded ((1S,5S,6S)-3-amino-5-(5-amino-2,3-difluorophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)methanol (**206**, 0.54 g, 1.80 mmol, 94% yield) as an off-white amorphous solid. *m/z* (ESI, +ve ion) 300.0 $(M+1)^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 6.68 (br., 1H), 6.33 (m, 1H), 5.85 (br., 2H), 5.09 (br., 2H), 5.00 (t, *J*=5.87 Hz, 1H), 3.52 (dd, *J*=6.36, 11.64 Hz, 1H), 3.41 (dd, *J*=5.58, 11.64 Hz, 1H), 1.58 (m, 1H), 1.53 (s, 3H), 0.79 (m, 1H), 0.46 (t, *J*=5.58 Hz, 1H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -140.52 (d, J=23.35 Hz, 1F), -155.98 (d, J=23.35 Hz, 1F).

((1S,5S,6S)-3-Amino-5-(5-amino-2-fluorophenyl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)methanol (207).



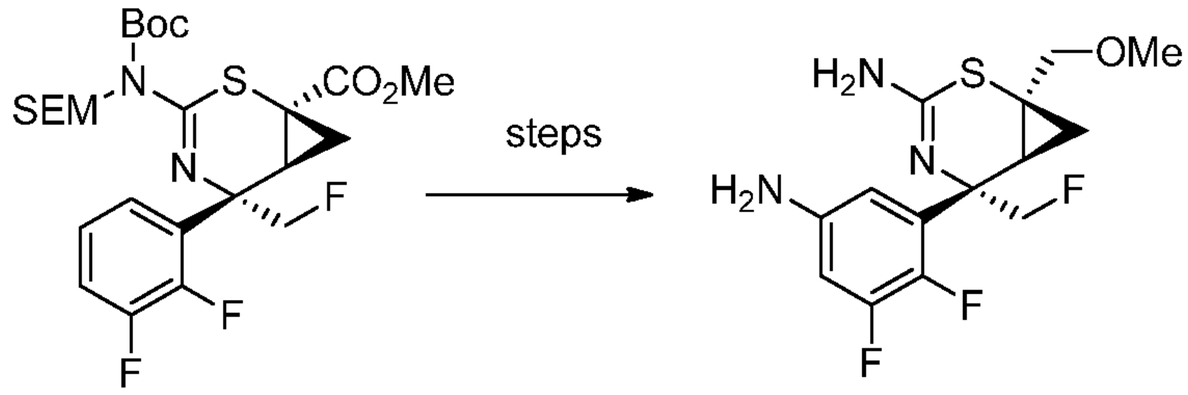
Preparation of Compound 207A. At RT, the mixture of diastereomers **210B** (3.92 g, 6.31 mmol) was treated with conc. sulfuric acid (25 mL, 0.47 mol), and stirred at RT for 10 min. The sticky mixture was added to ice (200 mL) and EtOAc (50 mL). The pH was adjusted to 9 with 10 M NaOH. The aqueous phase was extracted with EtOAc (3 x) and the combined organic extracts were washed with brine (1 x), dried over $MgSO_4$, filtered, and concentrated to give (5S)-methyl 3-amino-5-(5-bromo-2-fluorophenyl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylate (207A) as an off white foam that was used in the next step without further purification. LC/MS (ESI) *m/z* = 391.0 $(M+H)^+$.

Preparation of Compound 207B and Compound 207C. To a mixture of copper(I) iodide (0.241 g, 1.27 mmol), sodium azide (1.24 g, 19.1 mmol), and (5S)-methyl 3-amino-5-(5-bromo-2-fluorophenyl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylate (207A, material prepared as described above) at room temperature was added EtOH (9 mL) and water (4.5 mL). The reaction mixture was degassed by bubbling nitrogen through the solution for 5 min and N,N''-dimethylcyclohexane-1,2-diamine (0.200 mL, 1.27 mmol) was added. The reaction mixture was heated to 70 °C for 1.5 h and cooled to room temperature. The mixture was poured into 10:1 saturated NH_4Cl/ammonium hydroxide, and diluted with EtOAc. The aqueous phase was extracted with EtOAc (3 x) and the combined organic extracts were washed with brine (1 x), dried over $MgSO_4$, filtered, concentrated to give a dark yellow oil. The oil was dissolved in THF (20 mL) and water (7 mL) and trimethylphosphine (1.0 M solution in THF, 6.3 mL, 6.3 mmol) was added. The reaction mixture was stirred at RT

for 15 min, transferred to a separatory funnel, and diluted with water and EtOAc. The aqueous phase was extracted with EtOAc (3 x) and the combined organic extracts were washed with brine (1 x), dried over $MgSO_4$, filtered, and concentrated to give a yellow foam. Purification by flash column chromatography on silica gel (80 g, eluted with 50% to 100% EtOAc in heptane gradient) gave (1S,5S,6S)-methyl 3-amino-5-(5-amino-2-fluorophenyl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylate (**207B**, 1.62 g) as a white foam. LC/MS (ESI) *m/z* = 328.1 $(M+H)^+$. ^1H NMR (400 MHz, CHLOROFORM-d) δ ppm 6.92 (d, *J*=6.40 Hz, 1H), 6.86 (dd, *J*=11.64, 8.51 Hz, 1H), 6.56 (dt, *J*=8.51, 3.47 Hz, 1H), 4.93 (dd, *J*=8.61, 1.17 Hz, 1H), 4.82 (dd, *J*=8.61, 1.37 Hz, 1H), 4.72 (d, *J*=9.39 Hz, 1H), 4.66 (s br, 2H), 4.61 (d, *J*=8.61 Hz, 1H), 3.77 (s, 3H), 3.56 (s br, 2H), 2.50-2.57 (m, 1H), 1.69 (dd, *J*=9.98, 5.09 Hz, 1H), 1.02 (dd, *J*=7.24, 5.09 Hz, 1H). In addition, (1R,5S,6R)-methyl 3-amino-5-(5-amino-2-fluorophenyl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylate (**207C**, 0.280 g) was isolated as a yellow foam. LC/MS (ESI) *m/z* = 328.1 $(M+H)^+$. ^1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 6.81-6.88 (m, 1H), 6.53-6.59 (m, 2H), 4.66 (s br, 2H), 4.53-4.83 (m, 2H), 3.74 (s, 3H), 3.52 (s br, 2H), 2.79 (dd, *J*=9.78, 7.43 Hz, 1H), 1.71 (dd, *J*=9.49, 5.38 Hz, 1H), 1.42-1.60 (m, 1H).

Preparation of Compound 207. To a solution of (1S,5S,6S)-methyl 3-amino-5-(5-amino-2-fluorophenyl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylate (**207B**, 1.24 g, 3.79 mmol) in THF (15 mL) at RT was added lithium borohydride (2.0 M solution in THF, 5.70 mL, 11.4 mmol) and MeOH (1.20 mL, 29.6 mmol). The reaction mixture was stirred at room temperature for 4 h and quenched slowly with saturated NH_4Cl. After bubbling ceased, the mixture was transferred to a separatory funnel and diluted with water, EtOAc, and saturated NH_4Cl. The aqueous phase was extracted with EtOAc (4 x) and the combined organic extracts were washed with brine (1 x), dried over $MgSO_4$, filtered, concentrated. Purification by flash column chromatography on silica gel (40 g, eluted with 40% to 100% EtOAc [10% MeOH (2 M NH_3)] in heptane gradient) gave ((1S,5S,6S)-3-amino-5-(5-amino-2-fluorophenyl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)methanol (**207**, 1.06 g, 3.54 mmol, 93% yield) as a white solid. LC/MS (ESI) *m/z* = 300.0 $(M+H)^+$. ^1H NMR (400 MHz, DMSO-d6) δ ppm 6.84 (dd, *J*=6.85, 2.93 Hz, 1H), 6.79 (dd, *J*=12.32, 8.61 Hz, 1H), 6.43 (dt, *J*=8.22, 3.52 Hz, 1H), 6.12 (s, 2H), 5.02 (t, *J*=5.97 Hz, 1H), 4.84 (s, 2H), 4.66-4.74 (m, 1H), 4.54-4.61 (m, 1H), 3.53 (dd, *J*=11.54, 6.26 Hz, 1H), 3.39 (dd, *J*=11.54, 5.48 Hz, 1H), 1.54-1.60 (m, 1H), 0.95 (dd, J=9.49, 4.99 Hz, 1H), 0.41 (t, *J*=5.77 Hz, 1H).

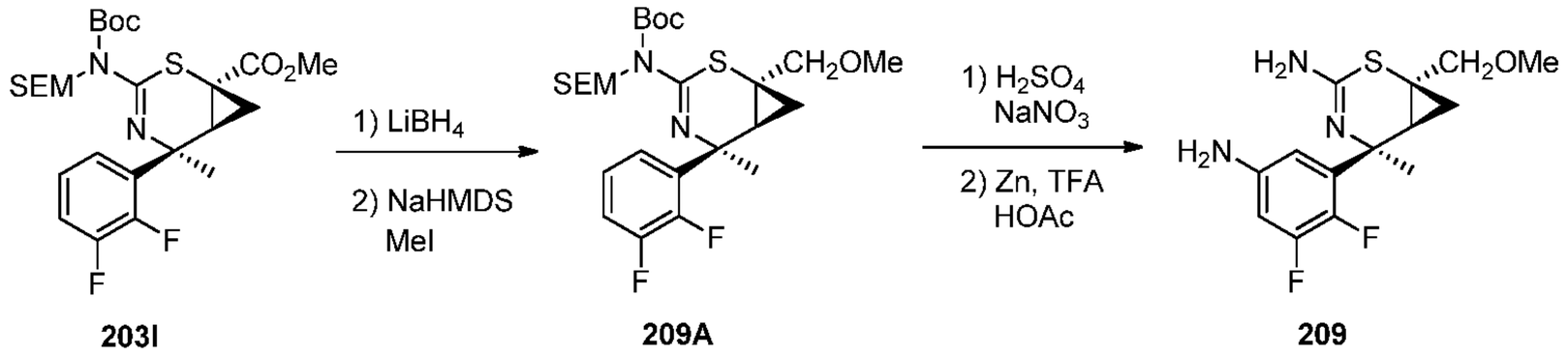
(1S,5S,6S)-Methyl 3-amino-5-(5-amino-2,3-difluorophenyl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylate (208).



201I **208**

The title compound was prepared from **201I** using the chemical procedures described for intermediate **209** (see below), except LHMDS was used in the place of NaHMDS. LC/MS (ESI$^-$) *m/z* = 332.0 $(M+H)^+$. ^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm (ddd, *J*=5.18, 2.93, 1.86 Hz, 1 H) 6.38 - 6.45 (m, 1 H) 4.56 - 4.91 (m, 3 H) 3.60 - 3.65 (m, 1 H) 3.39 (s, 3 H) 3.31 - 3.37 (m, 1 H) 1.69 - 1.75 (m, 1 H) 1.10 (dd, *J*=9.59, 5.67 Hz, 1 H) 0.74 (t, *J*=6.16 Hz, 1 H).

(1S,5S,6S)-5-(5-Amino-2,3-difluorophenyl)-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (209).



203I **209A** **209**

Preparation of Compound 209A. To a solution of (1S,5S,6S)-methyl 3-((*tert*-butoxycarbonyl)((2-(trimethylsilyl)ethoxy)methyl)amino)-5-(2,3-difluorophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylate (**203I**, 2.70 g, 4.98 mmol) in THF (20 mL) at 20 °C under nitrogen was added lithium borohydride (2.0 M in THF, 4.98 mL, 9.95 mmol) followed by MeOH (2.01 mL, 49.8 mmol). Gas evolution was noticed after addition of MeOH. After 15 min, the reaction was then cooled to 0 °C and carefully quenched with sat. NH_4Cl (20 mL). The reaction was then partitioned between 0.5 M $KHPO_4$ (40 mL) and 1:1 EtOAc/heptane (75 mL). The aqueous layer was further extracted with 1:1 EtOAc/heptane (25 mL). The combined organic extracts were washed with saturated NaCl (2 x 20 mL), dried over MgSO4, and then concentrated under

reduced pressure to afford the alcohol intermediate (2.70 g) as sticky oil. *m/z* (ESI, +ve ion) 515.2 $(M+1)^+$.

To a solution of crude alcohol intermediate (2.70 g) in THF (6 mL) at 0 ºC under nitrogen was added sodium bis(trimethylsilyl)amide (1.0 M in THF, 6.47 mL, 6.47 mmol) at a rate that did not exceed 5 ºC. The solution was stirred for 5 min at 0 ºC then iodomethane (0.433 mL, 6.97 mmol) added at a rate that did not exceed 7 ºC. The cooling bath was removed and reaction stirred for 2 h at 20 ºC. The LCMS suggested 95% conversion. The reaction was quenched with sat. NH_4Cl (10 mL) and then partitioned between 0.5 M $KHPO_4$ (20 mL) with 1 M HCl (20 mL) and 1:1 EtOAc/heptane (75 mL). The aqueous portion was further extracted with 1:1 EtOAc/heptane (25 mL). The combined organic extracts were washed with sat. NaCl (2 x 20 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (120 g) eluting with a gradient of 0-15% EtOAc/heptane to afford *tert*-butyl ((1S,5S,6S)-5-(2,3-difluorophenyl)-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (**209A**, 2.00 g, 3.78 mmol, 76% yield) as colorless oil. *m/z* (ESI, +ve ion) 529.3 $(M+1)^+$.

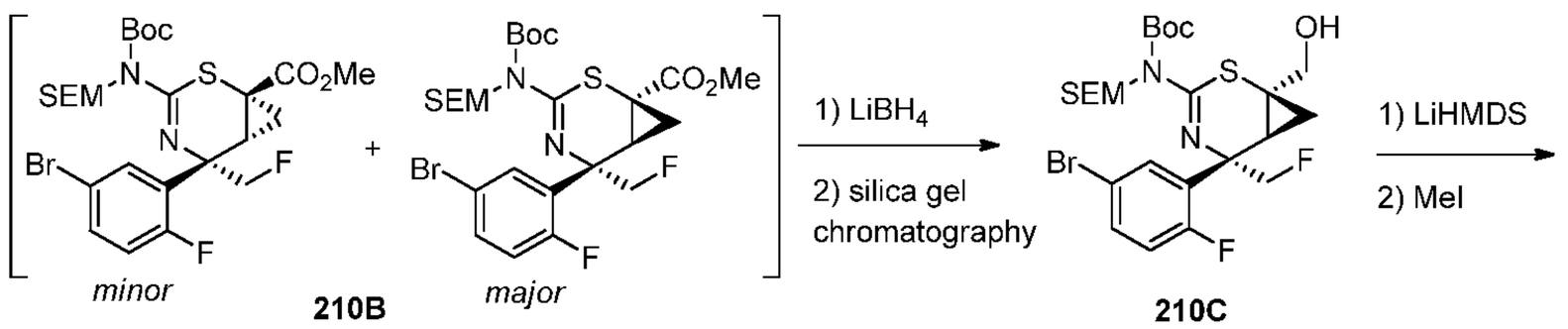
Preparation of Compound 209. At RT, to *tert*-butyl ((1S,5S,6S)-5-(2,3-difluorophenyl)-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (**209A**, 2.0 g, 3.78 mmol) in a 250 mL round bottom flask equipped with a magnetic stir bar and nitrogen line (no solvent) at 0 ºC was added chilled (0 ºC) neat sulfuric acid (15 mL). The internal temperature reached to 5 ºC, gas evolution was evident, and a red color developed. After 15 min, the reaction was cooled with an ice bath and treated with sodium nitrate (0.35 g, 4.16 mmol) in one portion. After 10 min, the reaction was poured onto wet ice (100 mL) contained in a 500 mL Erylmeyer flask. That flask was then jacketed with a wet ice cooling bath. To the mixture was added CH_2Cl_2 (50 mL) followed by dropwise addition of NaOH (4 M, 150 mL) at a rate that did not exceed an internal temp of 5 ºC until pH 14 was achieved. To the flask was added 9:1 $CHCl_3$/IPA (50 mL). The mixture was transferred to a separatory funnel and the layers were separated. The aqueous portion was further extracted with $CHCl_3$/IPA (2 x 50 mL). The combined organic extracts were dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (120 g) eluting with a 0-1.5% of 2 M NH_3 in MeOH in CH_2Cl_2 to

afford (1S,5S,6S)-5-(2,3-difluoro-5-nitrophenyl)-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (0.63 g, 1.83 mmol, 48% yield) as amber oil. *m/z* (ESI, +ve ion) 344.0 $(M+1)^+$.

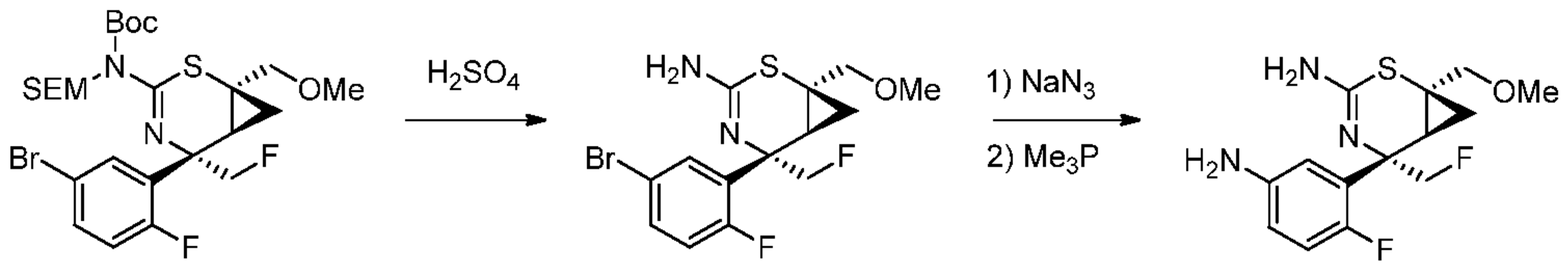
To a stirring solution of (1S,5S,6S)-5-(2,3-difluoro-5-nitrophenyl)-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (0.63 g, 1.83 mmol) in glacial HOAc (5 mL) and TFA (5 mL) at 20 °C was added nanopowder zinc (0.67 g, 10.29 mmol). After 90 min the reaction was concentrated under reduced pressure to a thick oil/suspension. The residue was partitioned between 9:1 $CHCl_3$/IPA (50 mL) and 10% NH_4OH (50 mL). The separated aqueous layer was further washed with 9:1 $CHCl_3$/IPA (20 mL). The combined organic solution was washed with sat. NaCl (20 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with a gradient of 1-6% of 2 M NH_3 in MeOH in DCM to afford (1S,5S,6S)-5-(5-amino-2,3-difluorophenyl)-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (**209**, 0.53 g, 1.69 mmol, 92% yield) as tan foam. *m/z* (ESI, +ve ion) 314.1 $(M+1)^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 6.67 (br., 1H), 6.36 (m, 1H), 5.92 (br., 2H), 5.12 (br. s., 2H), 3.55 (d, *J*=10.95 Hz, 1H), 3.36 (d, *J*=10.95 Hz, 1H), 3.32 (s, 3H), 1.61 (br., 1H), 1.56 (s, 3H), 0.87 (br., 1H), 0.57 (br., 1H).

(1S,5S,6S)-5-(5-Amino-2-fluorophenyl)-5-(fluoromethyl)-1-(methoxymethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (210).

204G **210A**



210B **210C**



210D **210E** **210**

Preparation of Compound 210A. To a solution of (S)-*tert*-butyl (4-(5-bromo-2-fluorophenyl)-4-(fluoromethyl)-4H-1,3-thiazin-2-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (204G, 40.2 g, 73.2 mmol) in THF (270 mL) under N_2 at -78 °C was added lithium diisopropylamide (2 M solution in THF/heptane/ethylbenzene, 36.6 mL, 73.2 mmol) dropwise at the rate where internal temperature did not exceed -50 °C. After addition, the mixture was then stirred at the same temperature for 45 min. CO_2 (gas) was bubbled into the mixture at the rate where internal temperature did not exceed -50 °C for 30 min. The mixture was warmed to RT and was quenched with saturated ammonium chloride. It was diluted with EtOAc and H_2O. The organic layer was separated, washed with HCl (1 N) followed by brine, dried over $MgSO_4$, and concentrated. The residue was dissolved in THF (220 mL) and MeOH (24.44 mL) and cooled with an ice bath. (Trimethylsilyl)diazomethane (2.0 M solutions in hexanes, 43.9 mL, 88 mmol) was added dropwise to the mixture. It was stirred at 0 °C for 20 min and quenched with HOAc (5 mL). The mixture was washed with saturated $NaHCO_3$, brine, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel flash column chromatography using ISCO instrument (0%-15% EtOAc/heptane) to give (S)-methyl 4-(5-bromo-2-fluorophenyl)-2-((*tert*-butoxycarbonyl)((2-

(trimethylsilyl)ethoxy)methyl)amino)-4-(fluoromethyl)-4H-1,3-thiazine-6-carboxylate (**210A**, 31.2 g, 51.4 mmol, 70% yield) as a white solid. LC/MS (ESI^-) *m/z* = 607.1, 609.0, 629.0, 631.1. ^1H NMR (CHLOROFORM-d) δ: 7.65 (dd, J=6.8, 2.5 Hz, 1H), 7.42 (ddd, J=8.6, 4.3, 2.5 Hz, 1H), 7.22 (d, J=4.5 Hz, 1H), 6.96 (dd, J=11.2, 8.6 Hz, 1H), 5.27-5.43 (m, 2H), 4.55-4.96 (m, 2H), 3.84 (s, 3H), 3.63-3.72 (m, 2H), 1.56 (s, 9H), 0.95-1.02 (m, 2H), 0.00 (s, 9H).

Preparation of Compound 210B. To a solution of trimethylsulfoxonium iodide (8.74 g, 39.7 mmol) in dimethyl sulfoxide (39 mL) at 0 °C under N_2 was added potassium *tert*-butoxide (4.19 g, 37.3 mmol) in two portions. The reaction mixture (A) was stirred at RT for 1 h. 20 mL of reaction mixture (A) was added to a solution of (S)-methyl 4-(5-bromo-2-fluorophenyl)-2-((*tert*-butoxycarbonyl)((2-(trimethylsilyl)ethoxy)methyl)amino)-4-(fluoromethyl)-4H-1,3-thiazine-6-carboxylate (**210A**, 12.06 g, 19.85 mmol) in DMSO (50 mL) dropwise. After addition, the mixture was then stirred RT for 1 h. LCMS showed some starting material. It was treated with additional 2 mL of the mixture A and stirred at RT for overnight. LCMS showed some starting material. It was treated with 4 mL of the mixture A and stirred at RT for 4.5 h. LCMS showed no starting material. The reaction mixture was quenched with saturated NH_4Cl and extracted with EtOAc (2 x). The organic solution was washed with brine, dried over $MgSO_4$, and concentrated to give 13.16 g of thick oil, 210B, as a mixture of (1R,5S,6R)-methyl 5-(5-bromo-2-fluorophenyl)-3-((*tert*-butoxycarbonyl)((2-(trimethylsilyl)ethoxy)methyl)amino)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylate (*minor product*) and (1S,5S,6S)-methyl-5-(5-bromo-2-fluorophenyl)-3-((*tert*-butoxycarbonyl)((2-(trimethylsilyl)ethoxy)methyl) amino)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylate (*major product*). LC/MS (ESI^-) *m/z* = 621.0, 623.2

Preparation of Compound 210C. To a solution of **210B** (6.1 g, 9.81 mmol) in THF (50 mL) at 0 °C under N_2 was added lithium borohydride (2 M solution in THF, 9.81 mL, 19.63 mmol) dropwise followed by MeOH (3.18 mL, 79 mmol). The mixture was stirred at 0 °C for 1 h and 45min. It was quenched with saturated ammonium chloride, washed with HCl (1 N), then saturated $NaHCO_3$, brine, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel flash column chromatography using ISCO instrument (0%-80% EtOAc/heptane) to give *tert*-butyl ((1S,5S,6S)-5-(5-bromo-2-fluorophenyl)-5-(fluoromethyl)-1-(hydroxymethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (**210C**, 4.6 g, 7.75 mmol, 79% yield)

as a light yellow oil. LC/MS (ESI^-) *m/z* = 593.2, 595.1. ^1H NMR (CHLOROFORM-d) δ: 7.77 (dd, J=6.8, 2.5 Hz, 1H), 7.40 (ddd, J=8.5, 4.3, 2.5 Hz, 1H), 6.96 (dd, J=11.5, 8.6 Hz, 1H), 5.28-5.31 (m, 1H), 5.07 (d, J=10.6 Hz, 1H), 4.82-4.99 (m, 1H), 4.61-4.79 (m, 1H), 3.49-3.87 (m, 4H), 1.88-1.95 (m, 1H), 1.52 (s, 9H), 0.94-1.07 (m, 3H), 0.73 (t, J=6.4 Hz, 1H), 0.00 (s, 9H)

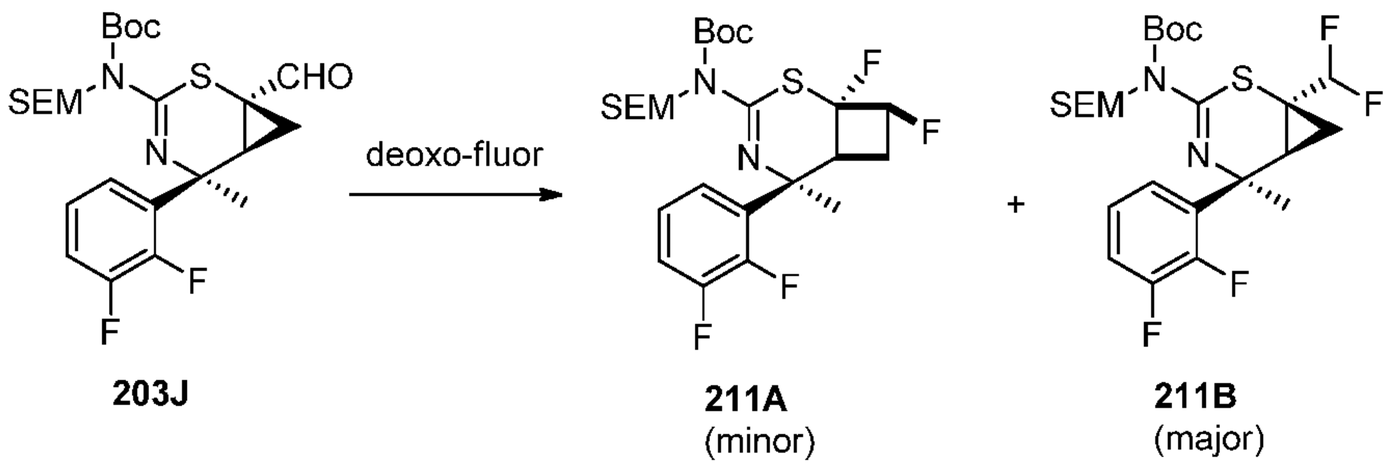
Preparation of Compound 210D. To a solution of *tert*-butyl ((1S,5S,6S)-5-(5-bromo-2-fluorophenyl)-5-(fluoromethyl)-1-(hydroxymethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (**210C**, 3.2 g, 5.39 mmol) in THF (20 mL) under N_2 at 0 °C was added lithium bis(trimethylsilyl)amide (1.0 M solution in THF, 8.09 mL, 8.09 mmol) dropwise. After addition, the mixture was stirred at 0 °C for 30 min and iodomethane (0.502 mL, 8.09 mmol) was added dropwise. It was stirred at 0 °C for 20 min followed by RT overnight. The mixture was quenched with saturated NH_4Cl and diluted with H_2O. It was extracted with EtOAc (2 x). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel flash column chromatography using ISCO instrument (10%-60% EtOAc/heptane) to give *tert*-butyl ((1S,5S,6S)-5-(5-bromo-2-fluorophenyl)-5-(fluoromethyl)-1-(methoxymethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (**210D**, 3.17 g, 5.22 mmol, 97 % yield) as a light yellow oil. LC/MS (ESI^-) *m/z* = 607.1, 609.0. ^1H NMR (CHLOROFORM-d) δ: 7.83 (dd, J=6.9, 2.4 Hz, 1H), 7.36-7.42 (m, 1H), 6.96 (dd, J=11.6, 8.7 Hz, 1H), 5.01-5.32 (m, 2H), 4.64-4.96 (m, 2H), 3.63-3.69 (m, 2H), 3.39 (s, 3H), 1.87 (t, J=7.1 Hz, 1H), 1.52 (s, 9H), 0.94-1.06 (m, 3H), 0.77 (t, J=6.2 Hz, 1H), 0.00 (s, 9H)

Preparation of Compound 210E. To a RBF containing *tert*-butyl ((1S,5S,6S)-5-(5-bromo-2-fluorophenyl)-5-(fluoromethyl)-1-(methoxymethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (**210D**, 3.17 g, 5.22 mmol) at 0 °C was added conc. sulfuric acid (13.90 mL, 261 mmol) dropwise. After the addition, the mixture was stirred at 0 °C for 30 min. It was adjusted to pH = 10-14 by 5 N NaOH. The mixture was extracted with EtOAc (2 x). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel flash column chromatography using ISCO instrument (0%-10% MeOH/DCM) to give (1S,5S,6S)-5-(5-bromo-2-fluorophenyl)-5-(fluoromethyl)-1-(methoxymethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (**210E**, 1.73 g, 4.59 mmol, 88% yield) as a yellow solid. LC/MS (ESI^-) *m/z* = 377.0, 379.0. ^1H NMR

(CHLOROFORM-d) δ: 7.78 (dd, J=7.0, 2.5 Hz, 1H), 7.38 (ddd, J=8.6, 4.2, 2.7 Hz, 1H), 6.94 (dd, J=11.5, 8.6 Hz, 1H), 5.30 (s, 1H), 4.52-4.92 (m, 3H), 3.62 (d, J=10.6 Hz, 1H), 3.39 (s, 3H), 3.35 (d, J=10.6 Hz, 1H), 1.77 (t, J=8.2 Hz, 1H), 1.08 (dd, J=9.6, 5.9 Hz, 1H), 0.74 (t, J=6.3 Hz, 1H)

Preparation of Compound 210. To a solution of (1S,5S,6S)-5-(5-bromo-2-fluorophenyl)-5-(fluoromethyl)-1-(methoxymethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (**210E**, 1.73 g, 4.59 mmol) in EtOH (3.0 mL), IPA (3.0 mL), and water (1.50 mL) was added sodium azide (0.894 g, 13.76 mmol), copper(i) iodide (0.218 g, 1.146 mmol), sodium L-ascorbate (0.227 g, 1.146 mmol), and *trans*-N,N'-dimethylcyclohexane-1,2-diamine (0.181 mL, 1.146 mmol). Then, N_2 was bubbled into the mixture for 5 min. The mixture was stirred at 70 °C under N_2 for 3 h. It was quenched with saturated NH_4Cl/NH_4OH (10:1), extracted with EtOAc (2 x). The combined organic extracts were dried over $MgSO_4$ and concentrated. The residue was dissolved in THF/H_2O (9:1, 20 mL) and trimethylphosphine (1.0M solution in THF) (4.59 mL, 4.59 mmol) was added. After the mixture was stirred at RT for 30 min, it was quenched with saturated $NaHCO_3$, and extracted with EtOAc. The organic solution was washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by silica gel flash column chromatography using ISCO instrument (0%-20% MeOH/DCM) to give (1S,5S,6S)-5-(5-amino-2-fluorophenyl)-5-(fluoromethyl)-1-(methoxymethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (**210**, 1.07 g, 3.41 mmol, 74.5 % yield) as a yellow solid. LC/MS (ESI^-) *m/z* =314.1. ^1H NMR (CHLOROFORM-d) δ: 6.89 (d, J=4.1 Hz, 1H), 6.84 (dd, J=11.6, 8.7 Hz, 1H), 6.54 (d, J=8.4 Hz, 1H), 4.58-4.93 (m, 2H), 3.63 (d, J=10.6 Hz, 1H), 3.38 (s, 3H), 3.33 (d, J=10.4 Hz, 1H), 1.75 (t, J=8.1 Hz, 1H), 1.04-1.11 (m, 1H), 0.72 (t, J=6.3 Hz, 1H).

(1S,5S,6S)-5-(5-Amino-2,3-difluorophenyl)-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (211).



203J

211A (minor)

211B (major)

211

Preparatipn of Compound 211B. At -10 °C (ice/salt), to a stirred solution of *tert*-butyl ((1S,5S,6S)-5-(2,3-difluorophenyl)-1-formyl-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (**203J**, 380 mg, 0.74 mmol) in 5 mL of DCM was added deoxo-fluor (0.48 mL, 2.59 mmol). It was stirred at 0 °C for 1 h then RT for 2 h. It was diluted with 30 mL of DCM, washed with 20 mL of sat $NaHCO_3$ followed by 5 mL of brine. The organic solution was dried over sodium sulfate and concentrated. The residue was purified on a silica gel column (5-10% EtOAc in hexanes) to give:

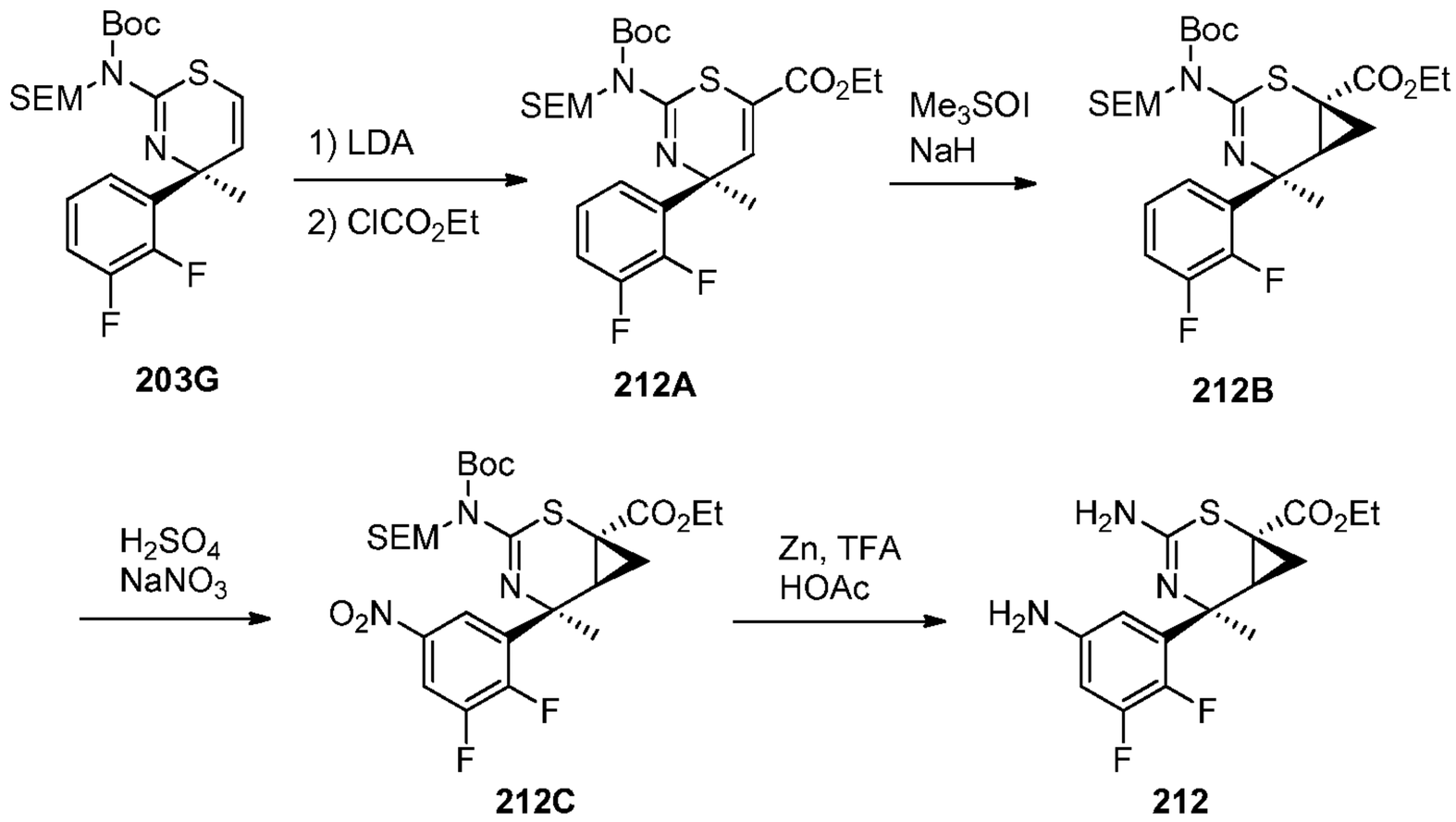
1) 1st eluent, *tert*-butyl ((1R,5S,6S,8S)-5-(2,3-difluorophenyl)-1,8-difluoro-5-methyl-2-thia-4-azabicyclo[4.2.0]oct-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl) carbamate (**211A**, 95 mg, 24% yield) as brown thick oil. *m/z* (ESI, +ve ion) 535.1 $(M+1)^+$. ^1H NMR (400 MHz, CHLOROFORM-d) δ 7.43 (t, *J*=7.40 Hz, 1H), 7.10 (m, 2H), 5.30 (d, *J*=10.76 Hz, 1H), 5.07-5.16 (m, 0.5H), 5.03 (d, *J*=8.61 Hz, 1H), 5.00 (m, 0.5H), 3.69 (m, 2H), 2.97 (m, 1H), 1.76 (m., 1H), 1.67 (s, 3H), 1.52 (s, 9H), 1.20 (m, 1H), 0.94 (m, 2H), 0.02 (s, 9H). ^{19}F NMR (376 MHz, CHLOROFORM-d) δ -112.71 (s, 1F), -138.50 (d, *J*=19.94 Hz, 1F), -139.76 (d, *J*=19.94 Hz, 1F), -173.68 (s, 1F).

2) 2nd eluent, *tert*-butyl ((1S,5S,6S)-1-(difluoromethyl)-5-(2,3-difluorophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl) carbamate (**211B**, 249 mg, 0.46 mmol, 62% yield) as brown sticky oil. *m/z* (ESI, +ve ion)

535.1 $(M+1)^+$. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.34 (m, 1H), 7.07 (m, 2H), 5.55-5.88 (m, 1H), 5.29 (d, *J*=10.37 Hz, 1H), 5.05 (d, *J*=10.56 Hz, 1H), 3.65 (m, 2H), 2.11 (dd, *J*=7.73, 9.29 Hz, 1H), 1.78 (s, 3H), 1.52 (s, 9H), 1.23 (m, 1H), 0.95 (m, 3H), 0.00 (s, 9H). ^{19}F NMR (376 MHz, CHLOROFORM-d) δ -118.00 (d, ^1J=280 Hz, 1F), -120.01 (d, ^1J=280 Hz, 1F), -138.73 (d, ^2J=19.94 Hz, 1F), -139.18 (d, ^2J=19.94 Hz, 1F).

Preparation of Compound 211. At RT, sulfuric acid (1 mL, 18.76 mmol) was added to *tert*-butyl ((1S,5S,6S)-1-(difluoromethyl)-5-(2,3-difluorophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (211B, 120 mg, 0.22 mmol). It was stirred at RT for 10 min. It was cooled with an ice bath and treated with sodium nitrate (24.80 mg, 0.29 mmol). Ice bath was removed. The mixture was stirred at RT for 2 h. It was cooled with an ice bath, treated with ice cube followed by 15 mL of DCM then potassium phosphate tribasic monohydrate (4.60 g, 20 mmol) in small portions. 2 mL of 2 N NaOH was added and pH was about 10. It was extracted with 2 x 20 mL of (9:1 = $CHCl_3$: iPrOH). The organic extracts were washed with 5 mL of brine and concentrated. The resulting brown residue containing (1S,5S,6S)-5-(2,3-difluoro-5-nitrophenyl)-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine was dissolved in 0.8 mL of glacial HOAc and 0.4 mL of TFA and treated with zinc (nanopowder, 88 mg, 1.34 mmol) at RT. It was stirred at RT for 3 h then concentrated under reduced pressure to remove TFA. The residue was basified with 2 N NaOH until pH was about 10. The mixture was extracted with 2 x 20 mL of (9:1 = $CHCl_3$: iPrOH). The organic extracts were washed with 5 mL of brine and concentrated. The residue was purified on a silica gel column (5% MeOH in DCM followed by 5% 2 M NH_3 in MeOH in DCM) to provide (1S,5S,6S)-5-(5-amino-2,3-difluorophenyl)-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (**211**, 47 mg, 0.15 mmol, 65% yield) as a brown amorphous solid. *m/z* (ESI, +ve ion) 320.0 $(M+1)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.52 (br., 1H), 6.38 (m, 2H), 6.23 (br., 1H), 5.77-6.04 (m, 1H), 5.14 (br., 2H), 1.84 (m, 1H), 1.59 (s, 3H), 1.30 (m, 1H), 0.67 (m, 1H). ^{19}F NMR (376 MHz, CHLOROFORM-d) δ -118.06 (d, ^1J=273 Hz, 1F), -115.47 (d, ^1J=273 Hz, 1F), -140.28 (d, ^2J=22.54 Hz, 1F), -155.35 (d, ^2J=22.64 Hz, 1F).

(1S,5S,6S)-Ethyl 3-amino-5-(5-amino-2,3-difluorophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylate (212).



Preparation of Compound 212A. In a 500 mL RBF, a solution of (S)-*tert*-butyl (4-(2,3-difluorophenyl)-4-methyl-4H-1,3-thiazin-2-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (3.05 g, 6.48 mmol) in 30 mL of THF at -78 ^{o}C was treated with lithium diisopropylamide (2 M solution in heptane/THF/ethylbenzene) (4.21 mL, 8.42 mmol) dropwise. The resulting mixture was stirred at -78 ^{o}C for 45 min and treated with ethyl chloroformate (1.852 mL, 19.44 mmol) via a syringe in one shot. The mixture was stirred for 30 min at -78 ^{o}C, then quenched with 50 mL of aq. NH_4Cl and warmed to RT. It was extracted with (2 x 100 mL) of EtOAc. The organic layers were combined, washed with 15 mL of brine, dried over sodium sulfate and concentrated. The residue was purified via flash chromatography on silica gel (80 g Grace column, eluted with 5-15% EtOAc in hexanes) to give (S)-ethyl 2-((*tert*-butoxycarbonyl)((2-(trimethylsilyl)ethoxy)methyl)amino)-4-(2,3-difluorophenyl)-4-methyl-4H-1,3-thiazine-6-carboxylate (**212A**, 2.5 g, 4.61 mmol, 71% yield) as a colorless viscous oil. *m/z* (ESI, +ve ion) 543.0 $(M+1)^{+}$. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.32 (m, 1H), 7.03-7.16 (m, 3H), 5.32 (d, *J*=10.37 Hz, 1H), 5.22 (d, *J*=10.37 Hz, 1H), 4.30 (m, 2H), 3.67 (m, 2H), 1.76 (s, 3H), 1.55 (s, 9H), 1.35 (t, *J*=7.14 Hz, 3H), 0.94 (m, 2H), 0.00 (s, 9H). ^{19}F NMR (377 MHz, CHLOROFORM-d) δ -137.70 (d, *J*=20.27 Hz, 1F), -138.25 (d, *J*=20.27 Hz, 1F).

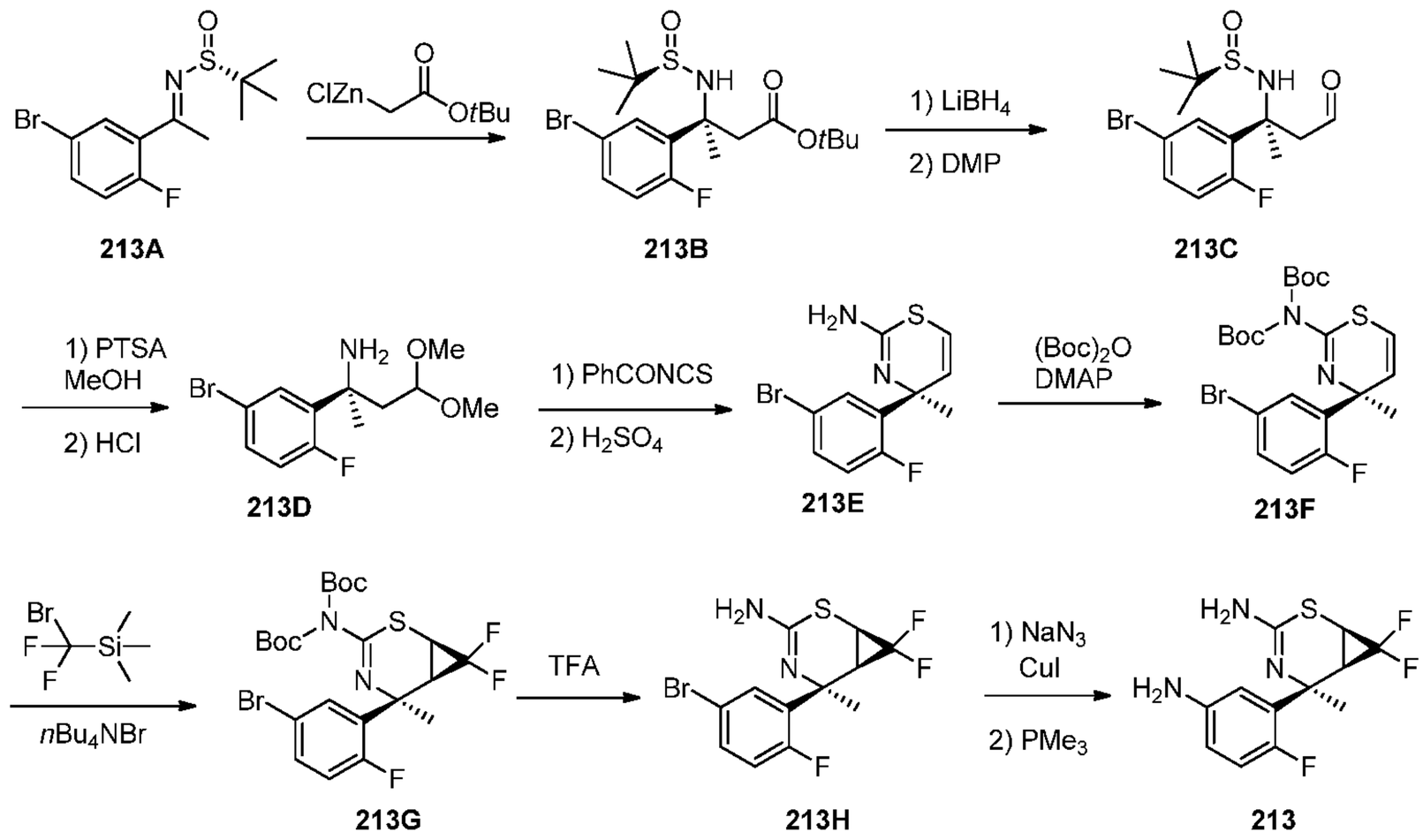
Preparation of Compound 212B. Preparation of Corey Chykovsky Reagent (0.25 M in DMSO): sodium hydride (60% wt.) (400 mg, 10 mmol) was added to a solution of trimethylsulfoxonium iodide (2.22 g, 10 mmol) in DMSO (40 mL) under argon. The mixture was stirred for 30 min before aliquots were used for cyclopropanation.

At RT, to a solution of (S)-ethyl 2-((*tert*-butoxycarbonyl)((2-(trimethylsilyl) ethoxy)methyl)amino)-4-(2,3-difluorophenyl)-4-methyl-4H-1,3-thiazine-6-carboxylate (**212A**, 2.5 g, 4.61 mmol) in 15 mL of THF was added freshly prepared Corey Chykovsky Reagent (0.25 M in DMSO) (27.6 mL, 6.91 mmol). The mixture was stirred at RT for 45 min. It was cooled with an ice bath and quenched with 50 mL of aq NH_4Cl, and extracted with (2 x 75 mL) EtOAc. The organic extracts were washed with 15 mL of brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified via flash chromatography on silica gel (40 g Grace column, elute with 1-15% EtOAc in hexanes) to provide (1S,5S,6S)-ethyl 3-((*tert*-butoxycarbonyl)((2-(trimethylsilyl)ethoxy)methyl)amino)-5-(2,3-difluorophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylate (**212B**, 2.11 g, 3.79 mmol, 82% yield) as a thick oil. *m/z* (ESI, +ve ion) 557.3 $(M+1)^+$.

Preparation of Compound 212C. At RT, sulphuric acid (5 mL, 94 mmol) was added to (1S,5S,6S)-ethyl 3-((*tert*-butoxycarbonyl)((2-(trimethylsilyl)ethoxy)methyl)amino)-5-(2,3-difluorophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylate (2.03 g, 3.65 mmol). It was stirred at RT for 10 min then cooled with an ice bath and treated with sodium nitrate (0.40 g, 4.74 mmol). Ice bath was removed. The mixture was stirred at RT for 45 min. It was cooled with an ice bath, treated with ice cube followed by 15 mL of DCM then potassium phosphate tribasic monohydrate (23.03 g, 100 mmol) in small portions. The mixture had a pH of about 8; 5 mL of 1 N NaOH was added and pH was about 10. It was extracted with (2 x 50 mL) (9:1 = $CHCl_3$: iPrOH). The organic extracts were concentrated and the residue was purified on a 40 g silica gel column (25-55% EtOAc in hexanes) to give (1S,5S,6S)-ethyl 3-amino-5-(2,3-difluoro-5-nitrophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylate (**212C**, 1.21 g, 3.26 mmol, 89% yield) as a brown amorphous solid. *m/z* (ESI, +ve ion) 372.0 $(M+1)^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.51-8.56 (m, 1H), 8.37 (dt, *J*=3.13, 6.36 Hz, 1H), 6.46 (s, 2H), 4.19 (q, *J*=7.11 Hz, 2H), 2.41 (t, *J*=8.51 Hz, 1H), 1.63 (s, 3H), 1.42 (dd, *J*=5.28, 9.59 Hz, 1H), 1.27 (m, 3H), 1.04 (m, 1H).

Preparation of Compound 212. Zinc (0.819 g, 12.52 mmol) was added to a stirred mixture of (1S,5S,6S)-ethyl 3-amino-5-(2,3-difluoro-5-nitrophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylate (0.93 g, 2.50 mmol) in HOAc (4 mL) and TFA (2 mL) at 0 °C. The reaction mixture was stirred at RT for 45 min then concentrated under reduced pressure (to remove the TFA). The residue was partitioned between 150 mL of EtOAc and 20 mL of 5 N NaOH. The organic solution was washed with 5 mL of brine and concentrated. The resulting crude product was purified via silica gel flash column chromatography eluting with 2-5% MeOH in DCM to give (1S,5S,6S)-ethyl 3-amino-5-(5-amino-2,3-difluorophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylate (**212**) (480 mg, 1.406 mmol, 56% yield) as a tan solid. *m/z* (ESI, +ve ion) 342.0 $(M+1)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.71 (d, *J*=5.73 Hz, 1H), 6.37 (m, 1H), 6.10 (s, 2H), 5.16 (s, 2H), 4.17 (q, *J*=7.11 Hz, 2H), 2.29 (m, 1H), 1.55 (s, 3H), 1.42 (dd, *J*=4.89, 9.78 Hz, 1H), 1.21 (t, *J*=7.14 Hz, 3H), 0.95 (dd, *J*=5.09, 7.24 Hz, 1H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -140.14 (d, *J*=20.20 Hz, 1F), -156.28 (d, *J*=20.20 Hz, 1F).

(1R,5S,6S)-5-(5-Amino-2-fluorophenyl)-7,7-difluoro-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (213).



Preparation of (S)-*tert*-butyl 3-(5-bromo-2-fluorophenyl)-3-((R)-1,1-dimethylethylsulfinamido)butanoate (213B). To a 3-L 3-neck RBF was added (R,E)-N-(1-(5-bromo-2-fluorophenyl)ethylidene)-2-methylpropane-2-sulfinamide (**213A**, 51 g, 159 mmol) and THF (400 mL). The flask was equipped with a temperature probe, and an

overhead stirrer. The solution was cooled in a dry ice / acetone bath to an internal temperature of -50.9 °C. (2-(*tert*-butoxy)-2-oxoethyl)zinc (II) chloride (0.5 M in ether, 796 mL, 398 mmol, Rieke Metals) was added slowly to the stirring solution over 45 min via cannula. After 20 min, the dry ice / acetone bath was removed and the reaction warmed to ambient temperature and stirred for 16 h. The flask was placed in an ice / water bath and cooled to 5 °C before slowly adding saturated ammonium chloride (aq.) solution (300 mL) and water (300 mL). The reaction was extracted with EtOAc (2 x 300 mL). The combined organic layers were washed sequentially with a 9:1 saturated ammonium chloride to saturated ammonium hydroxide solution (2 x) and brine before drying over magnesium sulfate and concentrating under reduced pressure to afford crude (S)-*tert*-butyl 3-(5-bromo-2-fluorophenyl)-3-((R)-1,1-dimethylethylsulfinamido)butanoate (74.44 g, 171 mmol, 213b, 107% yield) as a yellow oil which solidified upon sitting. The material was used in the next step without further purification assuming theoretical yield. MS *m/z* = 436.0 M^+.

Preparation of (R)-N-((S)-2-(5-bromo-2-fluorophenyl)-4-oxobutan-2-yl)-2-methylpropane-2-sulfinamide (213C). A 3-neck 3-L RBF was charged with a solution of (S)-*tert*-butyl 3-(5-bromo-2-fluorophenyl)-3-((R)-1,1-dimethylethylsulfinamido)butanoate (64.9 g, 149 mmol, 213b) in THF (400 mL). The flask was equipped with an overhead stirrer, a 250 mL addition funnel, and a temperature probe. The addition funnel was charged with $LiBH_4$ (2.0 M in THF, 186 mL, 372 mmol, Sigma Aldrich) via cannula. The $LiBH_4$ was added to the stirring solution at room temperature. The addition funnel was removed and replaced with a 125 mL addition funnel which was subsequently charged with MeOH (30.1 mL, 744 mmol). The MeOH was added dropwise to the stirring solution at RT via addition funnel. Evolution of gas observed and the internal temperature of the reaction rose to 47.5 °C over the course of the reaction and then began to subside. Upon reaching an internal temperature of 26 °C, a 250 mL addition funnel was attached to the reaction flask and charged with an additional portion of $LiBH_4$ (186 mL of 2.0M in THF, 372 mmol, Sigma Aldrich) via cannula. The $LiBH_4$ was added to the reaction. The addition funnel was removed and replaced with a 125 mL addition funnel which was then with MeOH (30.1 mL, 744 mmol). The MeOH was added dropwise to the stirring solution. Evolution of gas was observed and the internal temperature increased to 35 °C and then subsided. After 20 min, the flask was placed in an ice / water bath and carefully quenched with saturated ammonium chloride (aq.) solution. The reaction was diluted with water and EtOAc and stirred for 16 h. The

solids were filtered off and washed with EtOAc. The filtrate and washes were combined and transferred to a separatory funnel. The organic layer was separated, washed with brine, dried over magnesium sulfate and concentrated under reduced pressure to afford (R)-N-((S)-2-(5-bromo-2-fluorophenyl)-4-hydroxybutan-2-yl)-2-methylpropane-2-sulfinamide (50.93 g) as a white solid. MS *m/z* = 366.0 M^+. This material was used as crude.

(R)-N-((S)-2-(5-bromo-2-fluorophenyl)-4-hydroxybutan-2-yl)-2-methylpropane-2-sulfinamide (5.5 g, 15.02 mmol) was taken up in DCM (400 mL). Dess-martinperiodinane (DMP) (6.37 g, 15.02 mmol, Sigma Aldrich) was added. After 30 min, the reaction was quenched with 50 mL of aq. $Na_2S_2O_3$ and 50 mL of aq. $NaHCO_3$. The mixture was stirred for 10 min before partitioning. The aqueous portion was extracted with DCM (100 mL) and the combined organic layers were dried over $MgSO_4$. Filtration and concentration under reduced pressure, followed by silica gel flash chromatography on silica gel using a gradient of 10-60% EtOAc in hexanes afforded (R)-N-((S)-2-(5-bromo-2-fluorophenyl)-4-oxobutan-2-yl)-2-methylpropane-2-sulfinamide (**213C,** 3.3 g, 9.06 mmol, 60% yield) as a clear oil. MS *m/z* = 364.0 M^+.

Preparation of (S)-2-(5-bromo-2-fluorophenyl)-4,4-dimethoxybutan-2-amine (213D). (R)-N-((S)-2-(5-bromo-2-fluorophenyl)-4-oxobutan-2-yl)-2-methylpropane-2-sulfinamide (3.3 g, 9.06 mmol, 213c) was taken up in MeOH (50 mL). p-toluenesulfonic acid monohydrate (0.086 g, 0.453 mmol, Sigma Aldrich) was added, and the mixture was heated to 75 °C. After 30 min, the mixture was cooled to RT and HCl (4.0 M in 1,4-dioxane, 3.40 mL, 13.59 mmol, Sigma Aldrich) was added. After 1 h, the solvent was removed under reduced pressure. The residue was partitioned between a solution of 9:1 chloroform:IPA (50 mL) and saturated aqueous $NaHCO_3$ (50 mL). The aqueous portion was extracted with 9:1 chloroform:IPA (50 mL). The combined organic extracts were dried over $MgSO_4$. Filtration and concentration under reduced pressure afforded (S)-2-(5-bromo-2-fluorophenyl)-4,4-dimethoxybutan-2-amine (213d, 2.7 g, 8.82 mmol, 97% yield) as a yellow oil. The product was carried on without additional purification. MS *m/z* = 306.1 M^+.

Preparation of (R)-4-(5-bromo-2-fluorophenyl)-4-methyl-4H-thiopyran-2-amine (213E). To a solution of (S)-2-(5-bromo-2-fluorophenyl)-4,4-dimethoxybutan-2-amine (25.03 g, 82 mmol, 213d) in DCM (164 mL) was added benzoyl isothiocyanate (11.00 mL, 82 mmol, Sigma Aldrich) at RT. The reaction was stirred for 30 min then concentrated under reduced pressure. The residue was taken up in sulfuric acid (96 mL,

1799 mmol) and the reaction was heated to 50 °C for 16 h. The reaction was cooled to room temperature then carefully poured into an Erlenmeyer flask containing wet ice. The flask was placed in a water bath and the reaction was carefully basified to pH = 14 by the slow addition of 10 N NaOH. The solution was extracted with DCM (3 x). The combined organic layers were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The crude residue was purified via silica gel flash chromatography using a gradient of 0-5% 2 M ammonia in MeOH in DCM) to afford (R)-4-(5-bromo-2-fluorophenyl)-4-methyl-4H-thiopyran-2-amine (**213E**, 12.5 g, 41.6 mmol, 51% yield) as a brown oil. MS *m/z* = 301.0 M^+.

Preparation of N,N-Bis Boc protected (S)-4-(5-bromo-2-fluorophenyl)-4-methyl-4H-1,3-thiazin-2-amine (213F). To a solution of di-*tert*-butyl dicarbonate (0.91 g, 4.16 mmol, Sigma Aldrich) in THF (4.6 mL) at room temperature was added a solution of (S)-4-(5-bromo-2-fluorophenyl)-4-methyl-4H-1,3-thiazin-2-amine (**213E**, 0.57 g, 1.89 mmol) and 4-(dimethylamino)-pyridine (5.78 mg, 0.05 mmol, Sigma Aldrich) in THF (4.6 mL) dropwise via syringe. The reaction was stirred for one h. The reaction was diluted with water and EtOAc. The organic layer was separated, washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The crude residue was purified via silica gel flash chromatography using a gradient of 0-20% EtOAc in Hexanes to afford N,N-Bis Boc protected (S)-4-(5-bromo-2-fluorophenyl)-4-methyl-4H-1,3-thiazin-2-amine (**213F**, 0.80 g, 1.59 mmol, 84% yield). MS *m/z* = 501.0 M^+.

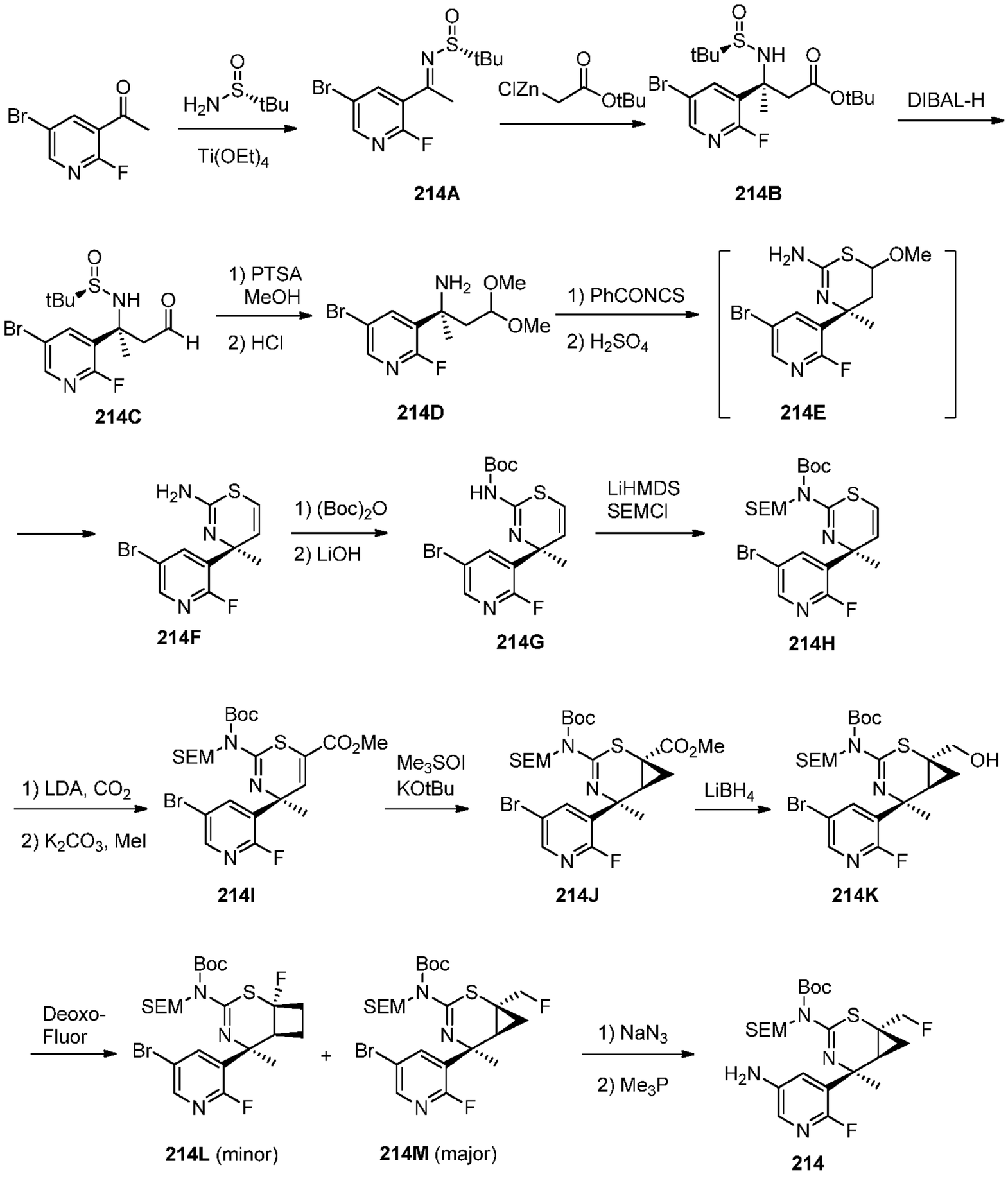
Preparation of N,N-Bis Boc protected (1R,5S,6R)-5-(5-bromo-2-fluorophenyl)-7,7-difluoro-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (213G). A sealable vial was charged with N,N-Bis Boc protected (S)-4-(5-bromo-2-fluorophenyl)-4-methyl-4H-1,3-thiazin-2-amine(1.04 g, 2.07 mmol, **213F**). THF was added to fully dissolve the starting material. The reaction was then concentrated to near dryness. Tetrabutylammonium bromide (0.07 g, 0.21 mmol, Sigma Aldrich) was added followed by (bromodifluoromethyl)trimethylsilane (2.11 g, 10.38 mmol, Synquest Laboratories). The vial was sealed and heated to 65 °C in an oil bath overnight. The reaction was diluted with water and EtOAc. The organic layer was separated, washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The crude residue was purified via silica gel flash chromatography using a gradient of 0-30% EtOAc in Hexanes to afford N,N-Bis Boc protected (1R,5S,6R)-5-(5-bromo-2-fluorophenyl)-7,7-difluoro-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (**213G**, 0.103 g, 0.188 mmol, 9% yield) as a pale yellow solid. MS *m/z* = 551.0 M^+.

Preparation of (1R,5S,6R)-5-(5-bromo-2-fluorophenyl)-7,7-difluoro-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (213H). To a solution of N,N-Bis Boc protected (1R,5S,6R)-5-(5-bromo-2-fluorophenyl)-7,7-difluoro-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (0.103 g, 0.187 mmol, 213g) in DCM (1.87 mL) was added TFA (0.475 mL, 6.16 mmol, Sigma Aldrich). The reaction was stirred at room temperature for 3 h. The reaction was concentrated under reduced pressure. The crude residue was taken up in EtOAc and washed with saturated sodium bicarbonate (aq.) solution and brine. The organic layer was dried over magnesium sulfate and concentrated under reduced pressure to afford (1R,5S,6R)-5-(5-bromo-2-fluorophenyl)-7,7-difluoro-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (**213H**, 69 mg, 0.195 mmol, 105% yield) as a yellow oil. It was used without further purification assuming theoretical yield. MS *m/z* = 350.9 M^+.

Preparation of (1R,5S,6R)-5-(5-azido-2-fluorophenyl)-7,7-difluoro-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (213). A sealable glass vial was charged with (1R,5S,6R)-5-(5-bromo-2-fluorophenyl)-7,7-difluoro-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (0.48 g, 1.37 mmol, **213H**), (+)-sodium L-ascorbate (0.054 g, 0.275 mmol, Sigma Aldrich), copper(I) iodide (79 mg, 0.413 mmol, Sigma Aldrich), and sodium azide (0.268 g, 4.13 mmol, Sigma Aldrich). The vial was sealed and evacuated / backfilled with Nitrogen (3 x). EtOH (4.8 mL) was added followed by water (2.0 mL) and (1R,2R)-(-)-N,N"-dimethylcyclohexane-1,2-diamine (0.043 mL, 0.27 mmol, Sigma Aldrich). The vial was stirred in a pre-heated 75 °C oil bath for 5.5 h. The reaction was cooled to room temperature. Additional sodium azide (0.268 g, 4.13 mmol), copper(I) iodide (79 mg, 0.413 mmol) and (1R,2R)-(-)-N,N"-dimethylcyclohexane-1,2-diamine (0.043 mL, 0.275 mmol) were added. The reaction was flushed with nitrogen and then stirred in a pre-heated 85 °C oil bath for an additional 1.5 h. The reaction was cooled to RT and poured into a separatory funnel containing a solution of 9:1 aqueous saturated ammonium chloride to aqueous saturated ammonium hydroxide. EtOAc was added and the organic phase was separated and washed sequentially with 9:1 saturated aqueous ammonium chloride to saturated aqueous ammonium hydroxide solution and brine. The organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The crude residue was taken up in THF (5.2 ml) and water (1.7 mL). Trimethylphosphine (1.0 M in THF, 1.376 mL, 1.376 mmol, Sigma Aldrich) was added at RT. The reaction was stirred for 5 min. The reaction was diluted with water and EtOAc. The organic layer was separated, washed with brine, dried over magnesium sulfate and

concentrated under reduced pressure. The crude residue was purified via silica gel flash chromatography using a gradient of 0-10% 2 M ammonia in MeOH in DCM to afford (1R,5S,6R)-5-(5-amino-2-fluorophenyl)-7,7-difluoro-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (**213**) (0.25 g, 0.86 mmol, 63% yield). ^{1}H NMR (300MHz, $CDCl_3$) δ = 7.04 (dd, *J*=2.9, 6.7 Hz, 1H), 6.87 (dd, *J*=8.5, 12.0 Hz, 1H), 6.54 (ddd, *J*=3.0, 3.8, 8.6 Hz, 1H), 2.89 (dd, *J*=8.3, 13.2 Hz, 1H), 2.74 - 2.60 (m, 1H), 1.69 (d, *J*=1.0 Hz, 3H) MS *m/z* = 288.0 M^+.

***tert*-Butyl ((1S,5S,6S)-5-(5-amino-2-fluoropyridin-3-yl)-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl) carbamate (214).**



Preparation of (R,Z)-N-(1-(5-bromo-2-fluoropyridin-3-yl)ethylidene)-2-methylpropane-2-sulfinamide (214A). A mixture of 1-(5-bromo-2-fluoropyridin-3-yl)ethanone (prepared according to procedures described in WO2009016460; 11.0 g, 50.5 mmol), (R)-2-methylpropane-2-sulfinamide (AK Scientific, 12.2 g, 101.0 mmol) and titanium(IV) ethoxide (Aldrich, 26.1 mL, 126.0 mmol) in THF (100 mL) was heated to reflux for 2 h. The mixture was cooled to room temperature, and brine (200 mL) was added. The suspension was vigorously stirred for 10 min. The suspension was filtered through a pad of silica gel and the organic phase was separated. The aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel chromatography (gradient 0-20% EtOAc/hexanes) to afford (R,Z)-N-(1-(5-bromo-2-fluoropyridin-3-yl)ethylidene)-2-methylpropane-2-sulfinamide (**214A**) as a bright yellow oil (16 g, 49.8 mmol, 99% yield). MS *m/z*= 320.8 $[M+H]^+$.

Preparation of (S)-*tert*-butyl 3-(5-bromo-2-fluoropyridin-3-yl)-3-((R)-1,1-dimethylethylsulfinamido)butanoate (214B). To a solution of (R,Z)-N-(1-(5-bromo-2-fluoropyridin-3-yl)ethylidene)-2-methylpropane-2-sulfinamide (**214A**, 41 g, 127 mmol) in THF (400 mL) in a 2 L flask at 0°C was cannulated slowly (2-(*tert*-butoxy)-2-oxoethyl)zinc(II) chloride (0.5 M in Et_2O, 611 mL, 305 mmol) within 1 h. The reaction mixture was stirred at RT overnight, and then quenched with 200 mL of saturated NH_4Cl solution. The layers were separated. The aqueous layer was extracted again with 200 mL of EtOAc. The combined organic layers were then dried (Na_2SO_4) and concentrated to give an orange oil that was purified by flash column (DCM to DCM/ethyl acetate = 10:1 to 5:1 to 3:1) to give (S)-*tert*-butyl 3-(5-bromo-2-fluoropyridin-3-yl)-3-((R)-1,1-dimethylethylsulfinamido)butanoate (**214B**, 43 g, 98 mmol, 77% yield). LC/MS (ESI^+) *m/z* = 458.9 (M+Na). ^1H NMR (300 MHz, CHLOROFORM-d) δ 8.17 (dd, *J*=1.61, 2.34 Hz, 1H), 8.03 (dd, *J*=2.48, 8.77 Hz, 1H), 5.44 (s, 1H), 3.18-3.29 (m, 1H), 2.98-3.11 (m, 1H), 1.82 (s, 3H), 1.33 (s, 9H), 1.30 (s, 9H).

Preparation of (R)-N-((S)-2-(5-bromo-2-fluoropyridin-3-yl)-4-oxobutan-2-yl)-2-methylpropane-2-sulfinamide (214C). A solution of (S)-*tert*-butyl 3-(5-bromo-2-fluoropyridin-3-yl)-3-((R)-1,1-dimethylethylsulfinamido)butanoate (**214B**, 42 g, 96 mmol) in 200 mL of anhydrous DCM in a 2 L round-bottom flask at -78 °C was treated with diisobutylaluminum hydride (1.0 M in hexanes) (211 mL, 211 mmol) via a syringe dropwise along the inner wall of the flask within 1.5 h. The stirring was continued for 1 h. The reaction was quenched at -78 °C by slow addition of 25 mL of MeOH along the

inner wall of the flask. The reaction mixture was then taken out of the dry ice-acetone bath, and treated with 300 mL of 1 M tartaric acid solution. The mixture was stirred at RT for 1 h. A clear two phase separation was achieved and the organic phase was isolated. The aqueous was extracted with DCM (3 x). The combined organic phase was evaporated to dryness. The residue was purified via silica gel chromatography (20-50% EtOAc in DCM) to gi®(R)-N-((S)-2-(5-bromo-2-fluoropyridin-3-yl)-4-oxobutan-2-yl)-2-methylpropane-2-sulfinamide (**214C**, 31 g, 85 mmol, 88% yield) as a yellow gum. LC/MS (ESI^+) *m/z* = 365.0 (M+H). ^1H NMR (300 MHz, CHLOROFORM-d) δ 9.70 (s, 1H), 8.16 (dd, *J*=1.68, 2.41 Hz, 1H), 8.04 (dd, *J*=2.41, 8.84 Hz, 1H), 4.89 (s, 1H), 3.59-3.73 (m, 1H), 3.35-3.48 (m, 1H), 1.77 (s, 3H), 1.29 (s, 9H).

Preparation of (S)-2-(5-bromo-2-fluoropyridin-3-yl)-4,4-dimethoxybutan-2-amine (214D). To a 1000 mL RBF equipped with a reflux condenser was added (R)-N-((S)-2-(5-bromo-2-fluoropyridin-3-yl)-4-oxobutan-2-yl)-2-methylpropane-2-sulfinamide (28.5 g, 78.0 mmol), MeOH (200 mL) and p-toluenesulfonic acid monohydrate (0.7 g, 3.9 mmol). The solution was stirred at 65 °C overnight. It was cooled to RT and treated with hydrogen chloride (4.0 M solution in 1,4-dioxane, 21.5 mL, 86.0 mmol) dropwise. After stirring at RT for 3 h, the mixture was concentrated *in vacuo*. The residue was diluted with 300 mL of chloroform and treated with 50 mL of sat. aq. $NaHCO_3$. The layers were separated and the aqueous layer was extracted with EtOAc (50 mL). The chloroform extracts were washed with 10 mL of brine. The EtOAc extracts were washed with 10 mL of brine. The combined organic extracts were dried over magnesium sulfate, filtered and concentrated *in vacuo* to give a light yellow oil. It was purified by silica gel chromatography (50-100% EtOAc in DCM) to give (*S*)-2-(5-bromo-2-fluoropyridin-3-yl)-4,4-dimethoxybutan-2-amine (**214D**, 20.6 g, 67.2 mmol, 86% yield) as a gum. LC/MS (ESI^+) *m/z* = 307.0 (M+H). ^1H NMR (300 MHz, CHLOROFORM-d) δ 8.26 (dd, *J*=2.48, 8.77 Hz, 1H), 8.12-8.19 (m, 1H), 4.10-4.19 (m, 1H), 3.23 (d, *J*=2.05 Hz, 6H), 2.24-2.45 (m, 1H), 1.79-2.14 (m, 1H), 1.75 (br. s., 2H), 1.54 (s, 3H)..

Preparation of (S)-4-(5-bromo-2-fluoropyridin-3-yl)-4-methyl-4H-1,3-thiazin-2-amine (214F). To a solution of (S)-2-(5-bromo-2-fluoropyridin-3-yl)-4,4-dimethoxybutan-2-amine (**214D**, 20.5 g, 66.7 mmol) in DCM (100 mL) at 0 ºC under nitrogen was added a solution of benzoyl isothiocyanate (9.4 mL, 70.1 mmol) in DCM (30 mL) dropwise. The reaction was kept below 5 ºC during the course of addition. After stirring at 0 ºC for 20 min, the reaction mixture was treated with MeOH (1 mL). The

solvents were removed under reduced pressure to afford a tan syrup. To the tan syrup at 0 ºC was added neat sulfuric acid (53.4 mL, 1001 mmol). The mixture was stirred at RT for 20 min then heated at 60 ºC for 5 h, then 80 ºC for 2 h, then 65 ºC overnight. LCMS indicated the ratio of 214E and 214F to be about 1:1. The mixture was heated at 85 ºC for 3 h. The reaction was cooled to 20 ºC then poured onto 200 g of ice. DCM (200 mL) was added to the slurry mixture. The resulting biphasic solution was chilled to 0 ºC with external wet ice bath, then basified to pH = 8 with very slow addition of 10 N NaOH solution. The organic layer was separated and the aqueous portion was extracted with DCM (3 x) and EtOAc (1 x). The combined organic extracts were dried over Na_2SO_4, filtered, and then concentrated under reduced pressure. The residue was purified by flash column (10-100% EtOAc in DCM) to give two compounds. The first eluent was (S)-4-(5-bromo-2-fluoropyridin-3-yl)-4-methyl-4H-1,3-thiazin-2-amine (**214F**, 12.0 g, 39.7 mmol, 59% yield) as a yellow solid. LC/MS (ESI^+) *m/z* = 302.0 (M+H). ^1H NMR (CHLOROFORM-d) δ: 8.12 (dd, J=2.5, 1.6 Hz, 1H), 8.02 (dd, J=8.6, 2.5 Hz, 1H), 6.30-6.39 (m, 1H), 6.17-6.27 (m, 1H), 1.66 (d, J=1.0 Hz, 3H). The second eluent was (4S)-4-(5-bromo-2-fluoropyridin-3-yl)-6-methoxy-4-methyl-5,6-dihydro-4H-1,3-thiazin-2-amine (214E, 6.0 g, 17.9 mmol).

A mixture of (4S)-4-(5-bromo-2-fluoropyridin-3-yl)-6-methoxy-4-methyl-5,6-dihydro-4H-1,3-thiazin-2-amine (**214E**, 6.0 g, 17.9 mmol) in 18 mL of H_2SO_4 was heated at 80 ºC overnight. The reaction mixture was cooled to 20 ºC then poured onto 200 g of ice. To the slurry was added DCM (200 mL), the resulting biphasic solution was chilled to 0 ºC with external wet ice bath, then basified to pH = 8 with very slow addition of 10 N NaOH solution. The organic layer was separated and the aqueous portion was extracted with DCM (3 x) and EtOAc (1 x). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column (10-30% EtOAc in DCM) to give (S)-4-(5-bromo-2-fluoropyridin-3-yl)-4-methyl-4H-1,3-thiazin-2-amine (**214F**, 4 g) as a yellow solid.

Preparation of (S)-*tert*-butyl (4-(5-bromo-2-fluoropyridin-3-yl)-4-methyl-4H-1,3-thiazin-2-yl)carbamate (214G). Using a procedure similar to that described for Intermediate **203F**, (S)-4-(5-bromo-2-fluoropyridin-3-yl)-4-methyl-4H-1,3-thiazin-2-amine (214F, 1.74 g, 5.76 mmol), 4-(dimethylamino)pyridine (0.04 g, 0.29 mmol), Boc anhydride (3.30 mL, 14.40 mmol) and lithium hydroxide monohydrate (1.21, 28.80 mmol) were combined to afford the title compound (2.17 g, 5.39 mmol, 94% yield).

LC/MS (ESI^+) *m/z* = 403.0 (M+H). ^1H NMR (300 MHz, CHLOROFORM-d) δ 8.14-8.20 (m, 1H), 8.00 (br. s., 1H), 6.30 (d, *J*=9.79 Hz, 1H), 6.14 (d, *J*=6.87 Hz, 1H), 1.69 (s, 3H), 1.54 (s, 9H).

Preparation of (S)-*tert*-butyl (4-(5-bromo-2-fluoropyridin-3-yl)-4-methyl-4H-1,3-thiazin-2-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (214H). Using a similar procedure described for **203G**, (S)-*tert*-butyl (4-(5-bromo-2-fluoropyridin-3-yl)-4-methyl-4H-1,3-thiazin-2-yl)carbamate (**214G**, 1.18 g, 2.93 mmol), lithium bis(trimethylsilyl)amide (3.8 mL of 1.0 M solution in THF, 3.8 mmol) and 2-(chloromethoxy)ethyltrimethylsilane (0.7 mL, 3.8 mmol) were combined to afford the title compound (**214H**, 1.5 g, 2.8 mmol, 95% yield). LC/MS (ESI^+) *m/z* = 532.0/534.0 (M+H). ^1H NMR (300 MHz, CHLOROFORM-d) δ 8.14-8.22 (m, 2H), 6.36 (d, *J*=9.50 Hz, 1H), 6.05-6.11 (m, 1H), 5.37 (d, *J*=10.38 Hz, 1H), 5.21 (d, *J*=10.38 Hz, 1H), 3.69 (dd, *J*=7.67, 8.84 Hz, 2H), 1.69 (d, *J*=1.17 Hz, 3H), 1.56 (s, 9H), 0.91-1.06 (m, 2H), 0.00 (s, 9H).

Preparation of (S)-methyl 4-(5-bromo-2-fluoropyridin-3-yl)-2-((*tert*-butoxycarbonyl)((2-(trimethylsilyl)ethoxy)methyl)amino)-4-methyl-4H-1,3-thiazine-6-carboxylate (214I). LDA (2.0 M heptane/THF/ethylbenzene) (0.92 mL, 1.83 mmol) was added dropwise to a solution of (S)-*tert*-butyl (4-(5-bromo-2-fluoropyridin-3-yl)-4-methyl-4H-1,3-thiazin-2-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (214H, 0.75 g, 1.41 mmol) in THF (10 mL) at -78 °C. The mixture was stirred for 25 min before CO_2 gas was bubbled through the reaction mixture at -78 °C. After 3 min, the cold bath was removed, the addition of CO_2 was stopped, and the reaction mixture was quenched with saturated NH_4Cl solution. The resulting solution was warmed to RT and extracted with EtOAc (2 x). The aqueous layer was acidified to pH 4 with 1 N HCl solution and extracted again with EtOAc. The combined extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give a yellow oil.

The oil was taken up in DMF (2.0 mL) and potassium carbonate (0.19 g, 1.41 mmol) and methyl iodide (0.09 mL, 1.41 mmol) were added. The mixture was stirred at RT for 2 h, diluted with water and extracted with EtOAc (2 x). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified on an ISCO column using 0-15% EtOAc in hexanes to afford (S)-methyl 4-(5-bromo-2-fluoropyridin-3-yl)-2-((*tert*-butoxycarbonyl)((2-(trimethylsilyl)ethoxy)methyl)amino)-4-methyl-4H-1,3-thiazine-6-carboxylate (**214I**, 0.40 g, 0.68 mmol, 48.1% yield). LC/MS (ESI^+) *m/z* = 590.0/592.0 (M+H). ^1H NMR (300 MHz, CHLOROFORM-d) δ

8.16-8.23 (m, 2H), 7.11 (d, *J*=3.07 Hz, 1H), 5.38 (d, *J*=10.38 Hz, 1H), 5.20 (d, *J*=10.38 Hz, 1H), 3.84 (s, 3H), 3.62-3.73 (m, 2H), 1.72 (d, *J*=1.02 Hz, 3H), 1.50-1.58 (m, 9H), 0.98 (dd, *J*=7.45, 8.92 Hz, 2H), -0.02 (s, 9H).

Preparation of (1S,5S,6S)-methyl 5-(5-bromo-2-fluoropyridin-3-yl)-3-((*tert*-butoxycarbonyl)((2-(trimethylsilyl)ethoxy)methyl)amino)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylate (214J). Using a similar procedure described for **210B**, trimethylsulfoxonium iodide (0.30 g, 1.36 mmol), potassium *tert*-butoxide (0.15 g, 1.35 mmol), and (S)-methyl 4-(5-bromo-2-fluoropyridin-3-yl)-2-((*tert*-butoxycarbonyl)((2-(trimethylsilyl)ethoxy)methyl)amino)-4-methyl-4H-1,3-thiazine-6-carboxylate (**214I**, 0.40 g, 0.68 mmol) were combined to afford (1S,5S,6S)-methyl 5-(5-bromo-2-fluoropyridin-3-yl)-3-((tert-butoxycarbonyl)((2-(trimethylsilyl)ethoxy)methyl)amino)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylate (**214J**, 0.27 g, 0.45 mmol, 65.9% yield). LCMS *m/z*= 604.0/606.0 $[M+H]^+$. ^{1}H NMR (300 MHz, CHLOROFORM-d) δ 8.17-8.27 (m, 2H), 5.30 (d, *J*=10.52 Hz, 1H), 5.03 (d, *J*=10.52 Hz, 1H), 3.82 (s, 3H), 3.62-3.74 (m, 2H), 2.68 (ddd, *J*=1.53, 7.71, 9.61 Hz, 1H), 1.75 (d, *J*=1.17 Hz, 3H), 1.51-1.57 (m, 9H), 1.24-1.36 (m, 1H), 1.16 (dd, *J*=5.26, 7.60 Hz, 1H), 0.85-1.07 (m, 2H), -0.06 (s, 9H). ^{19}F NMR (282 MHz, CHLOROFORM-d) δ -67.27 (s, 1F).

Preparation of *tert*-butyl ((1S,5S,6S)-5-(5-bromo-2-fluoropyridin-3-yl)-1-(hydroxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (214K). Using a similar procedure described for **210C**, (1S,5S,6S)-methyl 5-(5-bromo-2-fluoropyridin-3-yl)-3-((*tert*-butoxycarbonyl)((2-(trimethylsilyl)ethoxy)methyl)amino)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylate (**214J**, 0.46 g, 0.76 mmol) and lithium borohydride (2.0 M solution in THF, 0.76 mL, 1.52 mmol) and MeOH (0.12 mL, 3.04 mmol) were combined to afford the title compound (214K, 0.42 g, 0.73 mmol, 96% yield). LC/MS (ESI+) m/z = 576.0/578.0 (M+H).

Preparation of *tert*-butyl ((5S)-5-(5-bromo-2-fluoropyridin-3-yl)-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl) carbamate (214M). To a solution of *tert*-butyl ((5S)-5-(5-bromo-2-fluoropyridin-3-yl)-1-(hydroxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (0.46 g, 0.80 mmol) in hexanes (10.0 mL) at -78 °C was added Deoxo-Fluor (0.22 mL, 1.20 mmol) dropwise. The reaction mixture was warmed to RT for 30 min and quenched with

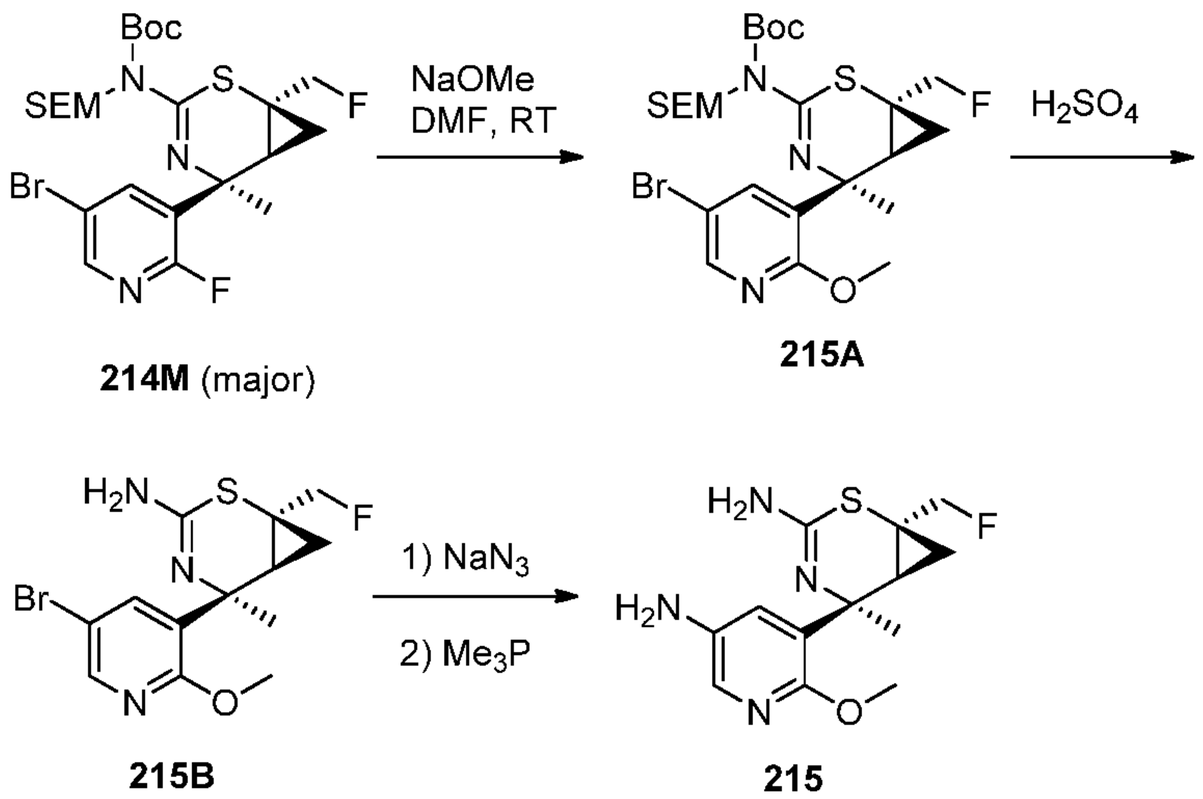
saturated $NaHCO_3$ solution. It was extracted with EtOAc (2 x). The organic extracts were concentrated under reduced pressure and the residue purified by silica gel chromatography eluting products with 0-20% EtOAc/heptane gradient to afford:

1st eluent, *tert*-butyl ((5S)-5-(5-bromo-2-fluoropyridin-3-yl)-1-fluoro-5-methyl-2-thia-4-azabicyclo[4.2.0]oct-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (**214L**, 0.13 g, 0.22 mmol, 28.2% yield). LC/MS (ESI+) m/z = 578.0/580.0 (M+H). ^{19}F NMR (282 MHz, CHLOROFORM-d) δ -67.71 (s, 1F), -102.44 (s, 1F).

2nd eluent, *tert*-butyl ((5S)-5-(5-bromo-2-fluoropyridin-3-yl)-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (**214M**, 0.17 g, 0.30 mmol, 37.0% yield). LC/MS (ESI+) m/z = 578.0/580.0 (M+H). ^{19}F NMR (282 MHz, CHLOROFORM-d) δ -67.71 (s, 1F), -213.42 (s, 1F).

Preparation of *tert*-butyl ((1S,5S,6S)-5-(5-amino-2-fluoropyridin-3-yl)-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl) carbamate (214). Using a similar procedure described for **210**, *tert*-butyl((5S)-5-(5-bromo-2-fluoropyridin-3-yl)-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (**214M**, 0.16 g, 0.28 mmol), sodium azide (0.05 g, 0.83 mmol), copper(I) iodide (13 mg, 0.07 mmol), sodium L-ascorbate (14 mg, 0.07 mmol), *trans*-N,N'-dimethyl-1,2-cyclohexanediamine (10.9 μL, 0.07 mmol) and trimethylphosphine (1 M solution in THF, 0.41 mL, 0.41 mmol) were combined to afford *tert*-butyl ((5S)-5-(5-amino-2-fluoropyridin-3-yl)-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (**214**, 72 mg, 0.14 mmol, 51% yield). LC/MS (ESI^-) *m/z* = 515.2 $(M+H)^+$.

(1S,5S,6S)-5-(5-Amino-2-methoxypyridin-3-yl)-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (215).



214M (major) **215A** **215B** **215**

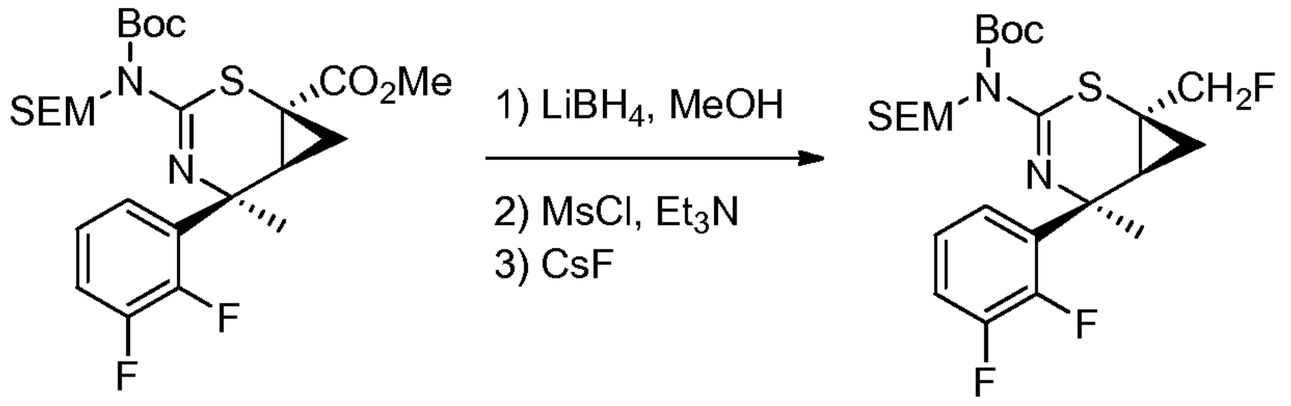
Preparation of Compound 215A. To a solution of *tert*-butyl ((1*S*,5*S*,6*S*)-5-(5-bromo-2-fluoropyridin-3-yl)-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (**214M**, 2.53 g, 4.37 mmol) in DMF (10 mL) was added sodium methoxide (2.36 g, 43.7 mmol) at RT. The suspension was stirred at RT for 6 h, diluted with water and extracted with EtOAc (2 x). The organic extracts were concentrated under reduced pressure and the residue was purified on a silica gel column (0-20% EtOAc/hexanes) to give *tert*-butyl ((1*S*,5*S*,6*S*)-5-(5-bromo-2-methoxypyridin-3-yl)-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (2.00 g, 3.39 mmol, 77% yield). LC/MS (ESI^+) *m/z* = 590.2/592.1 (M+H).

Preparation of Compound 215B. To a round bottom flask containing *tert*-butyl ((1*S*,5*S*,6*S*)-5-(5-bromo-2-methoxypyridin-3-yl)-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (**215A**, 2.0 g, 3.4 mmol) at 0 °C was added concentrated sulfuric acid (4 mL, 72.0 mmol) dropwise. After the addition, the mixture was stirred at RT for 30 min and the pH of the reaction mixture was adjusted to pH = 10-14 by the addition of 5 N NaOH solution. The mixture was extracted with EtOAc (2 x). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated to give (1*S*,5*S*,6*S*)-5-(5-bromo-2-methoxypyridin-3-yl)-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (1.2 g, 3.33 mmol, 98% yield). LC/MS (ESI^+) *m/z* = 360.2/362.0 (M+H).

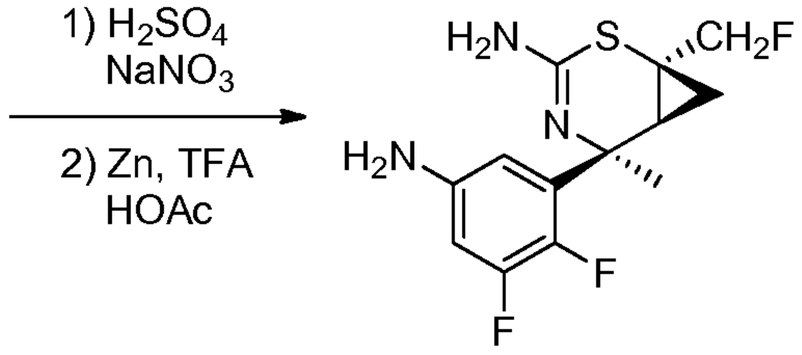
Preparation of Compound 215. A mixture of (1*S*,5*S*,6*S*)-5-(5-bromo-2-methoxypyridin-3-yl)-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (**215B**, 1.2 g, 3.33 mmol), sodium azide (1.08 g, 16.66 mmol), copper(i) iodide (63 mg, 0.33 mmol), (+)-sodium L-ascorbate (0.13 g, 0.67 mmol), and *trans*-N,N'-dimethylcyclohexane-1,2-diamine (0.10 mL, 0.67 mmol) in EtOH/H_2O (4:1, 20 mL) was heated in a closed capped vial at 85 °C for 2 h. The reaction mixture was cooled, diluted with water and extracted with EtOAc (2 x). The organic extracts were dried over Na_2SO_4 and concentrated.

The residue obtained was dissolved in a (8:2) mixture of THF/H_2O (10 mL) and trimethylphosphine (1 M solution in THF) (6.66 mL, 6.66 mmol) was added. After stirring at RT for 1 h, the reaction was quenched with saturated $NaHCO_3$, and extracted with EtOAc. The organic solution was concentrated and the residue was purified by silica gel flash column chromatography (0-15% MeOH/DCM) to give (1*S*,5*S*,6*S*)-5-(5-amino-2-methoxypyridin-3-yl)-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (0.25 g, 0.84 mmol, 25% yield). LC/MS (ESI^+) *m/z* = 297.2 (M+H). ^{1}H NMR (400 MHz, CHLOROFORM-d) δ: 7.54 (d, *J*=2.93 Hz, 1H), 7.40 (d, *J*=2.93 Hz, 1H), 4.46-4.62 (m, 1H), 4.34-4.46 (m, 1H), 4.11-4.34 (m, 2H), 3.93 (s, 3H), 3.70-3.00 (br., 2H), 2.13 (ddd, *J*=0.98, 6.94, 9.68 Hz, 1H), 1.69 (s, 3H), 0.92 (dd, *J*=5.87, 9.59 Hz, 1H), 0.71 (dt, *J*=4.30, 6.16 Hz, 1H). ^{19}F NMR (377 MHz, CHLOROFORM-d) δ -212.20.

(1S,5S,6S)-5-(5-Amino-2,3-difluorophenyl)-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (216).



203I **216A**



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Preparation of *tert*-butyl ((1S,5S,6S)-5-(2,3-difluorophenyl)-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (216A). At RT, to a solution of (1S,5S,6S)-methyl 3-((tert-butoxycarbonyl)((2-(trimethylsilyl)ethoxy)methyl)amino)-5-(2,3-difluorophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylate (**203I**, 34.6 g, 63.8 mmol) in 300 mL of THF was added lithium borohydride (2.0 M solution in THF, 63.8 mL, 128 mmol) dropwise via an addition funnel. MeOH (20.66 mL, 510 mmol) was the added slowly to the mixture over 20 min. The mixture was stirred at RT for 2 h, during which time it warmed slightly (estimated ~40 °C). The mixture was then chilled to 0 °C and quenched by dropwise addition of 250 mL of aq. NH_4Cl. The reaction mixture was then extracted with 500 mL of EtOAc and the organic extracts were washed with 250 mL of brine and dried over $MgSO_4$. Filtration and concentration under reduced pressure afforded tert-butyl ((1S,5S,6S)-5-(2,3-difluorophenyl)-1-(hydroxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (30.7 g, 59.6 mmol, 94% yield) as a viscous yellow oil. MS (ESI, positive ion) m/z: 515.3 (M+1). The crude material was used in the next step without further purification.

At 0 °C, *tert*-butyl ((1S,5S,6S)-5-(2,3-difluorophenyl)-1-(hydroxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (4.9 g, 9.52 mmol) in 50 mL of DCM was treated with TEA (1.72 mL, 12.38 mmol) followed by methanesulfonyl chloride (0.85 mL, 10.95 mmol). The mixture was stirred for 30 min, then quenched with 30 mL of aq. $NaHCO_3$ and 30 mL of water. The layers were separated and the aqueous portion was extracted with 25 mL of DCM. The combined organic extracts were dried over $MgSO_4$. Filtration and concentration under reduced pressure afforded an oil that was taken up in 20 mL of *t*BuOH. Cesium fluoride (4.34 g, 28.6 mmol) was added, and the mixture as heated at 75 °C for 10 h. The mixture was cooled to RT and partitioned between 100 mL of EtOAc and 100 mL of water. The organic portion was washed with 50 mL of brine and dried over $MgSO_4$. Filtration and concentration under reduced pressure, followed by flash chromatography on silica gel (5-25% EtOAc in heptanes) afforded *tert*-butyl ((1S,5S,6S)-5-(2,3-difluorophenyl)-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (**216A**) (4.34 g, 8.40 mmol, 88 % yield) as a clear oil. MS (ESI, positive ion) m/z: 517.3 (M+1).

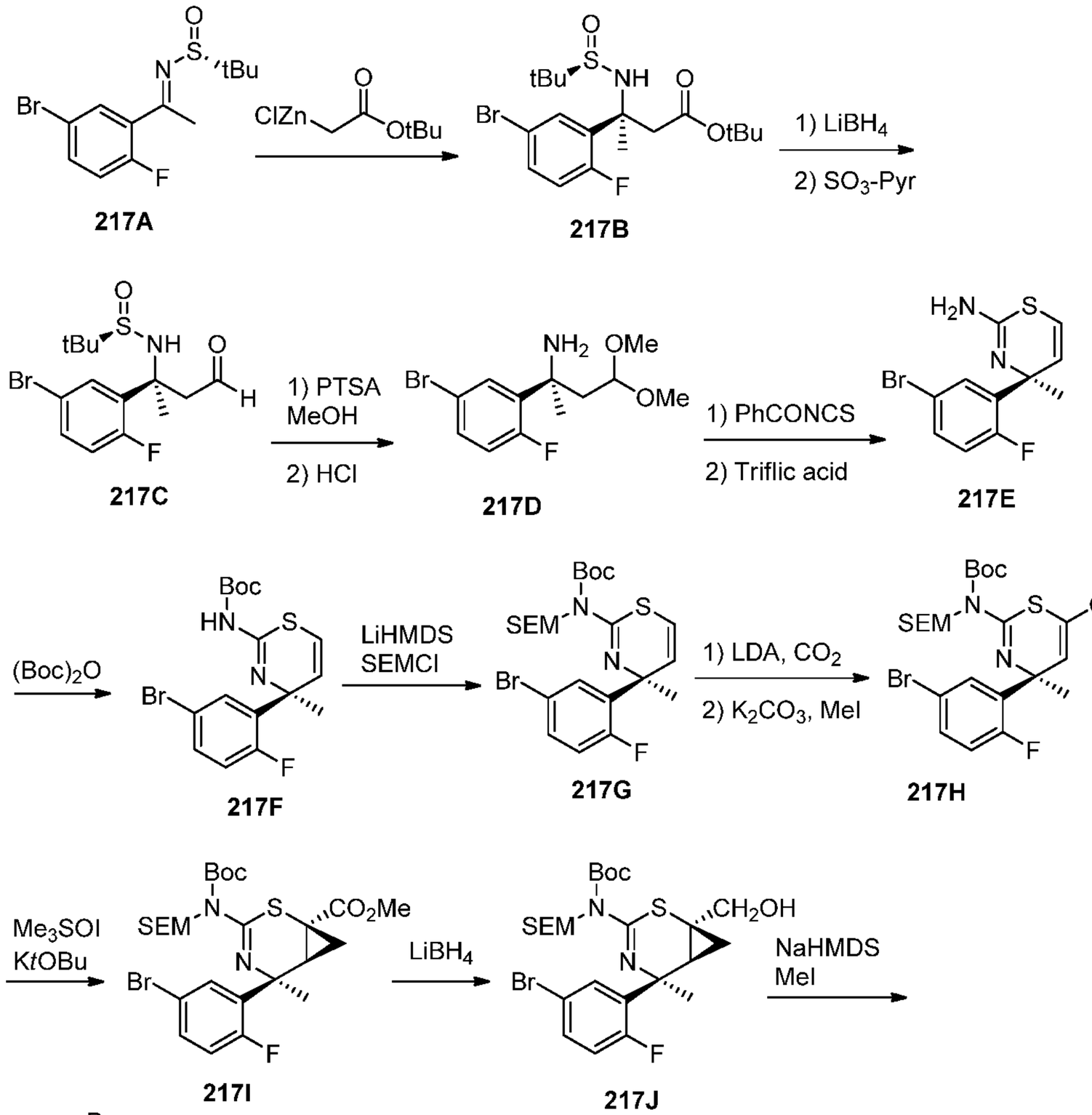
^{19}F NMR (376 MHz, DMSO-d_6) δ -139.35 (d, *J*=20.80 Hz, 1F), -139.82 (d, *J*=20.81 Hz, 1F), -212.18 (s, 1F).

Preparation of (1S,5S,6S)-5-(5-amino-2,3-difluorophenyl)-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (216). At 0 °C, *tert*-butyl ((1S,5S,6S)-5-(2,3-difluorophenyl)-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (4.3 g, 8.32 mmol) was treated with sulfuric acid (15.97 mL, 300 mmol) dropwise. The mixture was stirred for 5 min, then warmed to RT and stirred for 15 min. The mixture was chilled to 0 °C. Sodium nitrate (0.70 g, 8.32 mmol) was added. The mixture was warmed to RT and stirred for 40 min. The mixture was then chilled to 0 °C, and sodium nitrate (0.70 g, 8.32 mmol) was added. The mixture was warmed to RT. After 40 min, the mixture was chilled to 0 °C. 200 mL of wet ice was added to the flask. Potassium phosphate tribasic monohydrate (72.8 g, 316 mmol) was then added slowly over 15 min. 10 N aq. NaOH was then added until the mixture had reached a pH ~ 9.0. The mixture was diluted with 100 mL of water and 200 mL of chloroform:IPA (9:1), stirred for 5 min, then filtered to remove all solid material. The filtrate was transferred to a separatory funnel and the layers were separated. The aqueous portion was extracted with 100 mL of DCM. The combined organic extracts were then dried over $MgSO_4$. Filtration and concentration under reduced pressure, followed by flash chromatography on silica gel (5-50% EtOAc/heptanes) afforded (1S,5S,6S)-5-(2,3-difluoro-5-nitrophenyl)-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (1.44 g, 4.35 mmol, 52% yield) as a sticky yellow solid. MS (ESI, positive ion) m/z: 332.1 (M+1).

(1S,5S,6S)-5-(2,3-difluoro-5-nitrophenyl)-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (1.44 g, 4.35 mmol) was taken up in HOAc (6 mL, 104 mmol) and TFA (3 mL, 40.4 mmol). The mixture was cooled to 0 °C, and zinc (nanopowder, 0.85 g, 13.04 mmol) was added in four portions over 20 min. The mixture was warmed to RT and stirred for 1 h. The solvents were removed under reduced pressure and the residue was partitioned between 75 mL of 9:1 aq. NH_4Cl:NH_4OH and 75 mL of DCM. The aqueous portion was extracted with 50 mL of DCM and the combined organic extracts were dried over $MgSO_4$. Filtration and concentration under reduced pressure, followed by flash chromatography on silica gel (1-5% MeOH/DCM) afforded (1S,5S,6S)-5-(5-amino-2,3-difluorophenyl)-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (0.85 g, 2.82 mmol, 65% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.67 (m, 1H), 6.36 (m, 1H), 6.04 (br., 2H), 5.13 (br., 2H),

4.53 (m, 1H), 4.41 (m, 1H), 1.74 (m, 1H), 1.56 (s, 3H) 1.01 (m, 1H), 0.63 (m, 1H). ^{19}F NMR (377 MHz, DMSO-d_6) δ -140.38 (d, *J*=23.41Hz, 1F), -155.86 (d, *J*=23.41Hz, 1F), -211.45 (s, 1F). MS (ESI, positive ion) m/z: 302.0 (M+1).

(1S,5S,6S)-5-(5-amino-2-fluorophenyl)-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (217).



217A **217B** **217C** **217D** **217E** **217F** **217G** **217H** **217I** **217J** **217K** **217L** **217**

Preparation of (S)-tert-butyl (4-(5-bromo-2-fluorophenyl)-4-methyl-4H-1,3-thiazin-2-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (217G). This intermediate was prepared in 9 steps from Compound 217A in a fashion similar to that described for intermediate **204G**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.68 (dd, *J*=2.74, 7.04 Hz, 1H),

7.57 (ddd, *J*=2.74, 4.25, 8.66 Hz, 1H), 7.26 (dd, *J*=8.61, 11.54 Hz, 1H), 6.66 (d, *J*=9.39 Hz, 1H), 6.09 (dd, *J*=3.52, 9.39 Hz, 1H), 5.24 (d, *J*=10.56 Hz, 1H), 5.12 (d, *J*=10.76 Hz, 1H), 3.64 (m, 2H), 1.63 (s, 3H), 1.51 (s, 9H), 0.92 (m, 2H), -0.06 (s, 9H). ^{19}F NMR (377 MHz, DMSO-d_6) δ -113.44 (s, 1F). MS (ESI, positive ion) m/z: 531/535 (M+1).

Preparation of (S)-methyl 4-(5-bromo-2-fluorophenyl)-2-((tert-butoxycarbonyl)((2-(trimethylsilyl)ethoxy)methyl)amino)-4-methyl-4H-1,3-thiazine-6-carboxylate (217H). To a stirring solution of (S)-tert-butyl (4-(5-bromo-2-fluorophenyl)-4-methyl-4H-1,3-thiazin-2-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (**217G**) (15.0 g, 28.2 mmol) in THF (100 mL) at -78 ºC was added lithium diisopropylamide (14.1 mL of 2 M in THF, 28.2 mmol) at a rate that the reaction temperature did not exceed -65 ºC. The light orange solution was stirred for 20 min at -78 ºC. The reaction was then exposed to carbon dioxide (g), first as a stream above the level of the solvent for 2 min, followed by the gas bubbled through the solvent for 2 min. The reaction was then slowly quenched with sat. NH_4Cl (25 mL). Once the suspension reached RT, both EtOAc (200 mL) and water (25 mL) were added. The organic layer was separated and the aqueous layer was extracted with EtOAc (1x). The combined extracts were then dried over $MgSO_4$ and concentrated under reduced pressure to afford the crude (S)-4-(5-bromo-2-fluorophenyl)-2-((tert-butoxycarbonyl)((2-(trimethylsilyl)ethoxy)methyl)amino)-4-methyl-4H-1,3-thiazine-6-carboxylic acid as a thick oil. MS (ESI, positive ion) m/z: 575/577 (M+1).

The resulting thick oil was dissolved in DMF (100 mL) and treated with potassium carbonate (7.8 g, 56.4 mmol) followed by iodomethane (3.5 mL, 56.4 mmol) at RT. The mixture was then stirred for 3 d at RT. The reaction mixture was diluted with 100 mL of EtOAc, and then water (50 mL) was added. The resulting biphasic mixture was separated and the aqueous layer was extracted with EtOAc (1x). The combined organic extracts were washed with water (2 x), dried ($MgSO_4$), filtered, and concentrated in vacuo to give an oil. The crude material was loaded on a silica gel column and eluted with a gradient of 0-10% EtOAc in hexanes to afford (S)-methyl 4-(5-bromo-2-fluorophenyl)-2-((tert-butoxycarbonyl)((2-(trimethylsilyl)ethoxy)methyl)amino)-4-methyl-4H-1,3-thiazine-6-carboxylate (14.9 g, 46% yield) as a yellow viscous oil. ^{1}H NMR (CHLOROFORM-d) δ: 7.73 (dd, J=7.0, 2.5 Hz, 1H), 7.39 (ddd, J=8.7, 4.3, 2.5 Hz, 1H), 7.11 (d, J=3.1 Hz, 1H), 6.97 (dd, J=11.3, 8.6 Hz, 1H), 5.34 (d, J=10.4 Hz, 1H), 5.21 (d, J=10.4 Hz, 1H), 3.83 (s, 3H), 3.58-3.73 (m, 2H), 1.71 (s, 3H), 1.56 (s, 9H), 0.87-1.08

(m, 2H), 0.00 (s, 9H). MS (ESI, positive ion) m/z: 589/591 (M+1).

Preparation of (1S,5S,6S)-methyl 5-(5-bromo-2-fluorophenyl)-3-((tert-butoxycarbonyl)((2-(trimethylsilyl)ethoxy)methyl)amino)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylate (217I). Corey-Chaykovsky Reagent [~0.25 M in DMSO]: To a stirring solution of trimethylsulfoxonium iodide (12.46 g, 56.60 mmol) in DMSO (200 mL) at RT was added potassium tert-butoxide (6.35 g, 56.60 mmol) in one portion. The solution was stirred for 1 h and then used in the reaction outlined below.

To a stirring solution of (S)-methyl 4-(5-bromo-2-fluorophenyl)-2-((tert-butoxycarbonyl)((2-(trimethylsilyl)ethoxy)methyl)amino)-4-methyl-4H-1,3-thiazine-6-carboxylate (**217H**, 26.7 g, 45.3 mmol) in THF (200 mL) at RT was added freshly prepared Corey-Chaykovsky Reagent (56.60 mmol) via a syringe dropwise. The reaction mixture was stirred at RT for 1 h, then quenched with sat. NH_4Cl (300 mL) dropwise (exothermic!). It was extracted with of EtOAc (2 x 300 mL). The combined organic extracts were washed with water (2 x 30 mL) followed by brine (30 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The resulting oil was purified by silica gel chromatography (0-20% EtOAc in hexanes) to give Compound **217I** (24.05 g, 88% yield) as a light yellow oil. ^{1}H NMR (300 MHz, CHLOROFORM-d) δ 7.77 (dd, *J*=2.63, 7.02 Hz, 1H), 7.35 (ddd, *J*=2.63, 4.24, 8.62 Hz, 1H), 6.95 (dd, *J*=8.62, 11.55 Hz, 1H), 5.25 (d, *J*=10.52 Hz, 1H), 5.00 (d, *J*=10.52 Hz, 1H), 3.78 (s, 3H), 3.61-3.72 (m, 2H), 2.63 (ddd, *J*=1.39, 7.86, 9.61 Hz, 1H), 1.72 (d, *J*=1.17 Hz, 3H), 1.51 (s, 9H), 1.46 (dd, *J*=5.19, 9.87 Hz, 1H), 1.17 (dd, *J*=5.33, 7.53 Hz, 1H), 0.88-1.03 (m, 2H), 0.00 (s, 9H). MS (ESI, positive ion) m/z: 603/605 (M+1).

Preparation of *tert*-butyl ((1S,5S,6S)-5-(5-bromo-2-fluorophenyl)-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (217K). At RT, to a solution of (1S,5S,6S)-methyl 5-(5-bromo-2-fluorophenyl)-3-((tert-butoxycarbonyl)((2-(trimethylsilyl)ethoxy)methyl)amino)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylate (**217I**, 8.7 g, 14.41 mmol) in 70 mL of THF was added lithium borohydride (2 M solution in THF, 14.41 mL, 28.8 mmol) slowly. MeOH (4.66 mL, 115 mmol) was then added to the mixture. The mixture began to bubble and the temperature rose to ~40 °C over 15 min. After the mixture was stirred for 1 h, it was cooled to 0 °C and quenched with 70 mL of sat. aq. NH_4Cl. The mixture was extracted with 2 x 200 mL of EtOAc.

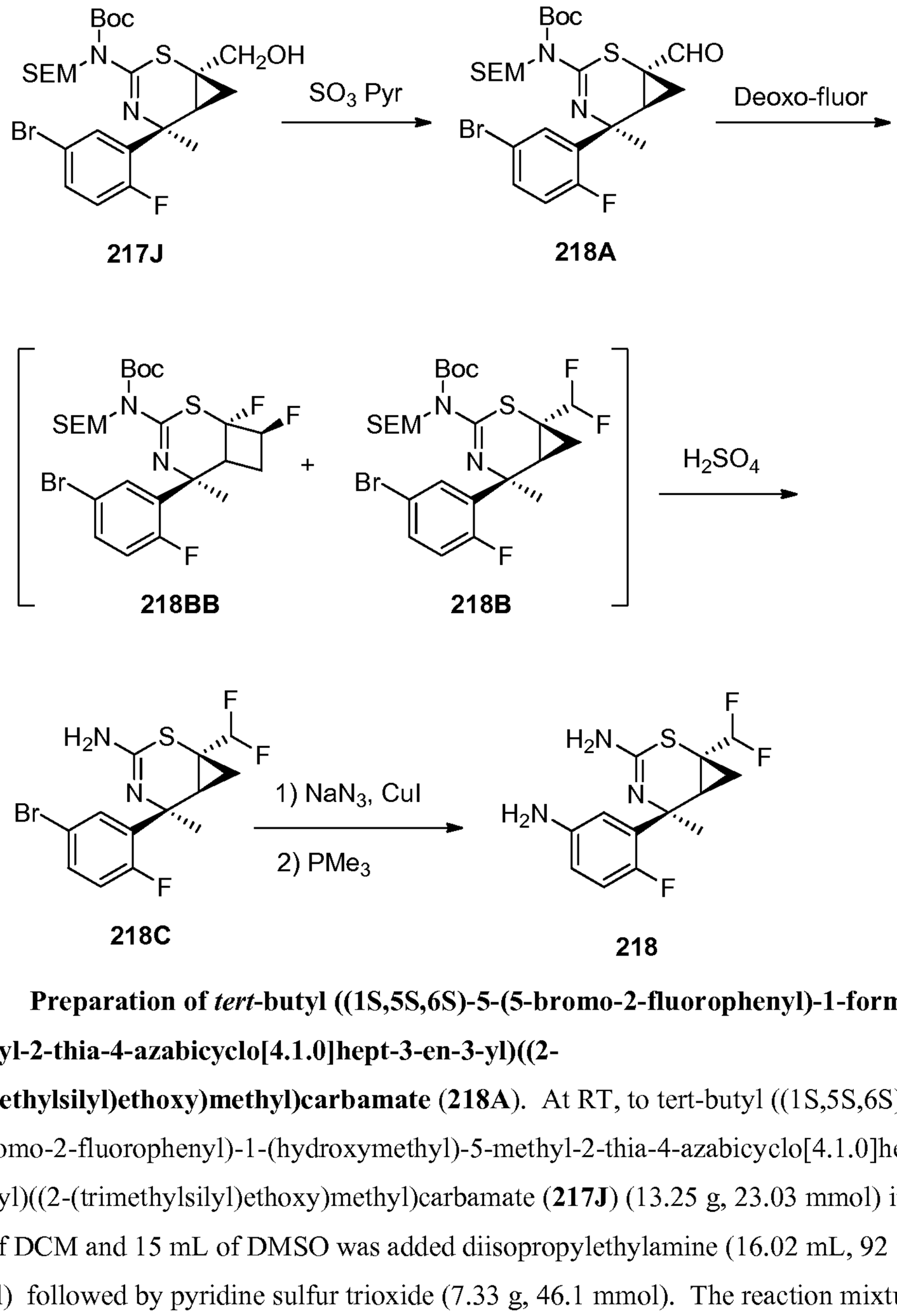
The organic extracts were washed with 50 mL of brine and dried over $MgSO_4$. Filtration and concentration under reduced pressure afforded tert-butyl ((1S,5S,6S)-5-(5-bromo-2-fluorophenyl)-1-(hydroxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (**217J**) as a light yellow oil. It was azeotroped with 2 x 5 mL of toluene. MS (ESI, positive ion) m/z: 575/577 (M+1).

At 0 °C, to the crude alcohol (**217J**) in 50 mL of THF was added sodium bis(trimethylsilyl)amide (16.58 mL of 1 M in THF solution, 16.58 mmol) dropwise. The resulting mixture was stirred at 0 °C for 15 min, then treated with iodomethane (1.12 mL, 18.02 mmol). The mixture was stirred at 0 °C for 1 h then RT for 15 h. It was diluted with DCM (400 mL) and washed with sat. NH_4Cl (50 mL) followed by brine (50 mL), dried over $MgSO_4$, filtered and concentrated. The crude material was purified by silica gel chromatography (5-15% EtOAc in hexanes) to give *tert*-butyl ((1S,5S,6S)-5-(5-bromo-2-fluorophenyl)-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (**217K**) (6.61 g, 11.21 mmol, 78% yield). ^{19}F NMR (376 MHz, DMSO-d_6) δ -114.48 (s, 1F). MS (ESI, positive ion) m/z: 589/591 $(M+H)^+$.

Preparation of Compound 217L. At RT, *tert*-butyl ((1S,5S,6S)-5-(5-bromo-2-fluorophenyl)-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (6.60 g, 11.19 mmol) was treated with sulfuric acid (5.97 mL, 112 mmol). The brown reaction mixture was stirred at RT for 10 min, then cooled with an ice bath and treated with 100 g of ice. Potassium phosphate tribasic monohydrate (27.6 g, 120 mmol) was added in small portions. The pH was then adjusted to 9 with 5 M NaOH. The mixture was extracted with EtOAc (3 x 200 mL) and the combined organic extracts were washed with brine (2 x 20 mL), dried over $MgSO_4$, filtered, and concentrated. Purification by flash column chromatography on silica gel column (25-65% EtOAc in DCM) gave (1S,5S,6S)-5-(5-bromo-2-fluorophenyl)-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (3.31 g, 9.21 mmol, 82% yield) as a pale yellow amorphous solid. ^{19}F NMR (376 MHz, DMSO-d_6) δ -113.99 (s, 1F). ^1H NMR (400 MHz, DMSO-d_6) δ 7.90 (dd, J=2.74, 7.24 Hz, 1H), 7.49 (m, 1H), 7.13 (m, 1H), 6.12 (br., 2H), 3.55 (d, J=10.95 Hz, 1H), 3.34 (d, J=11.15 Hz, 1H), 3.28 (s, 3H), 1.70 (m, 1H), 1.55 (s, 3H), 0.82 (m, 1H), 0.53 (m, 1H). MS (ESI, positive ion) m/z: 359/361 (M+1).

Preparation of (1S,5S,6S)-5-(5-amino-2-fluorophenyl)-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (217). To a mixture of copper (I) iodide (0.41 g, 2.16 mmol), sodium azide (1.97 g, 30.3 mmol), (+)-sodium L-ascorbate (0.09 g, 0.45 mmol), and (1S,5S,6S)-5-(5-bromo-2-fluorophenyl)-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (**217L**, 3.11 g, 8.66 mmol) at RT was added EtOH (20 mL) and water (10 mL). The reaction mixture was degassed by bubbling nitrogen through the solution for 5 min and (1R,2R)-(-)-N,N''-dimethylcyclohexane-1,2-diamine (0.31 g, 2.16 mmol) was added. The reaction mixture was heated to 70 °C for 1.5 h. The mixture was cooled to RT, poured into 30 mL of 10/1 mixed solution of saturated NH_4Cl/ammonium hydroxide, and extracted with EtOAc (2 x 150 mL). The combined organic extracts were washed with brine (15 mL), dried over $MgSO_4$, filtered, and concentrated to give a green sticky oil which contained (1S,5S,6S)-5-(5-azido-2-fluorophenyl)-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine. MS (ESI, positive ion) m/z: 322.0 (M+1). The green sticky oil was dissolved in THF (15 mL) and water (5 mL) and trimethylphosphine (1.0 M solution in THF, 8.66 mL, 8.66 mmol) was added. The reaction mixture was stirred at RT for 15 min, and then quenched by the addition of water (20 mL) and EtOAc (100 mL). The layers were separated. The aqueous phase was extracted with EtOAc (2 x 50 mL). The combined organic extracts were washed with brine (15 mL), dried over $MgSO_4$, filtered, and concentrated. Purification by flash column chromatography on silica gel (5-85% EtOAc in DCM followed by 5% MeOH in EtOAc) gave (1S,5S,6S)-5-(5-amino-2-fluorophenyl)-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (**217**) (1.96 g, 6.64 mmol, 77% yield) as a light yellow solid. MS (ESI, positive ion) m/z: 322.0 (M+1). ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.92 (dd, *J*=2.93, 7.24 Hz, 1H), 6.76 (dd, *J*=8.51, 12.42 Hz, 1H), 6.38 (td, *J*=3.45, 8.36 Hz, 1H), 5.87 (br., 2H), 4.79 (br., 2H), 3.55 (d, *J*=10.76 Hz, 1H), 3.38 (d, *J*=10.79 Hz, 1H), 3.35 (s, 3H), 1.63 (m, 1H), 1.54 (s, 3H), 0.81 (m, 1H), 0.54 (m, 1H). ^{19}F NMR (377 MHz, DMSO-d_6) δ -128.23 (s, 1F).

(1S,5S,6S)-5-(5-Amino-2-fluorophenyl)-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (218).



217J **218A** **218BB** **218B** **218C** **218**

Preparation of *tert*-butyl ((1S,5S,6S)-5-(5-bromo-2-fluorophenyl)-1-formyl-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (218A). At RT, to tert-butyl ((1S,5S,6S)-5-(5-bromo-2-fluorophenyl)-1-(hydroxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (**217J**) (13.25 g, 23.03 mmol) in 45 mL of DCM and 15 mL of DMSO was added diisopropylethylamine (16.02 mL, 92 mmol) followed by pyridine sulfur trioxide (7.33 g, 46.1 mmol). The reaction mixture was stirred at RT for 18 h. It was diluted with DCM (400 mL) and washed with sat. NH_4Cl (50 mL) followed by brine (50 mL), dried over $MgSO_4$, filtered and concentrated. The crude material was purified by silica gel chromatography (5-15% EtOAc in hexanes) to give *tert*-butyl ((1S,5S,6S)-5-(5-bromo-2-fluorophenyl)-1-formyl-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (**218A**,

10.68 g, 18.62 mmol, 81% yield) as a colorless viscous oil. MS (ESI, positive ion) m/z: 573/575 (M+1). ^{19}F NMR (377 MHz, DMSO-d_6) δ -114.00 (s, 1F).

Preparation of (1S,5S,6S)-5-(5-bromo-2-fluorophenyl)-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (218C). At -10 °C (ice/salt bath), to a stirring solution of tert-butyl ((1S,5S,6S)-5-(5-bromo-2-fluorophenyl)-1-formyl-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (**218A**, 10.67 g, 18.60 mmol) in 160 mL of hexanes was added Deoxo-Fluor (11.98 mL, 65.1 mmol). The reaction mixture was stirred at 0 °C for 1 h then RT overnight. The reaction mixture was diluted with EtOAc (400 mL), cooled with an ice bath and quenched with sat. $NaHCO_3$ (100 mL) slowly over a period of 30 min. The organic layer was separated, washed with brine (20 mL), dried over sodium sulfate, filtered and concentrated. The crude material was purified by column chromatography with 5-10% EtOAc in hexanes to give a mixture of two compounds (10.49 g) as a sticky oil, **218BB** : **218B**, in about 1:6 ratio. Both products had the mass of MS (ESI, positive ion) m/z: 595/597 (M+1). The major product, tert-butyl ((1S,5S,6S)-5-(5-bromo-2-fluorophenyl)-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (**218B**) had ^{19}F NMR (376 MHz, DMSO-d_6) δ -114.34 (s, 1F), -115.62 (d, ^1J=275.70 Hz, 1F), -118.55 (d, ^1J=275.70 Hz, 1F).

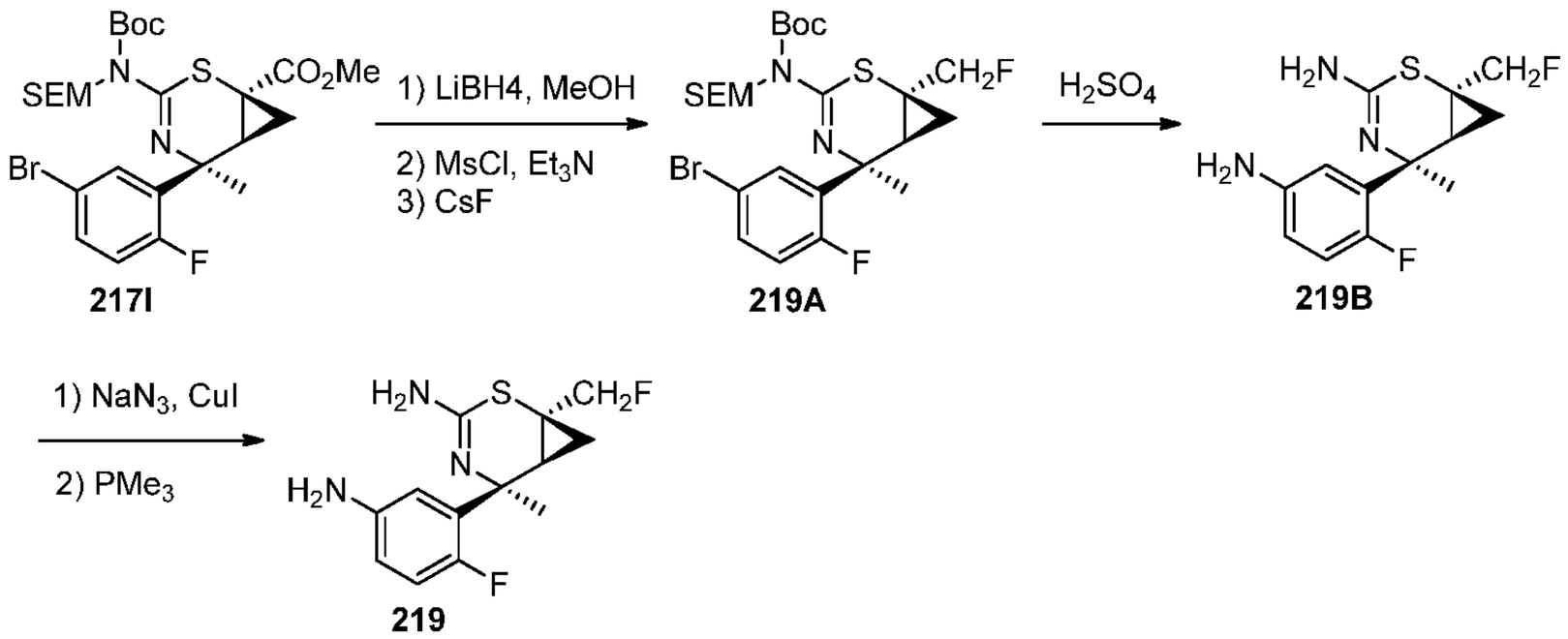
To the above mixture of **218BB** : **218B** (in about 1:6 ratio, 10.49 g) at RT was added sulfuric acid (9.91 mL, 186 mmol). The reaction mixture was stirred at RT for 10 min. It was poured onto 100 g of ice.

The brown mixture was cooled with an ice bath and treated with potassium phosphate tribasic monohydrate (43.8 g, 190 mmol) in small portions (pH was about 7). The pH was adjusted to 9 with 5 M NaOH. The aqueous phase was extracted with EtOAc (3 x 200 mL) and the combined organic extracts were washed with brine (2 x 20 mL), dried over $MgSO_4$, filtered, and concentrated. Purification by flash column chromatography on silica gel column (25-65% EtOAc in DCM) gave (1S,5S,6S)-5-(5-bromo-2-fluorophenyl)-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (**218C**, 3.69 g, 10.10 mmol, 54% yield) as a pale yellow foam. MS (ESI, positive ion) m/z: 365/367 (M+1).

Preparation of (1S,5S,6S)-5-(5-amino-2-fluorophenyl)-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (218). To a mixture of copper (I) iodide (0.48 g, 2.52 mmol), sodium azide (2.29 g, 35.3 mmol), (+)-sodium L-ascorbate

(0.09 g, 0.45 mmol), and (1S,5S,6S)-5-(5-bromo-2-fluorophenyl)-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (**218C**, 3.68 g, 10.08 mmol) at RT was added EtOH (25 mL) and water (12.5 mL). The reaction mixture was degassed by bubbling nitrogen through the solution for 5 min and (1R,2R)-(-)-N,N"-dimethylcyclohexane-1,2-diamine (0.36 g, 2.52 mmol) was added. The reaction mixture was heated to 70 °C for 1.5 h. LCMS indicated the presence of **218C**. Additional copper (I) iodide (0.24 g, 0.22 mmol) and (1R,2R)-(-)-N,N"-dimethylcyclohexane-1,2-diamine (0.18 g, 1.26 mmol) were added. Heating was resumed at 70 °C for 0.5 h. The mixture was cooled to RT, poured into 40 mL of 10:1 saturated NH_4Cl/ammonium hydroxide, and extracted with EtOAc (2 x 150 mL). The combined organic extracts were washed with brine (15 mL), dried over $MgSO_4$, filtered, and concentrated to give a brown sticky oil which contained (1S,5S,6S)-5-(5-azido-2-fluorophenyl)-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine. MS (ESI, positive ion) m/z: 328.0 (M+1). The brown sticky oil was dissolved in THF (15 mL) and water (5 mL) and trimethylphosphine (1.0 M solution in THF) (10.08 mL, 10.08 mmol) was added. The reaction mixture was stirred at RT for 15 min, and diluted with water (20 mL) and EtOAc (100 mL). The layers were separated. The aqueous phase was extracted with EtOAc (2 x 50 mL). The combined organic extracts were washed with brine (15 mL), dried over $MgSO_4$, filtered, and concentrated. Purification by flash column chromatography on silica gel column (5-85% EtOAc in DCM) gave: 1) <u>The 1st eluent</u> was the recovered (1S,5S,6S)-5-(5-bromo-2-fluorophenyl)-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (**218C**, 240 mg). MS (ESI, positive ion) m/z: 365/367 (M+1). 2) <u>The 2nd eluent</u> was (1S,5S,6S)-5-(5-amino-2-fluorophenyl)-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (**218**) (1.77 g, 5.87 mmol, 58% yield) as a light yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.75 (m, 2H), 6.36 (m, 1H), 6.17 (br., 2H), 5.76-6.04 (m, 1H), 4.80 (br., 2H), 1.81 (m, 1H), 1.57 (s, 3H), 1.25 (m, 1H), 0.63 (m, 1H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -114.65 (d, ^1J=274.10 Hz, 1F), -118.13 (d, ^1J=274.10 Hz, 1F), -127.65 (s, 1F). MS (ESI, positive ion) m/z: 302.1 (M+1).

(1S,5S,6S)-5-(5-Amino-2-fluorophenyl)-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (219).



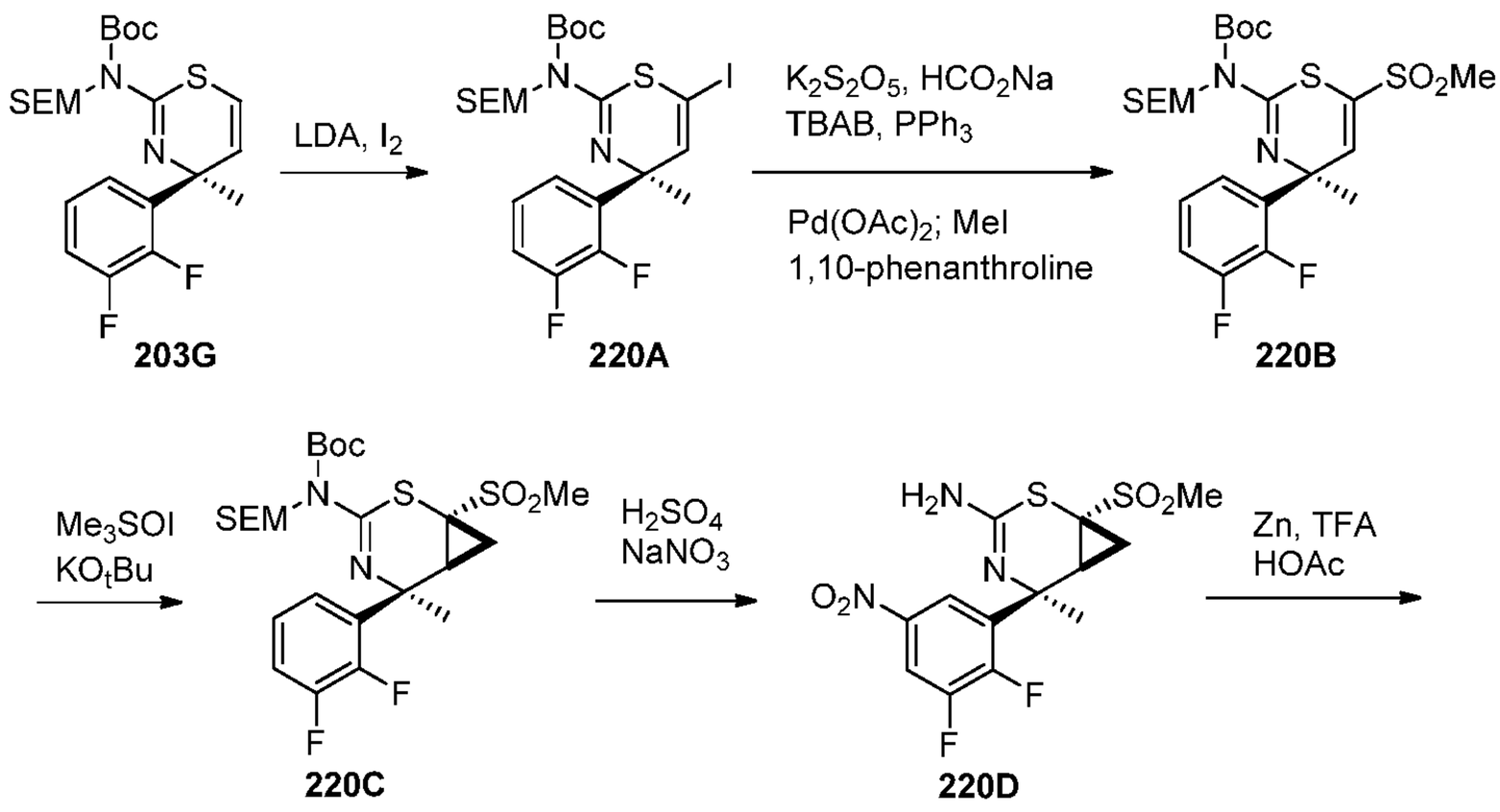
Preparation of tert-butyl ((1S,5S,6S)-5-(5-bromo-2-fluorophenyl)-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (219A). This compound (3.40 g, 5.89 mmol, 70% yield) as a light yellow sticky oil was prepared from **217I** (5.07 g, 8.40 mmol) according to the procedures similar to those described for intermediate **216A**. MS (ESI, positive ion) m/z: 577/579 (M+1). ^{19}F NMR (376 MHz, DMSO-d_6) δ -114.36 (s, 1F), -212.20 (s, 1F)

Preparation of (1S,5S,6S)-5-(5-amino-2-fluorophenyl)-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (219B). This compound (1.69 g, 4.87 mmol, 85% yield) as a pale yellow foam was prepared from *tert*-butyl ((1S,5S,6S)-5-(5-bromo-2-fluorophenyl)-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (**219A**, 3.30 g, 5.71 mmol) according to the procedures similar to those described for intermediate **217L**. ^{19}F NMR (376 MHz, DMSO-d_6) δ -113.80 (s, 1F), -211.59 (s, 1F). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.89 (dd, *J*=2.74, 7.24 Hz, 1H), 7.46 (m, 1H), 7.17 (dd, *J*=8.61, 11.93 Hz, 1H), 6.23 (br., 2H), 4.34-4.65 (m, 2H), 1.86 (m, 1H), 1.59 (s, 3H), 0.89 (m, 1H), 0.60 (m, 1H). MS (ESI, positive ion) m/z: 347/349 (M+1).

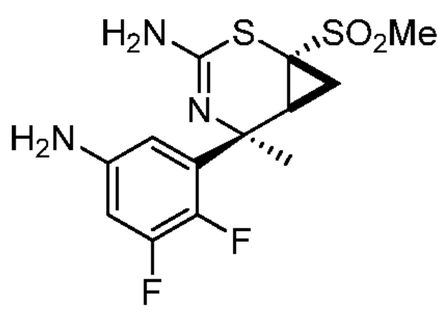
Preparation of (1S,5S,6S)-5-(5-amino-2-fluorophenyl)-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (219). This compound (1.08 g, 3.81 mmol, 79% yield) as a brown amorphous solid was prepared from (1S,5S,6S)-5-(5-bromo-2-fluorophenyl)-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (**219B**, 1.68 g, 4.84 mmol) according to the procedures similar to those described for intermediate **217**. ^{19}F NMR (376 MHz, DMSO-d_6) δ -128.09 (s, 1F), -211.32 (s, 1F).

^{1}H NMR (400 MHz, DMSO-d_6) δ 6.88 (dd, *J*=2.74, 7.04 Hz, 1H), 6.76 (dd, *J*=8.51, 12.42 Hz, 1H), 6.39 (td, *J*=3.42, 8.41 Hz, 1H), 5.98 (br., 2H), 4.79 (br., 2H), 4.32-4.57 (m, 2H), 1.78 (m, 1H), 1.54 (s, 3H), 0.95 (m, 1H), 0.59 (q, *J*=5.15 Hz, 1H). MS (ESI, positive ion) m/z: 284.0 (M+1).

(1R,5S,6S)-5-(5-Amino-2,3-difluorophenyl)-5-methyl-1-(methylsulfonyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (220).



203G **220A** **220B** **220C** **220D**



220

Preparation of (S)-tert-butyl (4-(2,3-difluorophenyl)-6-iodo-4-methyl-4H-1,3-thiazin-2-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (220A). A solution of lithium diisopropylamide (2.0 M in THF/heptane/ethylbenzene) (4.2 mL, 8.4 mmol) was added dropwise to a stirring solution of (S)-tert-butyl (4-(2,3-difluorophenyl)-4-methyl-4H-1,3-thiazin-2-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (**203G**, 3.3 g, 7.0 mmol) in THF (70 mL) under a nitrogen atmosphere at -78 ºC. The solution was stirred at -78 ºC for 15 min and then a solution of iodine (2.1 g, 8.4 mmol) in THF (15 mL) was added dropwise. The dark red mixture was stirred at -78 ºC for another 10 min and the reaction was quenched with saturated aqueous $Na_2S_2O_3$ solution (40 mL). The mixture was allowed to warm to RT and then diluted with water (40 mL) and extracted with EtOAc (2 x 75 mL). The combined organic extracts were washed with brine (40 mL), dried over

Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by silica gel chromatography eluting with a gradient of 2.5-10% EtOAc/heptane to give (S)-tert-butyl (4-(2,3-difluorophenyl)-6-iodo-4-methyl-4H-1,3-thiazin-2-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate as a yellow oil (**220A**, 4.2 g, 100%). LC/MS (ESI^+) *m/z* = 597.0 (M+H). ^1H NMR (400 MHz, chloroform-d) δ 7.24-7.30 (m, 1H), 6.98-7.15 (m, 2H), 6.68 (d, J=3.13 Hz, 1H), 5.30-5.37 (m, 1H), 5.20-5.27 (m, 1H), 3.65 (t, J=8.31 Hz, 2H), 1.72 (s, 3H), 1.55 (s, 9H), 0.91-0.96 (m, 2H), 0.00 (s, 9H).

Preparation of (S)-*tert*-butyl (4-(2,3-difluorophenyl)-4-methyl-6-(methylsulfonyl)-4H-1,3-thiazin-2-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (220B). (S)-*tert*-Butyl (4-(2,3-difluorophenyl)-6-iodo-4-methyl-4H-1,3-thiazin-2-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (**220A**, 4.2 g, 7.0 mmol), potassium metabisulfite (3.13 g, 14.1 mmol), tetrabutylammonium bromide (2.50 g, 7.74 mmol), sodium formate (1.05 g, 15.5 mmol), palladium(ii) acetate (0.079 g, 0.35 mmol), triphenylphosphine (0.277 g, 1.06 mmol), 1,10-phenanthroline (0.190 g, 1.06 mmol) and DMSO (20 mL) were combined under a nitrogen atmosphere. The mixture was degassed by bubbling nitrogen through it for 10 min. The mixture was then heated at 70 ºC for 1 h. The mixture was allowed to cool to RT and then methyl iodide (0.66 mL, 10.6 mmol) was added. The mixture was stirred at RT for 1 h. The reaction was then diluted with water (40 mL) and extracted with EtOAc (3 x 30 mL). The combined organic extracts were washed with brine (40 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by silica gel chromatography eluting with a gradient of 0-35% EtOAc/heptane to give (S)-*tert*-butyl (4-(2,3-difluorophenyl)-4-methyl-6-(methylsulfonyl)-4H-1,3-thiazin-2-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate as a yellow oil (**220B**, 1.8 g, 47%). LC/MS (ESI^+) *m/z* = 549.0 (M+H). ^1H NMR (400 MHz, chloroform-d) δ 7.29-7.32 (m, 1H), 7.04-7.18 (m, 3H), 5.32-5.37 (m, 1H), 5.22-5.28 (m, 1H), 3.65 (t, J=8.22 Hz, 2H), 3.03 (s, 3H), 1.79 (s, 3H), 1.57 (s, 9H), 0.91-0.95 (m, 2H), -0.01 (s, 9H).

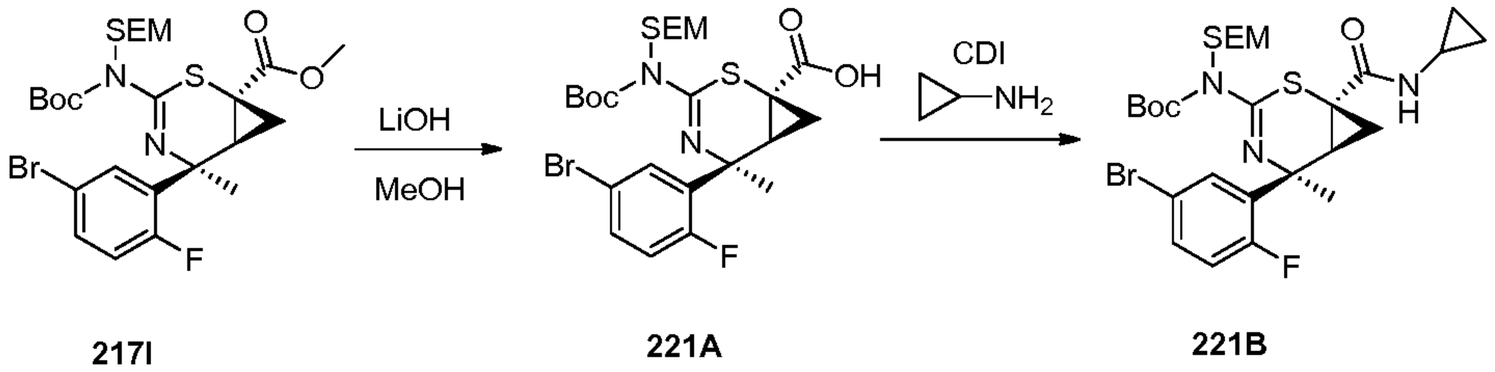
Preparation of *tert*-butyl ((1R,5S,6S)-5-(2,3-difluorophenyl)-5-methyl-1-(methylsulfonyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (220C). Potassium *tert*-butoxide (0.41 g, 3.6 mmol) was added to a solution of trimethylsulfoxonium iodide (0.81 g, 3.6 mmol) in DMSO (10 mL) at RT. The solution was stirred at RT for 1 h and then added dropwise over 5 min by addition funnel to a solution of (S)-*tert*-butyl (4-(2,3-difluorophenyl)-4-methyl-6-(methylsulfonyl)-4H-1,3-thiazin-2-yl)((2-

(trimethylsilyl)ethoxy)methyl)carbamate (**220B**, 1.80 g, 3.28 mmol) in THF (10 mL). The solution was stirred at RT for 1 h. The reaction was quenched with saturated aqueous NH_4Cl (20 mL) and diluted with water (20 mL). The mixture was extracted with 3:1 heptane:EtOAc (2 x 50 mL) and the combined organic extracts were washed with water (30 mL), brine (30 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by silica gel chromatography eluting with a gradient of 3-30% EtOAc/heptane to give *tert*-butyl ((1R,5S,6S)-5-(2,3-difluorophenyl)-5-methyl-1-(methylsulfonyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate as a yellow oil (**220C**, 1.55 g, 84%). LC/MS (ESI^+) *m/z* = 563.2 (M+H). ^1H NMR (400 MHz, chloroform-d) δ 7.30 (s, 1H), 7.01-7.19 (m, 2H), 5.37 (d, J=10.37 Hz, 1H), 5.13 (d, J=10.37 Hz, 1H), 3.66 (dt, J=2.54, 8.22 Hz, 2H), 3.12 (s, 3H), 2.55 (dd, J=7.92, 10.07 Hz, 1H), 1.93 (dd, J=6.16, 10.47 Hz, 1H), 1.84 (s, 3H), 1.55 (s, 9H), 1.15 (t, J=6.85 Hz, 1H), 0.91-0.98 (m, 2H), 0.02 (s, 9H).

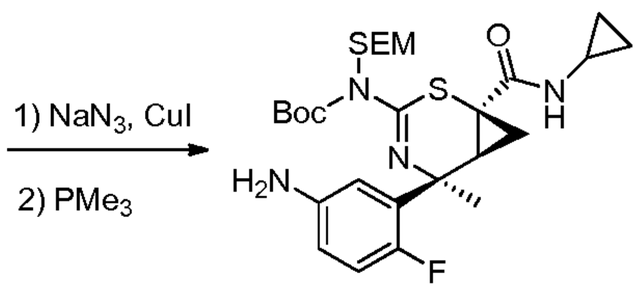
Preparation of (1R,5S,6S)-5-(2,3-difluoro-5-nitrophenyl)-5-methyl-1-(methylsulfonyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (220D). This compound (900 mg, 89% yield) as a yellow solid was prepared from intermediate **220C** (1.5 g, 2.67 mmol) using the procedures similar to those described for intermediate **203L**. LC/MS (ESI^+) *m/z* = 378.0 (M+H). ^1H NMR (400 MHz, chloroform-d) δ 8.26 (ddd, J=1.96, 2.84, 5.77 Hz, 1H), 8.04 (ddd, J=2.74, 6.36, 9.10 Hz, 1H), 4.78 (br. s., 2H), 3.06 (s, 3H), 2.47 (ddd, J=0.98, 7.73, 10.27 Hz, 1H), 2.04 (dd, J=6.26, 10.37 Hz, 1H), 1.83 (d, J=1.37 Hz, 3H), 1.03-1.09 (m, 1H).

Preparation of (1R,5S,6S)-5-(5-amino-2,3-difluorophenyl)-5-methyl-1-(methylsulfonyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (220). This compound (420 mg, 51% yield) as a yellow crystalline solid was prepared from intermediate **220D** (900 mg, 2.39 mmol) using the procedures similar to those described for intermediate **203**. LC/MS (ESI^+) *m/z* = 348.1 (M+H). ^1H NMR (400 MHz, chloroform-d) δ 6.39 (ddd, J=2.74, 6.16, 11.25 Hz, 1H), 6.27-6.34 (m, 1H), 3.61 (br. s., 2H), 3.01 (s, 3H), 2.34 (dd, J=7.63, 10.37 Hz, 1H), 2.14 (dd, J=6.16, 10.27 Hz, 1H), 1.82 (d, J=0.98 Hz, 3H), 1.01-1.09 (m, 1H).

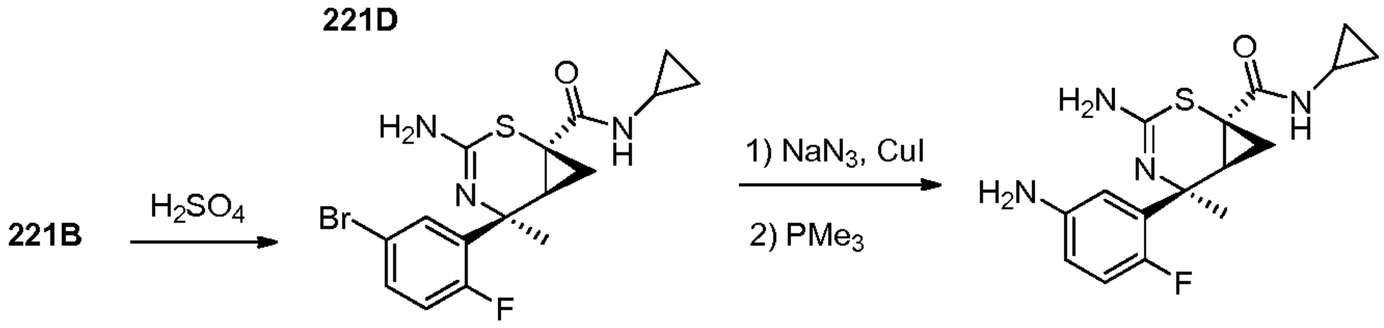
(1S,5S,6S)-3-Amino-5-(5-amino-2-fluorophenyl)-N-cyclopropyl-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide (221) and *tert*-butyl ((1S,5S,6S)-5-(5-amino-2-fluorophenyl)-1-(cyclopropylcarbamoyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (221D).



217I **221A** **221B**



221D



221C **221**

Preparation of acid 221A. A mixture of (1S,5S,6S)-methyl 5-(5-bromo-2-fluorophenyl)-3-((*tert*-butoxycarbonyl)((2-(trimethylsilyl)ethoxy)methyl)amino)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylate (**217I**, 4.0 g, 6.63 mmol), and lithium hydroxide (19.88 mL of 1 M aqueous solution, 19.88 mmol) in MeOH (60 mL) was stirred at RT in 16 h. The reaction mixture was concentrated, diluted with H_2O, cooled in an ice bath and acidified with 5 N HCl. The solid (3.9 g, 100%) was collected, washed with H_2O, dried and used in the next step. MS (ESI, positive ion) m/z: 589/591 (M+1).

Preparation of *tert*-butyl ((1S,5S,6S)-5-(5-bromo-2-fluorophenyl)-1-(cyclopropylcarbamoyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy) methyl)carbamate (221B). To a solution of (1S,5S)-5-(5-bromo-2-fluorophenyl)-3-((*tert*-butoxycarbonyl)((2-(trimethylsilyl)ethoxy)methyl)amino)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylic acid (**221A**, 5.3 g, 9.0 mmol) in 40 mL dry THF was added 1,1'-carbonyldiimidazole (2.2 g, 13.5 mmol), and the resulting cloudy mixture was stirred for

1 h. Additional 1,1'-carbonyldiimidazole (0.7 g) was added. It was stirred for 30 min then treated with cyclopropylamine (5 mL, 71.3 mmol). After the mixture was stirred for 1.5 h, it was treated with 100 mL of EtOAc and 100 mL of brine. The layers were separated. The organic layer was washed 1 N HCl (10 mL) followed by with brine (2 x 10 mL), dried over Na_2SO_4, filtered, and concentrated to give the title compound (**221B**, 5.4 g, 96%). MS (ESI, positive ion) m/z: 628/630 (M+1).

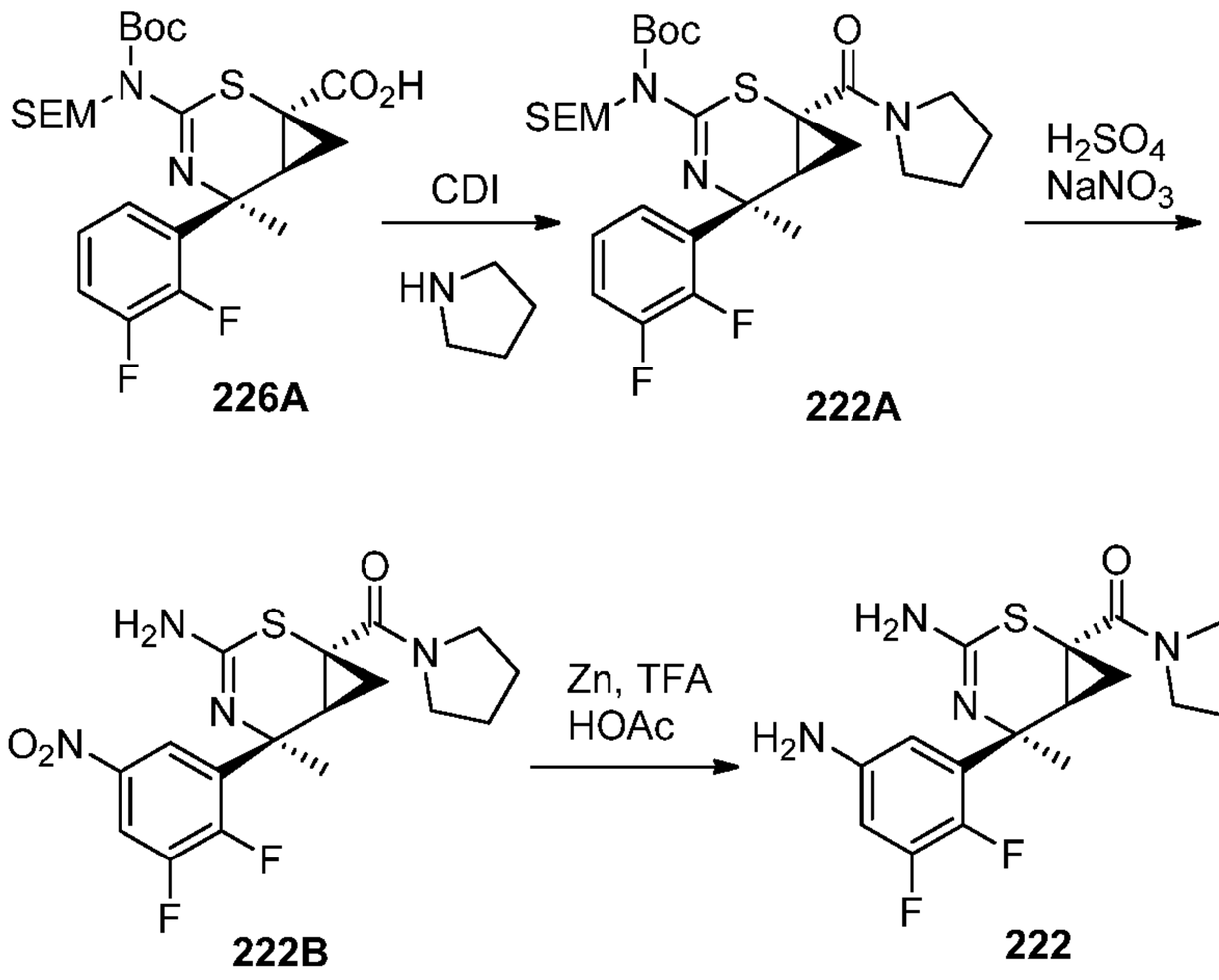
Preparation of (1S,5S,6S)-3-amino-5-(5-bromo-2-fluorophenyl)-N-cyclopropyl-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide (221C). At RT, concentrated sulfuric acid (20 mL) was added to *tert*-butyl ((1S,5S)-5-(5-bromo-2-fluorophenyl)-1-(cyclopropylcarbamoyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (**221B**, 5.43 g, 8.64 mmol) dropwise. After the brown sticky mixture was stirred for 10 min, it was added slowly to a mixture of 400 mL of DCM and 200 g of ice cooled with an ice bath. Solid K_3PO_4 was added in small portions untill pH was about 7. 500 mL of water was added, and the mixtured was partitioned. The layers were separated. The aqueous solution was extracted with a mixed solvent of (400 mL DCM + 50 mL MeOH). The combined organic extracts were dried over Na_2SO_4 and evaporated to give the title compound (1.23 g, 36%). MS (ESI, positive ion) m/z: 398/400 (M+1).

Preparation of *tert*-butyl ((1S,5S,6S)-5-(5-amino-2-fluorophenyl)-1-(cyclopropylcarbamoyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (221D). A mixture o f *tert*-butyl ((1S,5S,6S)-5-(5-bromo-2-fluorophenyl)-1-(cyclopropylcarbamoyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (**221B**, 3.5 g, 5.57 mmol), sodium azide (1.08 g, 16.70 mmol), copper(i) iodide (318 mg, 1.67 mmol), (+)-sodium L-ascorbate (0.33 g, 1.67 mmol), and (1R,2R)-(-)-N,N"-dimethylcyclohexane-1,2-diamine (0.26 mL, 1.67 mmol) in EtOH/H_2O (4:1, 50 mL) was heated at 90 °C for 2 h. The reaction mixture was cooled to RT and treated with NH_4Cl/NH_4OH (9:1, 20 mL) and stirred for 10 min. The mixture was extracted with $CHCl_3$ (3 x). The organic extracts were concentrated to dryness and dissolved in THF/H_2O (9:1, 40 mL) and added trimethylphosphine (1.0 M solution in THF, 8.35 mL, 8.35 mmol) and the mixture was stirred at RT overnight. It was treated with saturated aqueous NH_4Cl and extracted with $CHCl_3$ (3 x). The extracts were dried over Na_2SO_4 and

concentrated to give the title compound (3.1 g, 99%). MS (ESI, positive ion) m/z: 564/566 (M+1).

Preparation of (1S,5S,6S)-3-amino-5-(5-amino-2-fluorophenyl)-N-cyclopropyl-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide (221). A mixture of (1S,5S,6S)-3-amino-5-(5-bromo-2-fluorophenyl)-N-cyclopropyl-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide (**221C**, 1.2 g, 3.01 mmol), sodium azide (0.59 g, 9.04 mmol), copper(I) iodide (0.14 g, 0.75 mmol), sodium (R)-2-((S)-1,2-dihydroxyethyl)-4-hydroxy-5-oxo-2,5-dihydrofuran-3-olate (0.15 g, 0.75 mmol), and (1R,2R)-N1,N2-dimethylcyclohexane-1,2-diamine (0.147 ml, 0.753 mmol) in EtOH/H_2O (5:1, 18 mL) was heated at 90 °C for 16 h. The reaction mixture was cooled to RT and partitioned between NH_4Cl/NH_4OH (9:1, 10 mL) and DCM (100 mL). The organic layer was concentrated and the residue was dissolved in THF/H_2O (9:1, 20 mL). To this stirring solution was added trimethylphosphine (3.01 mL of 1 M in THF solution, 3.01 mmol). After the addition, the mixture was stirred for 1 h, diluted with EtOAc, washed with H_2O, brine, dried over $MgSO_4$, concentrated and the residue was purified by silica gel column (10-20% MeOH/DCM) to give the title product (0.41 g, 41%). MS (ESI, positive ion) m/z: 335 (M+1).

((1S,5S,6S)-3-Amino-5-(5-amino-2,3-difluorophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)(pyrrolidin-1-yl)methanone (222).



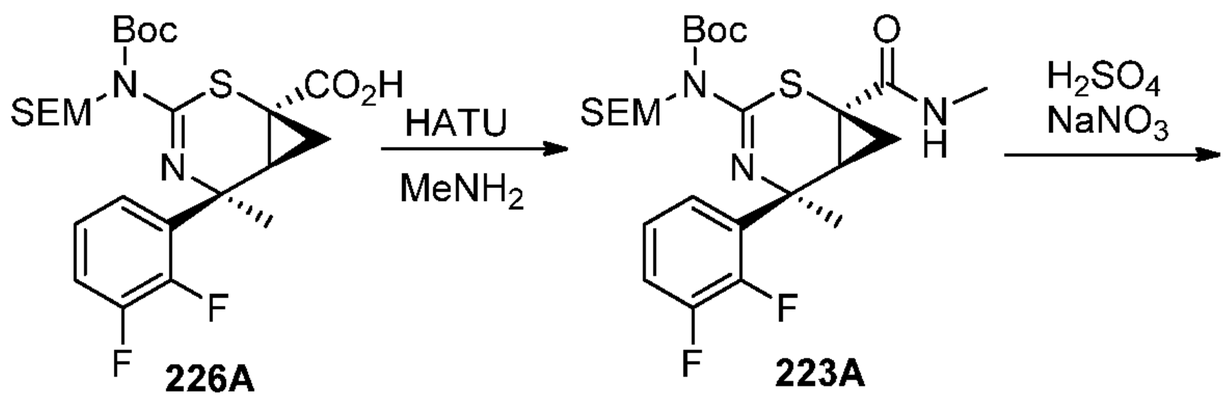
tert-Butyl ((1S,5S,6S)-5-(2,3-difluorophenyl)-5-methyl-1-(pyrrolidine-1-carbonyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-

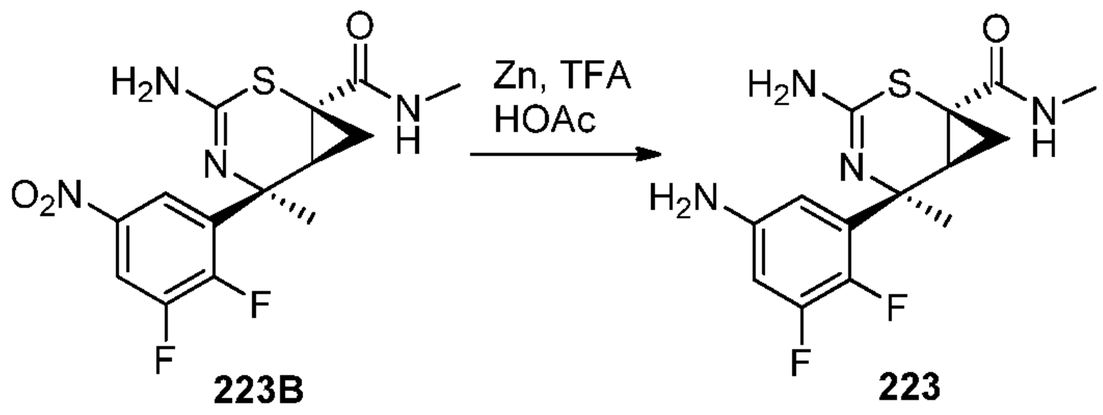
(trimethylsilyl)ethoxy)methyl)carbamate (**222A**, 3.1 g, 5.30 mmol, 100% yield) as colorless oil was prepared according to the procedures described for intermediate **226B**, starting from (1S,5S,6S)-3-((*tert*-butoxycarbonyl)((2-(trimethylsilyl)ethoxy)methyl)amino)-5-(2,3-difluorophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylic acid (**226A**, 2.8 g, 5.30 mmol), CDI (1.29 g, 7.94 mmol) and pyrrolidine (1.33 mL, 15.89 mmol). LC/MS (ESI^-) *m/z* = 582.2 $(M+H)^+$.

((1S,5S,6S)-3-Amino-5-(2,3-difluoro-5-nitrophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)(pyrrolidin-1-yl)methanone (**222B**, 1.29 g, 3.25 mmol, 63% yield) as off white solid was prepared according to the procedures described for intermediate **226C**, starting from *tert*-butyl ((1S,5S,6S)-5-(2,3-difluorophenyl)-5-methyl-1-(pyrrolidine-1-carbonyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (**222A**, 3.0 g, 5.16 mmol). LC/MS (ESI^-) *m/z* = 397.1 $(M+H)^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.31-8.38 (m, 2H), 6.51 (s, 2H), 3.60 (br., 2H), 3.28 (br., 2H), 2.14-2.20 (m, 1H), 1.83-1.93 (m, 2H), 1.81 (m, 2H), 1.70 (s, 3H), 1.31 (dd, *J*=5.58, 9.49 Hz, 1H), 0.71-0.76 (m, 1H).

((1S,5S,6S)-3-Amino-5-(5-amino-2,3-difluorophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)(pyrrolidin-1-yl)methanone (**222**) (0.78 g, 2.1 mmol, 98% yield) as white solid was prepared according to the procedures described for intermediate **226**, starting from ((1S,5S,6S)-3-amino-5-(2,3-difluoro-5-nitrophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)(pyrrolidin-1-yl)methanone (**222B**, 850 mg, 2.14 mmol). LC/MS (ESI^-) *m/z* = 367.1 (M+H). ^1H NMR (400 MHz, DMSO-d_6) δ 6.47-6.52 (m, 1H), 6.34 (ddd, *J*=2.84, 6.31, 12.57 Hz, 1H), 6.17 (br. s., 2H), 5.11 (s, 2H), 3.59 (d, *J*=18.78 Hz, 2H), 3.29 (d, *J*=9.00 Hz, 2H), 1.95-2.03 (m, 1H), 1.86 (br. s., 2H), 1.80 (br. s., 2H), 1.63 (s, 3H), 1.30 (dd, *J*=5.28, 9.39 Hz, 1H), 0.60-0.67 (m, 1H).

(1S,5S,6S)-3-Amino-5-(5-amino-2,3-difluorophenyl)-N,5-dimethyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide (223).





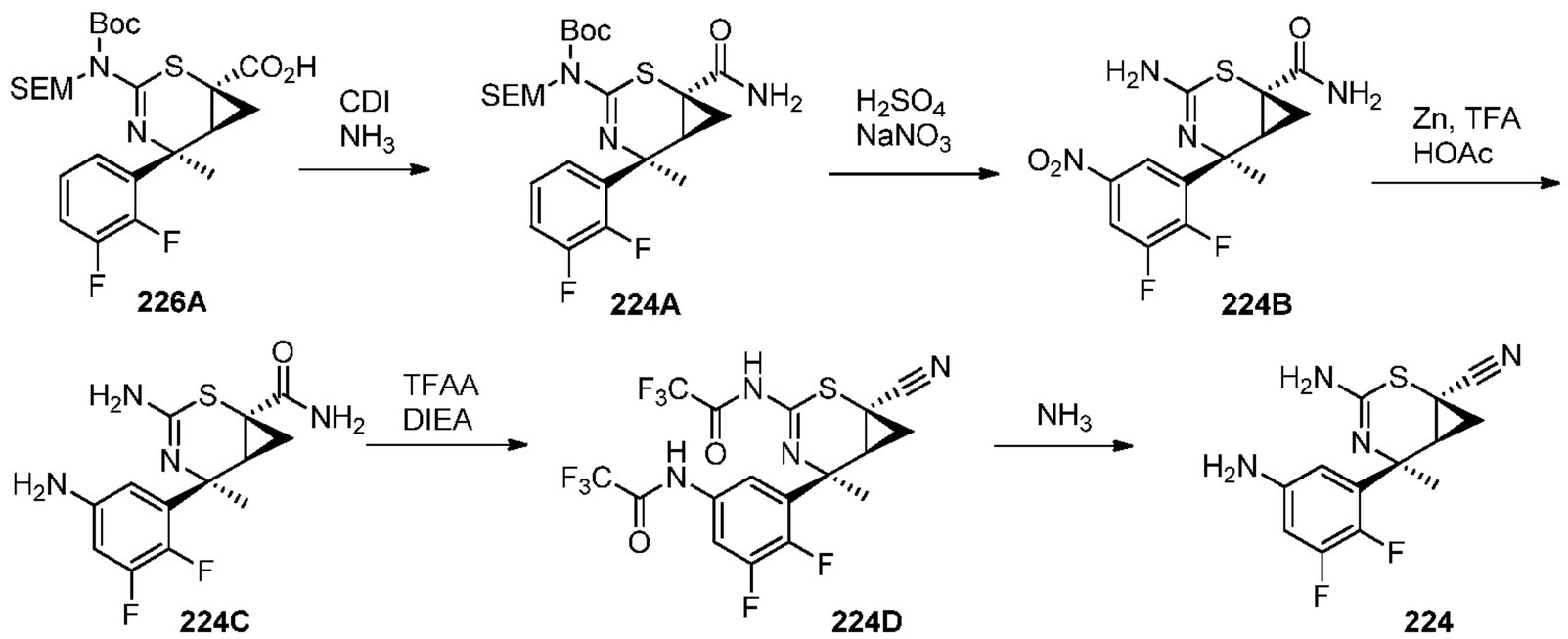
Preparation of Compound 223A. To a stirring solution of (1S,5S,6S)-3-((*tert*-butoxycarbonyl)((2-(trimethylsilyl)ethoxy)methyl)amino)-5-(2,3-difluorophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylic acid (**226A**, **13.0** g, 24.59 mmol) and N,N-diisopropylethylamine (5.35 ml, 30.7 mmol) in $CHCl_3$ (50 mL) and ACN (50 mL) at 20 °C was added HATU (10.75 g, 28.3 mmol). The solution was stirred for 45 min at 20 °C. To the reaction was added methylamine (2.0 M in THF, 36.9 mL, 73.8 mmol). After 30 min the reaction was partitioned between EtOAc (300 mL) and sat. $NaHCO_3$ (200 mL). The organic layer was washed sequentially with 1 M NaOH (150 mL), 1 M HCl (150 mL), and brine (50 mL). The organic extract was then dried over $MgSO_4$, filtered, then concentrated under reduced pressure to afford light oil. The material was then purified by silica gel chromatography (330 g) eluting products with 0-25% EtOAc/heptane to afford *tert*-butyl ((1S,5S,6S)-5-(2,3-difluorophenyl)-5-methyl-1-(methylcarbamoyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (**223A**, 11.1 g, 20.49 mmol, 83% yield) as colorless tar. LC/MS (ESI$^+$) *m/z* = 542.2 (M+H).

Preparation of Compound 223B. To a 500 mL flask containing *tert*-butyl ((1S,5S,6S)-5-(2,3-difluorophenyl)-5-methyl-1-(methylcarbamoyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (**223A**, 5.5 g, 10.15 mmol) at 0 °C under nitrogen was added sulfuric acid (16.24 mL, 305 mmol).

Gas evolution was evident. After 15 min, the reaction flask was removed from cooling bath, swirled by hand, then allowed to stir at 20 ºC for 30 min. The mixture was chilled to 0 ºC and sodium nitrate (0.86 g, 10.15 mmol) was added. The reaction was stirred for 15 min at 0 ºC then more sodium nitrate (0.86 g, 10.15 mmol) added. The reaction was stirred at 20 ºC for 45 min. The reaction was then slowly poured onto wet ice (700 mL) and the mixture along with CH_2Cl_2 (150 mL). To a rapidly stirred mixture was added potassium phosphate tribasic monohydrate (105 g, 457 mmol) over 40 min (pH ~8). The suspension was filtered and the filtrate was transferred to a separatory funnel. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (100 mL). The combined organic extracts were dried over $MgSO_4$, filtered, concentrated under reduced pressure, then purified via silica gel chromatography (120 g) eluting the products with a gradient of 0-50% EtOAc/CH_2Cl_2 to afford (1S,5S,6S)-3-amino-5-(2,3-difluoro-5-nitrophenyl)-N,5-dimethyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide (**223B**, 2.2 g, 6.17 mmol, 60.8 % yield) as off white solid. LC/MS (ESI^-) *m/z* = 357.0 (M+H). ^1H NMR (400 MHz, DMSO-d_6) δ 8.45-8.50 (m, 1H), 8.36 (ddd, *J*=2.93, 6.36, 9.49 Hz, 1H), 7.73 (t, *J*=5.63 Hz, 1H), 6.41 (s, 2H), 2.64 (d, *J*=4.50 Hz, 3H), 2.25 (t, *J*=8.22 Hz, 1H), 1.64 (s, 3H), 1.39 (dd, *J*=5.28, 9.59 Hz, 1H), 0.84 (dd, *J*=5.48, 7.04 Hz, 1H). ^{19}F NMR (377 MHz, DMSO-d_6) δ -126.77 (d, *J*=21.16 Hz, 1F), -134.13 (d, *J*=21.16 Hz, 1F).

Preparation of Compound 223. To a stirring solution of (1S,5S,6S)-3-amino-5-(2,3-difluoro-5-nitrophenyl)-N,5-dimethyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide (**223B**, 2.2 g, 6.17 mmol) in HOAc (20 mL) and TFA (5 mL) at 20 ºC was added zinc dust (1.61 g, 24.69 mmol) in 4 portions over the period of 15 min. After 1 h, the suspension was filtered through a pad of Celite® filter aid and the metallic residue was extensively washed with CH_2Cl_2 (100 mL). The filtrate was then chilled to 0 ºC and 30% NH_4OH (50 mL) was added drop wise via addition funnel over a 10 min period. The mixture was partitioned, and the aqueous portion was further extracted with CH_2Cl_2 (50 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford (1S,5S,6S)-3-amino-5-(5-amino-2,3-difluorophenyl)-N,5-dimethyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide (**223**, 1.91 g, 5.85 mmol, 95% yield) as yellow foam. LC/MS (ESI^-) *m/z* = 327.1 (M+H).

(1S,5S,6S)-3-Amino-5-(5-amino-2,3-difluorophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carbonitrile (224).



Preparation of Compound 224A. To a solution of (1S,5S,6S)-3-((*tert*-butoxycarbonyl)((2-(trimethylsilyl)ethoxy)methyl)amino)-5-(2,3-difluorophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylic acid (**226A**, 4 g, 7.57 mmol) in THF (40 mL) at 20 ºC was added 1,1'-carbonyldiimidazole (1.84 g, 11.35 mmol). The suspension was stirred for 1 h at 20 ºC. The solution was chilled to 0 ºC and ammonia was introduced from a lecture bottle. After 30 min, the reaction was partitioned between EtOAc (30 mL) and 1 M HCl (30 mL). The organic extracts were washed with brine (25 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford *tert*-butyl ((1S,5S,6S)-1-carbamoyl-5-(2,3-difluorophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (**224A**, 4 g, 7.58 mmol, 100% yield) as colorless oil. LC/MS (ESI^-) *m/z* = 528.2 (M+H).

(1S,5S,6S)-3-Amino-5-(2,3-difluoro-5-nitrophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide (**224B**, 1.4 g, 4.1 mmol, 54% yield) as tan foam was prepared according to the procedures described for intermediate **223B**, starting from *tert*-butyl ((1S,5S,6S)-1-carbamoyl-5-(2,3-difluorophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (**224A**, 4.0 g, 7.58 mmol). LC/MS (ESI^-) *m/z* = 343.0 (M+H). ^1H NMR (400 MHz, DMSO-d_6) δ 8.49 (d, *J*=5.60 Hz, 1H), 8.35 (ddd, *J*=2.93, 6.36, 9.49 Hz, 1H), 7.32 (br. s., 1H), 7.25 (br. s., 1H), 6.36 (s, 2H), 2.28 (t, *J*=8.41 Hz, 1H), 1.63 (s, 3H), 1.37 (dd, *J*=5.28, 9.59 Hz, 1H), 0.86 (dd, *J*=5.58, 6.94 Hz, 1H).

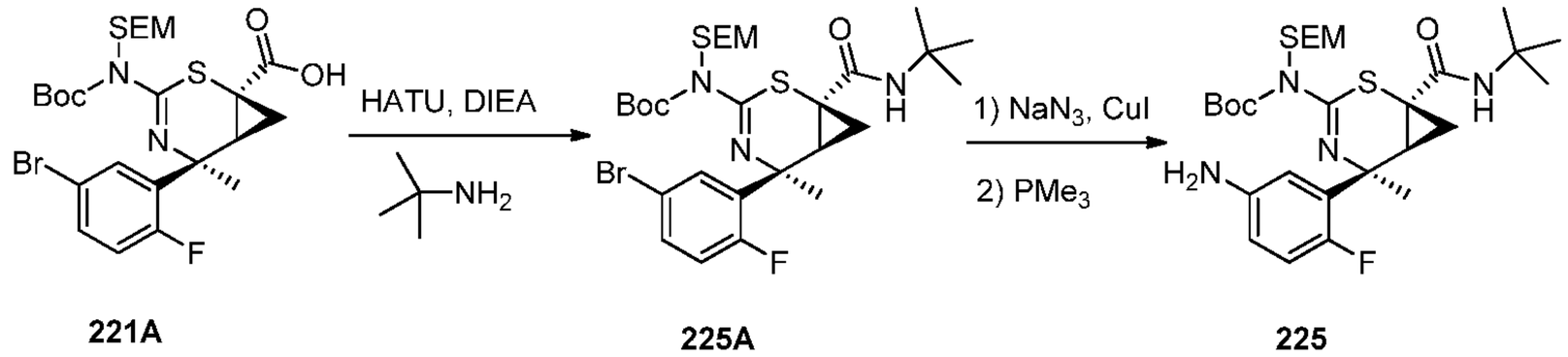
Preparation of Compound 224C. To a stirring solution of (1S,5S,6S)-3-amino-5-(2,3-difluoro-5-nitrophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide (**224B**, 280 mg, 0.82 mmol) in glacial HOAc (3 mL) and TFA (0.5 mL) at

20 °C was added zinc dust (270 mg, 4.09 mmol) in 5 portions. The suspension was stirred for 30 min at 20 °C then filtered. The metal residue was extensively washed with CH_2Cl_2 (10 mL). The filtrate was then chilled to 0 °C and 30% NH_4OH (5 mL) was added drop wise via addition funnel over a 10 min period. After separation of the organic the aqueous was further extracted with 9:1 $CHCl_3$/IPA (3 x 20 mL). The combined organics were dried over $MgSO_4$ and concentrated under reduced pressure to afford (1S,5S,6S)-3-amino-5-(5-amino-2,3-difluorophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide (**224C**, 295 mg, 0.944 mmol, 115 % yield) as yellow foam. LC/MS (ESI^-) *m/z* = 313.1 (M+H).

Preparation of Compound 224D. To a stirring solution of (1S,5S,6S)-3-amino-5-(5-amino-2,3-difluorophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide (**224C**, 250 mg, 0.80 mmol) and N,N-diisopropylethylamine (2.08 mL, 12.01 mmol) in THF (10 mL) at -70 °C under nitrogen was added trifluoroacetic anhydride (1.33 mL, 9.60 mmol). After 1 h, the reaction was quenched with sat. NH_4Cl (1 mL). The mixture was partitioned between EtOAc (10 mL) and 5% $NaHCO_3$ (10 mL). The organic layer was dried over $MgSO_4$, filtered, then concentrated under reduced pressure to afford N-((1S,5S,6S)-1-cyano-5-(2,3-difluoro-5-(2,2,2-trifluoroacetamido)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)-2,2,2-trifluoroacetamide (**224D**, 450 mg, 0.92 mmol, 116% yield) as tan oil. LC/MS (ESI^-) *m/z* = 487.0 (M+H).

Preparation of Compound 224. A solution of N-((1S,5S,6S)-1-cyano-5-(2,3-difluoro-5-(2,2,2-trifluoroacetamido)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)-2,2,2-trifluoroacetamide (**224D**, 375 mg, 0.771 mmol) in 2 M NH_3 in MeOH (10 mL) was stirred for 18 h at 42 °C in a closed screw top vial. The solvent was removed under reduced pressure and the residue was purified by silica gel chromatography (12 g) eluting products with a gradient of 1-5% 2 M NH_3 in MeOH/CH_2Cl_2 to afford (1S,5S,6S)-3-amino-5-(5-amino-2,3-difluorophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carbonitrile (**224**, 100 mg, 0.34 mmol, 44% yield) as yellow film. LC/MS (ESI^-) *m/z* = 295.1 (M+H). ^1H NMR (400 MHz, DMSO-d_6) δ 6.49 (br. s., 2H), 6.34-6.44 (m, 2H), 5.11-5.21 (m, 2H), 2.29 (dd, *J*=8.02, 9.59 Hz, 1H), 1.87 (dd, *J*=5.87, 9.78 Hz, 1H), 1.68 (s, 3H), 0.96 (t, *J*=6.65 Hz, 1H).

***tert*-butyl ((1S,5S,6S)-5-(5-Amino-2-fluorophenyl)-1-(*tert*-butylcarbamoyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (225).**

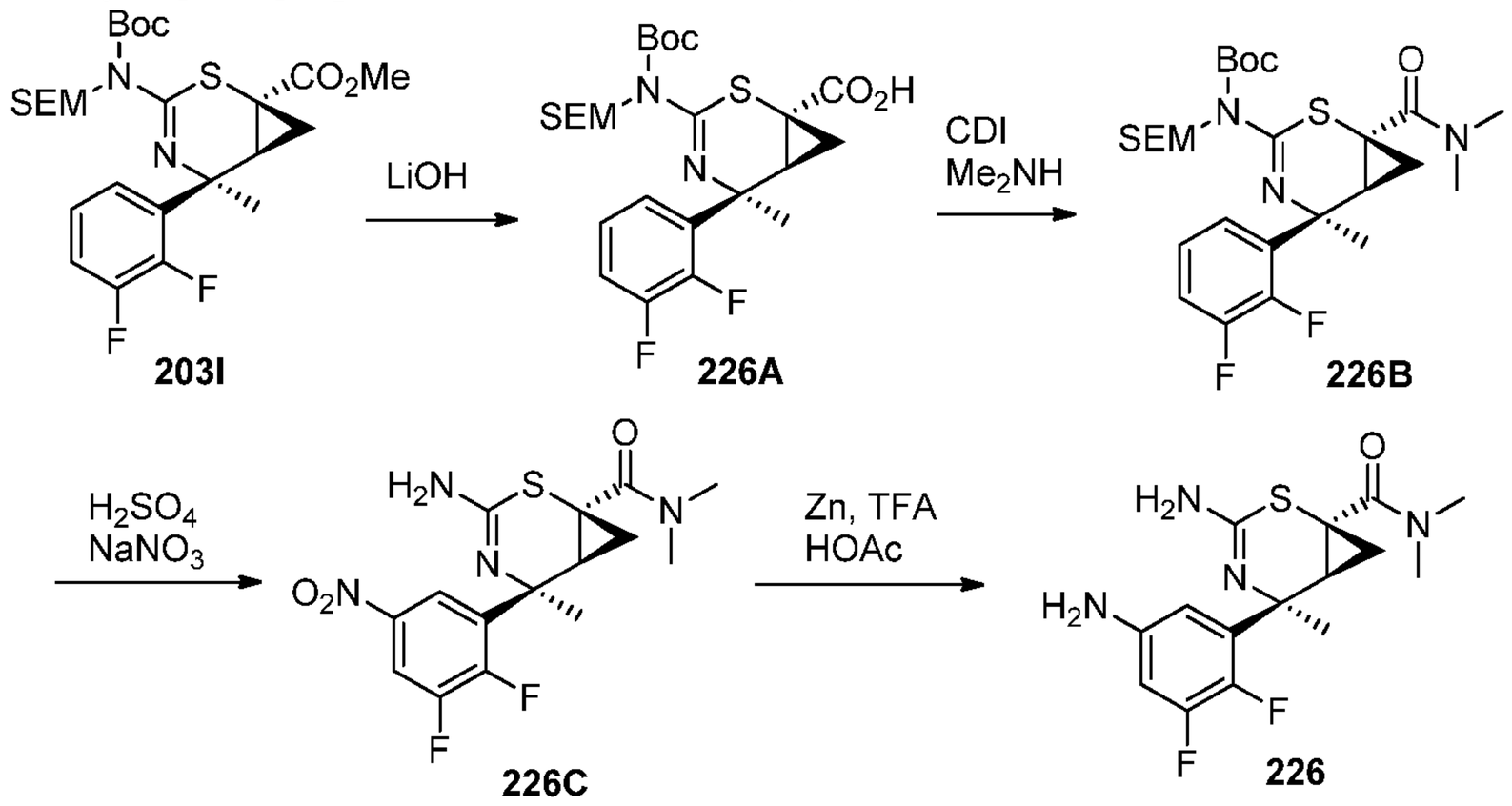


221A **225A** **225**

Preparation of *tert*-butyl ((1S,5S,6S)-5-(5-bromo-2-fluorophenyl)-1-(*tert*-butylcarbamoyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (225A). To a mixture of (1S,5S,6S)-5-(5-bromo-2-fluorophenyl)-3-((*tert*-butoxycarbonyl)((2-(trimethylsilyl)ethoxy)methyl)amino)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylic acid (**221A**, 5.19 g, 8.82 mmol), *tert*-butylamine (1.20 mL, 11.47 mmol), and DIEA (2.03 mL, 11.47 mmol) in DMF (30 ML) was added HATU (4.02 g, 10.58 mmol). After the addition, the mixture was stirred for 2 h. It was partitioned between H_2O (50 mL) and DCM (150). The extracts were dried over Na_2SO_4, and concentrated to give the title compound (5.6 g, 100%). MS (ESI, positive ion) m/z: 644/646 (M+1).

Preparation of *tert*-butyl ((1S,5S,6S)-5-(5-amino-2-fluorophenyl)-1-(*tert*-butylcarbamoyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (225). The title compound (3.63 g, 71%) was prepared according to the procedures described for intermediate **221D**, starting from *tert*-butyl ((1S,5S,6S)-5-(5-bromo-2-fluorophenyl)-1-(*tert*-butylcarbamoyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (**225A**, 5.69 g, 8.83 mmol). MS (ESI, positive ion) m/z: 581 (M+1).

(1S,5S,6S)-3-Amino-5-(5-amino-2,3-difluorophenyl)-N,N,5-trimethyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide (226).



Preparation of Compound 226A. To a stirring solution of (1S,5S,6S)-methyl 3-((*tert*-butoxycarbonyl)((2-(trimethylsilyl)ethoxy)methyl)amino)-5-(2,3-difluorophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylate (**203I**, 13.4 g, 24.7 mmol) in THF (100 mL) and MeOH (50 mL) was added a solution of lithium hydroxide monohydrate (3.1 g, 74.1 mmol) in water (50 mL). The reaction was rapidly stirred at 35 ºC for 1 h. The reaction mixture was then partitioned between EtOAc (400 mL) and 1 M HCl (200 mL). The organic layer was washed with brine (2 x 50 mL), dried over $MgSO_4$, filtered, then concentrated under reduced pressure to afford (1S,5S,6S)-3-((*tert*-butoxycarbonyl)((2-(trimethylsilyl)ethoxy)methyl)amino)-5-(2,3-difluorophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylic acid (**226A**, 13 g, 24.59 mmol, 100% yield) as colorless oil. LC/MS (ESI^-) *m/z* = 529.1 $(M+H)^+$.

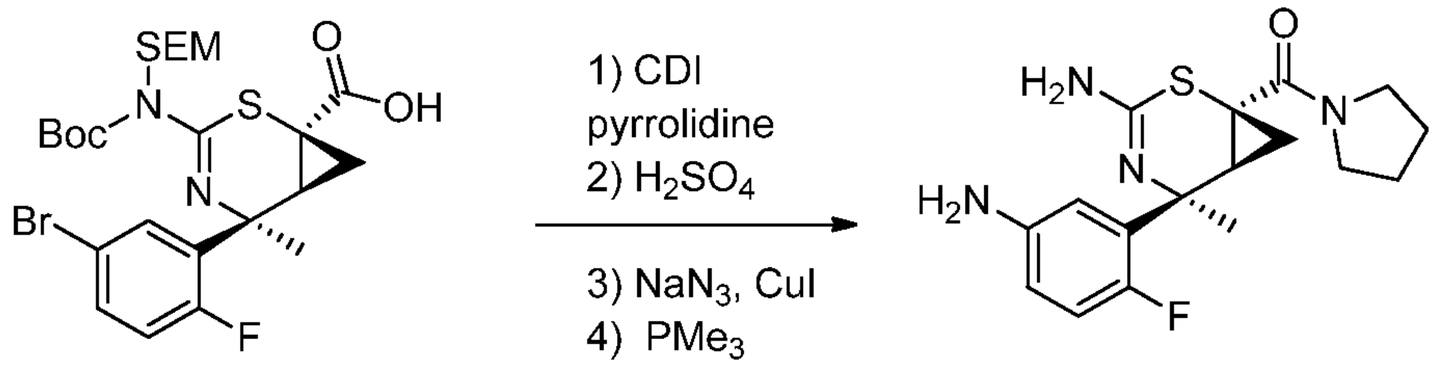
Preparation of Compound 226B. To a stirring solution of (1S,5S,6S)-3-((*tert*-butoxycarbonyl)((2-(trimethylsilyl)ethoxy)methyl)amino)-5-(2,3-difluorophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylic acid (**226A**, 2.0 g, 3.8 mmol) in THF (20 mL) at RT under nitrogen was added 1,1'-carbonyldiimidazole (0.9 g, 5.6 mmol). The cloudy solution was stirred for 90 min at RT followed by addition of dimethylamine (2.0 M in THF, 9.46 mL, 18.91 mmol). After 2 h the reaction mixture was partitioned between EtOAc (60 mL) and 1 M HCl (60 mL). The organic layer was washed with brine (25 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford *tert*-butyl((1S,5S,6S)-5-(2,3-difluorophenyl)-1-(dimethylcarbamoyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-

(trimethylsilyl)ethoxy)methyl)carbamate (**226B**, 2.1 g, 3.78 mmol) as colorless oil. LC/MS (ESI^-) *m/z* = 556.3 $(M+H)^+$.

Preparation of Compound 226C. To a 500 mL flask containing *tert*-butyl ((1S,5S,6S)-5-(2,3-difluorophenyl)-1-(dimethylcarbamoyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (**226B**, 2.0 g, 3.60 mmol) at 0 ºC was added sulfuric acid (14.39 mL, 270 mmol). The reaction was periodically removed from cooling bath, swirled by hand, and then allowed to stir at RT for 1 hr. The material was chilled to 0 ºC and sodium nitrate (0.31 g, 3.60 mmol) was added. The reaction was stirred for 15 min at 0 ºC then more sodium nitrate (0.31 g, 3.60 mmol) added. The reaction was stirred at RT for 45 min, then poured onto wet ice (700 mL) and the mixture along with CH_2Cl_2 (150 mL). To a rapidly stirred mixture was added potassium phosphate tribasic monohydrate (83 g, 360 mmol) over 20 min. The suspension was filtered and the filtrate transferred to a separatory funnel. The organic layer was separated, and the aqueous layer was extracted with 9:1 $CHCl_3$/IPA (2 x 50 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated under reduced pressure, then purified via silica gel flash column chromatography (40 g) eluting the products with a gradient of 0-50% EtOAc/CH_2Cl_2 to afford (1S,5S,6S)-3-amino-5-(2,3-difluoro-5-nitrophenyl)-N,N,5-trimethyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide (**226C**, 0.89 g, 2.40 mmol, 66.8 % yield) as off white solid. LC/MS (ESI^-) *m/z* = 371.0 $(M+H)^+$. ^1H NMR (400 MHz, CHLOROFORM-d) δ 8.32 (br. s., 1H), 8.01 (ddd, *J*=2.74, 6.26, 9.00 Hz, 1H), 3.05 (br. s., 6H), 2.43 (t, *J*=8.31 Hz, 1H), 1.90 (s, 3H), 1.40 (br. s., 1H), 0.99 (t, *J*=6.65 Hz, 1H).

Preparation of Compound 226. To a stirring solution of (1S,5S,6S)-3-amino-5-(2,3-difluoro-5-nitrophenyl)-N,N,5-trimethyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide (**226C**, 200 mg, 0.540 mmol) in glacial HOAc (2 mL) and TFA (0.5 mL) was added zinc nano powder (177 mg, 2.70 mmol) in five portions. The reaction was stirred for 2 h at 20 ºC. The reaction was then partitioned between 9:1 $CHCl_3$/IPA (30 mL) and 30% NH_4OH (20 mL). The aqueous was further extracted with 9:1 $CHCl_3$/IPA (2 x 15 mL). The organics were then washed with brine (10 mL), dried over $MgSO_4$, filtered, then concentrated under reduced pressure to afford (1S,5S,6S)-3-amino-5-(5-amino-2,3-difluorophenyl)-N,N,5-trimethyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide (**226**, 170 mg, 0.50 mmol, 92% yield) as colorless film. LC/MS (ESI^-) *m/z* = 341.0 $(M+H)^+$.

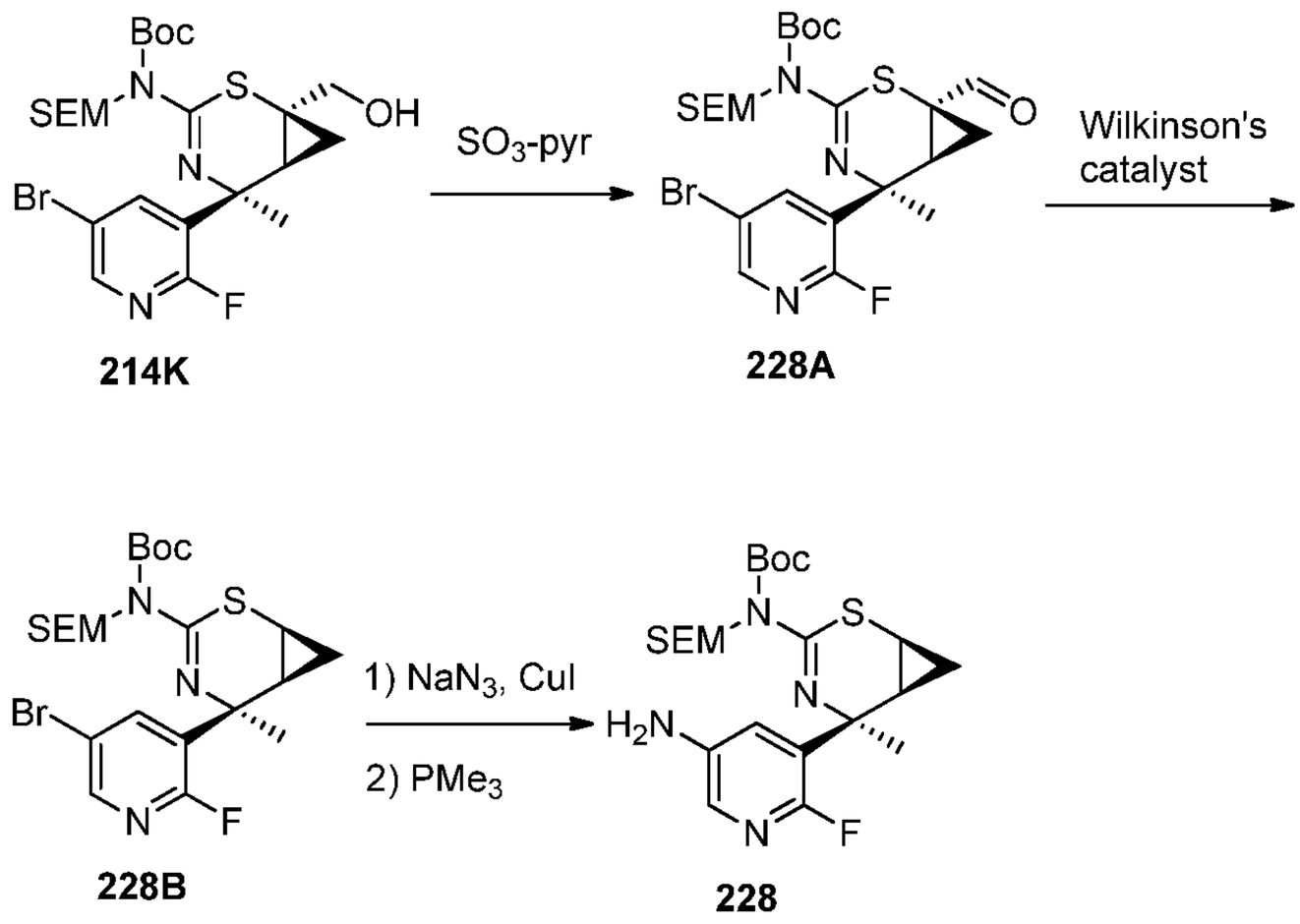
((1S,5S,6S)-3-Amino-5-(5-amino-2-fluorophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)(pyrrolidin-1-yl)methanone (227).



221A **227**

The title compound was prepared according to the synthetic sequence described for intermediate **221**, starting from (1S,5S,6S)-5-(5-bromo-2-fluorophenyl)-3-((*tert*-butoxycarbonyl)((2-(trimethylsilyl)ethoxy)methyl)amino)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylic acid (**221A).** MS (ESI, positive ion) m/z: 349.0 (M+1). ^{1}H NMR (CHLOROFORM-d) δ: 6.82 (dd, J=11.6, 8.5 Hz, 1H), 6.76 (dd, J=6.6, 2.8 Hz, 1H), 6.49 (dt, J=8.2, 3.2 Hz, 1H), 3.65 (d, J=16.6 Hz, 4H), 3.46 (br. s., 2H), 2.11-2.26 (m, 1H), 1.91 (d, J=18.6 Hz, 4H), 1.81 (s, 3H), 1.43 (dd, J=9.7, 5.6 Hz, 1H), 0.79 (t, J=6.3 Hz, 1H).

***tert*-Butyl ((1S,5S,6S)-5-(5-amino-2-fluoropyridin-3-yl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (228).**



214K **228A** **228B** **228**

Preparation of *tert*-butyl ((1S,5S,6S)-5-(5-bromo-2-fluoropyridin-3-yl)-1-formyl-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (228A). To a solution of *tert*-butyl

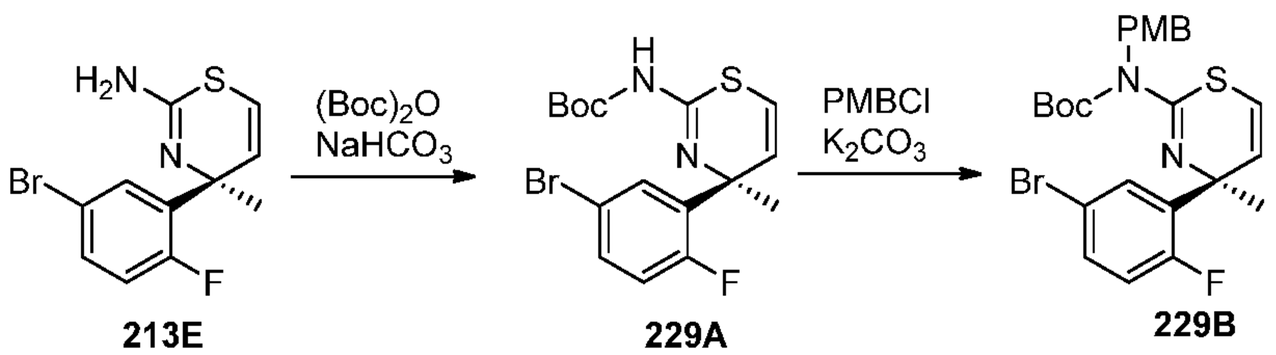
((1S,5S,6S)-5-(5-bromo-2-fluoropyridin-3-yl)-1-(hydroxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (**214K**, 3.0 g, 5.20 mmol) in DCM (30 mL) and DMSO (10 mL) was added diisopropylethylamine (3.8 mL, 21.85 mmol) and pyridine sulfur trioxide (1.8 g, 11.31 mmol). After 18 h, the mixture was diluted with EtOAc (200 mL) and washed with water (4 x 50 mL), brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by chromatography on silica using EtOAc in heptane (5-35%) as eluent to give the desired product as a colorless oil (2.31 g, 77%). LCMS (ESI, pos.) 574.0/576.0 (M+1). ^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.96 (s, 1H), 8.25 (dd, *J*=2.54, 8.61 Hz, 1H), 8.15-8.20 (m, 1H), 5.23-5.33 (m, 1H), 5.03 (d, *J*=10.56 Hz, 1H), 3.58-3.70 (m, 2H), 2.59 (ddd, *J*=1.17, 7.82, 9.59 Hz, 1H), 1.71 (d, *J*=0.98 Hz, 3H), 1.58 (dd, *J*=5.97, 9.88 Hz, 1H), 1.52 (s, 9H), 1.30-1.41 (m, 1H), 0.91-1.01 (m, 2H), 0.00 (s, 9H). ^{19}F NMR (376 MHz, CHLOROFORM-d) δ -67.51 (s).

Preparation of *tert*-butyl ((1S,5S,6S)-5-(5-amino-2-fluoropyridin-3-yl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (228B). A stream of Ar was bubbled through a solution of *tert*-butyl ((1S,5S,6S)-5-(5-bromo-2-fluoropyridin-3-yl)-1-formyl-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (0.99 g, 1.72 mmol) in 1,2-dichloroethane (8 mL) for 5 min before Wilkinson's catalyst (1.59 g, 1.72 mmol) was added. The mixture was heated at 90 °C under N_2. After 18 h, the mixture was allowed to cool to RT and filtered. The filtrate was loaded directly on a 220 g silica gel column. The remaining solids were washed with DCM (5 x 3 mL) and the mother liquid was concentrated and the residue was loaded to the silica gel column. The column was eluted with EtOAc in heptane (5-25%) to give the title compound as a colorless oil (0.60 g, 64%). LCMS (ESI, pos.) 546.0/548.0 (M+1). ^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.20 (dd, *J*=2.45, 8.51 Hz, 1H), 8.14 (s, 1H), 5.26 (d, *J*=10.56 Hz, 1H), 4.99 (d, *J*=10.56 Hz, 1H), 3.61-3.73 (m, 2H), 2.21 (dt, *J*=5.18, 8.26 Hz, 1H), 1.97-2.08 (m, 1H), 1.74 (s, 3H), 1.52 (s, 9H), 0.98 (dd, *J*=7.43, 9.19 Hz, 2H), 0.81-0.92 (m, 1H), 0.63 (q, *J*=5.74 Hz, 1H), 0.01 (s, 9H). ^{19}F NMR (377 MHz, CHLOROFORM-d) δ -67.82 (s).

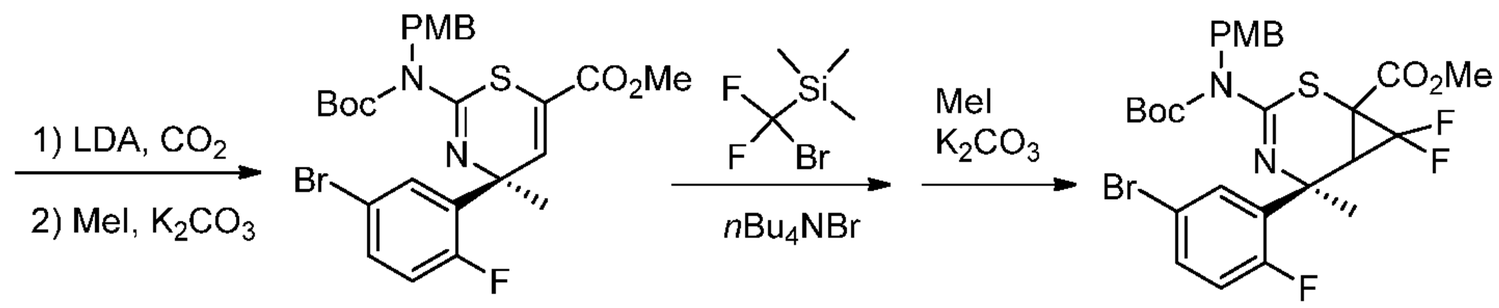
Preparation of *tert*-butyl ((1S,5S,6S)-5-(5-amino-2-fluoropyridin-3-yl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (228). A mixture of (+)-sodium L-ascorbate (50 mg, 0.25 mmol), sodium azide (200 mg, 3.08 mmol), trans-N,N'-dimethyl-1,2-

cyclohexanediamine (20 mg, 0.14 mmol), copper(I) iodide (30 mg, 0.16 mmol) and *tert*-butyl ((5S)-5-(5-bromo-2-fluoropyridin-3-yl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (600 mg, 1.10 mmol) was purged with N_2 through vacuum-back fill three times. EtOH (10 mL) and water 2.5 mL) were added. The blue mixture was heated at 95 °C under N_2. After 1 h, more (+)-sodium L-ascorbate (50 mg, 0.25 mmol), sodium azide (200 mg, 3.08 mmol), trans-N,N'-dimethyl-1,2-cyclohexanediamine (20 mg, 0.14 mmol) and copper(I) iodide (30 mg, 0.158 mmol) were added. The mixture was degassed with a stream of Ar for 5 min. The mixture was heated at 95 °C under N_2. After 30 min, the mixture was allowed to cool to RT. EtOAc (50 mL) was added and the mixture was washed with ammonium hydroxide (5 mL) followed by saturated NH_4Cl (20 mL). The aqueous layer was extracted with DCM (2 x 10 mL). The combined organic phases were concentrated. The crude residue was suspended in THF (10 mL) and treated with trimethylphosphine (1.0 M solution in THF, 1.5 mL, 1.5 mmol). After 2 h at RT, EtOAc (50 mL) was added. The mixture was washed with saturated NH_4Cl (20 mL) and brine (10 mL). The aqueous layer was washed with DCM (2 x 10 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated. The residue was purified by chromatography on silica using EtOAc in heptane (10-70%) as eluent to give the title compound (0.49 g, 86%). ^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.51 (d, *J*=2.35 Hz, 1H), 7.44 (dd, *J*=2.93, 8.41 Hz, 1H), 5.27 (d, *J*=10.56 Hz, 1H), 5.01 (d, *J*=10.56 Hz, 1H), 3.58-3.72 (m, 2H), 2.19 (dt, *J*=4.89, 8.31 Hz, 1H), 1.99-2.08 (m, 1H), 1.73 (d, *J*=0.78 Hz, 3H), 0.91-1.00 (m, 2H), 0.85 (dd, *J*=7.53, 15.16 Hz, 1H), 0.65 (q, *J*=5.87 Hz, 1H), 0.02 (s, 9H). ^{19}F NMR (376 MHz, CHLOROFORM-d) δ -77.66 (br. s.).

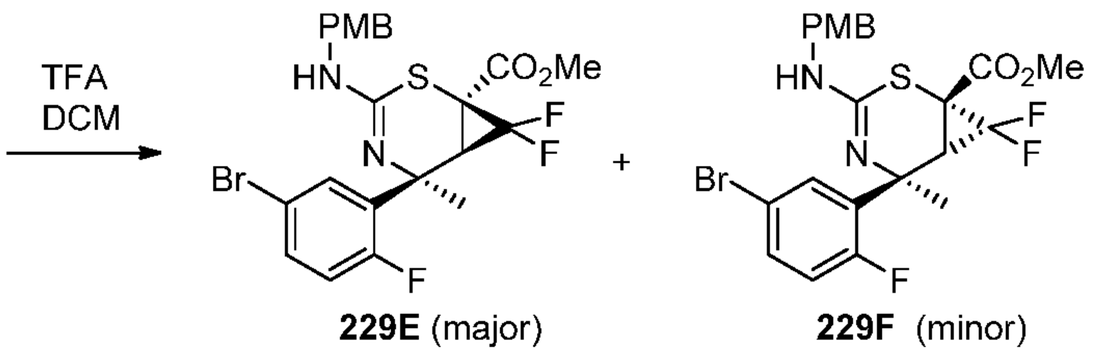
((1S,5S,6R)-3-Amino-5-(5-amino-2-fluorophenyl)-7,7-difluoro-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)methanol (229).



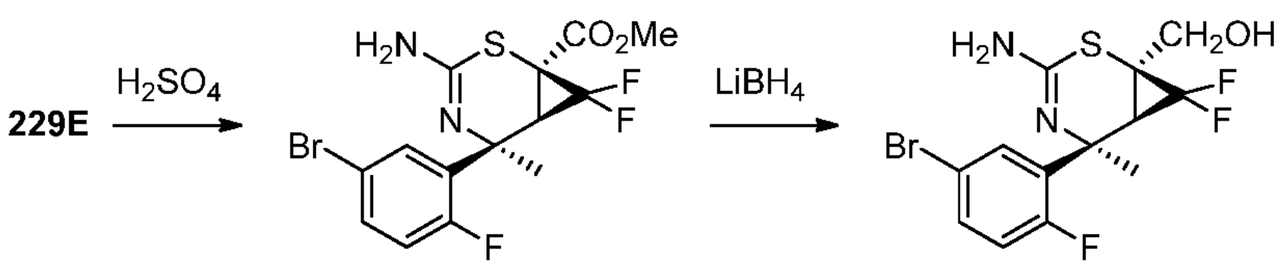
213E **229A** **229B**



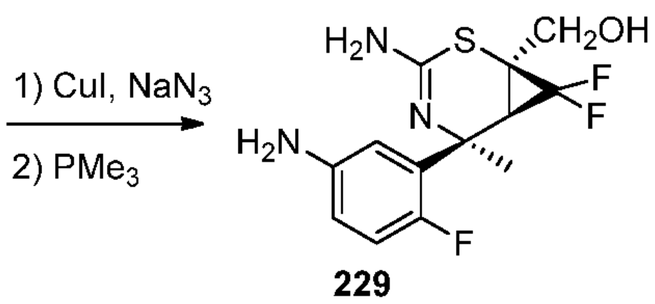
229C **229D**



229E (major) **229F** (minor)



229G **229H**



229

Preparation of (S)-*tert*-butyl (4-(5-bromo-2-fluorophenyl)-4-methyl-4H-1,3-thiazin-2-yl)carbamate (229A). To a 250 mL round bottom flask charged with (S)-4-(5-bromo-2-fluorophenyl)-4-methyl-4H-1,3-thiazin-2-amine (**213E**, 1.66 g, 5.51 mmol) and di-*tert*-butyl dicarbonate (1.20 g, 5.50 mmol, Sigma-Aldrich) was added THF (36 mL) and saturated sodium bicarbonate aqueous solution (36 mL). The reaction was stirred under Nitrogen for 48 h at RT. The reaction mixture was diluted with water and EtOAc.

The organic layer was separated, washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified via silica gel flash chromatography eluting with a gradient of 0-30% EtOAc in hexanes to afford Compound **229A** (2.08 g, 5.18 mmol, 94% yield) as a light yellow oil. MS *m/z* = 401.0/403 $[M+H]^+$.

Preparation of (S)-*tert*-butyl (4-(5-bromo-2-fluorophenyl)-4-methyl-4H-1,3-thiazin-2-yl)(4-methoxybenzyl)carbamate (229B). To a solution of (S)-*tert*-butyl (4-(5-bromo-2-fluorophenyl)-4-methyl-4H-1,3-thiazin-2-yl)carbamate (**229A**, 2.00 g, 4.98 mmol) in DMF (12.46 mL) was added potassium carbonate (0.96 g, 6.98 mmol, Sigma-Aldrich), followed by 4-methoxybenzyl chloride (0.81 mL, 5.98 mmol, Sigma-Aldrich). The reaction stirred at ambient temperature for 6 h. The reaction was diluted with water and EtOAc and allowed to sit at RT for 72 h. The organic layer was separated, washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified via silica gel flash chromatography eluting with a gradient of 0-25% EtOAc in hexanes to afford (S)-*tert*-butyl (4-(5-bromo-2-fluorophenyl)-4-methyl-4H-1,3-thiazin-2-yl)(4-methoxybenzyl)carbamate (2.4 g, 4.60 mmol, 92% yield) as a clear oil. MS *m/z* = 521.0/523 $[M+H]^+$.

Preparation of (S)-methyl 4-(5-bromo-2-fluorophenyl)-2-((*tert*-butoxycarbonyl)(4-methoxybenzyl)amino)-4-methyl-4H-1,3-thiazine-6-carboxylate (229C). A flame dried round bottom flask was charged with (S)-*tert*-butyl (4-(5-bromo-2-fluorophenyl)-4-methyl-4H-1,3-thiazin-2-yl)(4-methoxybenzyl)carbamate (0.53 g, 1.02 mmol) and THF (6 ml). The solution was cooled to -78 °C. Lithium diisopropylamide (2.0 M in heptane/THF/ethylbenzene, 0.66 mL, 1.33 mmol, Sigma-Aldrich) was added drop wise and the mixture was stirred for 15 min. CO_2 (generated by evaporation of dry ice) was passed over the reaction head space for 15 min. The reaction was carefully quenched with saturated ammonium chloride aqueous solution and the mixture was warmed to RT. The mixture was diluted with 1.0 N HCl and extracted with EtOAc. The organic layer was separated, washed with brine, dried over $_{MgSO4}$ and concentrated under reduced pressure. The material was taken up in DMF (10 mL). Potassium carbonate (0.14 g, 1.02 mmol, Sigma-Aldrich) and methyl iodide (0.06 mL, 1.02 mmol, Sigma-Aldrich) were added. The reaction was stirred at ambient temperature for 1.5 h. The reaction was diluted with water and EtOAc. The organic layer was separated and washed sequentially with 1 M LiCl aqueous solution and brine, dried over $_{MgSO4}$ and concentrated under reduced pressure. The crude residue was purified via silica gel flash chromatography eluting with a gradient of 0-30% EtOAc in hexanes to afford (S)-methyl

4-(5-bromo-2-fluorophenyl)-2-((*tert*-butoxycarbonyl)(4-methoxybenzyl)amino)-4-methyl-4H-1,3-thiazine-6-carboxylate (0.44 g, 0.75 mmol, 73% yield). MS *m/z* = 578.9/580.9 $[M+H]^+$.

Preparation of diastereomers 229D. A flame dried sealed tube was charged with a solution of (S)-methyl 4-(5-bromo-2-fluorophenyl)-2-((*tert*-butoxycarbonyl)(4-methoxybenzyl)amino)-4-methyl-4H-1,3-thiazine-6-carboxylate (**229C**, 3.03 g, 5.23 mmol) in toluene (20.9 mL). The vial was sealed and nitrogen was bubbled through the solution for 5 min. Tetrabutylammonium bromide (0.08 g, 0.26 mmol, Sigma-Aldrich) was added followed by trimethyl(bromodifluoromethyl)silane (2.12 g, 10.46 mmol, SynQuest Laboratories). The reaction was flushed with nitrogen and tightly sealed. The reaction was heated to 110 °C for 16 h then cooled to RT. It was diluted with water and EtOAc. The organic layer was separated, washed with brine, dried over $_{MgSO4}$ and concentrated under reduced pressure to afford an approximately 2:1:1 ratio of gemdifluorocyclopropyl carboxylic acid to gemdifluorocyclopropyl methyl ester to unreacted starting material by LC/MS. The crude material was taken up in DMF (35 mL). Potassium carbonate (0.72 g, 5.23 mmol, Sigma-Aldrich) was added followed by methyl iodide (0.33 mL, 5.23 mmol, Sigma-Aldrich). The reaction was stirred at RT for 2 h. The reaction was diluted with water and EtOAc. The organic layer was separated, washed with brine, and dried over $MgSO_4$. The crude material was purified via silica gel flash chromatography eluting with a gradient of 0-30% EtOAc in hexanes to afford 3.3 g of a mixture of (1S,5S,6R)-methyl 5-(5-bromo-2-fluorophenyl)-3-((*tert*-butoxycarbonyl)(4-methoxybenzyl)amino)-7,7-difluoro-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylate (**229D**: MS *m/z* = 572.8/574.8 $[M+H]^+$) as a mixture of diastereomers and (S)-methyl 4-(5-bromo-2-fluorophenyl)-2-((*tert*-butoxycarbonyl)(4-methoxybenzyl)amino)-4-methyl-4H-1,3-thiazine-6-carboxylate (**229C**: MS *m/z* = 578.9/580.9 M^+). Note: the observed mass to charge ratio of 572.8/574.8 corresponds to the mass of the desired product (629.5) minus the *tert*-butyl group of the Boc which is commonly observed under the standard LC/MS method. The mixture was carried forward without further purification.

Preparation of (1S,5S,6R)-methyl 5-(5-bromo-2-fluorophenyl)-7,7-difluoro-3-((4-methoxybenzyl)amino)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylate (229E) and (1R,5S,6R)-methyl 5-(5-bromo-2-fluorophenyl)-7,7-difluoro-3-((4-methoxybenzyl)amino)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylate (229F). To a flask charged with 3.3 g of the mixture containing (5S)-methyl

5-(5-bromo-2-fluorophenyl)-3-((*tert*-butoxycarbonyl)(4-methoxybenzyl)amino)-7,7-difluoro-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylate (**229D**) and **229C** from the previous step was added DCM (35 mL) followed by TFA (13. 3 mL, 173 mmol). The reaction was stirred at RT for 1 h. The reaction was concentrated under reduced pressure. The crude material was taken up in EtOAc (100 mL) and washed with saturated sodium bicarbonate aqueous solution and brine. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified via silica gel flash chromatography eluting with DCM to afford (1S,5S,6R)-methyl 5-(5-bromo-2-fluorophenyl)-7,7-difluoro-3-((4-methoxybenzyl)amino)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylate (1.4 g, 2.64 mmol, **229E**, 50% yield and the diastereomer (1R,5S,6S)-methyl 5-(5-bromo-2-fluorophenyl)-7,7-difluoro-3-((4-methoxybenzyl)amino)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylate (0.3 g, 0.567 mmol, **229F**, 11% yield). For both diastereomers: MS *m/z* = 528.9/530.9 $[M+H]^+$.

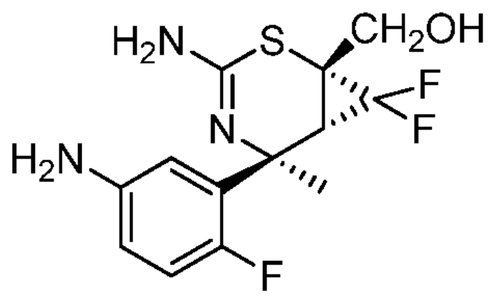
Preparation of (1S,5S,6R)-methyl 3-amino-5-(5-bromo-2-fluorophenyl)-7,7-difluoro-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylate (229G). To a solution of (1S,5S,6R)-methyl 5-(5-bromo-2-fluorophenyl)-7,7-difluoro-3-((4-methoxybenzyl)amino)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylate (**229E**, 1.4 g, 2.6 mmol) in TFA (17.6 mL) was added anisole (0.87 mL, 7.93 mmol) followed by drop wise addition of sulfuric acid (1.4 mL, 26.4 mmol). The reaction was stirred at RT for 2 h. The sticky mixture was poured into an Erlenmeyer flask containing wet ice. 10 N NaOH was added to basify the reaction to pH = 14. The basic aqueous layer was extracted with EtOAc twice and the combined organic layers were washed with brine, dried over $_{MgSO4}$ and concentrated under reduced pressure. The crude residue was purified via silica gel flash chromatography eluting with a gradient of 10-55% EtOAc in hexanes to afford (1S,5S,6R)-methyl 3-amino-5-(5-bromo-2-fluorophenyl)-7,7-difluoro-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylate (**229G**, 0.94 g, 2.29 mmol, 87% yield) as a white solid. MS *m/z* = 408.9/410.9 $[M+H]^+$.

Preparation of ((1S,5S,6R)-3-amino-5-(5-bromo-2-fluorophenyl)-7,7-difluoro-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)methanol (229H). To a solution of (1S,5S,6R)-methyl 3-amino-5-(5-bromo-2-fluorophenyl)-7,7-difluoro-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylate (**229G**, 0.98 g, 2.40 mmol) in THF (17 mL) was added lithium borohydride (2.0 M solution in THF, 2.40 ml, 4.80 mmol) followed by MeOH (0.78 mL, 19.22 mmol). The solution was stirred at ambient

temperature for 2 h. The reaction was quenched with water and EtOAc. The organic layer was separated, washed with brine, dried over $_{MgSO4}$ and concentrated under reduced pressure to afford ((1S,5S,6R)-3-amino-5-(5-bromo-2-fluorophenyl)-7,7-difluoro-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)methanol (0.83 g, 2.18 mmol, 91% yield) as a white solid. MS *m/z* = 380.8/382.8 $[M+H]^+$.

Preparation of ((1S,5S,6R)-3-amino-5-(5-amino-2-fluorophenyl)-7,7-difluoro-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)methanol (229). To a mixture of copper(I) iodide (0.05 g, 0.27 mmol, Sigma-Aldrich), sodium azide (0.27 g, 4.11 mmol, Sigma-Aldrich), and ((1S,5S,6R)-3-amino-5-(5-bromo-2-fluorophenyl)-7,7-difluoro-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)methanol (**229H**, 0.52 g, 1.37 mmol) at RT was added EtOH (4.8 mL) and water (2.1 mL). The reaction mixture was degassed by bubbling nitrogen through the solution for 5 min then (1R,2R)-(-)-N,N''-dimethylcyclohexane-1,2-diamine (0.04 mL, 0.27 mmol, Sigma-Aldrich) was added. The reaction mixture was heated to 80 °C for 1.5 h then cooled to RT. The reaction was poured into a separatory funnel containing a 9:1 solution of aqueous saturated ammonium chloride to ammonium hydroxide. EtOAc was added and the phases were mixed. The organic layer was separated, washed sequentially with 9:1 saturated ammonium chloride to saturated ammonium hydroxide solution and brine, then dried over $_{MgSO4}$ and concentrated under reduced pressure. The crude residue was taken up in THF (6 mL) and water (3 mL). Trimethylphosphine (1.37 mL of 1.0 M solution in THF, 1.37 mmol) was added and the reaction was stirred at RT for 1 h. It was diluted with water and EtOAc. The organic layer was separated, washed with brine and dried over $_{MgSO4}$ to afford ((1S,5S,6R)-3-amino-5-(5-amino-2-fluorophenyl)-7,7-difluoro-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)methanol (0.37 g, 1.12 mmol, 86% yield) as a glassy brown solid. MS *m/z* = 318.0 $[M+H]^+$. ^{19}F NMR (282 MHz, CHLOROFORM-d) δ -126.35 (s, 1F), -130.07 (d, *J*=157.75 Hz, 1F), -141.94 (d, *J*=158.32 Hz, 1F). ^1H NMR (300MHz, $CDCl_3$) δ 7.03 (dd, *J*=2.9, 6.7 Hz, 1H), 6.87 (dd, *J*=8.6, 11.9 Hz, 1H), 6.55 (td, *J*=3.4, 8.5 Hz, 1H), 4.04 - 3.85 (m, 2H), 2.47 (dd, *J*=3.7, 15.8 Hz, 1H), 1.64 (s, 3H).

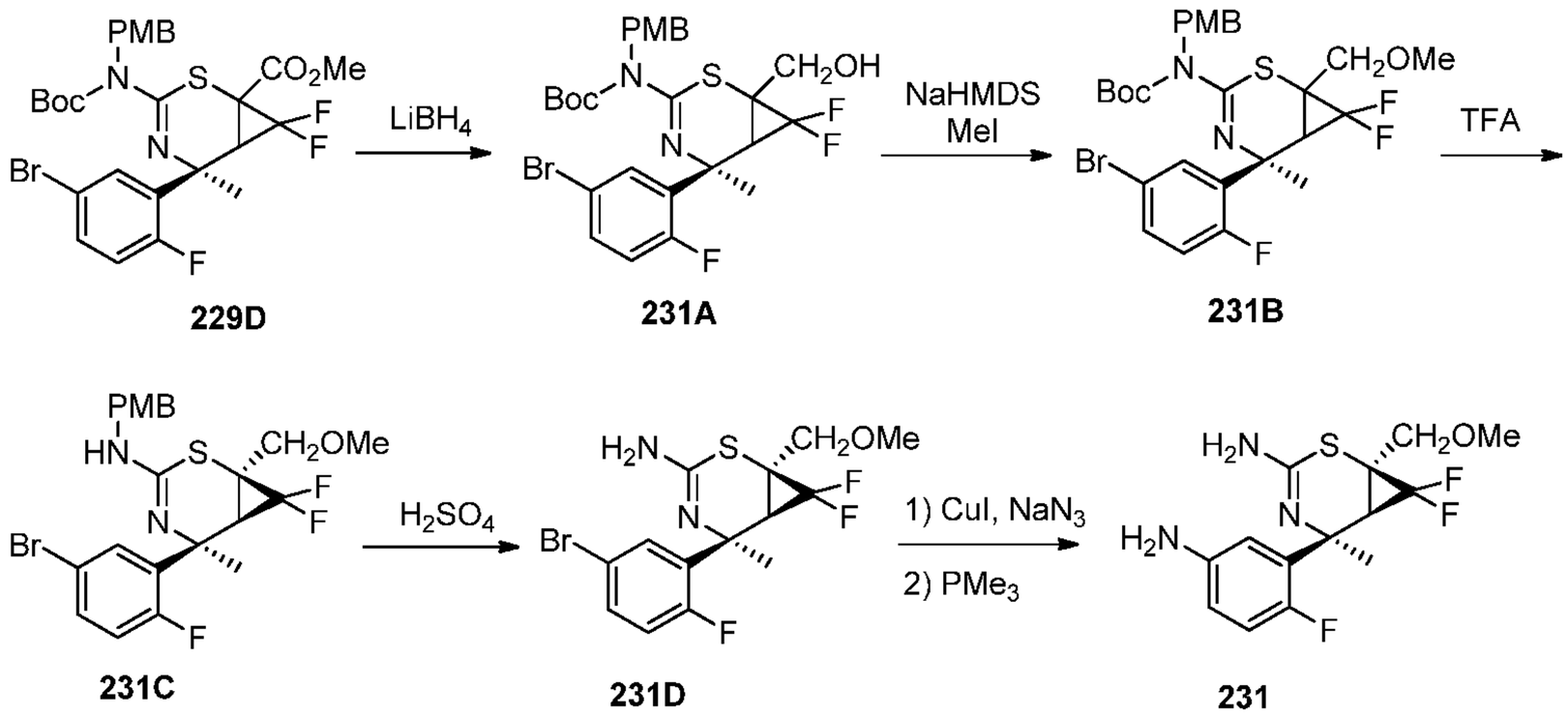
((1R,5S,6S)-3-Amino-5-(5-amino-2-fluorophenyl)-7,7-difluoro-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)methanol (230).



230

The title compound (**230**) was prepared following the procedures described for intermediate **229**, starting with intermediate **229F**. MS *m/z* = 318.0 $[M+H]^+$. ^1H NMR (300MHz, $CDCl_3$) δ 6.87 (dd, *J*=8.6, 11.9 Hz, 1H), 6.68 (dd, *J*=3.0, 6.8 Hz, 1H), 6.54 (ddd, *J*=3.0, 3.8, 8.6 Hz, 1H), 3.91 - 3.76 (m, 2H), 2.41 (dd, *J*=3.2, 16.2 Hz, 1H), 1.74 (s, 3H).

(1S,5S,6R)-5-(5-Amino-2-fluorophenyl)-7,7-difluoro-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (231).



Preparation of *tert*-butyl ((5S)-5-(5-bromo-2-fluorophenyl)-7,7-difluoro-1-(hydroxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)(4-methoxybenzyl)carbamate (231A). To a flask containing 0.94 g of intermediate **229D** (not pure: contaminated with **229C**) in THF (10 mL) at RT was added lithium borohydride (2.0 M solution in THF, 1.49 mL, 2.99 mmol). MeOH (0.48 mL, 11.95 mmol) was added dropwise. Evolution of gas was observed. The reaction was stirred at RT for 15 min. It was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over $_{MgSO4}$ and concentrated under reduced pressure. The crude residue was purified via silica gel flash chromatography eluting with a gradient of 0-40% EtOAc in hexanes to afford 0.9 g of a mixture of *tert*-butyl ((5S)-5-(5-bromo-2-

fluorophenyl)-7,7-difluoro-1-(hydroxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)(4-methoxybenzyl)carbamate as a mixture of diastereomers (**231A**). MS *m/z* = 544.8/546.8 $[M+H]^+$. Note 1: the observed mass to charge ratio of 544.8/546.8 corresponds to the mass of the desired product (601.5) minus the *tert*-butyl group of the Boc which is commonly observed under the standard LC/MS method. Note 2: The product mixture contains some of the allylic alcohol resulting from the reduction of Compound **229C** which was brought forward from the impure starting material.

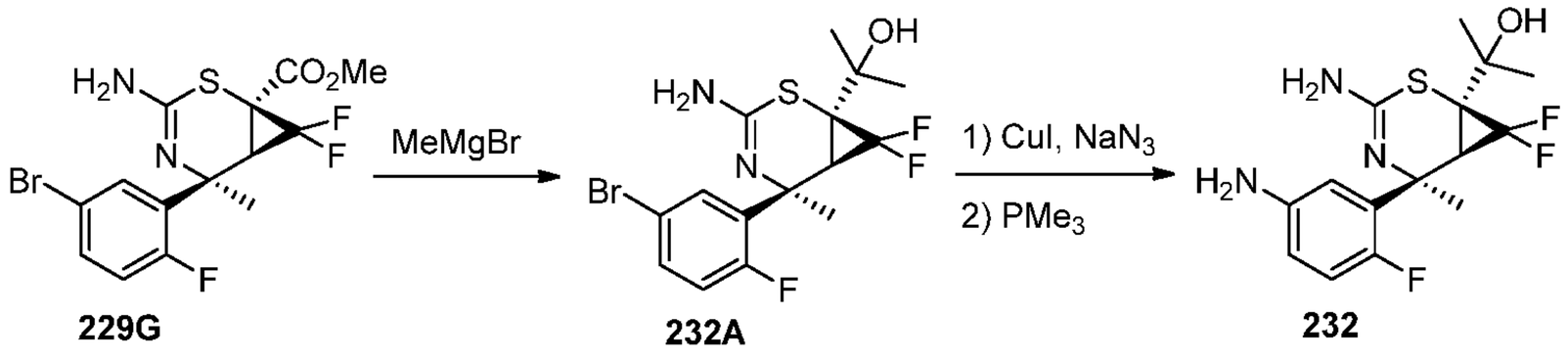
Preparation of *tert*-butyl ((5S)-5-(5-bromo-2-fluorophenyl)-7,7-difluoro-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)(4-methoxybenzyl)carbamate (231B). A solution of 0.9 g the above obtained intermediate **231A** in THF (7.5 mL) was cooled to 0 °C. Sodium bis(trimethylsilyl)amide (2.1 mL of 1.0 M solution in THF, 2.1 mmol, Sigma-Aldrich) was added drop wise to the stirring solution under nitrogen. The reaction was stirred for 20 min at 0 °C then methyl iodide (0.12 mL, 1.95 mmol) was added drop wise. The reaction was stirred at RT for 16 h. It was quenched with aqueous saturated ammonium chloride and diluted with water and EtOAc. The organic layer was separated, washed with brine, dried over $_{MgSO4}$ and concentrated under reduced pressure. The crude residue was purified via silica gel flash chromatography eluting with a gradient of 0-30% EtOAc in hexanes) to afford 0.77 g product mixture containing *tert*-butyl ((5S)-5-(5-bromo-2-fluorophenyl)-7,7-difluoro-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)(4-methoxybenzyl)carbamate as a mixture of diastereomers (**231B**). MS *m/z* = 615.0/617.0 $[M+H]^+$.

Preparation of (1S,5S,6R)-5-(5-bromo-2-fluorophenyl)-7,7-difluoro-N-(4-methoxybenzyl)-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (231C). To a solution of 0.77 g of the above obtained intermediate **221**C in DCM (10 mL) was added TFA (3.8 mL, 49.3 mmol). The reaction was stirred at RT for 30 min then concentrated under reduced pressure. The crude residue was taken up in EtOAc and washed with saturated sodium bicarbonate 3 times followed by brine, dried over $MgSO_4$ and concentrated under reduced pressure. The material was purified via silica gel flash chromatography eluting with DCM to afford (1S,5S,6R)-5-(5-bromo-2-fluorophenyl)-7,7-difluoro-N-(4-methoxybenzyl)-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (**231C**, 0.41 g, 0.79 mmol, 63% yield) as a single diastereomer MS *m/z* = 515.0 $[M+H]^+$.

Intermediate **231D** was prepared following the procedure described in intermediate **229G**, starting with intermediate **231C**. MS *m/z* = 395/397 $[M+H]^+$.

Preparation of (1S,5S,6R)-5-(5-amino-2-fluorophenyl)-7,7-difluoro-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (231). This compound was prepared following the procedure described in intermediate **229**, starting with intermediate **231D**. MS *m/z* = 332.0 $[M+H]^+$. ^1H NMR (300MHz, $CDCl_3$) δ 7.05 (dd, *J*=2.9, 6.7 Hz, 1H), 6.87 (dd, *J*=8.5, 12.0 Hz, 1H), 6.63 - 6.50 (m, 1H), 4.02 - 3.93 (m, 1H), 3.54 (dd, *J*=2.3, 11.3 Hz, 1H), 3.41 (s, 3H), 2.38 (dd, *J*=3.7, 15.4 Hz, 1H), 1.64 (d, *J*=1.0 Hz, 3H).

2-((1S,5S,6R)-3-Amino-5-(5-amino-2-fluorophenyl)-7,7-difluoro-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)propan-2-ol (232).



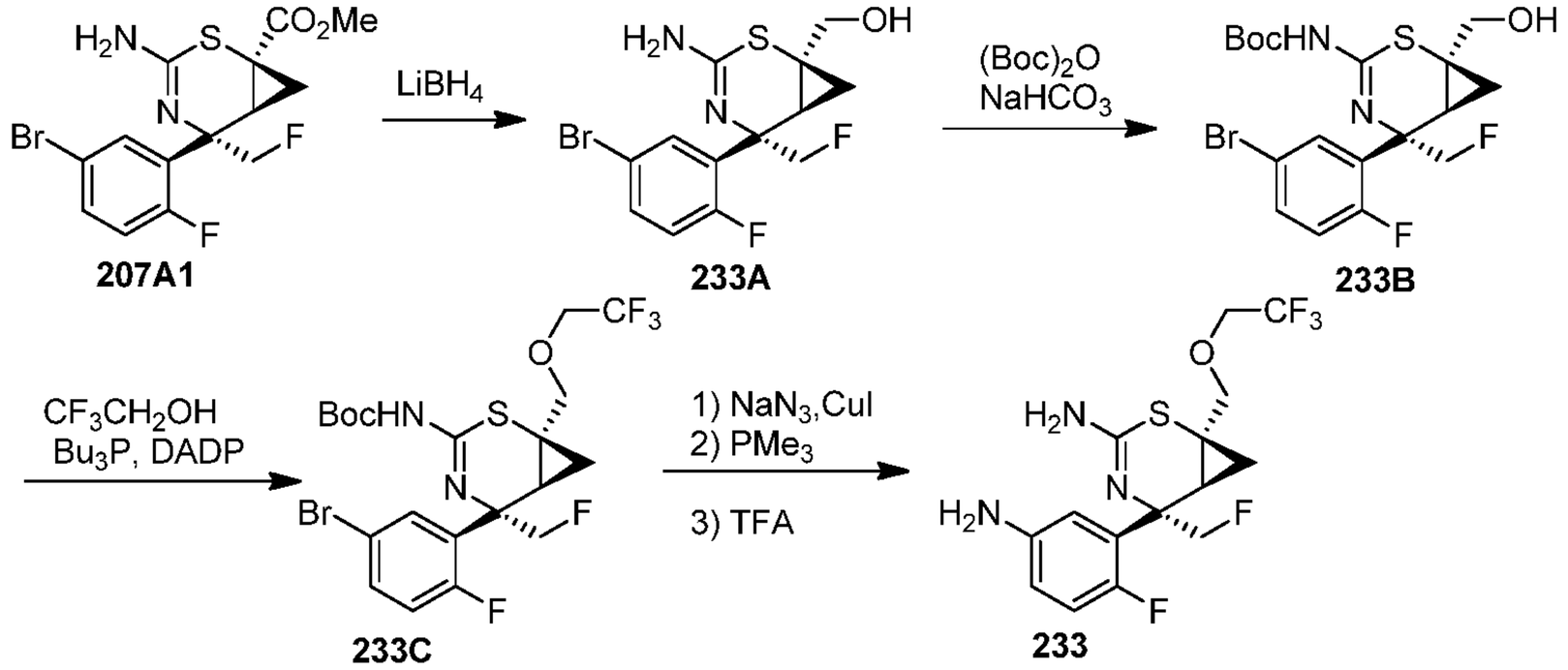
229G **232A** **232**

Preparation of intermediate 232A. A flame dried round bottom flask was charged with (1S,5S,6R)-methyl 3-amino-5-(5-bromo-2-fluorophenyl)-7,7-difluoro-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylate (**229G**, 0.28 g, 0.67 mmol). THF (11.20 mL) was added and the solution was cooled to 0 °C. Methylmagnesium bromide (3.0 M in Et_2O, 2.24 mL, 6.72 mmol, Sigma-Aldrich) was added drop wise to the stirring solution and the reaction was stirred at 0 °C for 5 min. The reaction was carefully quenched with saturated ammonium chloride and diluted with water and EtOAc. The organic layer was separated, washed with brine, dried over $_{MgSO4}$ and concentrated under reduced pressure. Purification via silica gel flash chromatography eluting with a gradient of 0-10% 2 M ammonia solution in MeOH in DCM afforded 2-((1S,5S,6R)-3-amino-5-(5-bromo-2-fluorophenyl)-7,7-difluoro-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)propan-2-ol (0.22 g, 0.55 mmol, 82% yield) as a pale yellow solid. MS *m/z* = 409.0/411.0 $[M+H]^+$.

2-((1S,5S,6R)-3-Amino-5-(5-amino-2-fluorophenyl)-7,7-difluoro-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)propan-2-ol (232) was prepared following the procedure described for intermediate **229**, starting with intermediate **232A**. MS *m/z* = 346.0 $[M+H]^+$. ^1H NMR (300MHz, $CDCl_3$) δ 6.96 (dd, *J*=3.1, 6.8 Hz, 1H), 6.88 (dd,

J=8.5, 11.8 Hz, 1H), 6.55 (td, *J*=3.6, 8.2 Hz, 1H), 3.12 - 3.01 (m, 1H), 1.68 (d, *J*=1.0 Hz, 3H), 1.49 (s, 3H), 1.47 (s, 3H).

(1S,5S,6S)-5-(5-Amino-2-fluorophenyl)-5-(fluoromethyl)-1-((2,2,2-trifluoroethoxy)methyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (233).



Preparation of Compound 233A. To a solution of (1S,5S,6S)-methyl 3-amino-5-(5-bromo-2-fluorophenyl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylate (**207A1** purified from intermediate **207A** via silica gel chromatography) (2.5 g, 6.39 mmol) in THF (60 mL) under N_2 was added lithium borohydride (2 M solution in THF, 6.39 mL, 12.78 mmol) via syringe followed by dropwise addition of MeOH (2.07 mL, 51.10 mmol). The mixture was stirred at RT for 30 min. It was quenched with saturated NH_4Cl, diluted with water, and then extracted with EtOAc (3 x). The combined organic extracts were washed with water and brine, dried over Na_2SO_4 and then filtered. The filtrate was concentrated and purified by silica gel chromatography (1-8% MeOH (2 M NH_3) in DCM) to afford ((1S,5S,6S)-3-amino-5-(5-bromo-2-fluorophenyl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)methanol (**233A**, 1.85 g, 5.09 mmol, 80% yield) as white solid. LC/MS (ESI^+) *m/z* = 363.0/365.0 (M+H).

Preparation of Compound 233B. To a solution of ((1S,5S,6S)-3-amino-5-(5-bromo-2-fluorophenyl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)methanol (1.5 g, 4.13 mmol) in 1,4-dioxane (30 mL) was added di-*tert*-butyl dicarbonate (4.74 mL, 20.65 mmol) followed by saturated sodium bicarbonate (12 mL). The reaction was stirred at ambient temperature for 16 h. The resulted mixture was diluted with water and then extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated and purified by silica gel chromatography (0-70% EtOAc/hexanes) to afford *tert*-butyl ((1S,5S,6S)-5-(5-bromo-

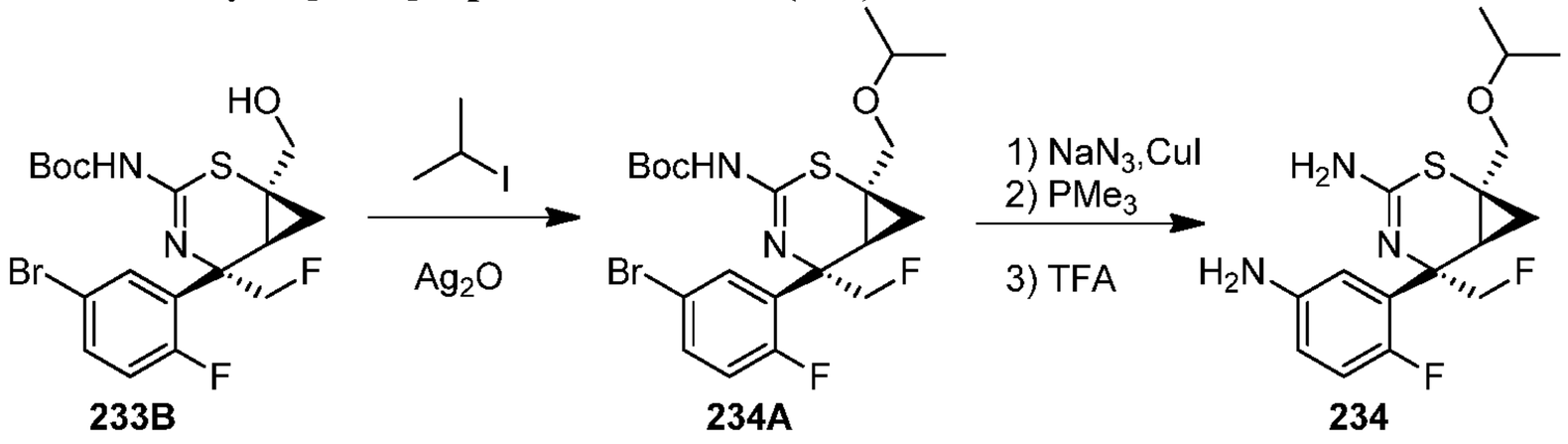
2-fluorophenyl)-5-(fluoromethyl)-1-(hydroxymethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)carbamate (1.77 g, 3.82 mmol, 93% yield) as white foam. LC/MS (ESI^+) *m/z* = 463.0/465.0 (M+H).

Preparation of Compound 233C. To a solution of *tert*-butyl ((1S,5S,6S)-5-(5-bromo-2-fluorophenyl)-5-(fluoromethyl)-1-(hydroxymethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)carbamate (0.10 g, 0.21 mmol) and (*E*)-diazene-1,2-diylbis(piperidin-1-ylmethanone) (0.11 g, 0.43 mmol) in toluene (5 mL) at ambient temperature was added tributylphosphine (0.11 mL, 0.43 mmol). After 10 min, 2,2,2-trifluoroethanol (0.16 mL, 2.16 mmol) was added and the mixture was heated at 65 °C for 2 h until the starting material was fully consumed. The mixture was concentrated and the residue was purified by Shimadzu HPLC to afford *tert*-butyl ((1S,5S,6S)-5-(5-bromo-2-fluorophenyl)-5-(fluoromethyl)-1-((2,2,2-trifluoroethoxy)methyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)carbamate (40 mg, 0.07 mmol, 34% yield). LC/MS (ESI^+) *m/z* = 545.0/547.0 (M+H).

Preparation of Compound 233. To a pressure vial was charged *tert*-butyl ((1S,5S,6S)-5-(5-bromo-2-fluorophenyl)-5-(fluoromethyl)-1-((2,2,2-trifluoroethoxy)methyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)carbamate (0.040 g, 0.073 mmol), sodium azide (0.014 g, 0.220 mmol), copper(I) iodide (2.79 mg, 0.015 mmol), (+)-sodium L-ascorbate (3.34 mg, 0.017 mmol), water (0.400 mL) and EtOH (2 mL). After purged with N_2, (1R,2R)-N1,N2-dimethylcyclohexane-1,2-diamine (2 μL, 0.015 mmol) was added. The mixture was heated to 80 °C for 1.5 h. The reaction was quenched with saturated NH_4Cl and extracted with EtOAc. The organic extracts were concentrated. The residue in THF (2 mL) and water (0.6 mL) was treated with trimethylphosphine (1.0 M solution in THF, 0.073 mL, 0.073 mmol). After stirred at RT for 5 min, the reaction was quenched with water and extracted with EtOAc. The organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was dissolved in DCM (3 mL) and treated with TFA (0.3 mL) at ambient temperature. After stirred for 25 min, the mixture was concentrated and purified by Shimadzu HPLC to afford (1S,5S,6S)-5-(5-amino-2-fluorophenyl)-5-(fluoromethyl)-1-((2,2,2-trifluoroethoxy)methyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (6.0 mg, 0.016 mmol, 21% yield). LC/MS (ESI^+) *m/z* = 382.1 $[M+H]^+$. ^1H NMR (400 MHz, CHLOROFORM-d) δ 6.77-6.91 (m, 2H), 6.54 (td, *J*=3.42, 8.41 Hz, 1H), 4.51-4.97 (m, 2H), 3.84-3.97 (m, 2H), 3.79 (d, *J*=10.56 Hz, 1H), 3.62 (d, *J*=10.76 Hz, 1H), 1.79 (m,

1H), 1.13 (dd, *J*=5.87, 9.59 Hz, 1H), 0.73 (t, *J*=6.26 Hz, 1H). The 2 sets of NH_2 have broad peaks.

(1S,5S,6S)-5-(5-Amino-2-fluorophenyl)-5-(fluoromethyl)-1-(isopropoxymethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (234).

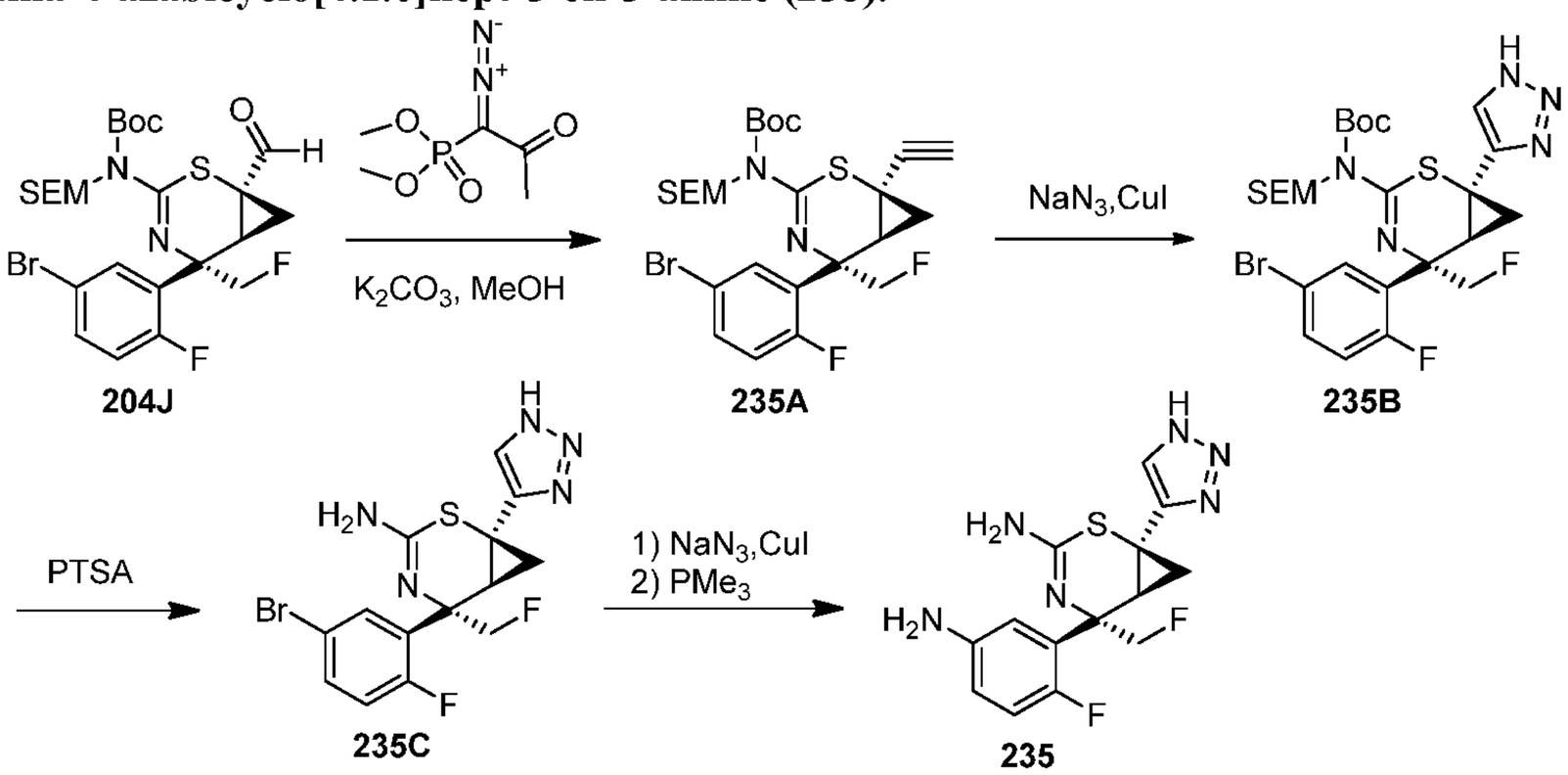


233B **234A** **234**

Preparation of Compound 234A. To a 20 mL pressure vial was charged *tert*-butyl ((1S,5S,6S)-5-(5-bromo-2-fluorophenyl)-5-(fluoromethyl)-1-(hydroxymethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)carbamate (0.58 g, 1.252 mmol), 2-iodopropane (1.00 mL, 10.01 mmol) and silver(i) oxide (0.58 g, 2.50 mmol). After purged with N_2 for 5 min, the vial was sealed and stirred at ambient temperature with protection from light for 140 h. At this point, LCMS detected no starting material. The mixture was diluted with ether and DCM, and then filtered. The filtrate was concentrated and purified by silica gel chromatography (0-20% EtOAc/hexane) to afford *tert*-butyl ((1S,5S,6S)-5-(5-bromo-2-fluorophenyl)-5-(fluoromethyl)-1-(isopropoxymethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)carbamate (0.20 g, 0.40 mmol, 31% yield). LC/MS (ESI^+) *m/z* = 505.1/507.1 $(M+H)^+$.

Intermediate 234 was synthesized using procedures analogous to those described for intermediate **233**, but using *tert*-butyl ((1S,5S,6S)-5-(5-bromo-2-fluorophenyl)-5-(fluoromethyl)-1-(isopropoxymethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)carbamate (**234A**). LC/MS (ESI^+) *m/z* = 342.2 $(M+H)^+$.

(1S,5S,6S)-5-(5-Amino-2-fluorophenyl)-5-(fluoromethyl)-1-(1H-1,2,3-triazol-4-yl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (235).



Preparation of Compound 235A. *tert*-butyl ((1S,5S,6S)-5-(5-bromo-2-fluorophenyl)-5-(fluoromethyl)-1-formyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (**204J**, 3.85 g, 6.51 mmol) in MeOH (50 mL) was treated with potassium carbonate (1.80 g, 13.02 mmol) followed by dimethyl (1-diazo-2-oxopropyl)phosphonate (1.5 g, 7.81 mmol) at ambient temperature. After stirred for 1.5 h, the reaction was quenched with saturated $NaHCO_3$ and extracted with EtOAc (2 x). The organic extracts were washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated and purified by silica gel chromatography (0-15% EtOAc in heptane) to afford *tert*-butyl ((1S,5S,6S)-5-(5-bromo-2-fluorophenyl)-1-ethynyl-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (3.44 g, 5.86 mmol, 90% yield) as colorless oil. LC/MS (ESI^+) *m/z* = 609.0/611.0 $(M+Na)^+$.

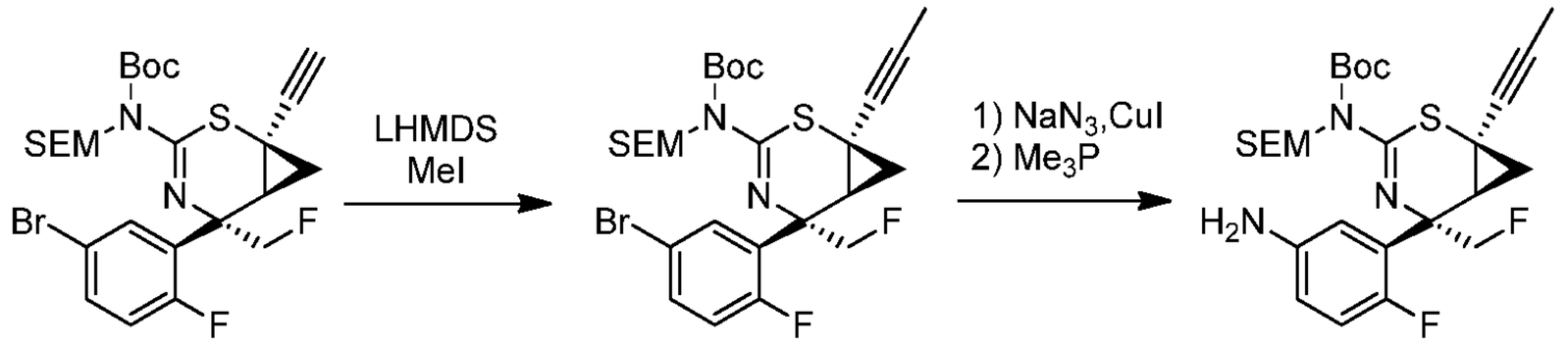
Preparation of Compound 235B. To a pressure flask charged with *tert*-butyl ((1S,5S,6S)-5-(5-bromo-2-fluorophenyl)-1-ethynyl-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (2.19 g, 3.73 mmol), sodium azide (0.73 g, 11.18 mmol), copper(I) iodide (0.14 g, 0.74 mmol), (+)-sodium L-ascorbate (0.17 g, 0.85 mmol), water (4.00 mL) and EtOH (20 mL). After purged with N_2, (1R,2R)-N1,N2-dimethylcyclohexane-1,2-diamine (0.12 mL, 0.74 mmol) was added. The reaction was heated to 75 °C for 2 h, and then allowed to cool to RT. The reaction was quenched with saturated NH_4Cl and extracted with EtOAc. The organic extracts were washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated and purified by silica gel chromatography on ISCO (0-30% EtOAc in

heptane) to afford *tert*-butyl ((1S,5S,6S)-5-(5-bromo-2-fluorophenyl)-5-(fluoromethyl)-1-(1H-1,2,3-triazol-4-yl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (1.27 g, 2.01 mmol, 54% yield). LC/MS (ESI^+) *m/z* = 630.2/632.2 $(M+H)^+$.

Preparation of Compound 235C. To a pressure flask was charged *tert*-butyl ((1S,5S,6S)-5-(5-bromo-2-fluorophenyl)-5-(fluoromethyl)-1-(1H-1,2,3-triazol-4-yl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (1.26 g, 1.99 mmol), p-toluenesulfonic acid monohydrate (3.80 g, 19.98 mmol) and isopropanol (20 mL). The vial was then sealed and heated in an 80 °C oil bath for 16 h, then at 90 °C for additional 5 h until the reaction progressed no further. The reaction mixture was allowed to cool to RT and partitioned between EtOAc and water. The separated aqueous layer was back extracted with EtOAc. The organic layers were combined, washed with brine, dried over Na_2SO_4 and then filtered. The filtrate was concentrated and purified by silica gel chromatography (0-80% EtOAc in heptane) to afford (1S,5S,6S)-5-(5-bromo-2-fluorophenyl)-5-(fluoromethyl)-1-(1H-1,2,3-triazol-4-yl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (0.49 g, 1.22 mmol, 61% yield) as light yellow oil. LC/MS (ESI^+) *m/z* = 400.0/402.0 $(M+H)^+$.

Preparation of Compound 235. To a pressure flask charged with (1S,5S,6S)-5-(5-bromo-2-fluorophenyl)-5-(fluoromethyl)-1-(1H-1,2,3-triazol-4-yl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (0.49 g, 1.22 mmol), sodium azide (0.24 g, 3.67 mmol), copper(I) iodide (47 mg, 0.24 mmol), (+)-sodium L-ascorbate (56 mg, 0.28 mmol), water (1.50 mL) and EtOH (7.50 mL). After purged with N_2, (1R,2R)-N1,N2-dimethylcyclohexane-1,2-diamine (0.04 mL, 0.24 mmol) was added. The mixture was heated to 75 °C for 23 h. The reaction was quenched with saturated NH_4Cl and extracted with EtOAc. The organic extracts were washed with brine and concentrated. To the residue in THF (10 mL) and water (3 mL) was added trimethylphosphine (1.0 M solution in THF, 1.22 mL, 1.22 mmol). After stirred for 50 min, the reaction was quenched with water and extracted with EtOAc. The organic extracts were concentrated. The residue was triturated with DCM and then filtered (repeated 3 times). The filter cake was rinsed with DCM and dried in air to afford (1S,5S,6S)-5-(5-amino-2-fluorophenyl)-5-(fluoromethyl)-1-(1H-1,2,3-triazol-4-yl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (0.31 g, 0.91 mmol, 74% yield) as brown solid. LC/MS (ESI^+) *m/z* = 337.1 $(M+H)^+$.

tert-Butyl ((1S,5S,6S)-5-(5-amino-2-fluorophenyl)-5-(fluoromethyl)-1-(prop-1-yn-1-yl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (236).



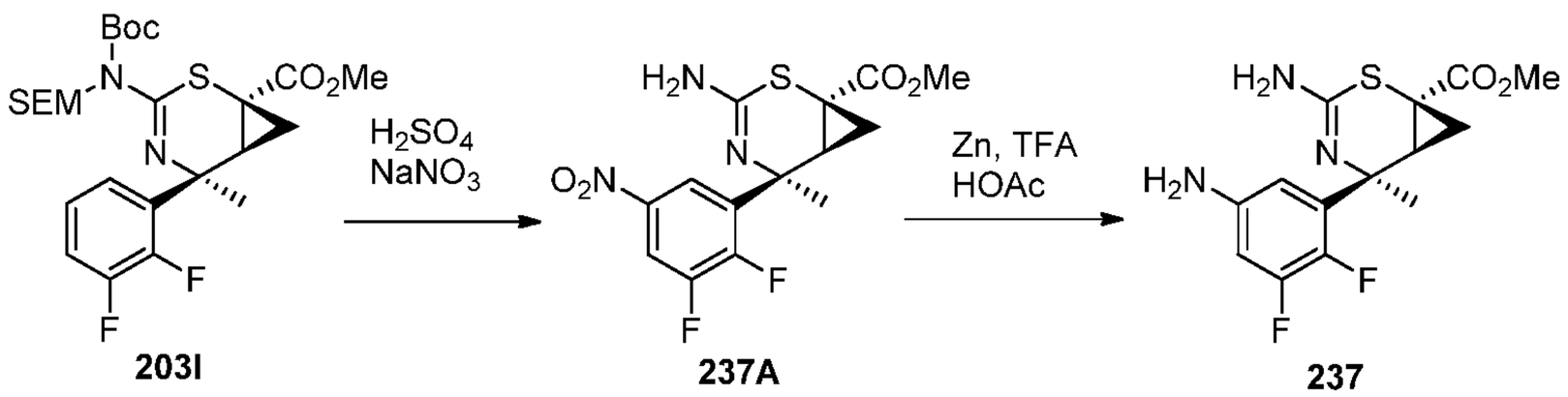
235A **236A** **236**

Preparation of Compound 236A. To a cooled (ice bath) solution of *tert*-butyl ((1S,5S,6S)-5-(5-bromo-2-fluorophenyl)-1-ethynyl-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (**235A**, 0.24 g, 0.401 mmol) in THF (4.0 mL) was added lithium bis(trimethylsilyl)amide (0.61 mL of 1 M in THF, 0.61 mmol). After stirred for 10min, iodomethane (0.04 mL, 0.61 mmol) was added and the mixture stirred for 1 h. The reaction was quenched with water and extracted with EtOAc. The organic extracts were washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated and purified by silica gel chromatography on ISCO (0-15% EtOAc in heptane) to afford *tert*-butyl ((1S,5S,6S)-5-(5-bromo-2-fluorophenyl)-5-(fluoromethyl)-1-(prop-1-yn-1-yl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (0.25 g, 0.42 mmol, 100% yield) as light yellow oil, LC/MS (ESI^+) *m/z* = 601.1/603.1 $(M+H)^+$.

Preparation of Compound 236. To a pressure flask charged with *tert*-butyl ((1S,5S,6S)-5-(5-bromo-2-fluorophenyl)-5-(fluoromethyl)-1-(prop-1-yn-1-yl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (0.25 g, 0.41 mmol), sodium azide (0.08 g, 1.24 mmol), copper(I) iodide (16 mg, 0.08 mmol), (+)-sodium L-ascorbate (19 mg, 0.09 mmol), water (0.4 mL) and EtOH (2.0 mL). After purged with N_2, (1R,2R)-N1,N2-dimethylcyclohexane-1,2-diamine (0.013 mL, 0.083 mmol) was added. The mixture was heated at 75 °C for 2 h. The reaction was quenched with saturated NH_4Cl and extracted with EtOAc. The organic extracts were washed with brine and concentrated. The residue was purified by silica gel chromatography on ISCO (0-30% EtOAc in heptane) to afford *tert*-butyl ((1S,5S,6S)-5-(5-bromo-2-fluorophenyl)-5-(fluoromethyl)-1-(5-methyl-1H-1,2,3-triazol-4-yl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate as colorless oil. LC/MS (ESI^+) *m/z* = 564.2 $(M+H)^+$. To the colorless oil in THF (2 mL) and water (0.6 mL) was added

trimethylphosphine (0.41 mL of 1 M in THF, 0.41 mmol). After 50 min, the reaction was quenched with water and extracted with EtOAc. The organic extracts were concentrated and dried in vacuum to afford *tert*-butyl ((1S,5S,6S)-5-(5-amino-2-fluorophenyl)-5-(fluoromethyl)-1-(prop-1-yn-1-yl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (114 mg, 0.21 mmol, 51% yield). This material was used without further purification. LC/MS (ESI^+) *m/z* = 538.3 $(M+H)^+$.

(1S,5S,6S)-Methyl 3-amino-5-(5-amino-2,3-difluorophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylate (237).

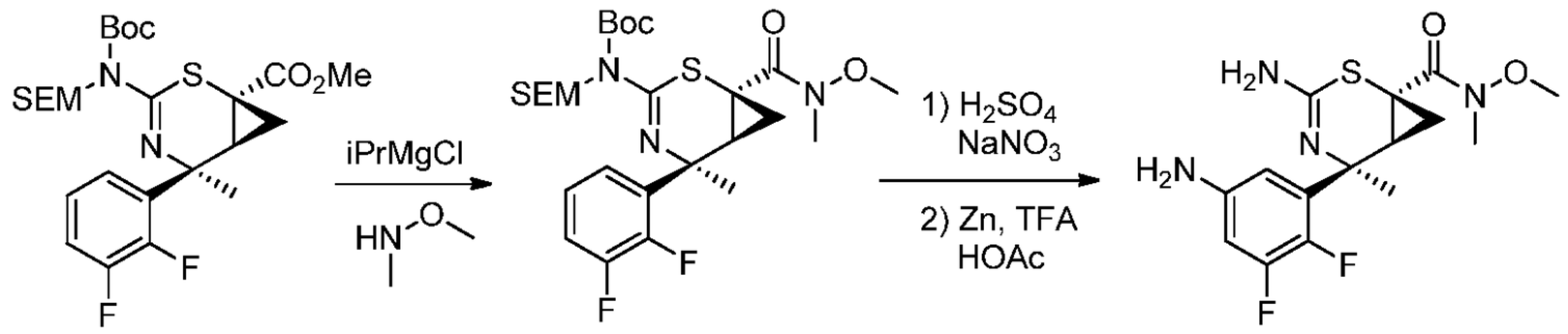


203I **237A** **237**

Preparation of Compound 237A. To a 250 mL flask containing(1S,5S,6S)-methyl 3-((*tert*-butoxycarbonyl)((2-(trimethylsilyl)ethoxy)methyl)amino)-5-(2,3-difluorophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylate (**203I**, 2.00 g, 3.69 mmol) at 0 ºC under nitrogen was added sulfuric acid (8.84 mL, 166 mmol). After 15 min, the ice bath was removed and syrup stirred for 30 min at 20 ºC. The reaction was cooled to 0 ºC and sodium nitrate (0.44 g, 5.16 mmol) was added. It was stirred at 0 °C for 1 h then RT for 24 h. The sticky mixture was pour onto ice (100 g). The mixture was cooled with an ice bath, diluted with CH_2Cl_2 (50 mL) and rapidly stirred. Solid potassium phosphate tribasic (23.47 g, 111 mmol) was added in small portions (over 20 min), and the mixture was then brought to pH ~8 with 1 M NaOH. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (50 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated under reduced pressure, then purified via silica gel flash column chromatography (0-25% EtOAc in heptane) to afford (1S,5S,6S)-methyl 3-amino-5-(2,3-difluoro-5-nitrophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylate (**237A**, 1.17 g, 3.27 mmol, 89% yield) as tan oil. LC/MS (ESI^-) *m/z* = 485.1 $(M+H)^+$. ^1H NMR (400 MHz, CHLOROFORM-d) δ 8.51 (br. s., 1H), 8.02 (ddd, *J*=2.84, 6.31, 9.05 Hz, 1H), 4.26-4.91 (m, 2H), 3.79-3.83 (m, 3H), 1.70-1.82 (m, 3H), 1.49-1.66 (m, 1H), 1.03-1.26 (m, 1H), 0.92 (br. s., 1H).

Preparation of Compound 237. To a stirring solution of (1S,5S,6S)-methyl 3-amino-5-(2,3-difluoro-5-nitrophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylate (**237A**, 1.17 g, 3.27 mmol) in glacial HOAc (6 mL) and TFA (6 mL) at 20 ºC was added zinc nanopowder (0.84 g, 13 mmol). After 90 min the reaction was concentrated under reduced pressure to a thick oil/suspension. The reaction was then partitioned between 9:1 $CHCl_3$/IPA (50 mL) and 10% NH_4OH (50 mL). The separated aqueous layer was further extracted with 9:1 $CHCl_3$/IPA (20 mL). The combined organics were then washed with brine (20 mL). The organic was dried over $MgSO_4$, concentrated under reduced pressure, then purified by silica gel chromatography (1-5% of 2 M NH_3 in MeOH in CH_2Cl_2) to afford (1S,5S,6S)-Methyl 3-amino-5-(5-amino-2,3-difluorophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylate (0.77 g, 2.35 mmol, 72 % yield) as white foam. LC/MS (ESI^-) *m/z* = 328.1 $(M+H)^+$. ^1H NMR (400 MHz, CHLOROFORM-d) δ 6.74 (d, *J*=5.24 Hz, 1H), 6.39 (ddd, *J*=2.93, 6.06, 11.35 Hz, 1H), 3.89-4.84 (m, 2H), 3.78 (s, 3H), 3.60 (br. s., 2H), 2.50-2.56 (m, 1H), 1.68-1.72 (m, 3H), 1.55 (dd, *J*=5.09, 9.78 Hz, 1H), 1.11 (dd, *J*=5.48, 7.43 Hz, 1H).

(1S,5S,6S)-3-Amino-5-(2,3-difluoro-5-nitrophenyl)-N-methoxy-N,5-dimethyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide (238).



203I **238A** **238**

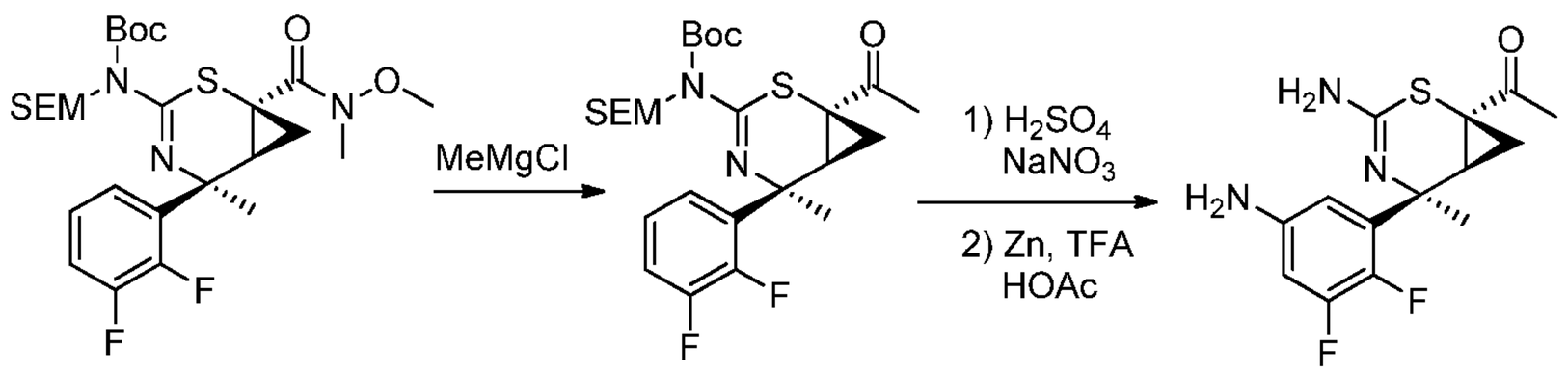
Preparation of Compound 238A. To a stirring suspension of (1S,5S,6S)-methyl 3-((*tert*-butoxycarbonyl)((2-(trimethylsilyl)ethoxy)methyl)amino)-5-(2,3-difluorophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylate (**203I**, 90 mg, 0.16 mmol) and N,O-dimethylhydroxylamine hydrochloride (32 mg, 0.33 mmol) in THF (2 mL) at -20 ºC under nitrogen was added isopropylmagnesium chloride (0.50 mL of 2 m in THF, 1.00 mmol) at a rate that did not exceed -15 ºC internal temperature. After 15 min at -10 ºC the reaction was quenched with sat NH_4Cl. The reaction was then portioned between 1:1 EtOAc/heptane (20 mL) and 5% $NaHCO_3$ (10 mL). The organic was dried over $MgSO_4$, concentrated under reduced pressure, then purified by silica gel chromatography (0-20% EtOAc in heptane) to afford *tert*-butyl ((1S,5S,6S)-5-(2,3-

difluorophenyl)-1-(methoxy(methyl)carbamoyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (**238A**, 57 mg, 0.10 mmol, 60% yield) as colorless film. LC/MS (ESI^-) *m/z* = 572.2 $(M+H)^+$.

Preparation of (1S,5S,6S)-3-amino-5-(5-amino-2,3-difluorophenyl)-N-methoxy-N,5-dimethyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide (238).

This compound (22 mg, 70 yield) as colorless film was prepared according to the procedures described for intermediate **237**, but starting from *tert*-butyl ((1S,5S,6S)-5-(2,3-difluorophenyl)-1-(methoxy(methyl)carbamoyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (**238A**, 50 mg). LC/MS (ESI^-) *m/z* = 357.0 $(M+H)^+$.

1-((1S,5S,6S)-3-Amino-5-(5-amino-2,3-difluorophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)ethanone (239).

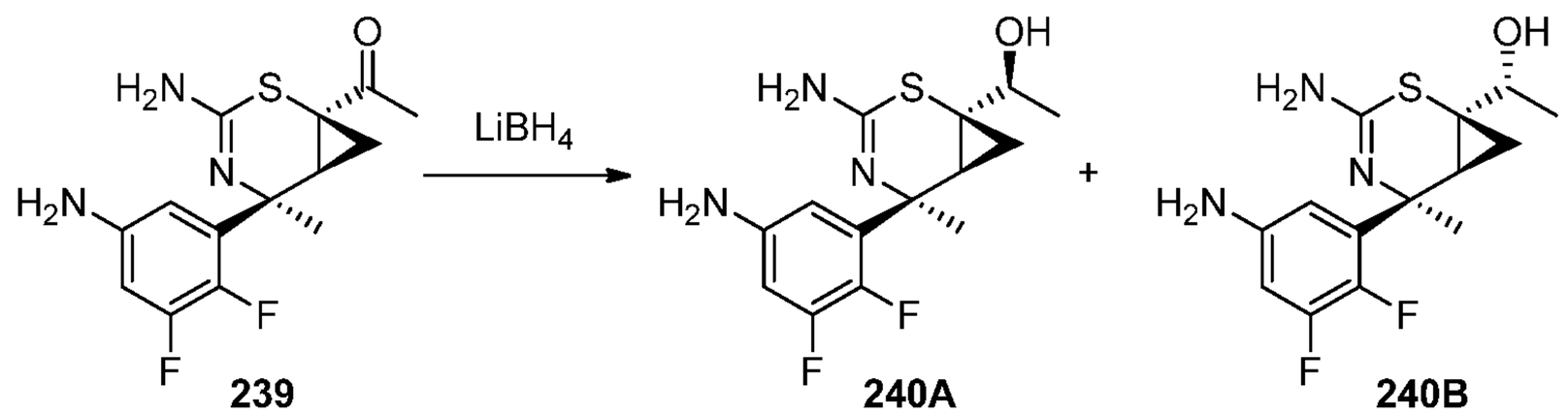


238A **239A** **239**

Preparation of Compound 239A. To a stirring solution of *tert*-butyl ((1S,5S,6S)-5-(2,3-difluorophenyl)-1-(methoxy(methyl)carbamoyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (**238A**, 1.04 g, 1.82 mmol) in THF (10 mL) at 0 ºC under nitrogen was added methylmagnesium bromide (2.42 mL of 3.0 M in Et_2O, 7.28 mmol). After stirring for 15 min at 0 ºC the reaction was slowly quenched with dropwise addition of sat. NH_4Cl (10 mL). The reaction was then partitioned between EtOAc (75 mL) and 5% $NaHCO_3$ (50 mL) along with water (50 mL). The separated aqueous was extracted with EtOAc (25 mL). The combined organics were dried over $MgSO_4$, filtered, then concentrated under reduced pressure to afford *tert*-butyl ((1S,5S,6S)-1-acetyl-5-(2,3-difluorophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (**239A**, 0.93 g, 1.76 mmol, 97% yield) as colorless oil. LC/MS (ESI^-) *m/z* = 527.2 $(M+H)^+$. ^1H NMR (400 MHz, CHLOROFORM-d) δ 7.38 (t, *J*=6.89 Hz, 1H), 7.02-7.13 (m, 2H), 5.27 (d, *J*=10.56 Hz, 1H), 5.04 (d, *J*=10.56 Hz, 1H), 3.60-3.70 (m, 2H), 2.53 (dd, *J*=8.02, 9.19 Hz, 1H), 2.25 (s, 3H), 1.67-1.83 (m, 3H), 1.57 (dd, *J*=5.38, 9.88 Hz, 1H), 1.54 (d, *J*=5.48 Hz, 1H), 1.49-1.52 (m, 9H), 0.89-0.97 (m, 2H), -0.02-0.01 (m, 9H).

Preparation of 1-((1S,5S,6S)-3-amino-5-(5-amino-2,3-difluorophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)ethanone (239). This compound (290 mg, 0.93 mmol, 51% yield) as tan foam was prepared according to the procedures described for intermediate **237**, but starting from *tert*-butyl ((1S,5S,6S)-1-acetyl-5-(2,3-difluorophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (**239A**, 0.95 g, 1.80 mmol). LC/MS (ESI$^-$) *m/z* = 312.1 $(M+H)^+$.

(S)-1-((1S,5S,6S)-3-amino-5-(5-amino-2,3-difluorophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)ethanol (240A) and (R)-1-((1S,5S,6S)-3-amino-5-(5-amino-2,3-difluorophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)ethanol (240B).

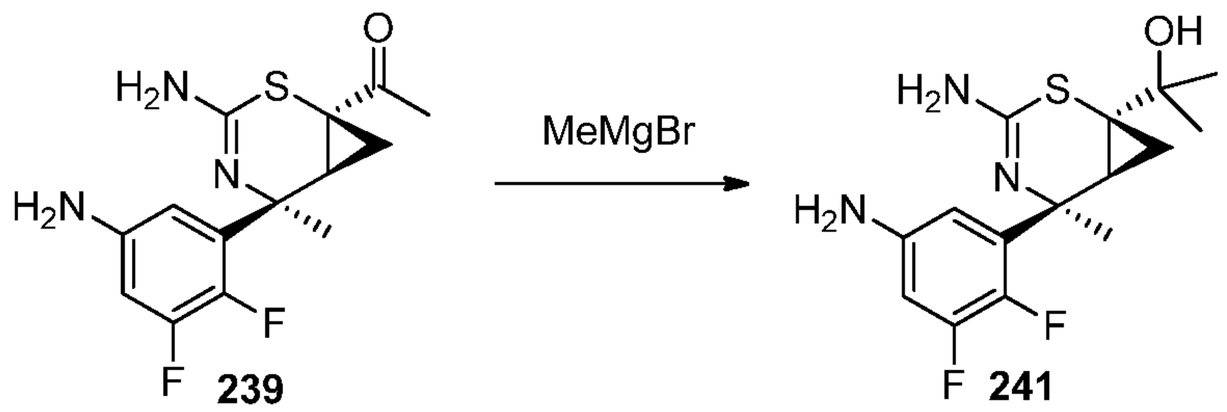


239 240A 240B

To a stirring solution of 1-((1S,5S,6S)-3-amino-5-(5-amino-2,3-difluorophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)ethanone (intermediate **239**, 104 mg, 0.33 mmol) in THF (3 mL) at RT under nitrogen was added lithium borohydride (0.33 mL of 2.0 M in THF, 0.66 mmol) at a rate that did not exceed an internal temperature of 25 °C. After 5 min, MeOH (0.13 mL, 3.34 mmol) was added drop wise. The reaction was cooled to 0 °C and quenched with sat'd aqueous NH_4Cl (2 mL). The mixture was then partitioned between 9:1 $CHCl_3$/IPA (30 mL) and 0.5 M K_2HPO_4 (10 mL). The aqueous was further extracted with 9:1 $CHCl_3$/IPA (2x5 mL). The organic solution was dried over $MgSO_4$, filtered, concentrated under reduced pressure. The residue was azeotroped with toluene (2 x 25 mL). The residue was then purified by silica gel chromatography (1-4% [2 M NH_3 in MeOH] in CH_2Cl_2) to afford separated diastereomers of arbitrary assignment. Oil observed: (R)-1-((1S,5S,6S)-3-amino-5-(5-amino-2,3-difluorophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)ethanol (intermediate **240B**, 45 mg, 0.14 mmol, 43% yield). LC/MS (ESI$^-$) *m/z* = 314.1 $(M+H)^+$. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ 6.59 (td, *J*=2.52, 4.94 Hz, 1H), 6.36 (ddd, *J*=2.93, 6.06, 11.35 Hz, 1H), 3.49-3.65 (m, 2H), 3.40-3.49 (m, 2H), 3.05-3.34 (m, 2H),

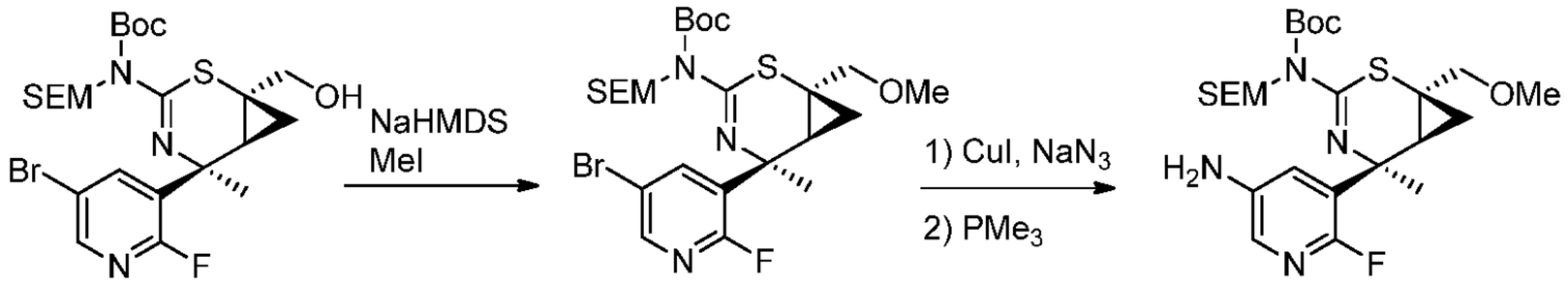
1.70-1.74 (m, 4H), 1.24-1.33 (m, 3H), 0.93 (dd, *J*=5.77, 9.49 Hz, 1H), 0.71 (t, *J*=6.26 Hz, 1H). Solid observed: (S)-1-((1S,5S,6S)-3-amino-5-(5-amino-2,3-difluorophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)ethanol (intermediate **240A**, 15 mg, 0.05 mmol, 14% yield). LC/MS (ESI$^-$) *m/z* = 314.1 $(M+H)^+$. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ 6.65-6.74 (m, 1H), 6.34-6.43 (m, 1H), 3.60 (br. s., 4H), 3.44-3.52 (m, 2H), 1.61-1.71 (m, 4H), 1.39 (d, *J*=6.26 Hz, 3H), 0.94 (dd, *J*=5.77, 9.49 Hz, 1H), 0.77 (t, *J*=6.06 Hz, 1H).

2-((1S,5S,6S)-3-Amino-5-(5-amino-2,3-difluorophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)propan-2-ol (241).



To a stirring solution of 1-((1S,5S,6S)-3-amino-5-(5-amino-2,3-difluorophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)ethanone (intermediate **239**, 82 mg, 0.26 mmol) in THF (3 mL) at 0 °C under nitrogen was added methylmagnesium bromide (3.0 M in Et_2O, 88 mL, 2.64 mmol) at a rate not to exceed an internal temperature of 7 °C. After 15 min, the reaction was slowly quenched with sat NH_4Cl then partitioned between 0.1 M K_2PO_4 (20 mL) and 9:1 $CHCl_3$/IPA (15 mL). The organic layer was dried over $MgSO_4$, concentrated under reduced pressure, then purified by silica gel chromatography (0-5% [2 M NH_3 in MeOH] in CH_2Cl_2) to afford Compound **241** (9 mg, 0.03 mmol, 10% yield) as colorless film. LC/MS (ESI$^-$) *m/z* = 328.1 $(M+H)^+$. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ 6.62-6.69 (m, 1H), 6.33-6.40 (m, 1H), 3.85-4.77 (br., 2H), 3.60 (br. s., 2H), 1.86 (dd, *J*=7.34, 9.68 Hz, 1H), 1.59-1.79 (m, 3H), 1.30-1.36 (m, 6H), 1.23-1.30 (m, 1H), 1.12 (dd, *J*=5.67, 9.78 Hz, 1H), 0.61 (t, *J*=6.26 Hz, 1H).

tert-butyl ((1S,5S,6S)-5-(5-Amino-2-fluoropyridin-3-yl)-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (242).



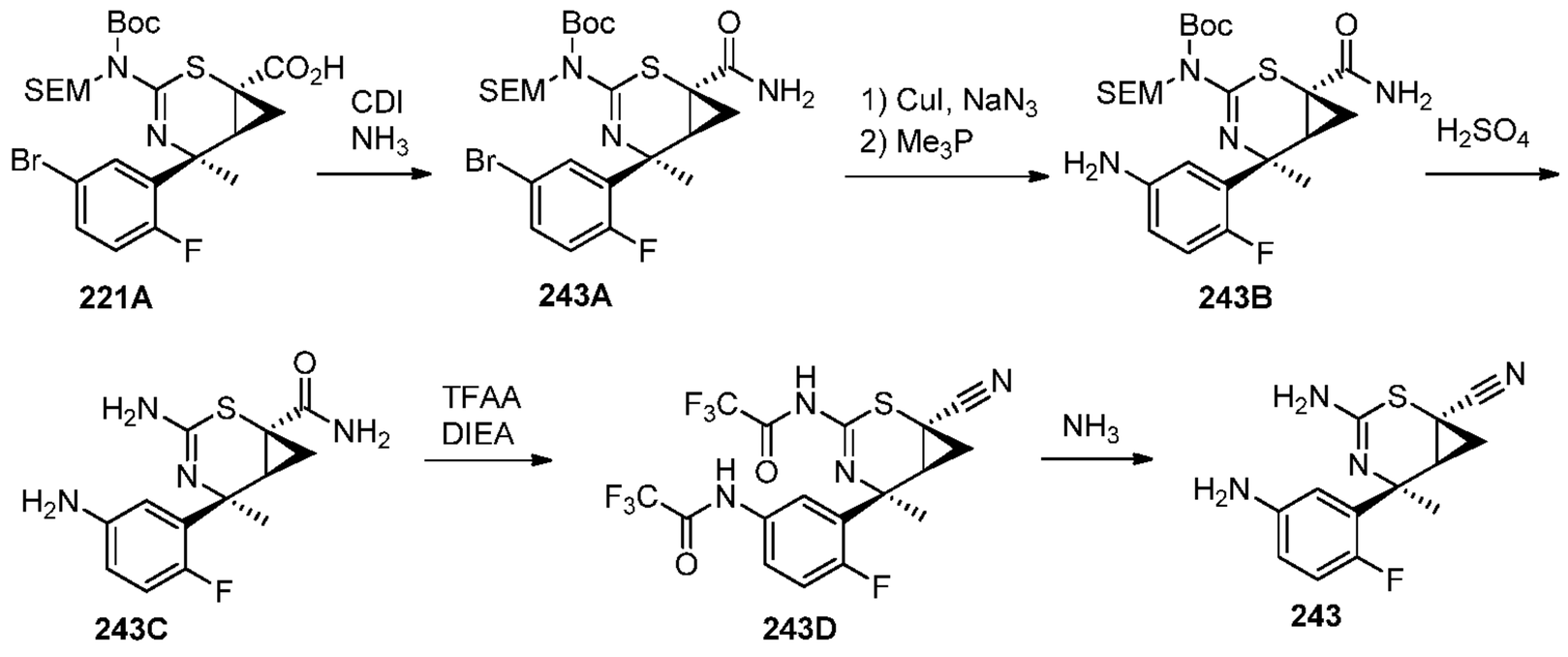
214K **242A** **242**

Preparation of Compound 242A. To a solution of *tert*-butyl ((1S,5S,6S)-5-(5-bromo-2-fluoropyridin-3-yl)-1-(hydroxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (**214K**, 310 mg, 0.538 mmol) in THF (15 mL) under N_2 at 0 °C was added lithium bis(trimethylsilyl)amide (1.0 M solution in THF, 0.86 mL, 0.86 mmol) dropwise. After addition, the mixture was stirred at 0 °C for 30 min and iodomethane (0.053 mL, 0.860 mmol) was added. The mixture was stirred at 0 °C for 20 min and at RT for overnight, then quenched with saturated NH_4Cl and diluted with H_2O. The mixture was extracted with EtOAc (2 x). The combined organic extracts were then washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel flash column chromatography (DCM/EtOAc = 5:1) to give *tert*-butyl ((1S,5S,6S)-5-(5-bromo-2-fluoropyridin-3-yl)-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (**242A**, 220 mg, 0.37 mmol, 69% yield) as a light yellow oil. LCMS (ESI^+) m/z = 590.5 (M+H).

Preparation of Compound 242. A microwave vial was charged with *tert*-butyl ((1S,5S,6S)-5-(5-bromo-2-fluoropyridin-3-yl)-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (**242A**, 220 mg, 0.372 mmol), sodium azide (121 mg, 1.862 mmol), copper(I) iodide (14.19 mg, 0.074 mmol), sodium (R)-2-((S)-1,2-dihydroxyethyl)-4-hydroxy-5-oxo-2,5-dihydrofuran-3-olate (14.76 mg, 0.074 mmol), EtOH (3 mL) and water (1 mL). It was purged with N_2 and sealed. Then (1R,2R)-N^1,N^2-dimethylcyclohexane-1,2-diamine (23 μL, 0.15 mmol) was added. The mixture was heated to 80 °C. The mixture was treated with saturated NH_4Cl and diluted with EtOAc. The organic layer was separated and the aqueous layer was extracted twice with EtOAc. The organic solution was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was dissolved in THF (3 mL) and water (1 mL) and treated with trimethylphosphine (1.0 M solution in THF, 0.45 mL, 0.45

mmol). The mixture was evaporated to dryness purified by a silica gel chromatography (DCM/EtOAc = 10:1 to 5:1) to give *tert*-butyl ((1S,5S,6S)-5-(5-amino-2-fluoropyridin-3-yl)-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (**242**, 130 mg, 0.25 mmol, 66% yield). LCMS (ESI^+) m/z = 527.2 (M+H).

(1S,5S,6S)-3-Amino-5-(5-amino-2-fluorophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carbonitrile (243).



Preparation of Compound 243A. To a stirring solution of (1S,5S,6S)-5-(5-bromo-2-fluorophenyl)-3-((*tert*-butoxycarbonyl)((2-(trimethylsilyl)ethoxy)methyl)amino)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylic acid (**221A**, 1.90 g, 3.22 mmol) in THF (20 mL) at 20 °C under nitrogen was added 1,1'-carbonyldiimidazole (0.784 g, 4.83 mmol). The cloudy solution was stirred for 1 hr at 20 °C followed by addition of ammonia (0.5 M in 1,4-dioxane, 19.34 mL, 9.67 mmol). After 1 h, the reaction mixture was partitioned between EtOAc (60 mL) and 1 M HCl (60 mL). The organic layer was washed with brine (25 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford *tert*-butyl ((1S,5S,6S)-5-(5-bromo-2-fluorophenyl)-1-carbamoyl-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (**243A**, 1.80 g, 3.06 mmol, 95% yield) as colorless oil. LC/MS (ESI^-) *m/z* = 588.0/590.0 $(M+H)^+$.

Preparation of Compound 243B. A mixture of *tert*-butyl ((1S,5S,6S)-5-(5-bromo-2-fluorophenyl)-1-carbamoyl-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (**243A**, 1.90 g, 3.23 mmol), sodium azide (0.63 g, 9.68 mmol), copper(i) iodide (0.18 g, 0.97 mmol), (1R,2R)-(-)-N,N''-dimethylcyclohexane-1,2-diamine (0.19 g, 0.97 mmol), (+)-sodium L-ascorbate (0.19 g,

0.97 mmol) in 5:1 EtOH/H_2O (20 mL) was purged with argon for 5 min. The blue suspension was then heated at 70 °C. After 1 h, the reaction mixture was chilled to 10 °C and quenched with 9:1 (20 mL) sat. NH_4Cl/NH_4OH (30%). The mixture was then extracted with EtOAc (60 mL). The organic solution was washed with sat. NH_4Cl (10 mL) followed by brine (10 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was dissolved in 5:1 THF/water (20 mL), chilled to 0 °C, then trimethylphosphine (4.84 mL of 1 M in THF, 4.84 mmol) was added. The ice bath was removed and reaction stirred for 20 min at 20 °C. It was partitioned between EtOAc (40 mL) and 5% $NaHCO_3$ (20 mL). The organic layer was dried over $MgSO_4$, concentrated under reduced pressure, then purified by silica gel chromatography (0-60% EtOAc in heptane) to afford *tert*-butyl ((1S,5S,6S)-5-(5-amino-2-fluorophenyl)-1-carbamoyl-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (**243B**, 0.81 g, 1.54 mmol, 48% yield) as colorless oil. LC/MS (ESI^-) *m/z* = 525.2 $(M+H)^+$.

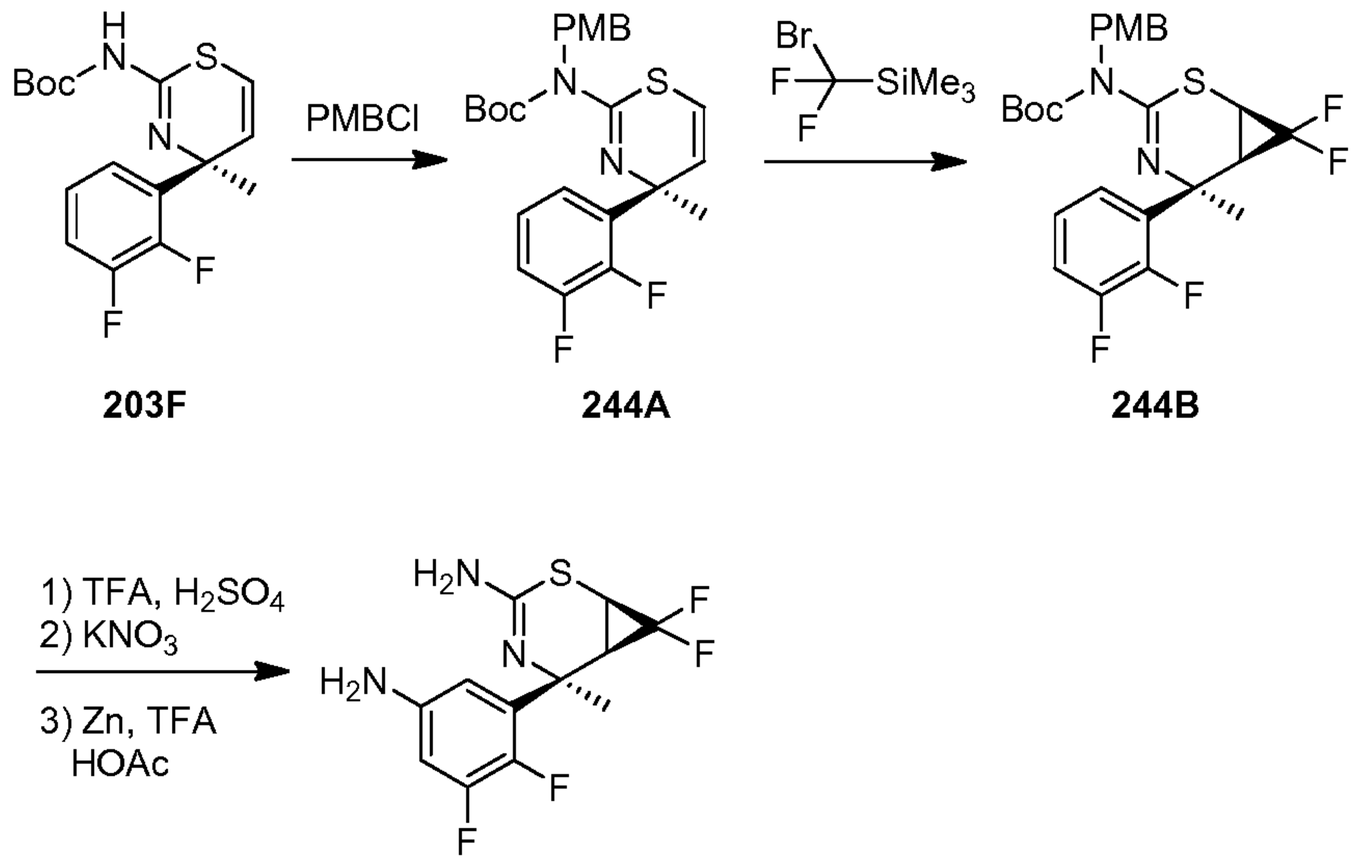
Preparation of Compound 243C. To a 100 mL flask containing *tert*-butyl ((1S,5S,6S)-5-(5-amino-2-fluorophenyl)-1-carbamoyl-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (**243B**, 0.78 g, 1.48 mmol) at 0 °C under nitrogen was added sulfuric acid (5.95 mL). The flask was periodically removed from cooling bath, swirled by hand, then allowed to stir at 20 °C for 1 h. The reaction mixture was then poured onto wet ice (300 mL) and the mixture along with DCM (100 mL). To the rapidly stirred mixture was added potassium phosphate tribasic monohydrate (42.8 g, 186 mmol). The suspension was filtered and the filtrate transferred to a separatory funnel. The organic layer was separated, and the aqueous layer was extracted with 9:1 $CHCl_3$/IPA (2 x 50 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated under reduced pressure, then purified via silica gel flash column chromatography (40 g) eluting the products with a gradient of 0-50% EtOAc/CH_2Cl_2 to afford (1S,5S,6S)-3-amino-5-(5-amino-2-fluorophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide (**243C**, 0.37 g, 1.25 mmol, 84% yield) as off white solid. LC/MS (ESI^-) *m/z* = 295.1 $(M+H)^+$.

Preparation of Compound 243D. To a stirring solution of (1S,5S,6S)-3-amino-5-(5-amino-2-fluorophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide (0.38 g, 1.291 mmol) and N,N-diisopropylethylamine (**243C**, 1.80 mL, 10.33 mmol) in THF (10 mL) at -70 °C under nitrogen was added 2,2,2-trifluoroacetic

anhydride (1.08 mL, 7.75 mmol). After 10 min, the reaction was quenched with sat. NH_4Cl (1 mL). The reaction was then partitioned between EtOAc (10 mL) and 5% $NaHCO_3$ (10 mL). The organic was dried over $MgSO_4$, filtered, then concentrated under reduced pressure to afford N-((1S,5S,6S)-1-cyano-5-(2-fluoro-5-(2,2,2-trifluoroacetamido)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)-2,2,2-trifluoroacetamide (**243D,** 0.60 g, 1.26 mmol) as tan solid. LC/MS (ESI^-) *m/z* = 421.0 $(M+H)^+$.

Preparation of Compound 243. A solution of N-((1S,5S,6S)-1-cyano-5-(2-fluoro-5-(2,2,2-trifluoroacetamido)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)-2,2,2-trifluoroacetamide (**243D**, 600 mg, 1.28 mmol) in 2 M NH_3 in MeOH (10 mL) was stirred for 18 h at 37 °C. The solvent was removed under reduced pressure and the residue was then purified by silica gel chromatography (12 g) eluting products with a gradient of 1-5% 2 M NH_3 in MeOH/DCM to afford (1S,5S,6S)-3-amino-5-(5-amino-2-fluorophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carbonitrile (235 mg, 0.85 mmol, 66% yield) as white foam. LC/MS (ESI^-) *m/z* = 277.1 $(M+H)^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 6.80 (dd, *J*=8.41, 12.13 Hz, 1H), 6.63 (dd, *J*=2.93, 7.04 Hz, 1H), 6.38-6.50 (m, 3H), 4.84 (s, 2H), 2.28 (dd, *J*=7.92, 9.68 Hz, 1H), 1.83 (dd, *J*=5.87, 9.78 Hz, 1H), 1.67 (s, 3H), 0.92 (t, *J*=6.46 Hz, 1H).

(1R,5S,6R)-5-(5-Amino-2,3-difluorophenyl)-7,7-difluoro-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (244).



203F **244A** **244B** **244**

Synthesis of (S)-*tert*-butyl (4-(2,3-difluorophenyl)-4-methyl-4H-1,3-thiazin-2-yl)(4-methoxybenzyl)carbamate (244A). To a solution of (S)-*tert*-butyl (4-(2,3-difluorophenyl)-4-methyl-4H-1,3-thiazin-2-yl)carbamate (**203F**, 1.00 g, 2.94 mmol) in DMF (6 mL) was added potassium carbonate (568 mg, 4.1 mmol), followed by 4-methoxybenzyl chloride (0.5 mL, 3.5 mmol). The reaction mixture was stirred overnight at RT. It was partitioned between water and EtOAc. The aqueous phase was separated and was back-extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, 0-30% EtOAc in hexanes) to afford the title compound (**244A,** 1.00 g, 2.25 mmol, 76% yield) as a yellow oil. LC/MS (ESI^+) *m/z* = 461.1 $(M+H)^+$; ^1H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.49 (s, 9 H) 1.69 (d, *J*=1.17 Hz, 3 H) 3.79 (s, 3 H) 5.06 (s, 2 H) 6.07 (dd, *J*=9.50, 3.65 Hz, 1 H) 6.26 (d, *J*=9.35 Hz, 1 H) 6.84 (m, 2 H) 6.89 - 7.13 (m, 3 H) 7.27 (m, 2 H).

Synthesis of *tert*-butyl ((1R,5S,6R)-5-(2,3-difluorophenyl)-7,7-difluoro-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)(4-methoxybenzyl)carbamate (244B). A sealable vial was charged with (S)-*tert*-butyl (4-(2,3-difluorophenyl)-4-methyl-4H-1,3-thiazin-2-yl)(4-methoxybenzyl)carbamate (**244A**, 440 mg, 0.96 mmol) and toluene under nitrogen atmosphere. Tetrabutylammonium bromide (9 mg, 0.029 mmol) was added, followed by trimethyl(bromodifluoromethyl)silane (SynQuest Laboratories, 291 mg, 1.43 mmol). The vial was sealed and heated to 110 °C for 6 h. The residue was partitioned between water and EtOAc. The aqueous phase was separated and was back-extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, 0-25% EtOAc in hexanes) to afford the title compound as an oil (**244B**, 116 mg, 0.23 mmol, 24%). LC/MS (ESI^+) *m/z* = 533.2 $(M+Na)^+$.

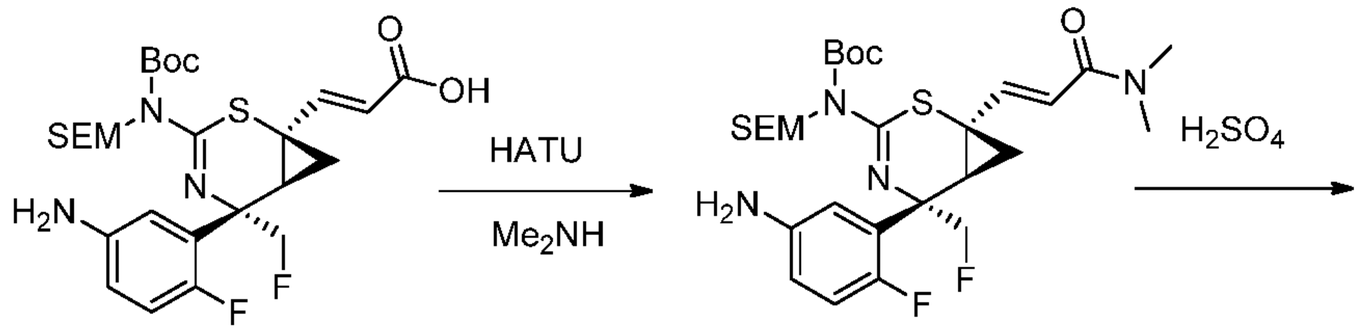
Synthesis of Compound 244C. A solution of *tert*-butyl ((1R,5S,6R)-5-(2,3-difluorophenyl)-7,7-difluoro-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)(4-methoxybenzyl)carbamate (**244B**, 380 mg, 0.74 mmol) in DCM (2.5 mL) was treated with TFA (1.7 mL, 22 mmol) at RT. After 1 h, anisole (0.12 mL, 1.1 mmol) was added to the reaction mixture, followed by drop-wise addition of concentrates sulfuric acid (0.4 mL, 7.4 mmol). After 20 min, the reaction mixture was poured into water and neutralized with aqueous, saturated bicarbonate solution. The reaction mixture was partitioned between water and EtOAc. The aqueous phase was separated and was back-extracted

with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated in vacuo. The crude material was purified by column chromatography (SiO_2, 5-55% EtOAc in hexanes) to afford (1R,5S,6R)-5-(2,3-difluorophenyl)-7,7-difluoro-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (87 mg, 0.30 mmol, 40% yield) as a waxy yellow solid. LC/MS (ESI^+) *m/z* = 291.0 $(M+H)^+$; ^1H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.75 (d, *J*=1.17 Hz, 3 H) 2.55 - 2.73 (m, 1 H) 2.84 - 3.01 (m, 1 H) 7.03 - 7.21 (m, 2 H) 7.39 - 7.50 (m, 1 H); ^{19}F NMR (282 MHz, CHLOROFORM-*d*) δ ppm -149.49 (d, *J*=158.90 Hz, 1 F) -140.44 - -138.72 (m, 1 F) -139.96 - -139.68 (m, 1 F) -139.26 - -139.04 (m, 1 F) -121.99 (d, *J*=158.90 Hz, 1 F); **The relative stereochemistry was confirmed by COSY, HMBC and NOESY correlations**.

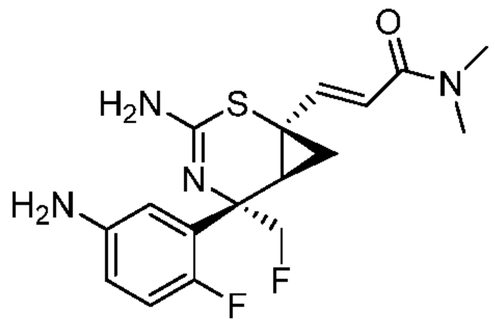
To a solution of (1R,5S,6R)-5-(2,3-difluorophenyl)-7,7-difluoro-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (87 mg, 0.30 mmol) in concentrated sulfuric acid (1 mL) at 0 °C was added potassium nitrate (45 mg, 0.45 mmol). The reaction was stirred at for 5 min at 0 °C and additional 5 min at RT. The reaction mixture was poured into ice-water and solid potassium carbonate was added portion wise until the reaction mixture reached pH >10. The aqueous phase was extracted with three times EtOAc. The combined organic extracts were dried over $MgSO_4$. The solution was filtered and concentrated in vacuo to give the crude (1R,5S,6R)-5-(2,3-difluoro-5-nitrophenyl)-7,7-difluoro-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (50 mg) as a yellow glass. The product was taken onto the next step without further purification. LC/MS (ESI^+) *m/z* = 336.0 $(M+H)^+$.

A flask containing a solution of (1R,5S,6R)-5-(2,3-difluoro-5-nitrophenyl)-7,7-difluoro-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (50 mg, 0.15 mmol) in HOAc (1 mL) was cooled in a water bath. TFA (0.08 mL) was added, followed by zinc dust (50 mg, 0.75 mmol) in one portion. After 10 min, the reaction mixture was basified with 1 N NaOH and then extracted with EtOAc. The organic phase was washed with aqueous, saturated NaCl solution, dried over $MgSO_4$ and filtered. The filtrate was concentrated to afford **intermediate 244** as a yellow residue which was taken on the next step without further purification. LC/MS (ESI^+) *m/z* = 306.0 $(M+H)^+$.

(E)-3-((1R,5S,6S)-3-Amino-5-(5-amino-2-fluorophenyl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)-N,N-dimethylacrylamide (246).



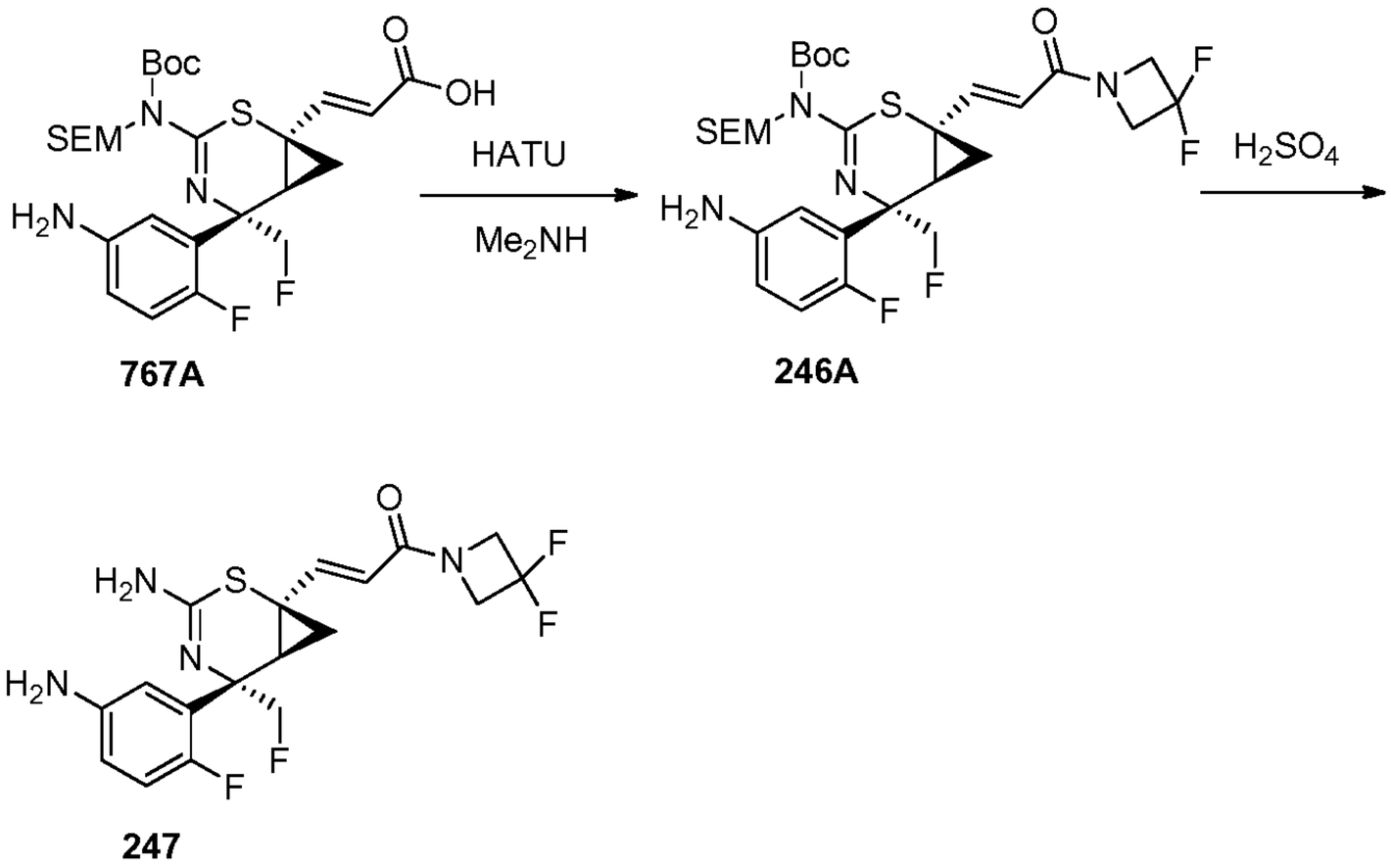
767A **246A**



246

The title compound was prepared according to the procedures describe for intermediate **767C** (see the synthesis of Example **767**). MS (ESI, positive ion) m/z: 367 $(M+1)^+$.

(E)-3-((1R,5S,6S)-3-Amino-5-(5-amino-2-fluorophenyl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)-1-(3,3-difluoroazetidin-1-yl)prop-2-en-1-one (247).

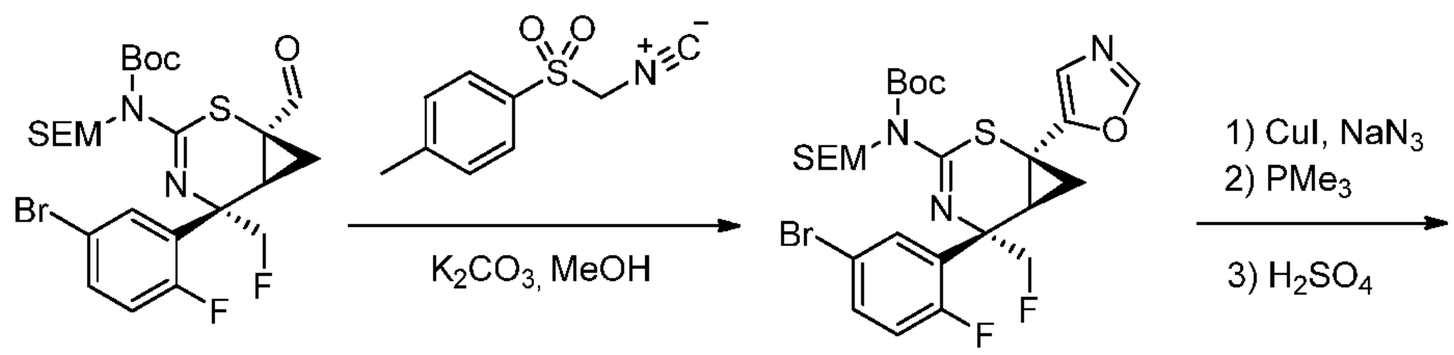


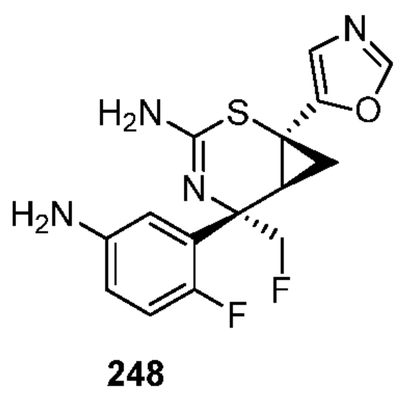
767A **246A**

247

The title compound was prepared according to the procedures describe for intermediate **767C** (see the synthesis of Example **767**). MS (ESI, positive ion) m/z: 415 $(M+1)^+$.

(1S,5S,6S)-5-(5-amino-2-fluorophenyl)-5-(fluoromethyl)-1-(oxazol-5-yl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (248).

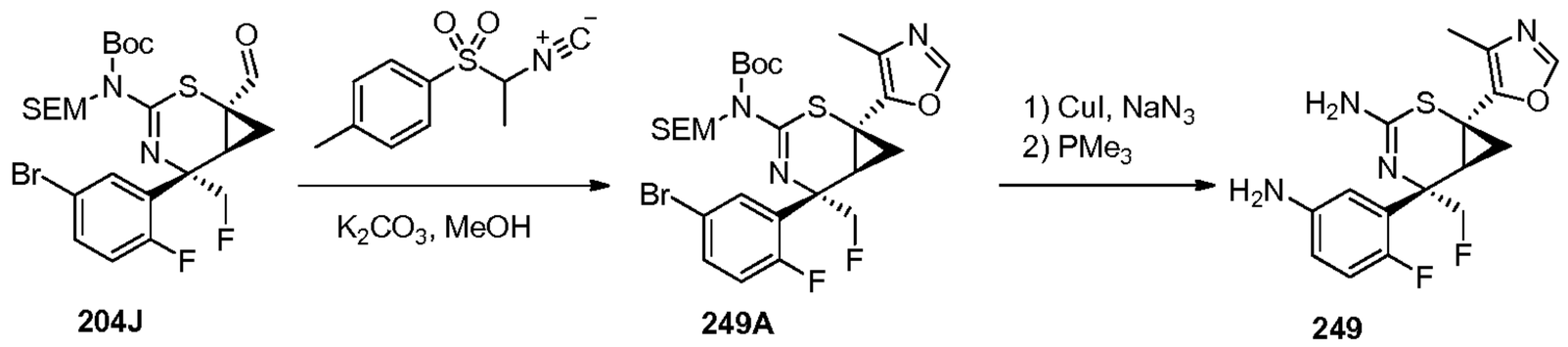




Preparation of Compound 248A. A mixture of p-toluenesulfonylmethyl isocyanide (0.79 g, 4.06 mmol), *tert*-butyl ((1S,5S,6S)-5-(5-bromo-2-fluorophenyl)-5-(fluoromethyl)-1-formyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl) ethoxy)methyl)carbamate (2.00 g, 3.38 mmol), and potassium carbonate (2.34 g, 16.90 mmol) in MeOH (4 mL) was stirred a RT for 16 h. The reaction mixture was concentrated to dryness. The residue was diluted with H_2O, and extracted with EtOAc (3 x). The organic extracts were dried over Na_2SO_4, concentrated and purified by silica gel column to give *tert*-butyl ((1S,5S,6S)-5-(5-bromo-2-fluorophenyl)-5-(fluoromethyl)-1-(oxazol-5-yl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (**248A**, 1.37 g, 64%). ^{1}H NMR (CHLOROFORM-d) δ: 7.86 (dd, J=6.8, 2.5 Hz, 1H), 7.80 (s, 1H), 7.42 (ddd, J=8.7, 4.3, 2.7 Hz, 1H), 7.01 (s, 1H), 6.98 (dd, J=11.5, 8.6 Hz, 1H), 5.36 (d, J=10.4 Hz, 1H), 5.10 (d, J=10.4 Hz, 1H), 4.89-5.06 (m, 1H), 4.68-4.85 (m, 1H), 3.62-3.72 (m, 2H), 2.30 (ddd, J=9.8, 7.4, 2.2 Hz, 1H), 1.53 (s, 9H), 1.50 (d, J=5.9 Hz, 1H), 1.12 (dd, J=7.0, 6.1 Hz, 1H), 0.98 (dd, J=9.0, 7.6 Hz, 2H), 0.00 (s, 9H). MS (ESI, positive ion) m/z: 630/632 $(M+1)^+$.

Preparation of (1S,5S,6S)-5-(5-amino-2-fluorophenyl)-5-(fluoromethyl)-1-(oxazol-5-yl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (248). The title compound (0.58 g, 79%) was prepared in the same method as described for **243C,** but starting from **248A** (1.37 g, 2.17 mmol). MS (ESI, positive ion) m/z: 337 $(M+1)^+$.

(1S,5S,6S)-5-(5-Amino-2-fluorophenyl)-5-(fluoromethyl)-1-(4-methyloxazol-5-yl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (249).

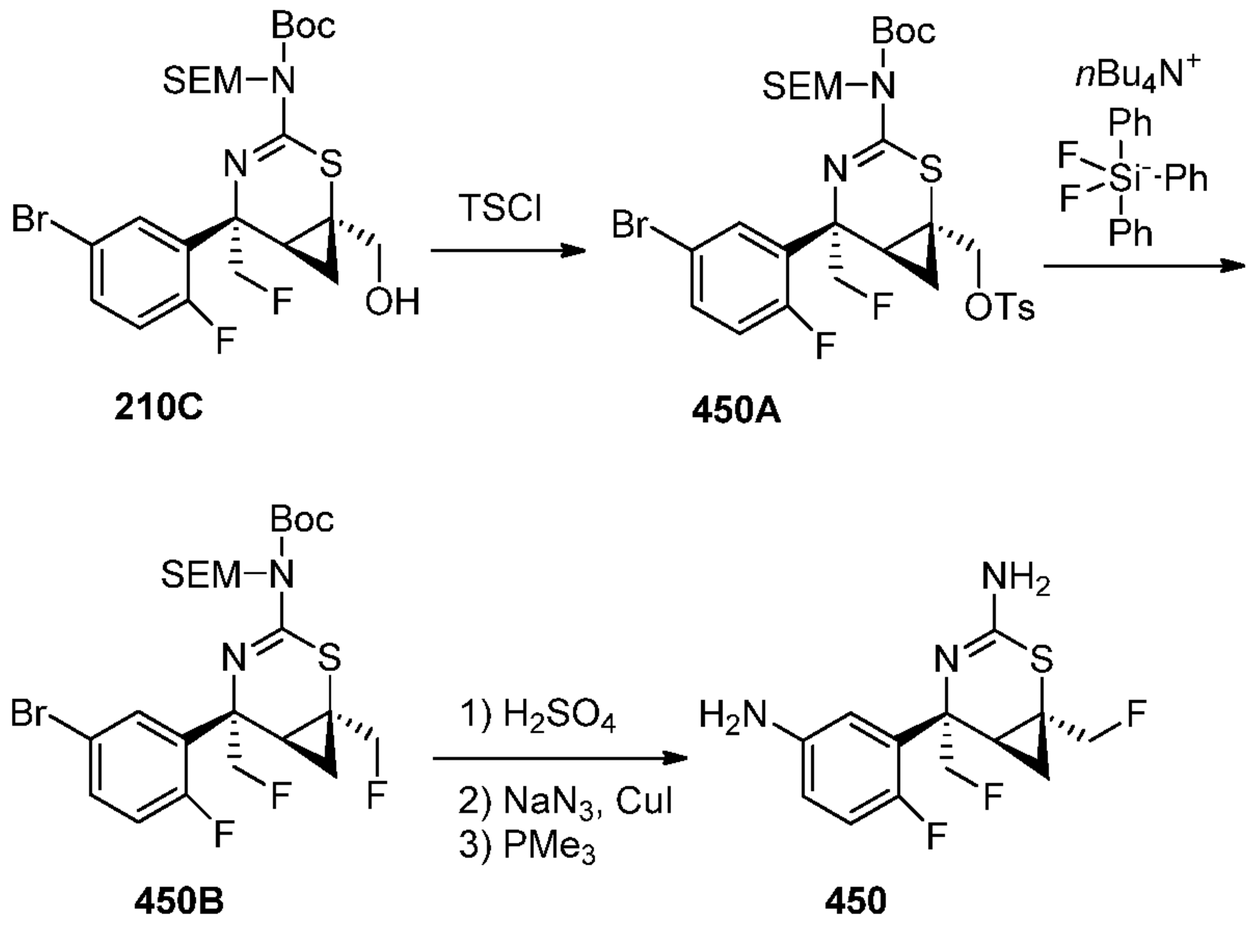


204J 249A 249

Preparation of *tert*-butyl ((1S,5S,6S)-5-(5-bromo-2-fluorophenyl)-5-(fluoromethyl)-1-(4-methyloxazol-5-yl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl) carbamate (249A). The title compound (2.41 g, 88%) was prepared in the same method as that described for **Example 248A**, but starting from *tert*-butyl ((1S,5S,6S)-5-(5-bromo-2-fluorophenyl)-5-(fluoromethyl)-1-formyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (**204J**, 2.50 g, 4.23 mmol), and 1-methyl-1-tosylmethyl isocyanide (1.06 g, 5.07 mmol). MS (ESI, positive ion) m/z: 644/646 $(M+1)^+$.

Compound **249** (2.41 g, 88%) was prepared in the same method as that described for intermediate **243C,** but starting from Compound **249A** (2.40 g, 3.71 mmol). MS (ESI, positive ion) m/z: 581 (M+1).

(1S,5S,6S)-5-(5-Amino-2-fluorophenyl)-1,5-bis(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (450).



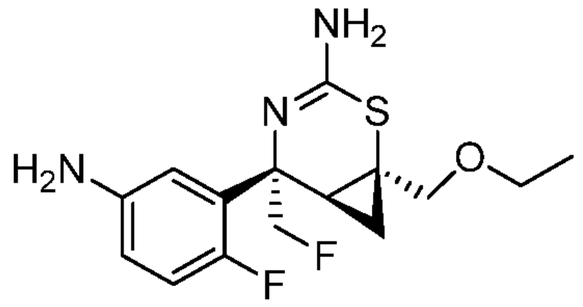
210C 450A 450B 450

Preparation of Compound 450A. To a solution of *tert*-butyl ((1S,5S,6S)-5-(5-bromo-2-fluorophenyl)-5-(fluoromethyl)-1-(hydroxymethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (**210C**, 1.4 g, 2.4 mmol) and TEA (0.5 mL, 3.5 mmol) in DCM (8 mL) at 0 °C was added 4-methylbenzenesulfonyl chloride (0.45 mL, 3.54 mmol) in DCM (7 mL). The resulting mixture was stirred at RT for 4 h. LCMS showed some starting material. 4-(dimethylamino)-pyridine (0.14 g, 1.18 mmol) was added and the mixture was stirred at RT for overnight. It was quenched saturated $NaHCO_3$. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel flash column chromatography (0-70% EtOAc/heptane) to give ((1S,5S,6S)-5-(5-bromo-2-fluorophenyl)-3-((*tert*-butoxycarbonyl)((2-(trimethylsilyl)ethoxy)methyl)amino)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)methyl 4-methylbenzenesulfonate (**450A**, 1.12 g, 1.50 mmol, 64% yield) as a colorless oil. MS (ESI, positive ion) m/z: 747/749 $(M+1)^+$.

Preparation of Compound 450B. To a solution of ((1S,5S,6S)-5-(5-bromo-2-fluorophenyl)-3-((*tert*-butoxycarbonyl)((2-(trimethylsilyl)ethoxy)methyl)amino)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)methyl 4-methylbenzenesulfonate (**450A**, 2.00 g, 2.67 mmol) (2.00 g, 2.67 mmol) in ACN (20 mL) at RT was added tetrabutylammonium difluorotriphenylsilicate (8.74 g, 16.19 mmol). The reaction mixture was heated to 75 °C for 1 d and cooled to RT. The mixture was diluted with EtOAc and transferred to a separatory funnel. The aqueous layer was discarded and the organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated. Purification by flash column chromatography on silica gel (5-10% EtOAc in heptane) gave *tert*-butyl ((1S,5S,6S)-5-(5-bromo-2-fluorophenyl)-1,5-bis(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (1.17 g, 1.96 mmol, 73% yield). MS (ESI, positive ion) m/z: 594/596 $(M+1)^+$.

Preparation of (1S,5S,6S)-5-(5-amino-2-fluorophenyl)-1,5-bis(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (450). The title compound was prepared in the same fashion as that described for intermediate **452**. MS (ESI, positive ion) m/z: 302.0 $(M+1)^+$.

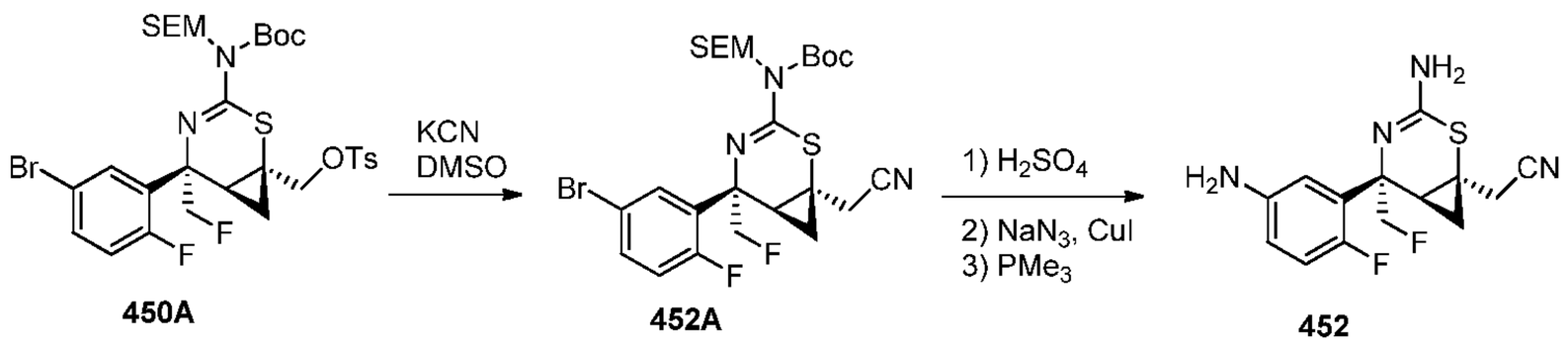
(1S,5S,6S)-5-(5-Amino-2-fluorophenyl)-1-(ethoxymethyl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (451).



451

The title compound was prepared in a fashion similar to that described for intermediate **210**. MS (ESI, positive ion) m/z: 328 $(M+1)^+$.

2-((1R,5S,6S)-3-Amino-5-(5-amino-2-fluorophenyl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)acetonitrile (452).



450A **452A** **452**

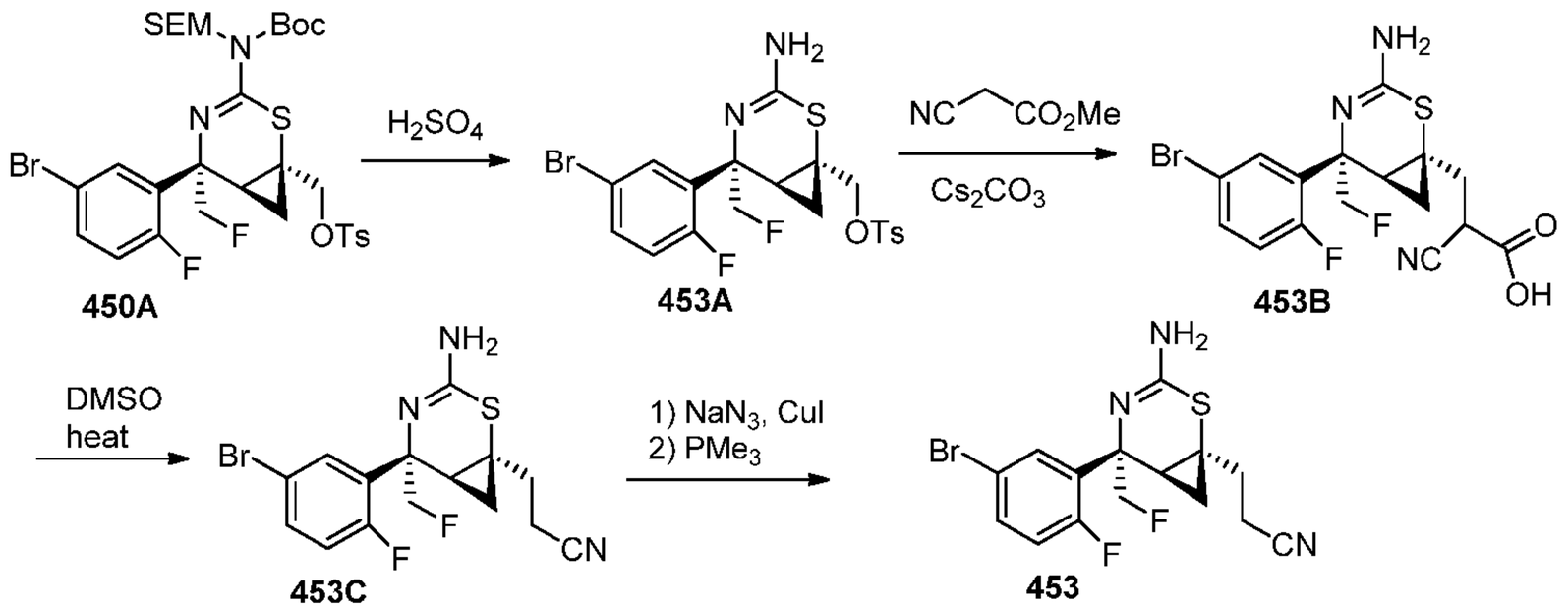
Preparation of Compound 452A. To a solution of ((1S,5S,6S)-5-(5-bromo-2-fluorophenyl)-3-((*tert*-butoxycarbonyl)((2-(trimethylsilyl)ethoxy)methyl)amino)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)methyl 4-methylbenzenesulfonate (**450A**, 1.02 g, 1.36 mmol) in DMSO (anhydrous, 9 mL) was added potassium cyanide (0.13 g, 2.04 mmol). The resulting mixture was stirred at 55 °C under N_2 overnight. It was cooled to RT, quenched with saturated $NaHCO_3$ (30 mL) and extracted with EtOAc (2 x 40 mL). The organic layer was then collected, washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel flash column chromatography using ISCO instrument (0-100% EtOAc/heptane) to give 783 mg of *tert*-butyl ((1R,5S,6S)-5-(5-bromo-2-fluorophenyl)-1-(cyanomethyl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate as a colorless oil. MS (ESI, positive ion) m/z: 602.2/604.1 $(M+1)^+$. ^1H NMR (CHLOROFORM-d) δ: 7.82 (dd, J=6.8, 2.5 Hz, 1H), 7.41 (dt, J=7.1, 4.3 Hz, 1H), 6.98 (dd, J=11.6, 8.7 Hz, 1H), 5.34 (d, J=10.4 Hz, 1H), 5.08 (d, J=10.4 Hz, 1H), 4.83-5.01 (m, 1H), 4.61-4.77 (m, 1H), 3.63-3.69 (m, 2H), 3.48 (s, 1H), 2.77 (q, J=17.4 Hz, 2H), 2.04 (t, J=7.5 Hz, 1H), 1.53 (s, 9H), 1.11 (dd, J=10.0, 6.3 Hz, 1H), 0.97 (dd, J=9.3, 7.3 Hz, 2H), 0.81 (t, J=6.7 Hz, 1H), 0.00 (s, 9H).

Preparation of Compound 452. To a round bottom flask containing *tert*-butyl ((1R,5S,6S)-5-(5-bromo-2-fluorophenyl)-1-(cyanomethyl)-5-(fluoromethyl)-2-thia-4-

azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (**452A**, 750 mg, 1.24 mmol) at 0 °C was added sulfuric acid (2 mL) dropwise. After addition, the mixture was stirred at 0 °C for 24 min and RT for 27 min. It was poured into 50 g of ice and the mixture was adjusted to pH >10 by saturated NaOH. The mixture was extracted with EtOAc (2 x 20 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated. The residue was purified by silica gel flash column chromatography using ISCO instrument (0-100% EtOAc/heptane) to give 2-((1R,5S,6S)-3-amino-5-(5-bromo-2-fluorophenyl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)acetonitrile (83 mg, 0.223 mmol, 18% yield) as a light yellow solid. MS (ESI, positive ion) m/z: 372.0/374.0 $(M+1)^+$.

To a solution of 2-((1R,5S,6S)-3-amino-5-(5-bromo-2-fluorophenyl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)acetonitrile (83 mg, 0.223 mmol) in EtOH (0.5 mL) and water (0.25 mL) was added sodium azide (44 mg, 0.67 mmol), (+)-sodium L-ascorbate (11.0 mg, 0.05 mmol), copper(i) iodide (10.6 mg, 0.05 mmol), and trans-N,N'-dimethylcyclohexane-1,2-diamine (8.8 μL, 0.05 mmol). Then, N_2 was bubbled in the solution mixture for 5 min. Then, the mixture was then stirred at 70 °C under N_2 for 1 h. LCMS showed 80% conversion. Then, copper(i) iodide (10 mg), (+)-sodium L-ascorbate (11 mg), and trans-N,N'-dimethylcyclohexane-1,2-diamine (8.8 μL) were added and the mixture was stirred at 70 °C for 45 min. LCMS showed no starting material. The mixture was cooled to RT, quenched with saturated NH_4Cl/NH_4OH (9:1, 5 mL), and extracted with EtOAc (2 x 10 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. The residue was dissolved in THF/H_2O (9:1, 1 mL) and trimethylphosphine (0.22 mL of 1.0 M solution in THF) was added. The resulting mixture was then stirred at RT overnight. It was diluted with EtOAc and washed with saturated $NaHCO_3$ (5 mL). The organic layer was collected, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel flash column chromatography using ISCO instrument (0-20% MeOH/DCM) to give 2-((1R,5S,6S)-3-amino-5-(5-amino-2-fluorophenyl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)acetonitrile (56 mg, 0.182 mmol, 81% yield) as a yellow solid. MS (ESI, positive ion) m/z: 309 $(M+1)^+$.

3-((1S,5S,6S)-3-Amino-5-(5-bromo-2-fluorophenyl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)propanenitrile (453).



Preparation of Compound 453A. At 0 °C, sulfuric acid (5 mL) was added dropwise to ((1S,5S,6S)-5-(5-bromo-2-fluorophenyl)-3-((*tert*-butoxycarbonyl)((2-(trimethylsilyl)ethoxy)methyl)amino)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)methyl 4-methylbenzenesulfonate (**250A**, 1.7 g, 2.3 mmol). The mixture was stirred at RT for 5 min then pour onto 50 g of ice. The pH of the mixture was adjusted to >12 with the addition of 5 N NaOH. The mixture was extracted with EtOAc (2 x 50 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated. The residue was purified by silica gel flash column chromatography using ISCO instrument (0-100% EtOAc/heptane) to give ((1S,5S,6S)-3-amino-5-(5-bromo-2-fluorophenyl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)methyl 4-methylbenzenesulfonate (851 mg, 1.64 mmol, 72% yield) as a light yellow solid. MS (ESI, positive ion) m/z: 517.0, 518.9 $(M+1)^+$. ^{1}H NMR (CHLOROFORM-d) δ: 7.80 (d, J=8.2 Hz, 2H), 7.61 (d, J=6.3 Hz, 1H), 7.43 (br. s., 1H), 7.38 (d, J=8.0 Hz, 2H), 6.91-7.00 (m, 1H), 4.57-4.87 (m, 2H), 4.01-4.17 (m, 2H), 1.89 (br. s., 1H), 1.25 (br. s., 1H), 0.80 (t, J=6.7 Hz, 1H).

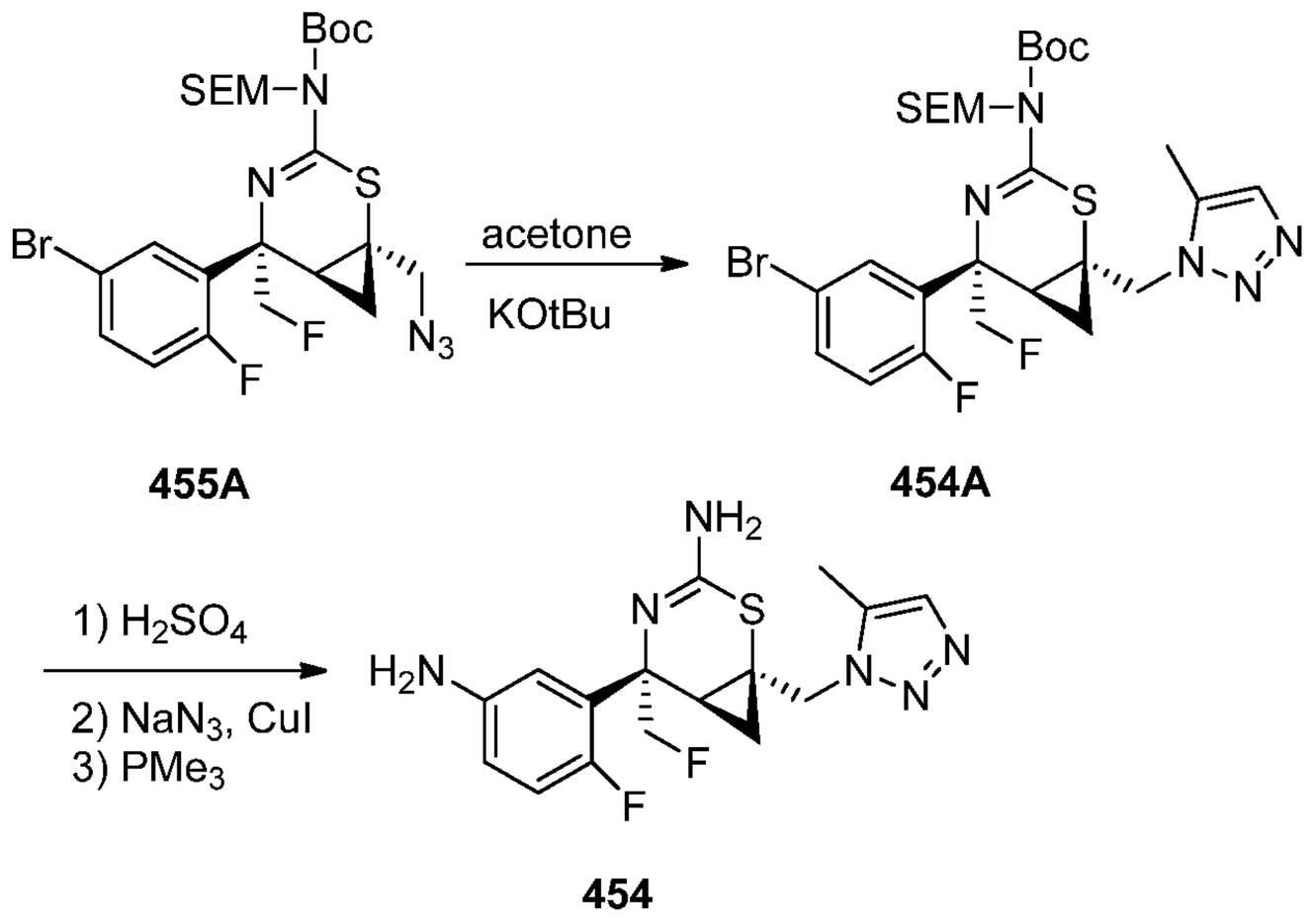
Preparation of Compound 453B. To a solution of ((1S,5S,6S)-3-amino-5-(5-bromo-2-fluorophenyl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)methyl 4-methylbenzenesulfonate (**453A**, 300 mg, 0.58 mmol) in DMF (3.7 mL) was added cesium carbonate (416 mg, 1.27 mmol) and methyl 2-cyanoacetate (86 mg, 0.87 mmol). The resulting mixture was stirred at RT overnight. It was quenched with saturated $NaHCO_3$ (7 mL) and extracted with EtOAc (2 x 20 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated. The residue was purified by silica gel flash column chromatography using ISCO instrument (0-40% EtOAc/heptane), then by

preparative HPLC (10% ACN 0.1% TFA/H_2O 0.1% TFA). The desired fractions were concentrated and the residue was treated with saturated $NaHCO_3$ and extracted with EtOAc (2 x 20 mL). The combined organic extracts were dried over $MgSO_4$, concentrated, and dried in vacuo to give a product as a mixture of (2R)-3-[(1R,5S,6S)-3-amino-5-(5-bromo-2-fluorophenyl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl]-2-cyanopropanoic acid and (2S)-3-[(1R,5S,6S)-3-amino-5-(5-bromo-2-fluorophenyl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl]-2-cyanopropanoic acid. MS (ESI, positive ion) m/z: 430, 432 $(M+1)^+$.

Preparation of Compound 453C. A mixture of (2R)-3-[(1R,5S,6S)-3-amino-5-(5-bromo-2-fluorophenyl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl]-2-cyanopropanoic acid and (2S)-3-[(1R,5S,6S)-3-amino-5-(5-bromo-2-fluorophenyl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl]-2-cyanopropanoic acid (**453B**, 249 mg, 0.58 mmol) in DMSO (1 mL) was stirred at 70 °C overnight. It was cooled to RT and saturated NaHCO3 (5 mL) was added. The mixture was extracted with EtOAc (2 x 10 mL). The combined organic extracts were dried over $MgSO_4$, concentrated and dried in vacuo to give 3-((1S,5S,6S)-3-amino-5-(5-bromo-2-fluorophenyl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)propanenitrile as a light yellow oil which was used in the next step without purification requirement. MS (ESI, positive ion) m/z: 386, 388 $(M+1)^+$.

Preparation of 3-((1S,5S,6S)-3-amino-5-(5-amino-2-fluorophenyl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)propanenitrile (453). The title compound (13 mg) as a yellow solid was prepared from intermediate **453C** (224 mg, 0.58 mmol) according to the procedures described for intermediate **452**. MS (ESI, positive ion) m/z: 323 $(M+1)^+$.

(1S,5S,6S)-5-(5-Amino-2-fluorophenyl)-5-(fluoromethyl)-1-((5-methyl-1H-1,2,3-triazol-1-yl)methyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (454).



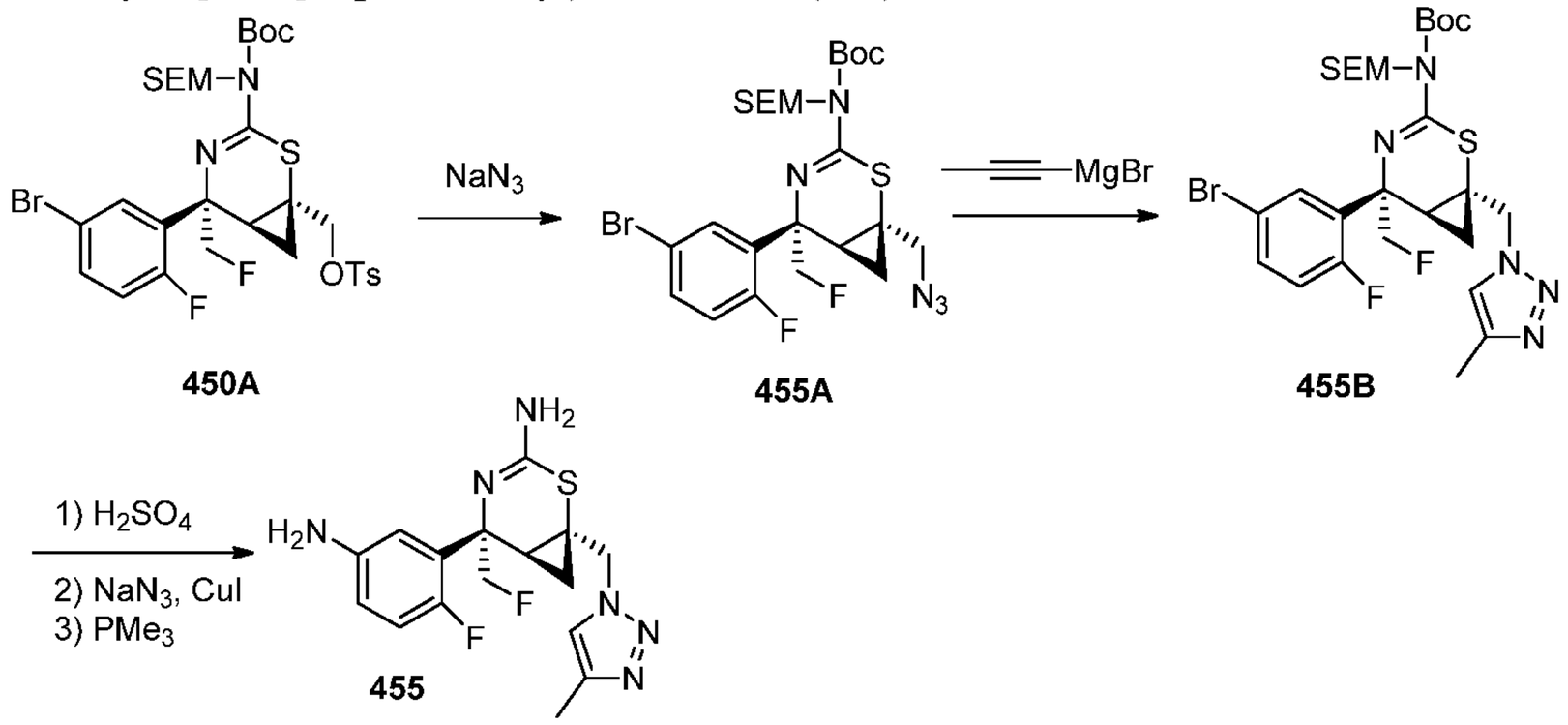
455A **454A**

454

Preparation of Compound 454A. To a solution of potassium t-butoxide (0.82 g, 7.27 mmol) in THF (8 mL) at 0 °C under N_2 was added a solution of *tert*-butyl ((1S,5S,6S)-1-(azidomethyl)-5-(5-bromo-2-fluorophenyl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (**455A**, 1.5 g, 2.42 mmol) in acetone (0.53 mL, 7.27 mmol) and THF (7 mL) dropwise. After addition, the mixture was stirred at 0 °C for 1 h and RT for 18 h. The mixture was poured onto ice bath (50 mL) and saturated $NaHCO_3$ (7 mL) was added. The mixture was extracted with EtOAc (2 x 10 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Chromatographic purification of the residue (silica gel, 0%-100% EtOAc/heptane) provided *tert*-butyl ((1S,5S,6S)-5-(5-bromo-2-fluorophenyl)-5-(fluoromethyl)-1-((5-methyl-1H-1,2,3-triazol-1-yl)methyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (**454A**, 226 mg, 0.34 mmol, 14% yield) as a yellow solid. MS (ESI, positive ion) m/z: 658.1/660.2 $(M+H)^+$.

Preparation of (1S,5S,6S)-5-(5-amino-2-fluorophenyl)-5-(fluoromethyl)-1-((5-methyl-1H-1,2,3-triazol-1-yl)methyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (454). The title compound (51 mg, 41% yield) as a yellow solid was prepared from intermediate **454A** (226 mg, 0.34 mmol) according to the procedures described for intermediate **452**. MS (ESI, positive ion) m/z: 365.0 $(M+1)^+$.

2-((1R,5S,6S)-3-Amino-5-(5-amino-2-fluorophenyl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)acetonitrile (455).



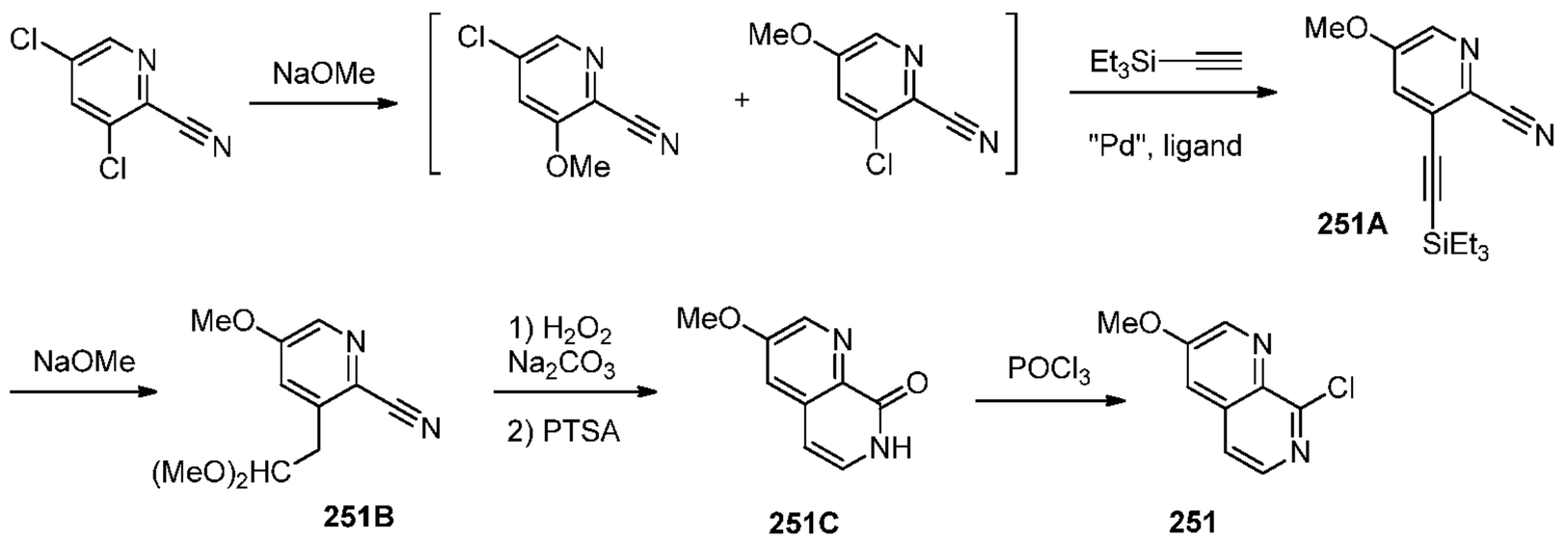
Preparation of Compound 455A. To a solution of ((1S,5S,6S)-5-(5-bromo-2-fluorophenyl)-3-((*tert*-butoxycarbonyl)((2-(trimethylsilyl)ethoxy)methyl)amino)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)methyl 4-methylbenzenesulfonate (**450A**, 606 mg, 0.81 mmol) in DMSO (4.0 mL) was added sodium azide (58 mg, 0.89 mmol). The resulting mixture was then stirred at RT overnight. The mixture was quenched with saturated NH_4Cl/NH_4OH (10:1, 10 mL) and extracted with EtOAc (2 x 15 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel flash column chromatography using ISCO instrument (0-100% EtOAc in heptane) to give *tert*-butyl ((1S,5S,6S)-1-(azidomethyl)-5-(5-bromo-2-fluorophenyl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (501 mg, 0.81 mmol, 100% yield) as a colorless oil. MS (ESI, positive ion) m/z: 618.0/620.2 $(M+1)^+$.

Preparation of Compound 455B. To a solution of *tert*-butyl ((1S,5S,6S)-1-(azidomethyl)-5-(5-bromo-2-fluorophenyl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (501 mg, 0.81 mmol) in MTBE (4 mL) under N_2 at 0 °C was added 1-propynylmagnesium bromide (0.5 M in THF, 2.43 mL, 1.21 mmol). After addition, the mixture was stirred at RT overnight. LCMS showed 15% conversion. Additional 1-propynylmagnesium bromide (0.5 M in THF, 2.43 mL, 1.21 mmol) was added and the mixture was then stirred at RT for 4 h. LCMS showed no starting material. The reaction was quenched with saturated NH_4Cl (50 mL) and extracted with EtOAc (2 x 70 mL). The combined organic extracts

were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel flash column chromatography using ISCO instrument (0%-100% EtOAc/heptane) to give *tert*-butyl ((1S,5S,6S)-5-(5-bromo-2-fluorophenyl)-5-(fluoromethyl)-1-((4-methyl-1H-1,2,3-triazol-1-yl)methyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (449 mg, 0.68 mmol, 84% yield) as colorless oil. MS (ESI, positive ion) m/z: 658.1/660.0 $(M+1)^+$. ^1H NMR (CHLOROFORM-d) δ: 7.77 (dd, J=6.9, 2.4 Hz, 1H), 7.50 (s, 1H), 7.40 (ddd, J=8.7, 4.3, 2.5 Hz, 1H), 6.97 (dd, J=11.5, 8.6 Hz, 1H), 5.27 (d, J=10.4 Hz, 1H), 5.03 (d, J=10.4 Hz, 1H), 4.57-4.82 (m, 2H), 4.39-4.50 (m, 2H), 3.64 (dd, J=9.1, 7.3 Hz, 2H), 2.43 (s, 3H), 2.24 (t, J=7.6 Hz, 1H), 1.50 (s, 9H), 1.22 (dd, J=9.9, 6.2 Hz, 1H), 0.95 (dd, J=9.1, 7.5 Hz, 2H), 0.85 (t, J=6.7 Hz, 1H), 0.00 (s, 9H).

Preparation of Compound 455. The title compound (185 mg, 87% yield) as a yellow solid was prepared from intermediate **455B** (449 mg, 0.68 mmol) according to the procedures described for intermediate **452**. MS (ESI, positive ion) m/z: 365.0 (M+1). ^1H NMR (CHLOROFORM-d) δ: 7.46 (s, 1H), 6.84 (dd, J=11.7, 8.6 Hz, 1H), 6.75 (dd, J=6.6, 2.8 Hz, 1H), 6.51-6.58 (m, 1H), 4.73-4.90 (m, 1H), 4.52-4.69 (m, 1H), 4.33-4.51 (m, 2H), 2.38 (s, 3H), 2.04-2.06 (m, 1H), 1.35 (dd, J=9.8, 6.3 Hz, 1H), 1.26 (t, J=7.1 Hz, 1H). The 2 sets of NH_2 have very broad peaks.

8-Chloro-3-methoxy-1,7-naphthyridine (251).



Preparation of 5-methoxy-3-((triethylsilyl)ethynyl)picolinonitrile (251A). To a solution of 3,5-dichloropicolinonitrile (22.5 g, 130 mmol) in DMF (500 mL) at 0 °C was added sodium methoxide (6.67 g, 124 mmol) slowly. The reaction was stirred for 5 min at 0 °C then stirred at RT for 30 min. The solution was partitioned between water and EtOAc. The organic layer was washed with water and concentrated. The crude product was purified via silica gel chromatography, eluting with 0-75% EtOAc in

heptane, to afford a 1: 1 ratio of the desired isomer 3-chloro-5-methoxypicolinonitrile and 5-chloro-3-methoxypicolinonitrile (7.0 g, 41.5 mmol). The material was used without further purification. MS *m/z* = 169 (M+H). A sealed vessel was charged with bis(acetonitrile)palladium (II) chloride (0.154 g, 0.593 mmol), dicyclohexyl(2',4',6'-triisopropyl-[1,1'-biphenyl]-2-yl)phosphine (0.848 g, 1.780 mmol), cesium carbonate (25.1 g, 77 mmol), the mixture (1: 1 ratio) of 3-chloro-5-methoxypicolinonitrile and 5-chloro-3-methoxypicolinonitrile (5 g, 29.7 mmol), and ACN (60 mL). The vessel was flushed with argon, and stirred at RT for 25 min. To the reaction was added triethyl(ethynyl)silane (5.41 g, 38.6 mmol), and the vessel was resealed and stirred at 90 °C for 3 h. The solution was concentrated, and the residue was purified via silica gel chromatography, eluting with 0-50% EtOAc in heptane, to afford the title compound (3.8 g, 13.9 mmol). MS *m/z* = 273 $(M+H)^+$.

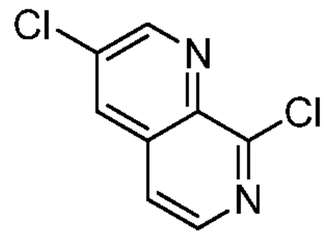
Preparation of 3-(2,2-dimethoxyethyl)-5-methoxypicolinonitrile (251B). A pressure vessel was charged with 5-methoxy-3-((triethylsilyl)ethynyl) picolinonitrile (251A, 3.8 g, 13.95 mmol) and sodium methoxide (0.5 M in MeOH, 69.7 mL, 34.9 mmol). The vessel was sealed and stirred at 55 °C for 2 h. The reaction was concentrated to afford the title intermediate (3.1 g, 13.95 mmol).

Preparation of 3-Methoxy-1,7-naphthyridin-8(7H)-one (251C). To a solution of 3-(2,2-dimethoxyethyl)-5-methoxypicolinonitrile (251B, 8.55 g, 38.5 mmol) in water (480 mL) and acetone (120 mL) was added an aqueous solution of sodium carbonate (3 M; 154 mL, 462 mmol) followed by hydrogen peroxide (35 wt.% solution in water; 138 mL, 1347 mmol). The tan mixture was stirred vigorously at RT for 2 h. The organic solvent was removed under reduced pressure and the aqueous residue was extracted with DCM (3x). The combined organic fractions were dried over sodium sulfate. The filtrate was concentrated under reduced pressure to afford 3-(2,2-dimethoxyethyl)-5-methoxypicolinamide (8.2 g, 34.1 mmol, 89% yield) as an off-white solid that was advanced without further purification. MS *m/z* = 263.2 $(M+Na)^+$.

To a mixture of 3-(2,2-dimethoxyethyl)-5-methoxypicolinamide (6.74 g, 28.1 mmol) in toluene (112 mL) was added 4-methylbenzene sulfonic acid (monohydrate; 0.534 g, 2.81 mmol). The reaction mixture was heated to reflux for 20 h. The reaction mixture was cooled to RT and concentrated *in vacuo* to a volume of ca. 15 mL. The residue was triturated with heptane and filtered to afford 3-methoxy-1,7-naphthyridin-8(7H)-one (251C, 4.53 g, 25.7 mmol, 92% yield) as a crude, tan solid that was advanced without further purification. MS *m/z* = 177.1 $[M+H]^+$

Preparation of 8-chloro-3-methoxy-1,7-naphthyridine (251). To a mixture of 3-methoxy-1,7-naphthyridin-8(7H)-one (4.50 g, 25.5 mmol) in ACN (102 mL) was added phosphorus oxychloride (11.69 mL, 128 mmol). The reaction mixture was heated to 85 °C for 5 h. The solution was cooled to RT and concentrated *in vacuo*. The resulting brown residue was partitioned between DCM and aqueous saturated $NaHCO_3$ solution; the aqueous layer was back-extracted with DCM (3x). The combined organic extracts were dried over sodium sulfate. The filtrate was concentrated *in vacuo*, and the residue was purified by silica gel chromatography (5-30% of (9:1 DCM:MeOH) in DCM) to give 8-chloro-3-methoxy-1,7-naphthyridine (3.00 g, 15.41 mmol, 60% yield) as an off-white solid. MS $m/z = 195$ $(M+H)^+$.

3,8-Dichloro-1,7-naphthyridine (252).



252

Preparation of 3-bromo-5-chloropicolinonitrile

A microwave vial was charged with copper(I) cyanide (1.089 g, 12.16 mmol), 2,3-dibromo-5-chloropyridine (3 g, 11.06 mmol), and propionitrile (15 mL). The vial was capped and irradiated in a microwave reactor at 150 °C for 2.5 h. The solution was concentrated, diluted with DCM (25 mL), and filtered. The filtrate was concentrated, and the residue was purified by silica gel chromatography, eluting with 0-30% EtOAc in heptane, to afford the title compound (2 g, 9.20 mmol). MS $m/z = 219$ $(M+H)^+$.

Preparation of 5-chloro-3-((trimethylsilyl)ethynyl)picolinonitrile

A pressure vessel was charged with TEA (7.65 mL, 55.2 mmol), ethynyltrimethylsilane (2.32 mL, 16.6 mmol), copper(I) iodide (0.263 g, 1.380 mmol), palladium (0) tetrakis(triphenylphosphine) (0.558 g, 0.483 mmol), 3-bromo-5-chloropicolinonitrile (3.0 g, 13.8 mmol), and DMF (50 mL). The vessel was flushed with argon, sealed, stirred at ambient temperature for 15 minutes, and then heated at 50 °C for 4 h. The solution was diluted with water and extracted with EtOAc. The combined organic layers were concentrated, and the residue was purified by silica-gel chromatography, eluting 0-50 % EtOAc in hexane, to afford the title compound (1.3 g, 5.5 mmol). MS $m/z = 235$ $(M+H)^+$.

Preparation of 5-chloro-3-(2,2-dimethoxyethyl)picolinonitrile

A pressure vessel was charged with 5-chloro-3-((trimethylsilyl)ethynyl)picolinonitrile (2g, 8.52 mmol) and sodium methoxide (0.5 M in MeOH, 42.6 mL, 21.30 mmol), sealed, and stirred at 55 °C for 1 h. The solution was concentrated, and the residue was purified via silica gel chromatography, eluting with 10% MeOH in DCM to afford the title compound (1.7 g, 7.50 mmol). MS *m/z* = 227 $(M+H)^+$.

Preparation of 3-chloro-1,7-naphthyridin-8(7*H*)-one

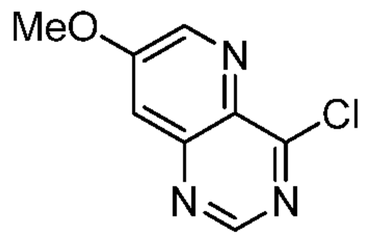
To a solution of 5-chloro-3-(2,2-dimethoxyethyl)picolinonitrile (1.7 g, 7.50 mmol) in acetone (50 mL) and water (150 mL) was added aqueous saturated sodium carbonate (37.5 mL, 113 mmol) and 30% aqueous hydrogen peroxide (38.3 mL, 375 mmol). The reaction was stirred at RT for one hour, concentrated to remove most of the acetone, and extracted with DCM. The combined organic layers were concentrated.

To a solution of this intermediate (1.8 g, 7.36 mmol) in benzene (20 mL) was added p-toluenesulfonic acid (0.350 g, 1.839 mmol) and the reaction was sonicated for 10 minutes. The solution was stirred overnight at 80 °C and concentrated. The crude product was purified via silica gel, eluting with 0-100% (80/20/1 EtOAc/MeOH/ ammonium hydroxide) in EtOAc, to the title intermediate (1.1 g, 6.1 mmol). MS *m/z* = 181 $(M+H)^+$.

Preparation of 3,8-dichloro-1,7-naphthyridine

A suspension of -chloro-1,7-naphthyridin-8(7*H*)-one (250 mg, 1.384 mmol) in phosphorus oxychloride (1.94 mL, 20.8 mmol) was stirred at 95 °C for one hour. The solution was concentrated to afford the title compound (276 mg, 1.39 mmol). MS *m/z* = 199 $(M+H)^+$.

5-Chloro-2-methoxypyrido[3,4-b]pyrazine (253).



253

Preparation of 5-chloropyrido[3,4-*b*]pyrazin-2(1*H*)-one

A suspension 2-chloropyridine-3,4-diamine (2.5 g, 17.41 mmol) and a 50% solution of ethyl glyoxalate in toluene (3.45 mL, 17.41 mmol) in EtOH (34.8 mL) was stirred at reflux for 24 h. The solution was cooled to -20 °C for 16 hours, and the

resulting precipitate was collected by vacuum filtration and rinsed with EtOH. The crude product was purified via reverse-phase HPLC, eluting with 5-50% ACN/0.1% TFA in water/0.1% TFA, to afford the title compound (570 mg, 3.14 mmol). MS *m/z* = 182 $(M+H)^+$.

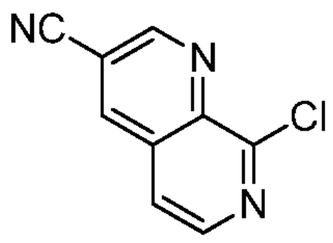
Preparation of 2,5-dichloropyrido[3,4-*b*]pyrazine

A suspension of 5-chloropyrido[3,4-*b*]pyrazin-2(1*H*)-one (0.57 g , 3.14 mmol) in phosphorus oxychloride (10.24 mL, 110 mmol) was stirred at 110 °C for two hours, and then concentrated. The residue was dissolved in DCM, washed with saturated sodium bicarbonate, dried over anhydrous sodium sulfate, filtered, and concentrated to afford the title compound (580 mg, 2.90 mmol). MS *m/z* = 200 $(M+H)^+$.

Preparation of 5-chloro-2-methoxypyrido[3,4-*b*]pyrazine

To a solution of 2,5-dichloropyrido[3,4-*b*]pyrazine (580 mg, 2.90 mmol) in *DMF* (10 mL) was added a 0.5 M solution of sodium methoxide in MeOH (6.09 mL, 3.04 mmol), and the reaction was stirred at RT for 5 min. The solution was diluted with water and extracted with EtOAc. The organic layer was dried with sodium sulfate, filtered and concentrated to afford the title compound (550 mg, 2.81 mmol). MS *m/z* = 196 $(M+H)^+$.

8-Chloro-1,7-naphthyridine-3-carbonitrile (254).

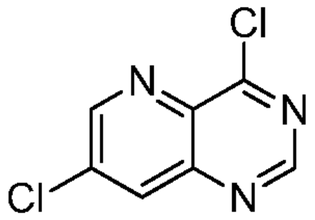


254

A screw-cap vial was charged with 3-chloro-1,7-naphthyridin-8(7*H*)-one (100 mg, 0.554 mmol), zinc cyanide (52.7 µL, 0.831 mmol), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (45.5 mg, 0.111 mmol), tris(dibenzylideneacetone)dipalladium(0) (40.6 mg, 0.044 mmol), DMF (2.74 mL) and water (28 µL). The vial was purged with argon, sealed, and stirred at 110 ºC for 1 hour. The mixture was filtered through a pad of Celite® filter aid, which was rinsed with MeOH and DMSO. The combined filtrates were concentrated, and a few drops of water were added. The resulting solids were collected by vacuum filtration, rinsed with water and dried. The solids were suspended in toluene (3.5 mL), and phosphorus oxychloride (98 µL, 1.052 mmol) and DIPEA (122 µL, 0.70 mmol) were added. The reaction was stirred at 120 ºC for 1.5 hours, cooled to RT, diluted with EtOAc, and washed with 2 M aqueous sodium carbonate. The organic portion was dried over anhydrous sodium sulfate, filtered and concentrated. The crude

material was purified by silica gel chromatography, eluting with 5-50% EtOAc in heptane, to provide the title compound (50 mg, 0.264 mmol) as a white solid. LC/MS (ESI^+) *m/z* = 190 $(M+H)^+$.

4,7-Dichloropyrido[3,2-*d*]pyrimidine (255).



255

Preparation of 3-amino-5-chloropicolinamide.

To a suspension of 5-chloro-2-cyano-3-nitropyridine (1.274 mL, 10.9 mmol) in water (22 mL) was added 28% aqueous NH_4OH (3.94 mL, 28.3 mmol), and the reaction was stirred at RT for 20 min. Sodium hydrosulfite (2.68 mL, 32.7 mmol) was added, and the reaction mixture was stirred at RT for 70 minutes. The yellow precipitate was collected by vacuum filtration to provide the title compound (1.097 g, 6.39 mmol) as yellow solid. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.88 (br. s, 1 H), δ 7.73 (s, 1 H), δ 7.39 (br. s, 1 H), δ 7.23 (s, 1 H), δ 7.06 (br. s, 2 H). LC/MS (ESI^+) *m/z* = 172 $(M+H)^+$.

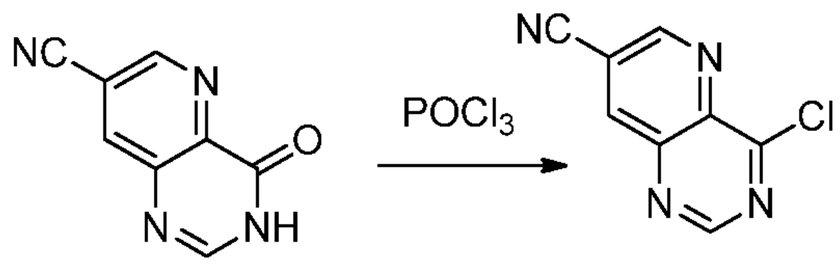
Preparation of 7-chloropyrido[3,2-*d*]pyrimidin-4(1*H*)-one.

A suspension of 3-amino-5-chloropicolinamide (1.1 g, 6.41 mmol) in triethyl orthoformate (15.99 mL, 96 mmol) was stirred at 155 °C for 22 h. After cooling to RT, the yellow precipitate was collected by vacuum filtration and washed with hexanes to yield the title intermediate (1.03 g, 5.67 mmol) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.20 (s, 1 H) 8.27 (d, *J*=2.35 Hz, 1 H) 8.80 (d, *J*=2.25 Hz, 1 H) 12.68 (br. s., 1 H). LC/MS (ESI^+) *m/z* = 182 $(M+H)^+$.

Preparation of 4,7-dichloropyrido[3,2-*d*]pyrimidine.

To a mixture of 7-chloropyrido[3,2-*d*]pyrimidin-4(1*H*)-one (250 mg, 1.377 mmol) in toluene (12 mL) were added DIPEA (0.73 mL, 4.20 mmol) and phosphorus oxychloride (0.391 mL, 4.27 mmol), and the reaction was stirred at reflux for 1 h. After cooling to RT, the reaction mixture was concentrated to provide the title compound. LC/MS (ESI^+) *m/z* = 200 $(M+H)^+$.

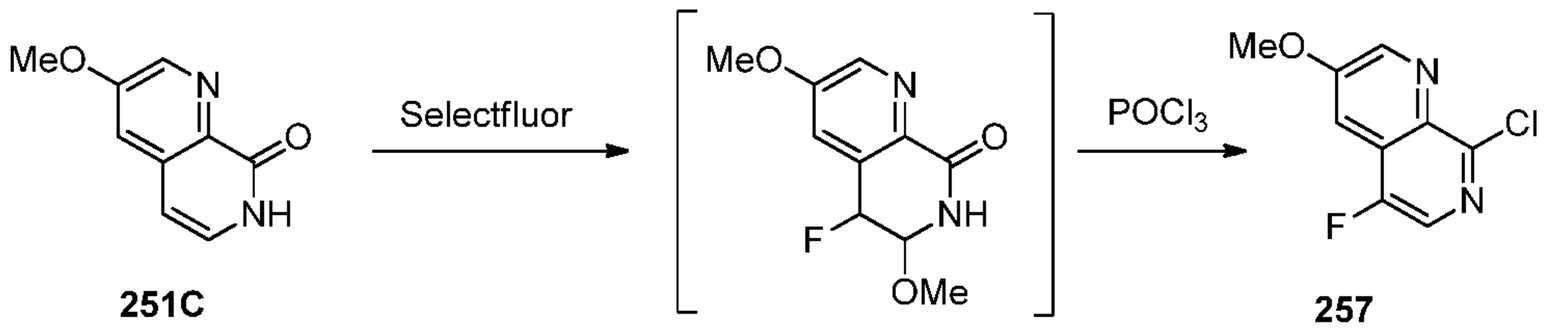
4-Chloropyrido[3,2-d]pyrimidine-7-carbonitrile (256).



256

To a mixture of 4-oxo-1,4-dihydropyrido[3,2-d]pyrimidine-7-carbonitrile (prepared according to the procedures described in US20090036430) (7.7g, 44.7 mmol) in toluene (249 mL) were added N,N-diisopropylethylamine (23.73 mL, 136 mmol) and phosphorus oxychloride (12.69 mL, 139 mmol). The resulting reaction mixture was refluxed at 130 °C for 20 min. It was concentrated under reduced pressure. The residue was dissolved in EtOAc (150 mL) and neutralized with sat. $NaHCO_3$ until pH = 6-7. It was diluted with water and filtered through a pad of silica in a fritted funnel. The filtrate was extracted with EtOAc (3 x 150 mL). The combined organic extracts were washed sequentially with water, brine and dried over $MgSO_4$. The solution was filtered and concentrated *in vacuo* to give a dark brown solid. It was triturated with 160 mL of heptane and 20 mL of EtOAc to yield 4-chloropyrido[3,2-d]pyrimidine-7-carbonitrile (5.7 g, 29.9 mmol, 67% yield) as an orange solid. The filtrate was concentrated down to ~50 mL and the precipitated solid was collected to yield 0.3 g of 4-chloropyrido[3,2-d]pyrimidine-7-carbonitrile. MS m/z = 191.0 $[M+H]^+$. ^1H NMR (300 MHz, CHLOROFORM-d) δ 9.27 (d, *J*=2.0 Hz, 1H), 9.26 (s, 1H), 8.77 (d, *J*=2.0 Hz, 1H).

8-Chloro-5-fluoro-3-methoxy-1,7-naphthyridine (257).



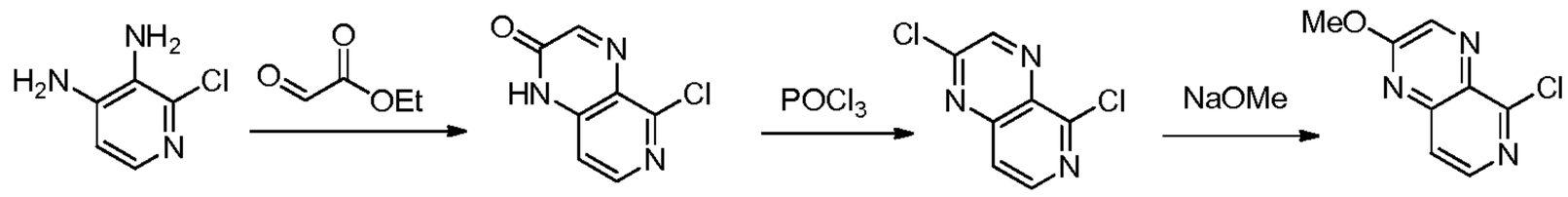
251C **257**

A mixture of 3-methoxy-1,7-naphthyridin-8(7H)-one (15.00 g, 85 mmol) and selectfluor fluorinating reagent (47.21 g, 133 mmol) in ACN (360 mL)/MeOH (90 mL) was heated at 45 °C for 3 h. It was cooled to RT and the solvents were removed *in vacuo*. The residue was partitioned between EtOAc (200 mL and saturated $NaHCO_3$ (200 mL). The aqueous layer was extracted with EtOAc (2 x 200 mL) and DCM (2 x 200 mL). A white solid precipitated from the combined organic layers and was filtered to give 5-

fluoro-3,6-dimethoxy-6,7-dihydro-1,7-naphthyridin-8(5H)-one (10.20 g, MS m/z = 227.0 $[M+H]^+$). The combined organic layers were dried over $MgSO_4$ where a white solid precipitate formed on the $MgSO_4$. The organic solution was filtered and the solid was washed consecutively with water then Et_2O. The remaining solid (1.24 g) contained product 5-fluoro-3,6-dimethoxy-6,7-dihydro-1,7-naphthyridin-8(5H)-one (MS m/z = 227.0 $[M+H]^+$). The combined dried organic layers were concentrated *in vacuo* to give 5-fluoro-3,6-dimethoxy-6,7-dihydro-1,7-naphthyridin-8(5H)-one (7.41 g) of a light-tan solid.

The three batches of solid (18.85 g) 5-fluoro-3,6-dimethoxy-6,7-dihydro-1,7-naphthyridin-8(5H)-one were slurried in toluene (150 mL), treated with phosphorus oxychloride (80 mL, 874 mmol) and heated at 75 °C overnight. The mixture was cooled to RT and the solvents were removed *in vacuo*. The residue was azeotroped with toluene, dissolved in DCM, evaporated onto silica gel and purified by flash chromatography eluting with EtOAc:hexanes (0:1 → 3:1) to give 8-chloro-5-fluoro-3-methoxy-1,7-naphthyridine (257) (11.21 g, 62% yield) of a sticky yellow solid. MS m/z = 212.9 $[M+H]^+$. ^1H NMR (300 MHz, $CDCl_3$) δ ppm 8.85 (d, *J*=2.92 Hz, 1 H), 8.23 (s, 1 H), 7.54 (d, *J*=2.92 Hz, 1 H), 4.05 (s, 3 H). ^{19}F NMR (282 MHz, $CDCl_3$) δ ppm -140.46.

5-Chloro-2-methoxypyrido[3,4-b]pyrazine (258).



258A **258B** **258**

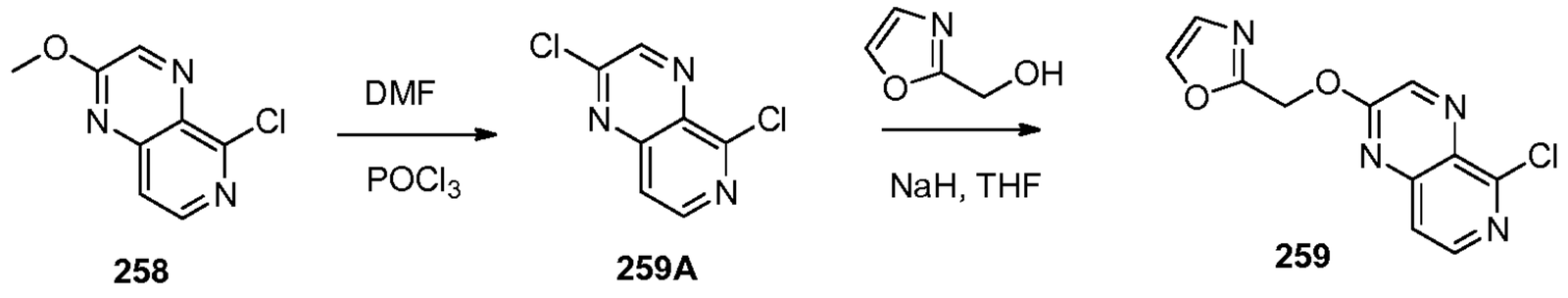
Preparation of 5-chloropyrido[3,4-*b*]pyrazin-2(1*H*)-one (258A). A suspension 2-chloropyridine-3,4-diamine (2.5 g, 17.41 mmol) and a 50% solution of ethyl glyoxalate in toluene (3.45 mL, 17.41 mmol) in EtOH (34.8 mL) was stirred at reflux for 24 h. The solution was cooled to -20 °C for 16 h, and the resulting precipitate was collected by vacuum filtration and rinsed with EtOH. The crude product was purified via reverse-phase HPLC, eluting with 5-50% ACN/0.1% TFA in water/0.1% TFA, to afford the title compound (570 mg, 3.14 mmol). MS *m/z* = 182 $(M+H)^+$.

Preparation of 2,5-dichloropyrido[3,4-*b*]pyrazine (258B). A suspension of 5-chloropyrido[3,4-*b*]pyrazin-2(1*H*)-one (0.57 g , 3.14 mmol) in phosphorus oxychloride (10.24 mL, 110 mmol) was stirred at 110 °C for two h, and then concentrated. The

residue was dissolved in DCM, washed with saturated sodium bicarbonate, dried over anhydrous sodium sulfate, filtered, and concentrated to afford the title compound (580 mg, 2.90 mmol). MS *m/z* = 200 $(M+H)^+$.

Preparation of 5-chloro-2-methoxypyrido[3,4-*b*]pyrazine (258). To a solution of 2,5-dichloropyrido[3,4-*b*]pyrazine (580 mg, 2.90 mmol) in *DMF* (10 mL) was added a 0.5 M solution of sodium methoxide in MeOH (6.09 mL, 3.04 mmol), and the reaction was stirred at RT for 5 min. The solution was diluted with water and extracted with EtOAc. The organic layer was dried with sodium sulfate, filtered and concentrated to afford the title compound (550 mg, 2.81 mmol). MS *m/z* = 196 $(M+H)^+$.

2-(((5-Chloropyrido[3,4-b]pyrazin-2-yl)oxy)methyl)oxazole (259).



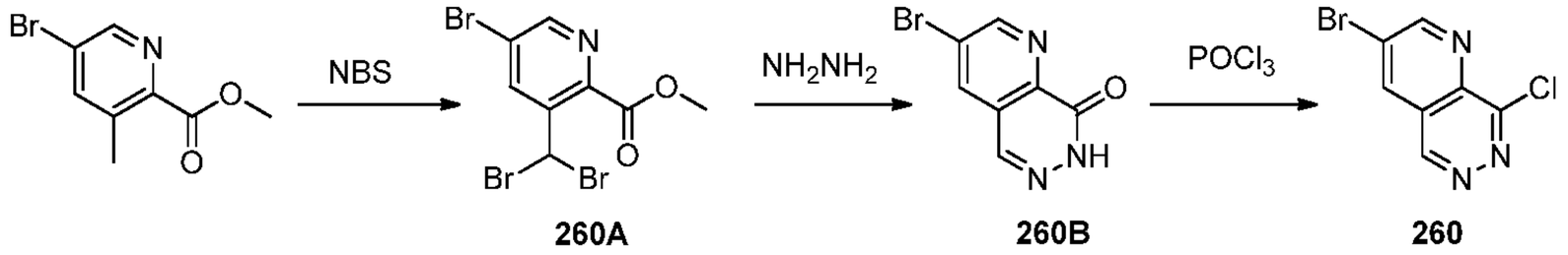
258 259A 259

Preparation of Compound 259A. A mixture of 5-chloro-2-methoxypyrido[3,4-b]pyrazine (258, 2.76 g, 14.11 mmol), phosphorus oxychloride (17.10 mL, 183 mmol) and DMF (1.09 mL, 14.12 mmol) was heated at 100 °C overnight. The mixture was concentrated *in vacuo*. The residue was diluted with EtOAc (150 mL) and cooled to 0 °C. It was treated with ice water followed by solid $NaHCO_3$ in small portions. The layers were separated. The basic aqueous layer was extracted with EtOAc. The combined organic solution was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to afford 2,5-dichloropyrido[3,4-b]pyrazine (259A, 2.57 g, 12.85 mmol, 91% yield) as a brown solid. LC/MS (ESI^-) *m/z* = 200, 202 $(M+H)^+$.

Preparation of Compound 259. At 0 °C, to a mixture of 2,5-dichloropyrido[3,4-b]pyrazine (**259A**, 1.64 g, 8.20 mmol), oxazol-2-ylmethanol (1.19 g, 8.85 mmol) in THF (50 mL) under N_2 was added sodium hydride (60% wt. dispersion in mineral oil) (0.35 g, 8.85 mmol) in batches. After 40 min, the reaction was quenched with saturated NH_4Cl (20 mL) and water (20 mL). The mixture was diluted with EtOAc (150 mL) and the organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The solid was suspended in heptane-EtOAc and filtered to afford 2-(((5-chloropyrido[3,4-b]pyrazin-2-yl)oxy)methyl)oxazole (**259**, 1.89 g, 7.20 mmol, 88% yield) as a brown powder. LC/MS (ESI^-) *m/z* = 263, 265 $(M+H)^+$. ^1H NMR

(400MHz, CHLOROFORM-d) δ = 8.70 (s, 1H), 8.51 (d, *J*=5.7 Hz, 1H), 7.74 (d, *J*=0.8 Hz, 1H), 7.69 - 7.64 (m, 1H), 7.21 (s, 1H), 5.68 (s, 2H).

3-Bromo-8-chloropyrido[2,3-d]pyridazine (260).



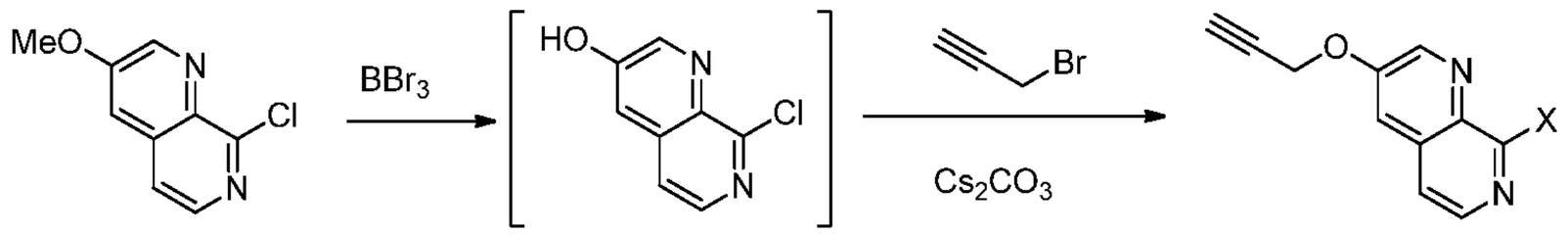
Preparation of Compound 260A. A vial was charged with methyl 5-bromo-3-methylpicolinate (2.03 g, 8.82 mmol), carbon tetrachloride (22 mL), benzoyl peroxide (0.107 g, 0.441 mmol) and NBS (3.14 g, 17.65 mmol). The mixture was heated at 80 °C for 2 h. Another equivalent of NBS and 50 mg benzoyl peroxide were added, and heating was continued for 16 h. Upon cooling to RT the mixture was filtered through Celite® filter aid and washed with DCM. The filtrate was concentrated, and the crude material was purified by silica gel chromatography (10-50% EtOAc/heptane) to provide methyl 5-bromo-3-(dibromomethyl)picolinate as a yellow oil (**260A**, 3.28 g, 8.46 mmol, 96% yield).

Preparation of 3-bromopyrido[2,3-d]pyridazin-8(7H)-one (260B). A pressure bottle was charged with methyl 5-bromo-3-(dibromomethyl)picolinate (3.28 g, 8.46 mmol), EtOH (16.91 mL) and hydrazine hydrate (4.19 mL, 85 mmol). The bottle was sealed, and the mixture was heated at 80 °C for 1.5 h. The mixture was heterogeneous upon cooling, so the solids were filtered, washed with MeOH and dried. The filtrate was concentrated and was triturated in MeOH. The solids were filtered, rinsed with MeOH and dried to give a second crop of product. The title compound (1.72 g, 7.61 mmol, 90% yield) was isolated as a yellow solid.

Preparation of 3-bromo-8-chloropyrido[2,3-d]pyridazine (260).

A vial was charged with 3-bromopyrido[2,3-d]pyridazin-8(7H)-one (500 mg, 2.212 mmol) and phosphorus oxychloride (4.1 mL, 44.2 mmol). The vial was capped and the mixture was heated at 90 °C for 2 h. The mixture was concentrated and used without further purification. MS *m/z* = 241 $(M + MeOH\ adduct)^+$.

8-Chloro-3-(prop-2-yn-1-yloxy)-1,7-naphthyridine and 8-chloro-3-(prop-2-yn-1-yloxy)-1,7-naphthyridine (261).

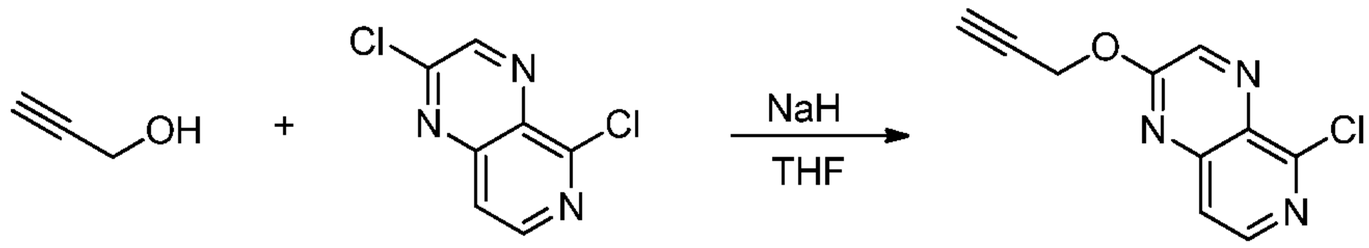


251 **261** (X = Cl & Br)

To a stirring solution of 8-chloro-3-methoxy-1,7-naphthyridine (**251**) (0.75 g, 3.85 mmol) in 1,2-dichloroethane (40 mL) at 20 °C under nitrogen was added boron tribromide (3.71 mL, 38.5 mmol) dropwise. The reaction mixture was then heated to 70 °C for 2 h. The solvents were removed under reduced pressure. The resulting solid was suspended in CH_2Cl_2 (10 mL) and collected by filtration. The solid was further washed with CH_2Cl_2 (10 mL). The solid was air dried for 30 min to afford crude 8-chloro-1,7-naphthyridin-3-ol (1.8 g, 9.97 mmol, 259% yield) as a tan solid which was used without further purification.

To a stirring suspension of the above crude 8-chloro-1,7-naphthyridin-3-ol (700 mg, 3.88 mmol) and cesium carbonate (6.31 g, 19.38 mmol) in DMF (5 mL) at 20 °C under nitrogen was added propargyl bromide (691 µL, 7.75 mmol) in one portion and stirred for 18 h. The reaction mixture was partitioned between EtOAc (25 mL) and 5% $NaHCO_3$ (50 mL). The organic layer was separated, washed with 5% $NaHCO_3$ (50 mL) and brine (20 mL). The organic solution was dried over $MgSO_4$, concentrated under reduced pressure, then purified by silica gel chromatography eluting with a gradient of 0-30% EtOAc/heptane to afford 540 mg of off-white solid, as a mixture of 8-chloro-3-(prop-2-yn-1-yloxy)-1,7-naphthyridine (MS m/z = 219.1 $[M+H]^+$) and 8-bromo-3-(prop-2-yn-1-yloxy)-1,7-naphthyridine (MS m/z = 263/265 $[M+H]^+$) in a ratio of about 3 : 2. ^1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.85 (d, *J*=2.74 Hz, 1 H), 8.29 - 8.35 (m, 1 H), 7.54 - 7.58 (m, 1 H), 7.47 - 7.52 (m, 1 H), 4.90 (d, *J*=2.54 Hz, 2 H), 2.64 (t, *J*=2.45 Hz, 1 H).

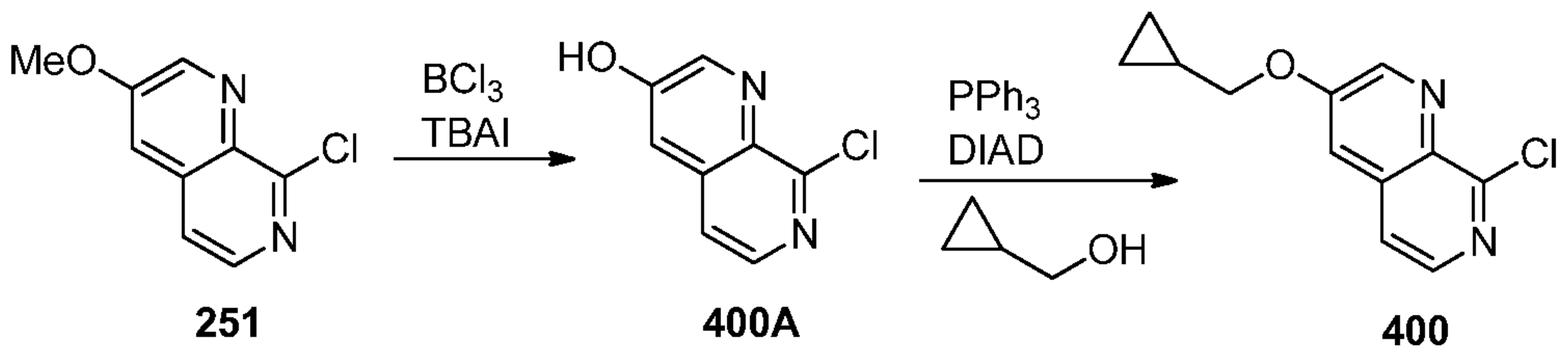
5-Chloro-2-(prop-2-yn-1-yloxy)pyrido[3,4-b]pyrazine (262).



259A **262**

A solution of 3-propynol (0.62 mL, 10.72 mmol) in THF (1 mL) was added under N_2 to a slurry of NaH (60% wt. dispersion in mineral oil) (0.43 g, 10.72 mmol) in THF (30 mL) at 0 °C. The slurry was stirred for 15 min then added to a mixture of 2,5-dichloropyrido[3,4-b]pyrazine (259A, 1.95 g, 9.75 mmol) in THF (20 mL) at 0 °C. After 20 min, the reaction was quenched with saturated NH_4Cl (20 mL) and water (20 mL). The mixture was diluted with EtOAc (200 mL) and the organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The solid (2.26 g) was suspended in heptane-DCM and filtered to afford the first batch of 5-chloro-2-(prop-2-yn-1-yloxy)pyrido[3,4-b]pyrazine as a brown powder (1.81 g). The filtrate was concentrated *in vacuo* and was purified by silica gel chromatography (40 g, 0-50% EtOAc in DCM) to afford the second batch of 5-chloro-2-(prop-2-yn-1-yloxy)pyrido[3,4-b]pyrazine as a white solid (0.32 g). LC/MS (ESI^-) *m/z* = 220, 222 $(M+H)^+$. ^1H NMR (400MHz, CHLOROFORM-d) δ = 8.66 (s, 1H), 8.50 (d, *J*=5.7 Hz, 1H), 7.67 (d, *J*=5.7 Hz, 1H), 5.18 (d, *J*=2.3 Hz, 2H), 2.58 (t, *J*=2.4 Hz, 1H).

8-Chloro-3-(cyclopropylmethoxy)-1,7-naphthyridine (400).



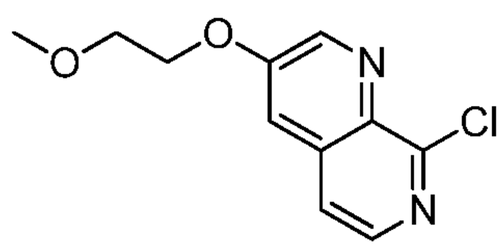
251 **400A** **400**

To a stirring solution of 8-chloro-3-methoxy-1,7-naphthyridine (**251**) (5.00 g, 25.7 mmol) and tetrabutylammonium iodide (12.3 g, 33.4 mmol) in DCM (86 mL) at RT under nitrogen was added a solution of boron trichloride (1.0 M in DCM, 128 mL, 128 mmol). The dark red solution was stirred at RT for 5 h and then cooled to 0 °C in an ice bath. The reaction was carefully quenched by dropwise addition of water until bubbling ceased with further addition of water. The ice bath was removed and the mixture was then stirred for 30 min. DCM (250 mL) and water (250 mL) were added and the mixture was carefully neutralized by portion wise addition of solid sodium bicarbonate. The layers

were then separated and the aqueous layer was extracted with DCM (3 x 150 mL). The combined organic extracts were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by silica gel chromatography eluting with a gradient of 50-100% EtOAc/heptane to give 8-chloro-1,7-naphthyridin-3-ol as a yellow solid (**400A**, 3.5 g, 75%). LC/MS (ESI^+) *m/z* = 181.1 $(M+H)^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 11.30 (s, 1H), 8.75 (d, J=2.74 Hz, 1H), 8.22 (d, J=5.48 Hz, 1H), 7.77 (d, J=5.67 Hz, 1H), 7.58 (d, J=2.74 Hz, 1H).

To a stirring suspension of 8-chloro-1,7-naphthyridin-3-ol (**400A**) (200 mg, 1.107 mmol) in THF (5 mL) under nitrogen, was added cyclopropanemethanol (0.27 mL, 3.32 mmol). The mixture was then cooled to 0 °C in an ice bath and triphenylphosphine (871 mg, 3.32 mmol) was added. The reaction mixture was stirred at 0 °C for 3 min then diisopropyl azodicarboxylate (0.65 mL, 3.32 mmol) was added dropwise by syringe over 2 min. The yellow solution was then stirred at RT for 10-120 min. The reaction was quenched with water (30 mL), and then diluted with EtOAc (25 mL). The layers were separated and the aqueous layer was extracted with EtOAc (20 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, filtered through a fritted funnel and concentrated in vacuo. The residue was purified by silica gel chromatography eluting with a gradient of 0-80% EtOAc/heptane to give 8-chloro-3-(cyclopropylmethoxy)-1,7-naphthyridine (**400**), contaminated with DIAD byproduct as a white solid (280 mg, 108%). LC/MS (ESI^+) *m/z* = 235.1 $(M+H)^+$. ^1H NMR (400 MHz, chloroform-d) δ 8.85 (d, J=2.74 Hz, 1H), 8.28 (dd, J=5.67, 6.65 Hz, 1H), 7.50 (dd, J=2.35, 5.48 Hz, 1H), 7.28 (d, J=2.74 Hz, 1H), 3.99 (d, J=7.04 Hz, 2H), 1.32 (m, 1H), 0.71-0.79 (m, 2H), 0.45 (q, J=5.02 Hz, 2H).

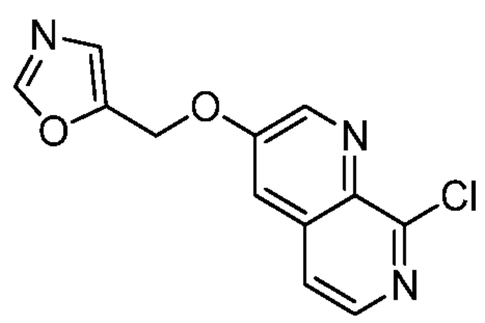
8-Chloro-3-(2-methoxyethoxy)-1,7-naphthyridine (401).



401

The title compound was synthesized according to the procedures similar to those described for intermediate **400**, using 2-methoxyethanol to react with compound **400A**. LC/MS (ESI^+) *m/z* = 239.1 $(M+H)^+$. ^1H NMR (400 MHz, chloroform-d) δ 8.88 (d, J=2.93 Hz, 1H), 8.30 (dd, J=5.67, 6.65 Hz, 1H), 7.52 (m, 1H), 7.36 (dd, J=2.93, 6.85 Hz, 1H), 4.27-4.35 (m, 2H), 3.82-3.90 (m, 2H), 3.50 (s, 3H).

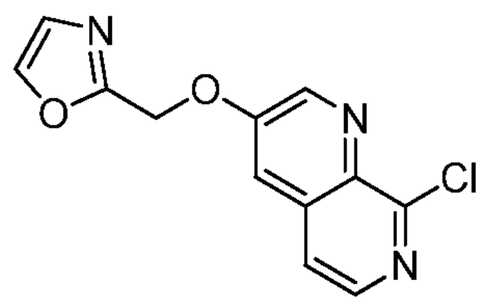
5-(((8-Chloro-1,7-naphthyridin-3-yl)oxy)methyl)oxazole (402).



402

The title compound was synthesized according to the procedures similar to those described for intermediate **400**, using 5-oxazolemethanol to react with compound **400A**. LC/MS (ESI^+) m/z = 262.0 $(M+H)^+$.

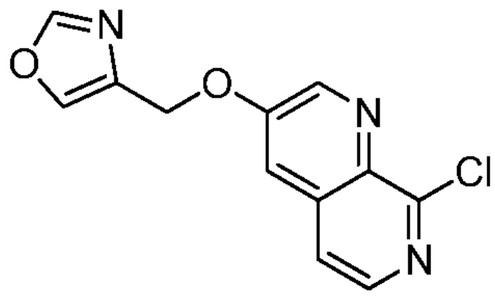
2-(((8-Chloro-1,7-naphthyridin-3-yl)oxy)methyl)oxazole (403).



403

The title compound was synthesized according to the procedures similar to those described for intermediate **400**, using 2-oxazolemethanol to react with compound **400A**. LC/MS (ESI^+) m/z = 262.1 $(M+H)^+$.

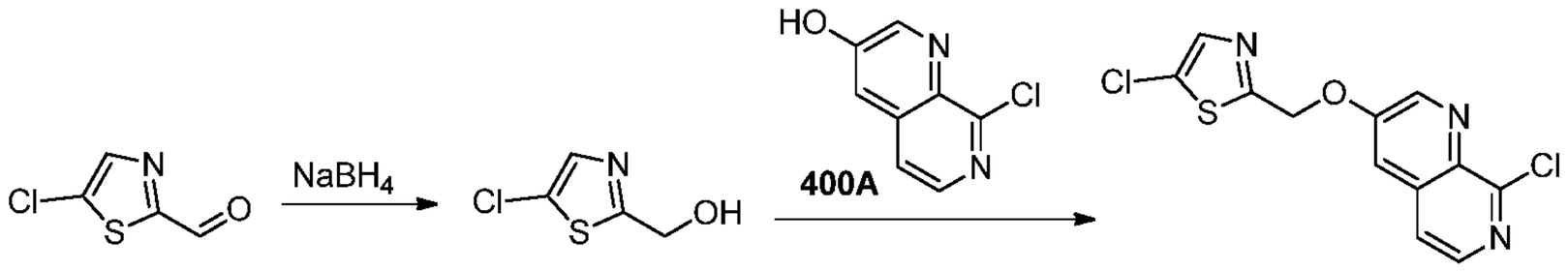
4-(((8-Chloro-1,7-naphthyridin-3-yl)oxy)methyl)oxazole (404).



404

The title compound was synthesized according to intermediate **400**, using oxazol-4-yl-methanol to react with compound **400A**. The product precipitated from the reaction mixture and was collected by filtration, washed with THF and used without further purification. LC/MS (ESI^+) m/z = 262.0 $(M+H)^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.87 (d, J=2.74 Hz, 1H), 8.46 (s, 1H), 8.30-8.38 (m, 2H), 8.07 (d, J=2.74 Hz, 1H), 7.85 (d, J=5.48 Hz, 1H), 5.29 (s, 2H).

5-Chloro-2-(((8-chloro-1,7-naphthyridin-3-yl)oxy)methyl)thiazole (405).

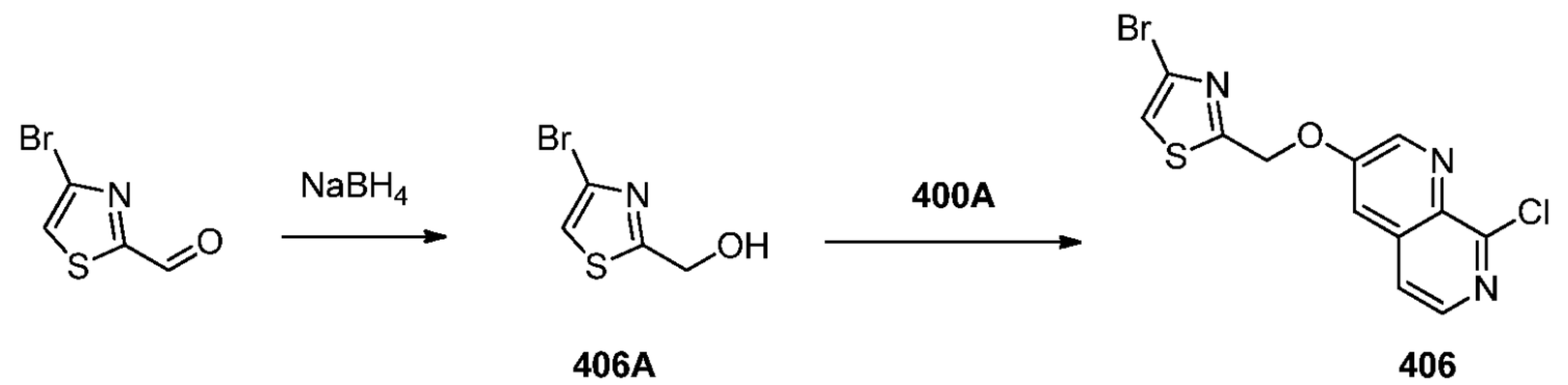


405A **405**

Sodium borohydride (0.128 g, 3.39 mmol) was added to a stirring solution of 5-chlorothiazole-2-carboxaldehyde (0.5 g, 3.39 mmol) in MeOH (6.78 mL) at RT. The mixture was stirred for 30 min at RT and then concentrated in vacuo. The residue was taken up in EtOAc (40 mL) and washed sequentially with water (30 mL) and brine (20 mL). The organic layer was then dried over Na_2SO_4, filtered and concentrated in vacuo to give (5-chlorothiazol-2-yl)methanol as a white solid that was used without further purification (**405A**, 511 mg, 101%). LC/MS (ESI^+) *m/z* = 150.1 $(M+H)^+$. ^1H NMR (400 MHz, chloroform-d) δ 7.54 (s, 1H), 4.88 (d, J=5.87 Hz, 2H), 2.57 (t, J=6.06 Hz, 1H).

The title compound was synthesized according to intermediate **400**, using (5-chlorothiazol-2-yl)methanol (**405A**) to react with Compound **400A**. LC/MS (ESI^+) *m/z* = 311.0 $(M+H)^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.94 (d, J=2.93 Hz, 1H), 8.34 (d, J=5.67 Hz, 1H), 8.08 (d, J=2.74 Hz, 1H), 7.93 (s, 1H), 7.85 (d, J=5.67 Hz, 1H), 5.66 (s, 2H).

4-Bromo-2-(((8-chloro-1,7-naphthyridin-3-yl)oxy)methyl)thiazole (406).

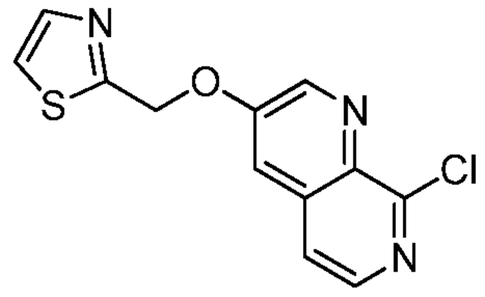


406A **406**

Sodium borohydride (99 mg, 2.60 mmol) was added to a stirring solution of 5-chlorothiazole-2-carboxaldehyde (500 mg, 2.60 mmol) in MeOH (5.2 mL) at RT. The mixture was stirred for 30 min at RT and then concentrated in vacuo. The residue was taken up in EtOAc (40 mL) and washed sequentially with water (30 mL) and brine (20 mL). The organic layer was then dried over Na_2SO_4, filtered and concentrated in vacuo to give (4-bromothiazol-2-yl)methanol as a brown oil that was used without further purification (**406A**, 499 mg, 99%). LC/MS (ESI^+) *m/z* = 194.0 $(M+H)^+$. ^1H NMR (400 MHz, chloroform-d) δ 7.23 (s, 1H), 4.97 (d, J=6.06 Hz, 2H), 2.51 (t, J=5.38 Hz, 1H).

The title compound was synthesized according to intermediate **400**, using (4-bromothiazol-2-yl)methanol (**406A**) to react with Compound **400A**. LC/MS (ESI^+) *m/z* = 358.0 $(M+H)^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.96 (d, J=2.93 Hz, 1H), 8.35 (d, J=5.48 Hz, 1H), 8.09 (d, J=2.93 Hz, 1H), 7.97 (s, 1H), 7.86 (d, J=5.67 Hz, 1H), 5.71 (s, 2H).

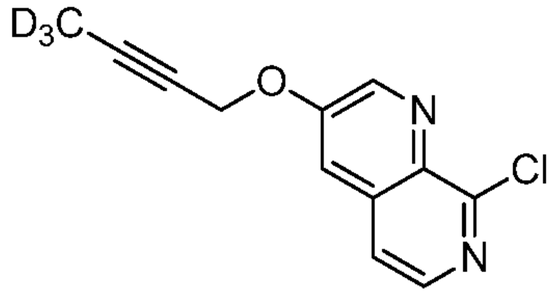
2-(((8-Chloro-1,7-naphthyridin-3-yl)oxy)methyl)thiazole (407).



407

The title compound was synthesized according to intermediate **400**, using 1,3-thiazol-2-ylmethanol to react with Compound **400A**. LC/MS (ESI^+) *m/z* = 278.1 $(M+H)^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.95 (d, J=2.93 Hz, 1H), 8.34 (d, J=5.48 Hz, 1H), 8.10 (d, J=2.93 Hz, 1H), 7.91 (d, J=3.13 Hz, 1H), 7.82-7.87 (m, 2H), 5.71 (s, 2H).

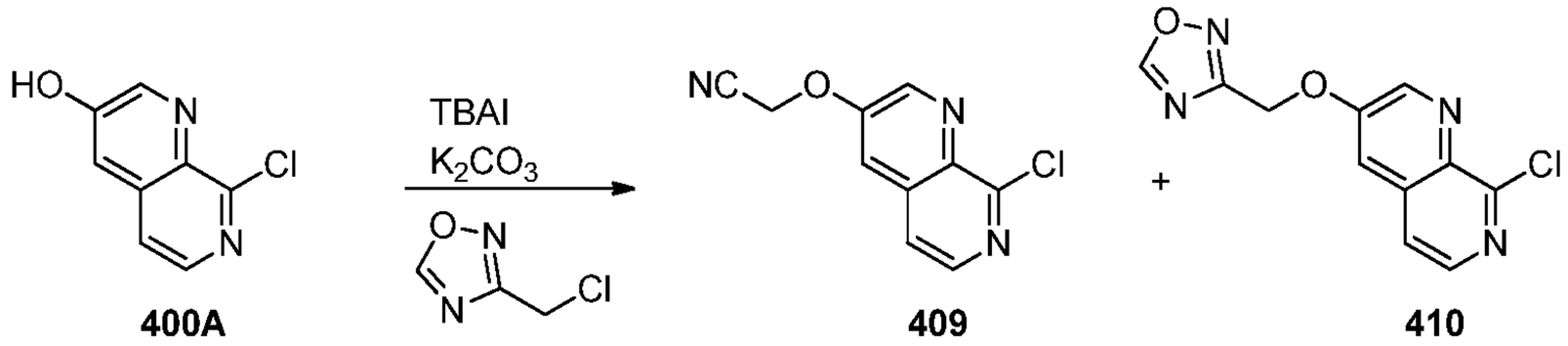
8-Chloro-3-((4,4,4-trideuterobut-2-yn-1-yl)oxy)-1,7-naphthyridine (408).



408

The title compound was synthesized according to intermediate **400**, using 4,4,4-trideuterobut-2-yn-1-ol (prepared according to the procedures reported in: *J. Org. Chem.* **2014**, *79*, 3572) to react with Compound **400A**. ^1H NMR (400 MHz, chloroform-d) δ 8.86 (d, J=2.93 Hz, 1H), 8.32 (d, J=5.48 Hz, 1H), 7.56 (d, J=5.48 Hz, 1H), 7.48 (d, J=2.74 Hz, 1H), 4.86 (s, 2H).

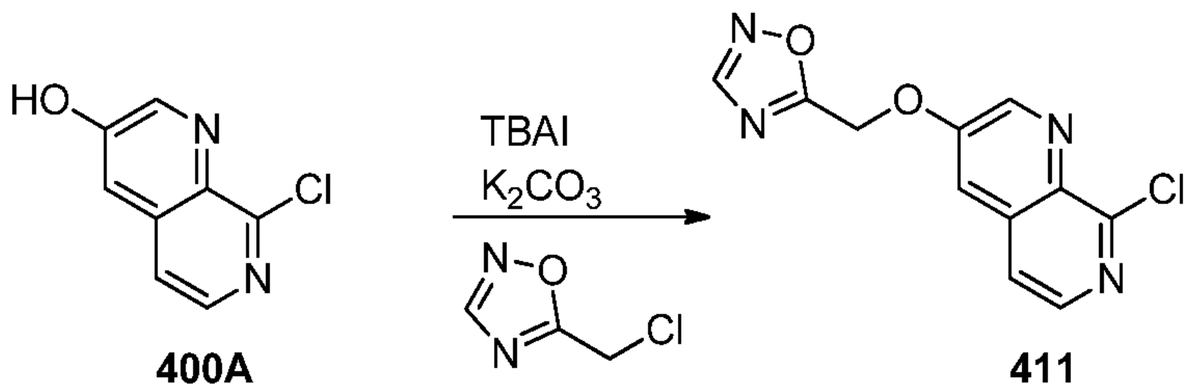
2-((8-Chloro-1,7-naphthyridin-3-yl)oxy)acetonitrile (409) and 3-(((8-chloro-1,7-naphthyridin-3-yl)oxy)methyl)-1,2,4-oxadiazole (410).



400A **409** **410**

To a stirring solution of 3-(chloromethyl)-1,2,4-oxadiazole (361 mg, 3.05 mmol) in DMF (13.8 mL) was added 8-chloro-1,7-naphthyridin-3-ol (**400A**) (500 mg, 2.77 mmol), tetrabutylammonium iodide (102 mg, 0.27 mmol) and potassium carbonate (765 mg, 5.54 mmol). The suspension was heated at 70 °C for 45 min and then cooled to RT. The mixture was diluted with EtOAc (75 mL) and water (150 mL). The layers were separated and the aqueous layer was extracted with EtOAc (75 mL). The combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by silica gel chromatography eluting with a gradient of 20-80% EtOAc/heptane to give twp products: the 1st eluent, 2-((8-chloro-1,7-naphthyridin-3-yl)oxy)acetonitrile (**409**) as a white solid (325 mg, 53%). LC/MS (ESI^+) *m/z* = 220.1 $(M+H)^+$. ^1H NMR (400 MHz, chloroform-d) δ 8.89 (d, J=2.93 Hz, 1H), 8.40 (d, J=5.48 Hz, 1H), 7.61 (d, J=5.48 Hz, 1H), 7.52 (d, J=2.93 Hz, 1H), 5.00 (s, 2H). The 2nd eluent, 3-(((8-chloro-1,7-naphthyridin-3-yl)oxy)methyl)-1,2,4-oxadiazole (**410**) as a white solid (149 mg, 20%). LC/MS (ESI^+) *m/z* = 263.0 $(M+H)^+$. ^1H NMR (400 MHz, chloroform-d) δ 8.92 (d, J=2.93 Hz, 1H), 8.84 (s, 1H), 8.34 (d, J=5.67 Hz, 1H), 7.53-7.59 (m, 2H), 5.47 (s, 2H).

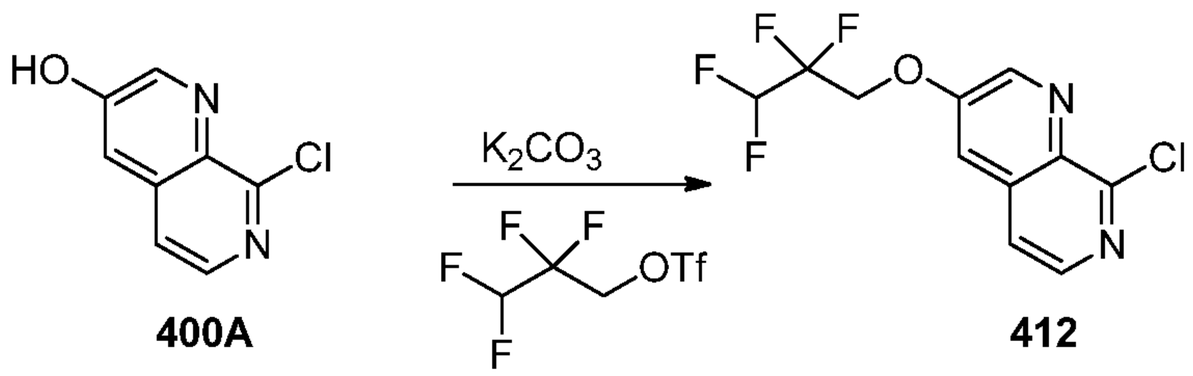
5-(((8-Chloro-1,7-naphthyridin-3-yl)oxy)methyl)-1,2,4-oxadiazole (411).



400A **411**

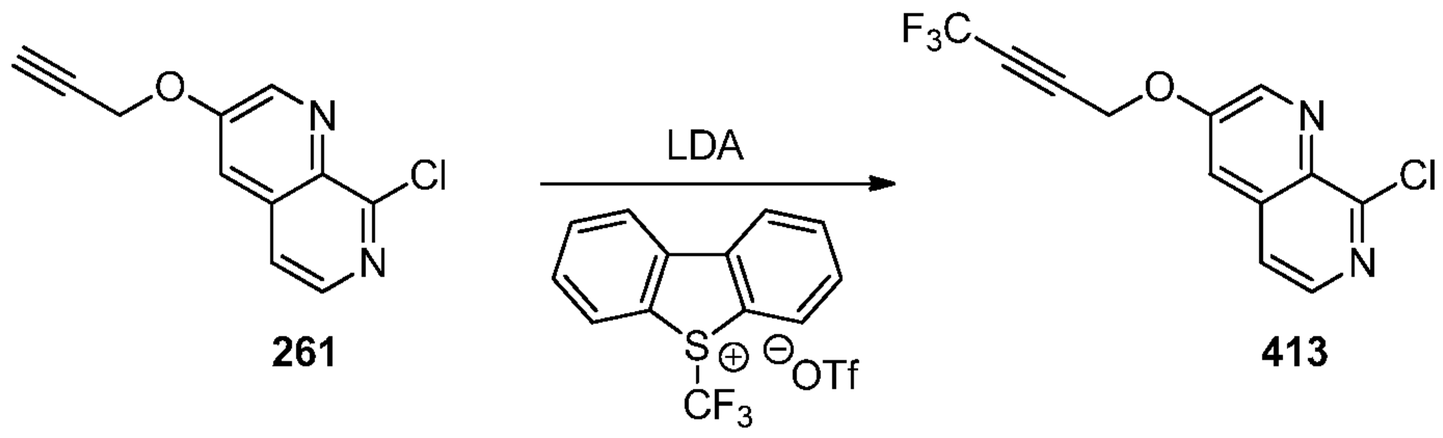
To a stirring solution of 5-(chloromethyl)-1,2,4-oxadiazole (361 mg, 3.05 mmol) in DMF (13.8 mL) was added 8-chloro-1,7-naphthyridin-3-ol (**400A**) (500 mg, 2.77 mmol), tetrabutylammonium iodide (205 mg, 0.554 mmol) and potassium carbonate (765 mg, 5.54 mmol). The suspension was heated at 70 °C for 4 h and then cooled to RT. The mixture was diluted with EtOAc (75 mL) and water (150 mL). The layers were separated and the aqueous layer was extracted with EtOAc (75 mL). The combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by silica gel chromatography eluting with a gradient of 0-20% MeOH/DCM to give 5-(((8-chloro-1,7-naphthyridin-3-yl)oxy)methyl)-1,2,4-oxadiazole (**411**) as an oil (100 mg, 14%). LC/MS (ESI^+) *m/z* = 263.2 $(M+H)^+$.

8-Chloro-3-(2,2,3,3-tetrafluoropropoxy)-1,7-naphthyridine (412).



To a stirring suspension of 2,2,3,3-tetrafluoroproyl trifluoromethanesulfonate (377 mg, 1.43 mmol) and 8-chloro-1,7-naphthyridin-3-ol (**400A**) (258 mg, 1.43 mmol) in acetone (4.5 mL) was added potassium carbonate (592 mg, 4.29 mmol). The suspension was stirred at RT for 6 h, then diluted with MTBE (25 mL) and filtered to remove the solids. The filtrate was concentrated in vacuo and the residue was purified by silica gel chromatography eluting with a gradient of 10-70% EtOAc/heptane to give 8-chloro-3-(2,2,3,3-tetrafluoropropoxy)-1,7-naphthyridine (**412**) as an off-white solid (343 mg, 81%). LC/MS (ESI^+) *m/z* = 295.1 $(M+H)^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.93 (d, J=2.93 Hz, 1H), 8.36 (d, J=5.48 Hz, 1H), 8.10 (d, J=2.93 Hz, 1H), 7.84 (d, J=5.67 Hz, 1H), 6.60-6.94 (m, 1H), 4.90 (t, J=13.50 Hz, 2H).

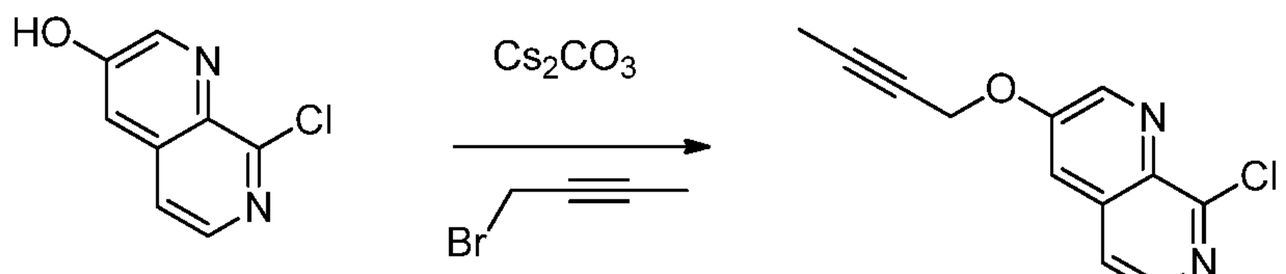
8-Chloro-3-((4,4,4-trifluorobut-2-yn-1-yl)oxy)-1,7-naphthyridine (413).



A solution of lithium diisopropylamide (2.0 M in THF/heptane/ethylbenzene) (0.73 mL, 1.47 mmol) was added dropwise to a stirring solution of 8-chloro-3-(prop-2-yn-1-yloxy)-1,7-naphthyridine (**261**) (292 mg, 1.33 mmol) in THF (13.4 mL) under nitrogen at -78 ºC. The solution was stirred at -78 ºC for 5 min and then solid S-(trifluoromethyl)dibenzothiophenium triflate (913 mg, 2.27 mmol) was added in one portion. The cold bath was removed and the mixture was allowed to warm to RT. The reaction was quenched with saturated aqueous ammonium chloride solution (20 mL) and then diluted with water (30 mL) and EtOAc (50 mL). The layers were separated and the organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography eluting with a gradient of 10-35% EtOAc/heptane to give 8-chloro-3-((4,4,4-trifluorobut-2-yn-1-yl)oxy)-1,7-naphthyridine (**413**) as a white

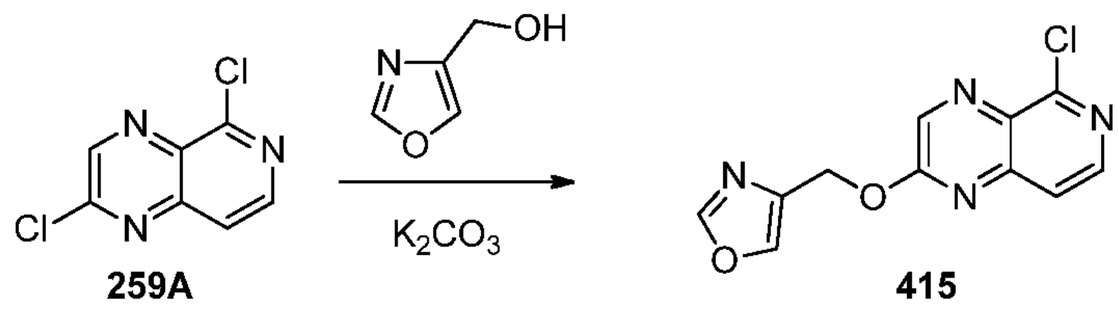
solid (88 mg, 23%). LC/MS (ESI^+) *m/z* = 287.1 $(M+H)^+$. ^1H NMR (400 MHz, chloroform-d) δ 8.88 (d, J=2.93 Hz, 1H), 8.37 (d, J=5.48 Hz, 1H), 7.59 (d, J=5.48 Hz, 1H), 7.44 (d, J=2.93 Hz, 1H), 5.02 (q, J=2.80 Hz, 2H). ^{19}F NMR (376 MHz, chloroform-d) δ -51.2.

3-(But-2-yn-1-yloxy)-8-chloro-1,7-naphthyridine (414).



A suspension of 8-chloro-1,7-naphthyridin-3-ol (0.50 g, 2.77 mmol) with cesium carbonate (4.51 g, 13.84 mmol) and 1-bromo-2-butyne (0.73 g, 5.54 mmol) was stirred at RT for 15 min then placed in a 40 ºC sand bath for 18 h. The reaction mixture was partitioned between EtOAc (25 mL) and 0.5 M K_2HPO_4 (50 mL). The organic layer was further washed with 0.5 M K_2HPO_4 (50 mL) and brine (20 mL). The organic layer was dried over $MgSO_4$, concentrated under reduced pressure, then purified by silica gel chromatography (40 g) eluting products with a gradient of 10-25% EtOAc/heptane to afford 3-(but-2-yn-1-yloxy)-8-chloro-1,7-naphthyridine (**414**) (370 mg) as a white solid: m/z (APCI, pos. ion) 233.0. This material contained a small amount of 8-bromo-3-(but-2-yn-1-yloxy)-1,7-naphthyridine: m/z (APCI, pos. ion) 277.

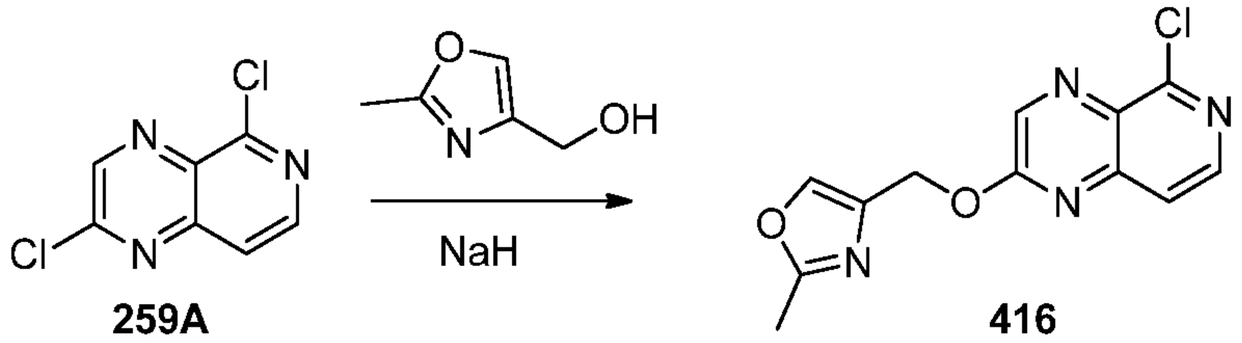
4-(((5-Chloropyrido[3,4-b]pyrazin-2-yl)oxy)methyl)oxazole (415).



A mixture of 2,5-dichloropyrido[3,4-b]pyrazine (1.07 g, 5.35 mmol), oxazol-4-yl-methanol (0.42 mL, 5.35 mmol), and potassium carbonate (1.48 g, 10.70 mmol) in DMF (18 mL) was heated at 50 °C for 5 h. The reaction mixture was diluted with water and extracted with EtOAc. The organic extract was washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product (1.2 g) was adsorbed onto a plug of silica gel and chromatographed through a Biotage SNAP Ultra silica gel column (50 g), eluting with isocratic 18% EtOH/EtOAc (25:75) in hexanes, to the title compound (0.74 g, 2.82 mmol, 53% yield). ^1H NMR (300 MHz, DMSO-d_6) δ ppm 5.51 (s, 2 H) 7.84 (d,

J=5.70 Hz, 1 H) 8.34 (d, *J*=0.73 Hz, 1 H) 8.45 (s, 1 H) 8.54 (d, *J*=5.70 Hz, 1 H) 8.80 (s, 1 H). LC/MS (ESI^+) m/z = 263.0 $[M+H]^+$.

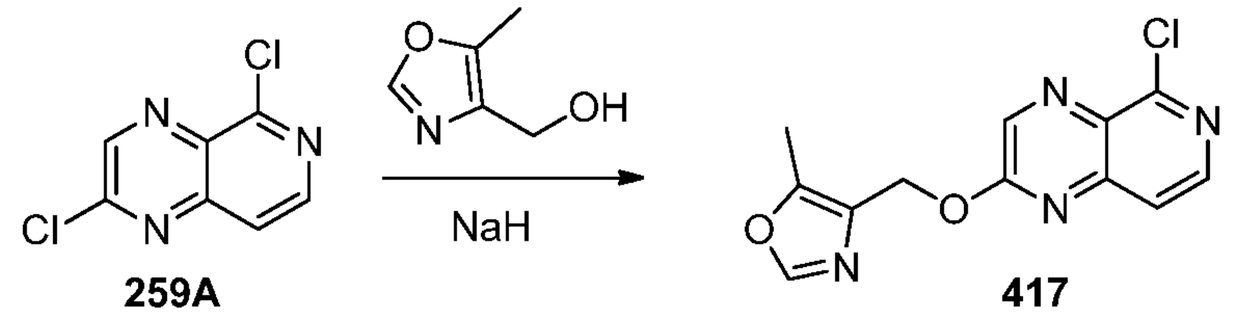
4-(((5-Chloropyrido[3,4-b]pyrazin-2-yl)oxy)methyl)-2-methyloxazole (416).



259A **416**

The title compound (0.94 g, 3.81 mmol, 73% yield) as a tan solid was prepared according to the procedures described for intermediate **259** using 2,5-dichloropyrido[3,4-b]pyrazine (**259A**, 0.99 g, 4.98 mmol) and (2-methyloxazol-4-yl)methanol (0.56 g, 4.98 mmol). ^1H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 2.50 (s, 3 H) 5.48 (s, 2 H) 7.66 (d, *J*=5.70 Hz, 1 H) 7.70 (s, 1 H) 8.50 (d, *J*=5.70 Hz, 1 H) 8.64 (s, 1 H). LC/MS (ESI^+) *m/z* = 277.0 $(M+H)^+$.

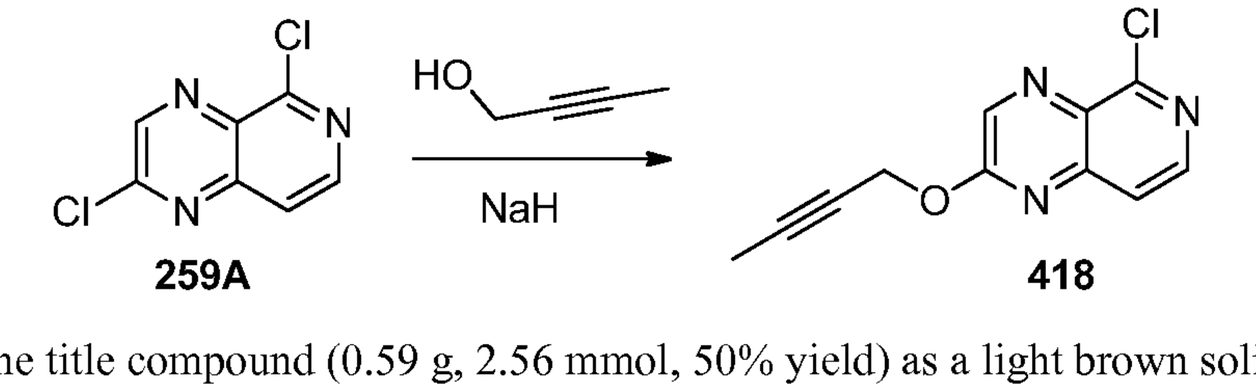
4-(((5-chloropyrido[3,4-b]pyrazin-2-yl)oxy)methyl)-5-methyloxazole (417).



259A **417**

The title compound (0.16 g, 0.58 mmol, 22% yield) as an off-white solid was prepared according to the procedures described for intermediate **259** using 2,5-dichloropyrido[3,4-b]pyrazine (**259A**, 0.51 g, 2.56 mmol) and (5-methyloxazol-4-yl)methanol (0.29 g, 2.56 mmol). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 2.47 (s, 3 H) 5.45 (s, 2 H) 7.81 (d, *J*=5.67 Hz, 1 H) 8.26 (s, 1 H) 8.53 (d, *J*=5.67 Hz, 1 H) 8.79 (s, 1 H). LC/MS (ESI^+) *m/z* = 277.1 $(M+H)^+$.

2-(But-2-yn-1-yloxy)-5-chloropyrido[3,4-b]pyrazine (418).

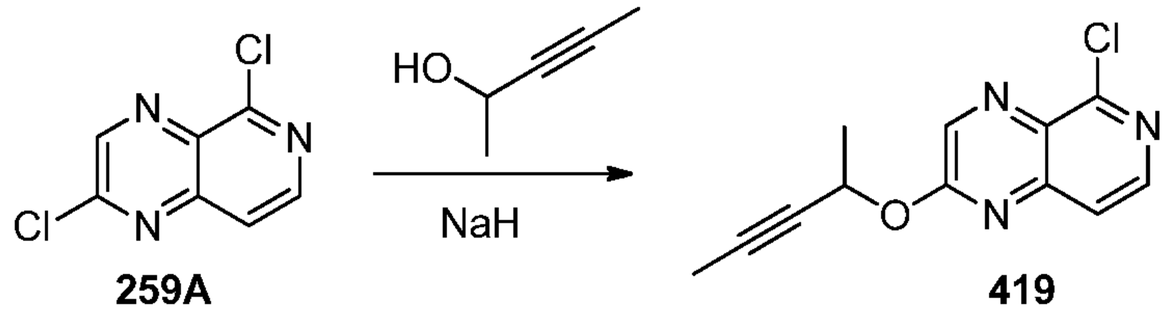


259A **418**

The title compound (0.59 g, 2.56 mmol, 50% yield) as a light brown solid was prepared according to the procedures described for intermediate **259** using 2,5-dichloropyrido[3,4-b]pyrazine (**259A**, 1.02 g, 5.11 mmol) and 3-pentyn-2-ol (0.48 mL,

5.11 mmol). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.88 (t, *J*=2.34 Hz, 3 H) 5.19 (q, *J*=2.34 Hz, 2 H) 7.81 (d, *J*=5.70 Hz, 1 H) 8.53 (d, *J*=5.55 Hz, 1 H) 8.82 (s, 1 H). LC/MS (ESI$^+$) *m/z* = 234.2 $(M+H)^+$.

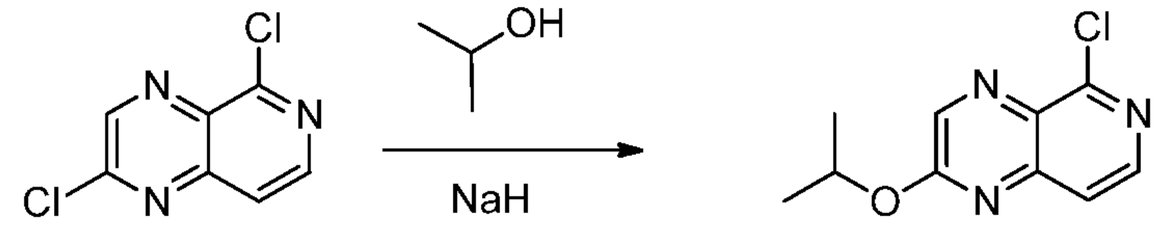
5-Chloro-2-(pent-3-yn-2-yloxy)pyrido[3,4-b]pyrazine (419).



259A **419**

The title compound (0.64 g, 2.61 mmol, 51% yield) as a solid was prepared according to the procedures described for intermediate **259** using 2,5-dichloropyrido[3,4-b]pyrazine (**259A**, 1.03 g, 5.15 mmol) and 2-butyn-1-ol (0.38 mL, 5.15 mmol). ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.70 (d, *J*=6.65 Hz, 3 H) 1.86 (d, *J*=2.15 Hz, 3 H) 5.98 (m, 1 H) 7.67 (d, *J*=5.67 Hz, 1 H) 8.49 (d, *J*=5.67 Hz, 1 H) 8.60 (s, 1 H). LC/MS (ESI$^+$) *m/z* = 247.9 $(M+H)^+$.

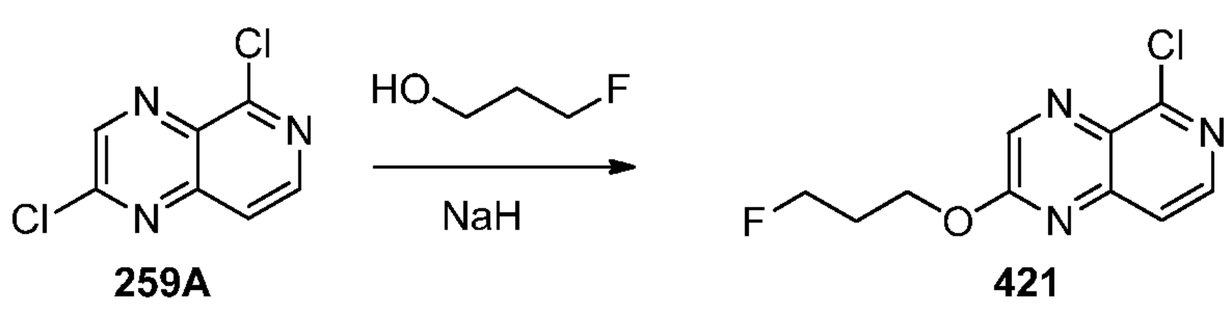
5-Chloro-2-isopropoxypyrido[3,4-b]pyrazine (420).



259A **420**

The title compound (0.56 g, 2.53 mmol, 100% yield) as a tan solid was prepared according to the procedures described for intermediate **259** using 2,5-dichloropyrido[3,4-b]pyrazine (**259A**, 0.50 g, 2.53 mmol) and isopropanol (0.19 mL, 2.53 mmol). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.47 (d, *J*=6.14 Hz, 6 H) 5.56 (dt, *J*=12.39, 6.16 Hz, 1 H) 7.61 (d, *J*=5.70 Hz, 1 H) 8.46 (d, *J*=5.70 Hz, 1 H) 8.53 (s, 1 H). LC/MS (ESI$^+$) *m/z* = 224.0 $(M+H)^+$.

5-Chloro-2-(3-fluoropropoxy)pyrido[3,4-b]pyrazine (421).

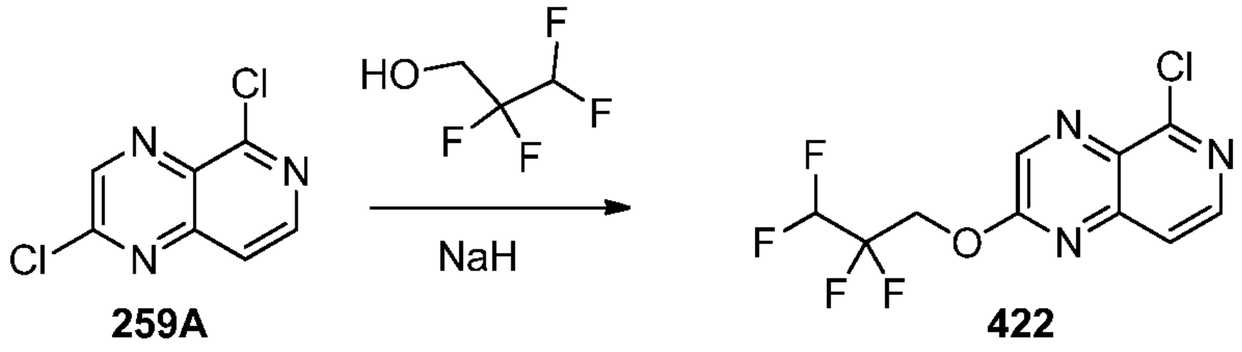


259A **421**

The title compound (0.40 g, 1.69 mmol, 66% yield) as a white solid was prepared according to the procedures described for intermediate **259** using 2,5-dichloropyrido[3,4-b]pyrazine (**259A**, 0.51 g, 2.54 mmol) and 3-fluoropropan-1-ol (0.19 mL, 2.54 mmol). ^{1}H

NMR (300 MHz, CHLOROFORM-*d*) δ ppm 2.18 - 2.41 (m, 2 H) 4.56 - 4.83 (m, 4 H) 7.64 (d, *J*=5.70 Hz, 1 H) 8.49 (d, *J*=5.70 Hz, 1 H) 8.61 (s, 1 H). LC/MS (ESI^+) *m/z* = 242.0 $(M+H)^+$.

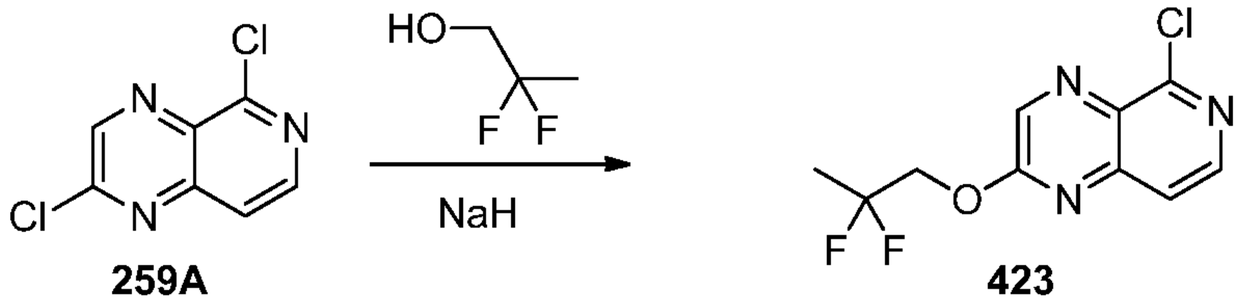
5-Chloro-2-(2,2,3,3-tetrafluoropropoxy)pyrido[3,4-b]pyrazine (422).



259A **422**

The title compound (0.63 g, 2.2 mmol, 85% yield) as a white solid was prepared according to the procedures described for intermediate **259** using 2,5-dichloropyrido[3,4-b]pyrazine (**259A**, 0.50 g, 2.53 mmol) and 1H,1H,3H-tetrafluoro-1-propanol (0.20 mL, 2.53 mmol). ^1H NMR (300 MHz, DMSO-d_6) δ ppm 5.11 (t, *J*=14.10 Hz, 2 H) 6.52 - 6.99 (m, 1 H) 7.83 (d, *J*=5.70 Hz, 1 H) 8.57 (d, *J*=5.70 Hz, 1 H) 8.92 (s, 1 H). LC/MS (ESI^+) *m/z* = 295.9 $(M+H)^+$.

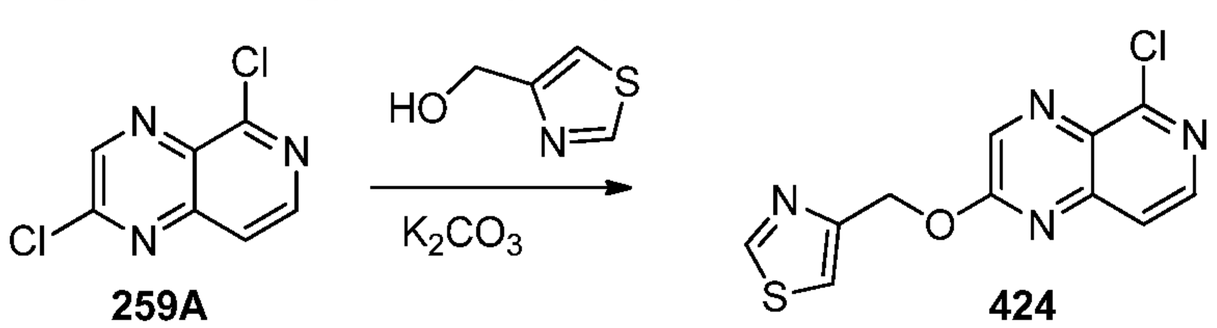
5-Chloro-2-(2,2-difluoropropoxy)pyrido[3,4-b]pyrazine (423).



259A **423**

The title compound (0.34 g, 1.33 mmol, 52% yield) as a white solid was prepared according to the procedures described for intermediate **259** using 2,5-dichloropyrido[3,4-b]pyrazine (**259A**, 0.51 g, 2.56 mmol) and 2,2-difluoro-propan-1-ol (0.20 mL, 2.56 mmol). ^1H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.83 (t, *J*=18.64 Hz, 3 H) 4.72 (t, *J*=11.84 Hz, 2 H) 7.65 (d, *J*=5.70 Hz, 1 H) 8.52 (d, *J*=5.55 Hz, 1 H) 8.71 (s, 1 H). LC/MS (ESI^+) *m/z* = 260.0 $(M+H)^+$.

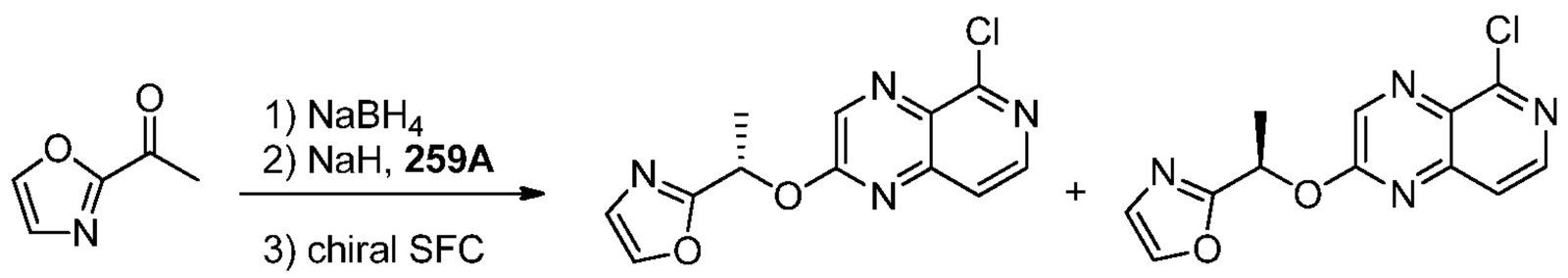
4-(((5-Chloropyrido[3,4-b]pyrazin-2-yl)oxy)methyl)thiazole (424).



259A **424**

The title compound (0.22 g, 0.78 mmol, 39% yield) as a tan solid was prepared according to the procedures described for intermediate **415** using 2,5-dichloropyrido[3,4-b]pyrazine (**259A**, 0.40 g, 2.00 mmol) and thiazole-4-methanol (0.23 g, 2.00 mmol). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 5.78 (s, 2 H) 7.55 (d, *J*=2.05 Hz, 1 H) 7.68 (d, *J*=5.70 Hz, 1 H) 8.51 (d, *J*=5.70 Hz, 1 H) 8.68 (s, 1 H) 8.91 (d, *J*=2.05 Hz, 1 H). LC/MS (ESI$^+$) *m/z* = 278.9 (M+H)$^+$.

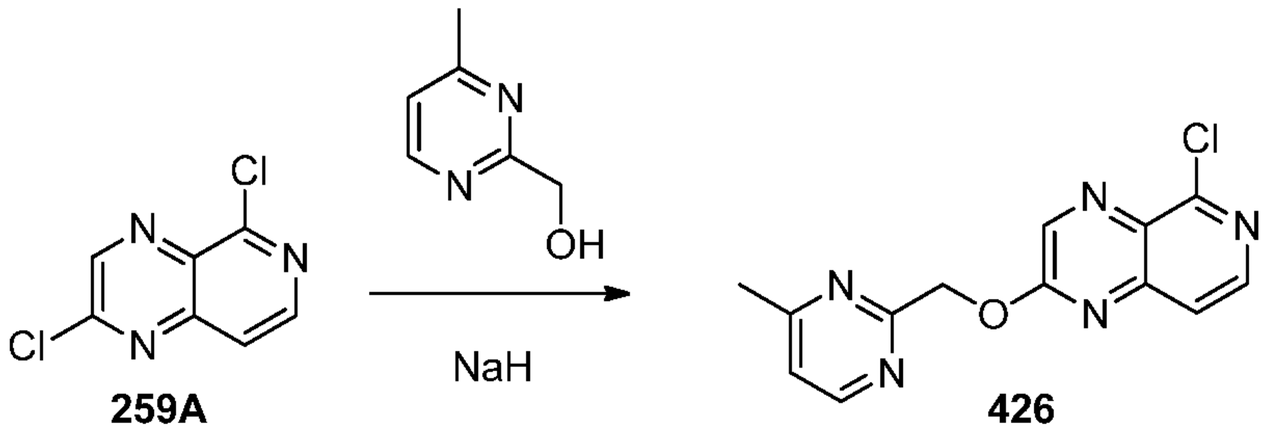
(*S*)-2-(1-((5-Chloropyrido[3,4-b]pyrazin-2-yl)oxy)ethyl)oxazole (425A) and (*R*)-2-(1-((5-chloropyrido[3,4-b]pyrazin-2-yl)oxy)ethyl)oxazole (425B).



At 0 °C, a solution of 1-(oxazol-2-yl)ethanone (1.0 g, 9.00 mmol, J&W Pharmlab) in MeOH (40 mL) was treated with sodium borohydride (0.39 g, 10.31 mmol) in 2 portions. After 15 min the reaction was allowed to warm to RT for 2 h. The reaction was quenched with water (5 mL). The mixture was partitioned between brine/DCM and the aqueous layer was extracted with DCM (2 x). The combined organic layers were washed brine, dried over Na_2SO_4 and concentrated under reduced pressure to give 920 mg (90%) of a light-yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.62 (d, *J*=0.88 Hz, 1 H), 7.07 (s, 1 H), 4.97 (q, *J*=6.58 Hz, 1 H), 1.62 (d, *J*=6.72 Hz, 3 H). LC/MS (ESI$^+$) m/z = 114.1 (M+H)$^+$.

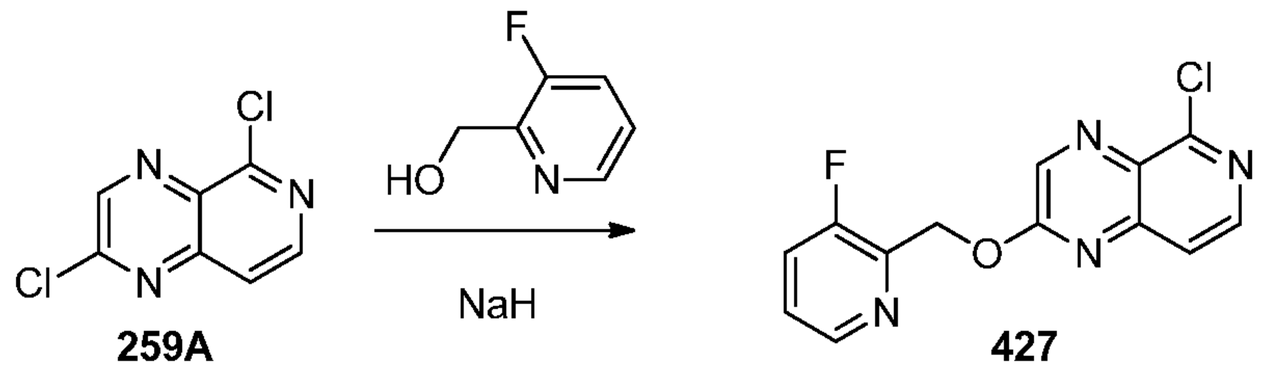
2-(1-((5-Chloropyrido[3,4-b]pyrazin-2-yl)oxy)ethyl)oxazole (6.00 g, 21.7 mmol, 88% yield) as a solid was prepared according to the procedures described for intermediate **259** using 2,5-dichloropyrido[3,4-b]pyrazine (**259A**, 4.91 g, 24.57 mmol) and 1-(oxazol-2-yl)ethanol (2.7794 g, 24.57 mmol). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.90 (d, *J*=6.72 Hz, 3 H) 6.58 (q, *J*=6.72 Hz, 1 H) 7.14 (s, 1 H) 7.63 (d, *J*=5.70 Hz, 1 H) 7.67 (d, *J*=0.73 Hz, 1 H) 8.49 (d, *J*=5.55 Hz, 1 H) 8.67 (s, 1 H). LC/MS (ESI$^+$) *m/z* = 277.1 (M+H)$^+$. The racemic mixture was chromatographed using supercritical CO_2 (Organic modifier, 40% MeOH) on a Chiracel AZ-H column (150 x 21 mm, 5 μm) eluting at a flow rate of 60 mL/min (220 bar pressure, 40 °C column temperature). **The stereochemistry was arbitrarily assigned**. (*S*)-2-(1-((5-Chloropyrido[3,4-b]pyrazin-2-yl)oxy)ethyl)oxazole (**425A**, the first eluent, 2.97 g) and (*R*)-2-(1-((5-chloropyrido[3,4-b]pyrazin-2-yl)oxy)ethyl)oxazole (**425B**, the second eluent, 3.02 g) were obtained.

5-Chloro-2-((4-methylpyrimidin-2-yl)methoxy)pyrido[3,4-b]pyrazine (426).



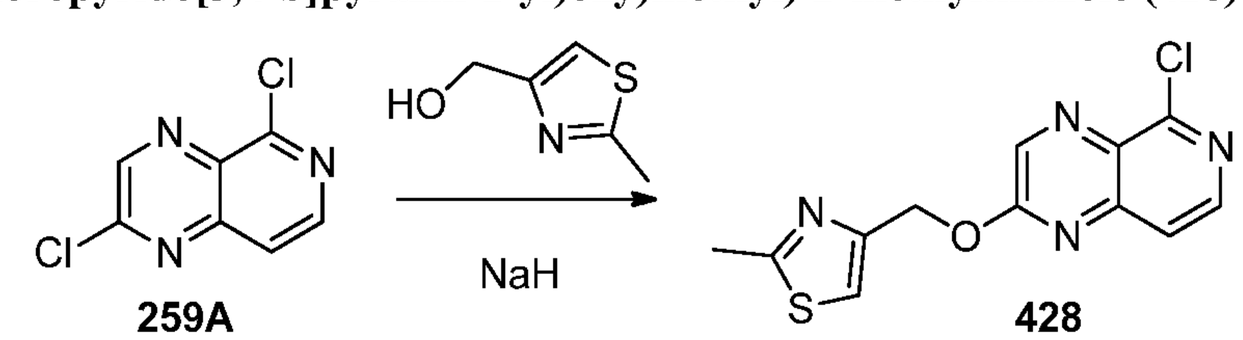
The title compound (0.45 g, 1.58 mmol, 56% yield) as a light yellow solid was prepared according to the procedures described for intermediate **259** using 2,5-dichloropyrido[3,4-b]pyrazine (**259A**, 0.56 g, 2.79 mmol) and 2-hydroxymethyl-4-methylpyrimidine (0.28 mL, 2.79 mmol). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.46 (s, 3 H) 5.73 (s, 2 H) 7.33 (d, *J*=5.28 Hz, 1 H) 7.69 (d, *J*=5.67 Hz, 1 H) 8.48 (d, *J*=5.67 Hz, 1 H) 8.62 (d, *J*=5.09 Hz, 1 H) 8.94 (s, 1 H). LC/MS (ESI$^+$) *m/z* = 287.9 (M+H)$^+$.

5-Chloro-2-((3-fluoropyridin-2-yl)methoxy)pyrido[3,4-b]pyrazine (427).



The title compound (0.74 g, 2.56 mmol, 101% yield) as a light yellow solid was prepared according to the procedures described for intermediate **259** using 2,5-dichloropyrido[3,4-b]pyrazine (**259A**, 0.51 g, 2.54 mmol) and (3-fluoropyridin-2-yl)methanol (0.25 mL, 2.54 mmol). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 5.74 (d, *J*=1.90 Hz, 2 H) 7.55 (dt, *J*=8.59, 4.40 Hz, 1 H) 7.74 - 7.90 (m, 2 H) 8.46 (dt, *J*=4.60, 1.42 Hz, 1 H) 8.52 (d, *J*=5.70 Hz, 1 H) 8.86 (s, 1 H). LC/MS (ESI$^+$) *m/z* = 290.9 (M+H)$^+$.

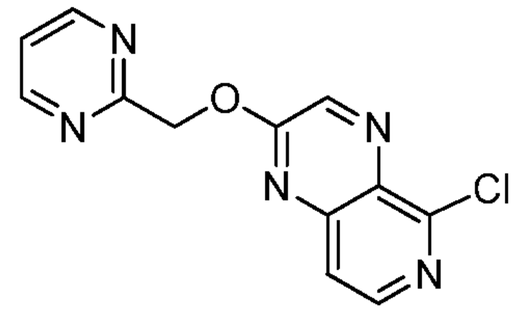
4-(((5-chloropyrido[3,4-b]pyrazin-2-yl)oxy)methyl)-2-methylthiazole (428)



The title compound (0.72 g, 2.48 mmol, 100% yield) as a tan solid was prepared according to the procedures described for intermediate **259** using 2,5-dichloropyrido[3,4-b]pyrazine (**259A**, 0.50 g, 2.49 mmol) and (2-methyl-1,3-thiazol-4-yl)methanol (0.32 g,

2.49 mmol). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 5.59 (s, 2 H) 7.71 (s, 1 H) 7.83 (d, *J*=5.70 Hz, 1 H) 8.53 (d, *J*=5.70 Hz, 1 H). LC/MS (ESI$^+$) *m/z* = 293.0 (M+H)$^+$.

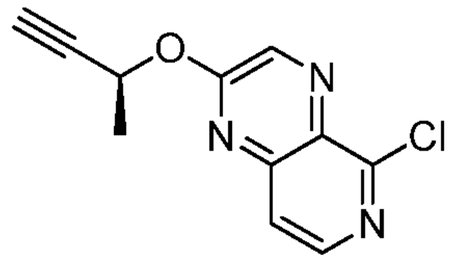
5-Chloro-2-(pyrimidin-2-ylmethoxy)pyrido[3,4-b]pyrazine (429).



429

The title compound (1.11 g, 4.06 mmol, 77% yield) as a tan crystalline solid was prepared according to the procedure described for intermediate **259** using 2,5-dichloropyrido[3,4-b]pyrazine (**259A**, 1.06 g, 5.30 mmol) and pyrimidin-2-ylmethanol (0.59 g, 5.35 mmol, Synthonix). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.81 (s, 1 H), 8.76 (d, *J*=4.89 Hz, 2 H), 8.45 (d, *J*=5.67 Hz, 1 H), 7.56 (d, *J*=5.67 Hz, 1 H), 7.27 - 7.31 (m, 1 H), 5.82 (s, 2 H). LC/MS (ESI$^+$) m/z = 274.1 (M+H)$^+$.

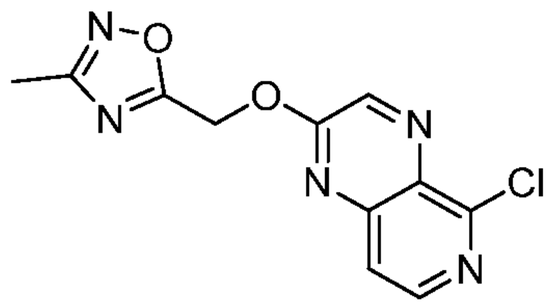
(*S*)-2-(But-3-yn-2-yloxy)-5-chloropyrido[3,4-b]pyrazine (430).



430

The title compound (0.87 g, 3.72 mmol, 62% yield) as a tan crystalline solid was prepared according to the procedure described for intermediate **259** using 2,5-dichloropyrido[3,4-b]pyrazine (**259A**, 1.2 g, 6.0 mmol) and (S)-(-)-3-butyn-2-ol (0.50 mL, 0.443 g, 6.31 mmol, Sigma-Aldrich). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.61 (s, 1 H), 8.49 (d, *J*=5.70 Hz, 1 H), 7.66 (d, *J*=5.70 Hz, 1 H), 5.98 (qd, *J*=6.67, 2.05 Hz, 1 H), 2.51 (d, *J*=2.05 Hz, 1 H), 1.75 (d, *J*=6.72 Hz, 3 H). LC/MS (ESI$^+$) m/z = 234.1 (M+H)$^+$.

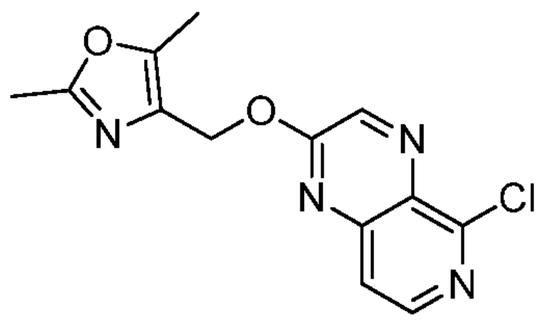
5-(((5-Chloropyrido[3,4-b]pyrazin-2-yl)oxy)methyl)-3-methyl-1,2,4-oxadiazole (431).



431

The title compound (0.95 g, 3.41 mmol, 68% yield) as a tan amorphous solid was prepared according to the procedure described for intermediate **259** using 2,5-dichloropyrido[3,4-b]pyrazine (**259A**, 1.0 g, 5.0 mmol) and (3-methyl-1,2,4-oxadiazol-5-yl)methanol (0.618 g, 5.42 mmol, Enamine). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.77 (s, 1 H) 8.52 (d, *J*=5.55 Hz, 1 H) 7.64 (d, *J*=5.70 Hz, 1 H) 5.78 (s, 2 H) 2.44 (s, 3 H). LC/MS (ESI^+) m/z = 278.0 $(M+H)^+$.

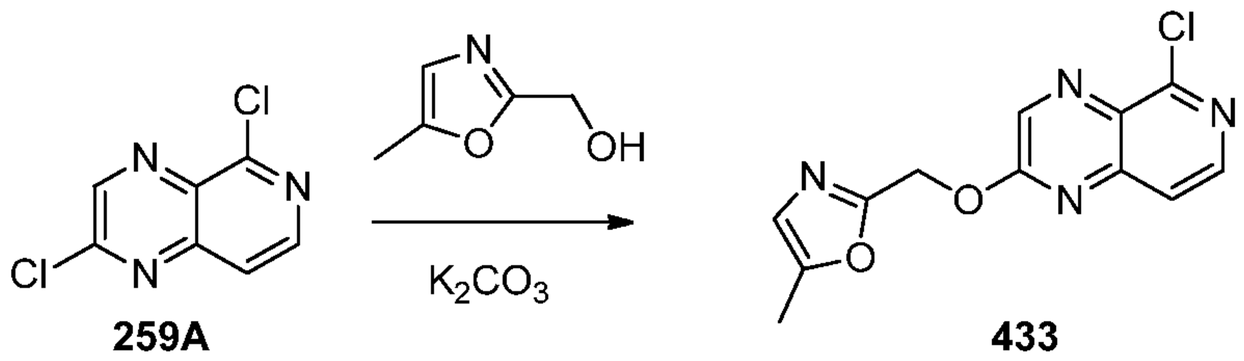
4-(((5-Chloropyrido[3,4-b]pyrazin-2-yl)oxy)methyl)-2,5-dimethyloxazole (432).



432

The title compound (0.631 g, 2.17 mmol, 83% yield) as a white crystalline solid was prepared according to the procedure described for intermediate **259** using 2,5-dichloropyrido[3,4-b]pyrazine (**259A**, 0.520 g, 2.60 mmol) and (2,5-dimethyloxazol-4-yl)methanol (0.380 g, 2.99 mmol, Frontier Scientific). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.63 (s, 1 H), 8.49 (d, *J*=5.70 Hz, 1 H), 7.64 (d, *J*=5.70 Hz, 1 H), 5.41 (s, 2 H), 2.44 (s, 3 H), 2.43 (s, 3 H). LC/MS (ESI^+) m/z = 291.0 $(M+H)^+$.

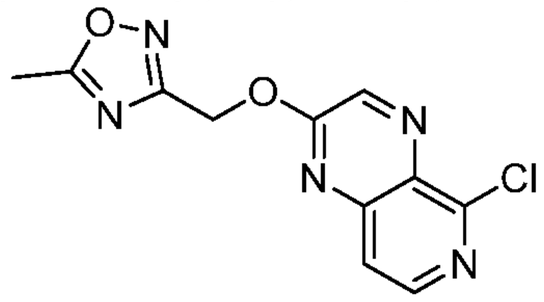
2-(((5-Chloropyrido[3,4-b]pyrazin-2-yl)oxy)methyl)-5-methyloxazole (433).



259A **433**

The title compound (0.87 g, 3.17 mmol, 80% yield) as a tan solid was prepared according to the procedures described for intermediate **415** using 2,5-dichloropyrido[3,4-b]pyrazine (**259A**, 0.79 g, 3.96 mmol) and (5-methyloxazol-2-yl)methanol (0.36 mL, 3.96 mmol). ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 2.37 (d, *J*=1.02 Hz, 4 H) 5.61 (s, 2 H) 6.81 (d, *J*=1.17 Hz, 1 H) 7.68 (d, *J*=5.70 Hz, 1 H) 8.52 (d, *J*=5.70 Hz, 1 H) 8.69 (s, 1 H) LC/MS (ESI^+) *m/z* = 2778.0 $(M+H)^+$.

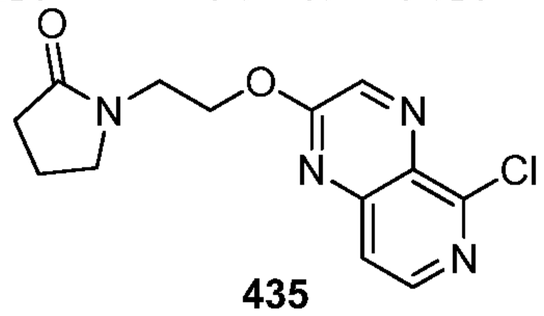
3-(((5-Chloropyrido[3,4-b]pyrazin-2-yl)oxy)methyl)-5-methyl-1,2,4-oxadiazole (434).



434

The title compound (1.349 g, 4.86 mmol, 88% yield) as a white crystalline solid was prepared according to the procedure described for intermediate **259** using 2,5-dichloropyrido[3,4-b]pyrazine (**259A**, 1.10, 5.50 mmol) and (5-methyl-1,2,4-oxadiazol-3-yl-methanol (0.656 g, 5.75 mmol, Enamine). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.72 (s, 1 H), 8.51 (d, *J*=5.70 Hz, 1 H), 7.66 (d, *J*=5.70 Hz, 1 H), 5.69 (s, 2 H), 2.65 (s, 3 H). LC/MS (ESI^+) m/z = 278.1 $(M+H)^+$.

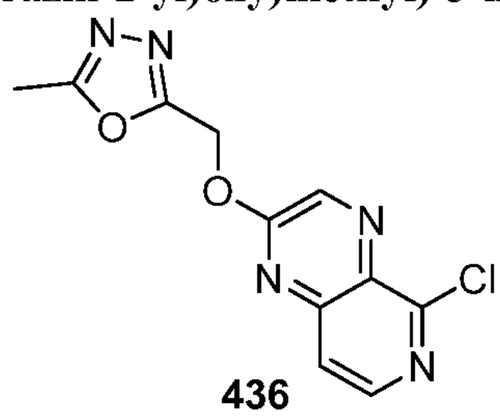
1-(2-((5-Chloropyrido[3,4-b]pyrazin-2-yl)oxy)ethyl)pyrrolidin-2-one (435).



435

The title compound (0.822 g, 2.81 mmol, 75% yield) as a light-yellow crystalline solid was prepared according to the procedure described for intermediate **259** using 2,5-dichloropyrido[3,4-b]pyrazine (**259A**, 0.750 g, 3.75 mmol) and 1-(2-hydroxyethyl)-2-pyrrolidinone (0.450 mL, 3.98 mmol, Sigma-Aldrich). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.59 (s, 1 H), 8.49 (d, *J*=5.55 Hz, 1 H), 7.62 (d, *J*=5.70 Hz, 1 H), 4.69 (t, *J*=5.41 Hz, 2 H), 3.79 (t, *J*=5.41 Hz, 2 H), 3.57 (t, *J*=7.02 Hz, 2 H), 2.34 - 2.47 (m, 2 H), 1.98 - 2.17 (m, 2 H). LC/MS (ESI^+) m/z = 293.0 $(M+H)^+$.

2-(((5-Chloropyrido[3,4-b]pyrazin-2-yl)oxy)methyl)-5-methyl-1,3,4-oxadiazole (436).

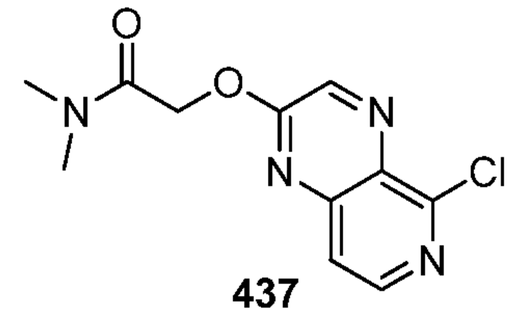


436

The title compound (0.860 g, 3.10 mmol, 68% yield) as a white crystalline solid was prepared according to the procedure described for intermediate **259** using 2,5-dichloropyrido[3,4-b]pyrazine (**259A**, 0.910 g, 4.55 mmol) and (5-methyl-1,3,4-oxadiazol-2-yl)methanol (0.597 g, 5.23 mmol, ChemBridge). ^{1}H NMR (300 MHz,

$CDCl_3$) δ ppm 8.71 (s, 1 H) 8.54 (d, *J*=5.70 Hz, 1 H) 7.69 (d, *J*=5.70 Hz, 1 H) 5.77 (s, 2 H) 2.60 (s, 3 H)LC/MS (ESI^+) m/z = 278.1 $(M+H)^+$.

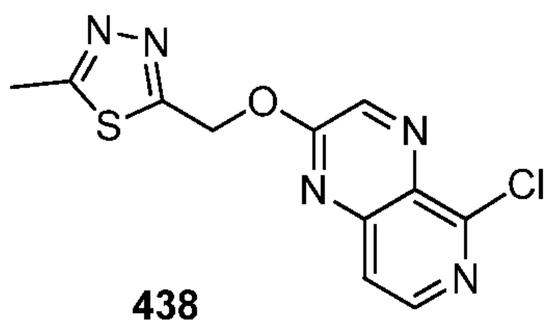
2-((5-Chloropyrido[3,4-b]pyrazin-2-yl)oxy)-N,N-dimethylacetamide (437).



437

The title compound (0.555 g, 2.08 mmol, 59% yield) as a light-orange crystalline solid was prepared according to the procedure described for intermediate **259** using 2,5-dichloropyrido[3,4-b]pyrazine (**259A**, 0.706 g, 3.53 mmol) and 2-hydroxy-N,N-dimethylacetamide (0.372 g, 3.61 mmol, Enamine). LC/MS (ESI^+) m/z = 267.0 $(M+H)^+$.

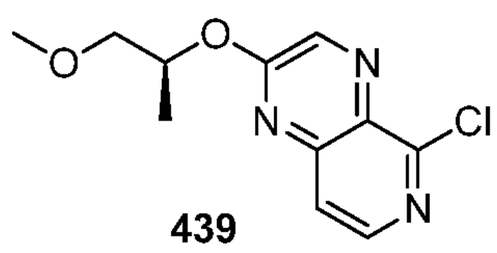
2-(((5-Chloropyrido[3,4-b]pyrazin-2-yl)oxy)methyl)-5-methyl-1,3,4-thiadiazole (438).



438

The title compound (0.191 g, 0.650 mmol, 34% yield) as a tan crystalline solid was prepared according to the procedure described for intermediate **259** using 2,5-dichloropyrido[3,4-b]pyrazine (**259A**, 0.380 g, 1.90 mmol) and (5-methyl-1,3,4-thiadiazol-2-yl)methanol (0.261 g, 2.00 mmol, Enamine). ^1H NMR (300 MHz, $CDCl_3$) δ ppm 8.68 (s, 1 H) 8.54 (d, *J*=5.70 Hz, 1 H) 7.70 (d, *J*=5.70 Hz, 1 H) 5.96 (s, 2 H) 2.81 (s, 3 H). LC/MS (ESI^+) m/z = 294.2 $(M+H)^+$.

(*S*)-5-Chloro-2-((1-methoxypropan-2-yl)oxy)pyrido[3,4-b]pyrazine (439).

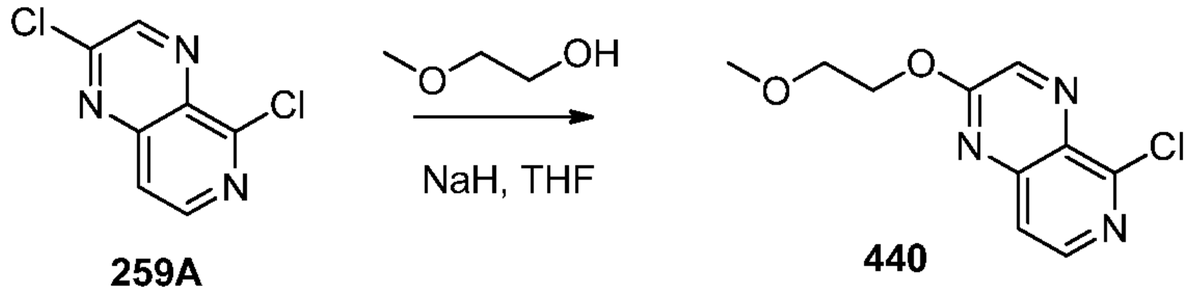


439

The title compound (0.794 g, 3.13 mmol, 84% yield) as a light-yellow crystalline solid was prepared according to the procedure described for intermediate **259** using 2,5-dichloropyrido[3,4-b]pyrazine (**259A**, 0.750 g, 3.75 mmol) and (S)-(+)-1-methoxy-2-propanol (0.380 mL, 3.88 mmol, Fluka). ^1H NMR (300 MHz, $CDCl_3$) δ ppm 8.59 (s, 1 H), 8.46 (d, J=5.70 Hz, 1 H), 7.60 (d, J=5.55 Hz, 1 H), 5.56 - 5.78 (m, 1 H), 3.68 (dd,

J=10.67, 5.99 Hz, 1 H), 3.62 (dd, J=10.67, 3.80 Hz, 1 H), 3.42 (s, 3 H), 1.45 (d, J=6.43 Hz, 3 H). LC/MS (ESI^+) m/z = 254.0 $(M+H)^+$.

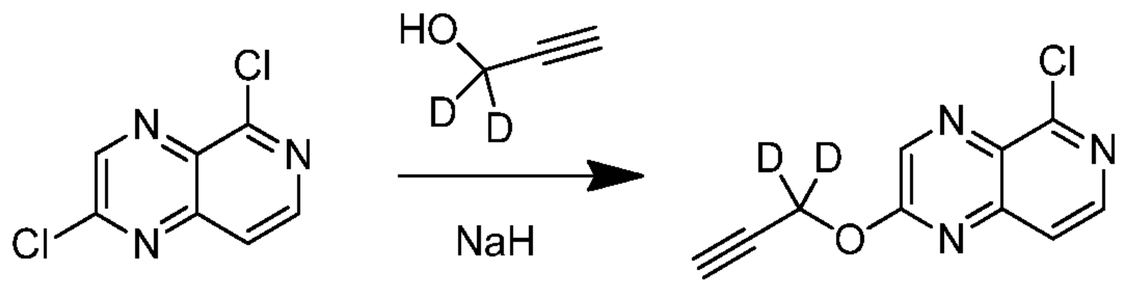
5-Chloro-2-(2-methoxyethoxy)pyrido[3,4-b]pyrazine (440).



259A **440**

To a solution of 2-methoxyethanol (0.09 mL, 1.10 mmol) in THF (1 mL) under nitrogen was added to a slurry of sodium hydride (60% dispersion in mineral oil, 44 mg, 1.10 mmol) in THF (3 mL) at 0 °C. The slurry was stirred for 15 min, then was added to the mixture of 2,5-dichloropyrido[3,4-b]pyrazine (0.20 g, 1.00 mmol) in THF (2 mL) at 0 °C. After 20 min, the reaction was quenched with saturated NH_4Cl solution (20 mL) and water (20 mL). The mixture was diluted with EtOAc (100 mL) and the organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated to give 5-chloro-2-(2-methoxyethoxy)pyrido[3,4-b]pyrazine (0.24 g, 1.01 mmol, 100% yield). This material was used without further purification. LC/MS (ESI^+) *m/z* = 240.1 $(M+H)^+$.

5-Chloro-2-((1,1-dideuteriumprop-2-yn-1-yl)oxy)pyrido[3,4-b]pyrazine (441).

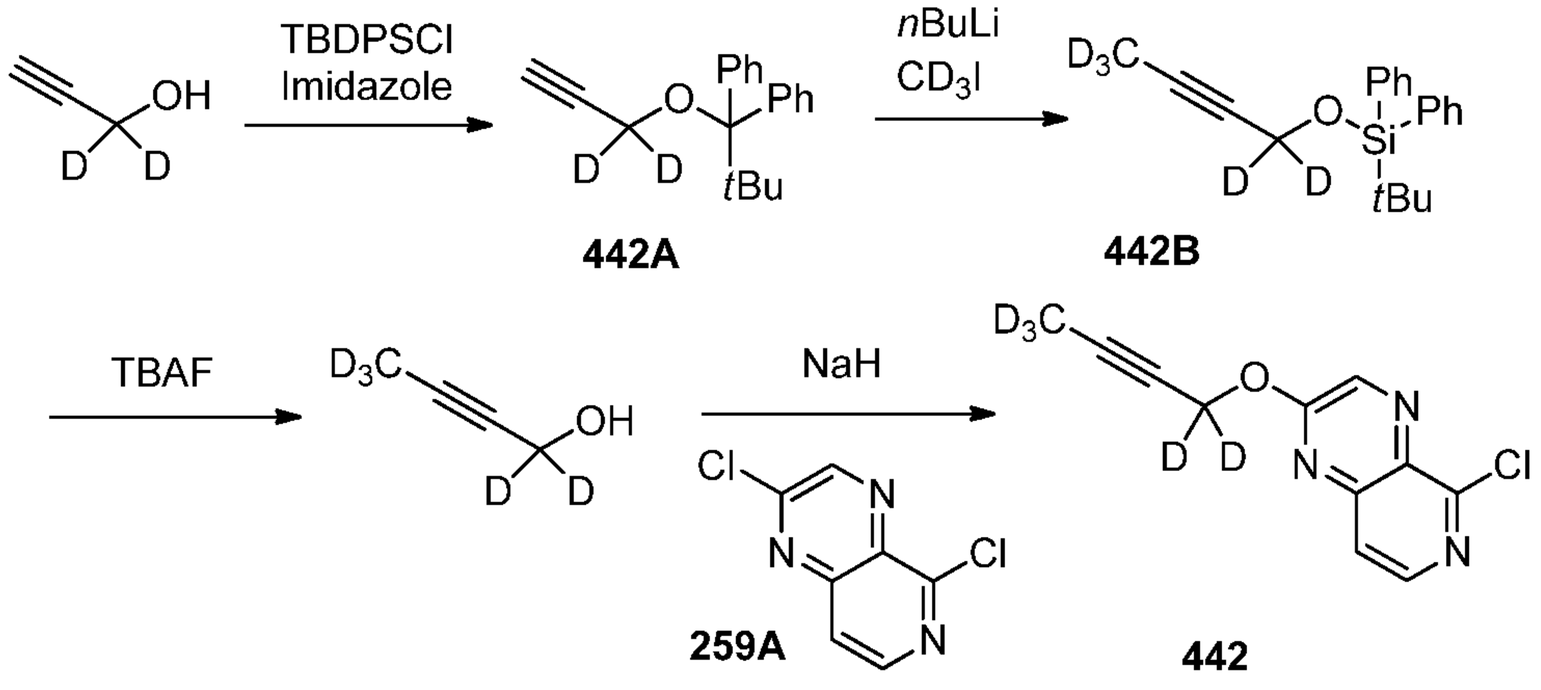


259A **441**

A solution of 1,1-dideuteriumprop-2-yn-1-ol (0.22 g, 3.8 mmol) in THF (1 mL) was added to a slurry of sodium hydride (60% dispersion in mineral oil, 0.11 g, 2.80 mmol) in THF (5 mL) at 0 °C. The slurry was stirred for 10 min. Solid 2,5-dichloropyrido[3,4-b]pyrazine (**259A**, 500 mg, 2.50 mmol) was added to the alkoxide followed by THF rinsing of the stock flask (~5 mL). After 10 min at 0 °C, the cooling bath was removed and the mixture was stirred at RT for 20 min. It was quenched with saturated NH_4Cl solution and was extracted with DCM (3 x). The combined organic extracts were dried over Na_2SO_4 and was passed through a silica gel pad with excess of DCM/ EtOAc = 10:1. The filtrate was concentrated and the resulting solid was triturated with hexanes-EtOAc (2:1, 6 mL, 5 times) and dried under vacuum to afford intermediate **441** (350 mg, 1.58 mmol, 63% yield) as an off-white powder. LCMS (ESI^+) m/z = 221.6

$(M+H)^+$. ^1H NMR (300 MHz, CHLOROFORM-d) δ 8.66 (s, 1H), 8.50 (d, *J*=5.70 Hz, 1H), 7.67 (d, *J*=5.70 Hz, 1H), 2.57 (s, 1H).

5-Chloro-2-((1,1,4,4,4-pentadeuterobut-2-yn-1-yl)oxy)pyrido[3,4-b]pyrazine (442).

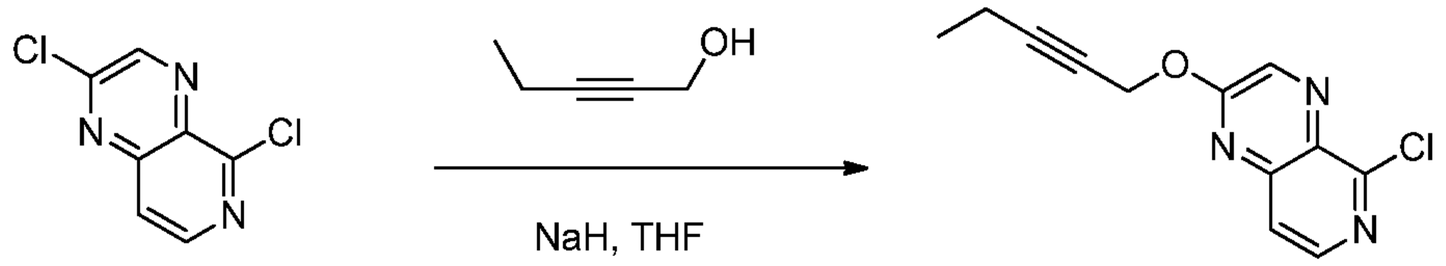


Preparation of Compound 442A. A solution of 1,1-dideutero-prop-2-yn-1-ol (0.8 g, 13.78 mmol) in DCM (5 mL) was added to a solution of *tert*-butyl(chloro)diphenylsilane (5.37 mL, 20.66 mmol) and imidazole (1.36 mL, 20.66 mmol) in DCM (5 mL) at RT. The mixture was stirred at RT for 18 h, diluted with water, and extracted with ether. The organic extract was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography eluting with a gradient of 0-10% EtOAc/heptane to give *tert*-butyl((1,1-dideuteroprop-2-yn-1-yl)oxy)diphenylsilane (1.7 g, 41.6 %) as a colorless oil. ^1H NMR (300 MHz, CHLOROFORM-d) δ 7.74 (dd, *J*=1.83, 7.67 Hz, 4H), 7.28-7.50 (m, 6H), 2.39 (s, 1H), 1.09 (s, 9H).

Preparation of Compound 442B. To a solution of *tert*-butyl((1,1-dideuteroprop-2-yn-1-yl)oxy)diphenylsilane (1.7 g, 5.73 mmol) in THF (10 mL) was slowly added *n*-butyllithium solution (1.6 M in hexanes) (4.66 mL, 7.45 mmol) at 0 °C. After 10 min, iodomethane-D3 (0.47 mL, 7.45 mmol) was slowly added and the resulting mixture was stirred at RT overnight. The mixture was diluted with EtOAc and washed with saturated aqueous NH_4Cl solution and then brine. The organic layer was dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel using 0-10% EtOAc in heptane to give *tert*-butyl((1,14,4,4-pentadeuterobut-2-yn-1-yl)oxy)diphenylsilane (1.23 g, 68.4 %) as a pale yellow oil. LC/MS (ESI^+) *m/z* = 314.0 $(M+H)^+$. ^1H NMR (300 MHz, CHLOROFORM-d) δ 7.64-7.88 (m, 4H), 7.34-7.56 (m, 6H), 0.97-1.15 (m, 9H).

Preparation of 5-Chloro-2-((1,1,4,4,4-pentadeuterobut-2-yn-1-yl)oxy)pyrido[3,4-b]pyrazine (442). To a solution of *tert*-butyl((1,14,4,4-pentadeuterobut-2-yn-1-yl)oxy)diphenylsilane in THF (5 mL) was added TBAF solution (1M in THF) (1.91 mL, 1.9 mmol). The solution was stirred at RT for 1 h, quenched with water and extracted with Et_2O (2 x). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated on the rotovap. The residue obtained which contained 1,1,4,4,4-pentadeutero-but-2-yn-1-ol was dissolved in THF (2 mL) at 0 °C and was added sodium hydride (38 mg, 0.96 mmol). The slurry was stirred for 10 min and solid 2,5-dichloropyrido[3,4-b]pyrazine (**259A**, 0.17 g, 0.83 mmol) was added. After stirring for 10 min at 0 °C, the cooling bath was removed and the mixture was stirred at RT for 20 min. The reaction mixture was quenched with saturated NH_4Cl solution and extracted with DCM. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography eluting with a gradient of 0-60% EtOAc/heptane to give 5-chloro-2-((1,1,4,4,4-pentadeuterobut-2-yn-1-yl)oxy)pyrido[3,4-b]pyrazine (0.035 g, 22.95 %). LCMS (ESI^+) *m/z* = 239.0 $(M+H)^+$. ^1H NMR (300 MHz, CHLOROFORM-d) δ 8.66 (s, 1H), 8.51 (d, *J*=5.70 Hz, 1H), 7.68 (d, *J*=5.70 Hz, 1H).

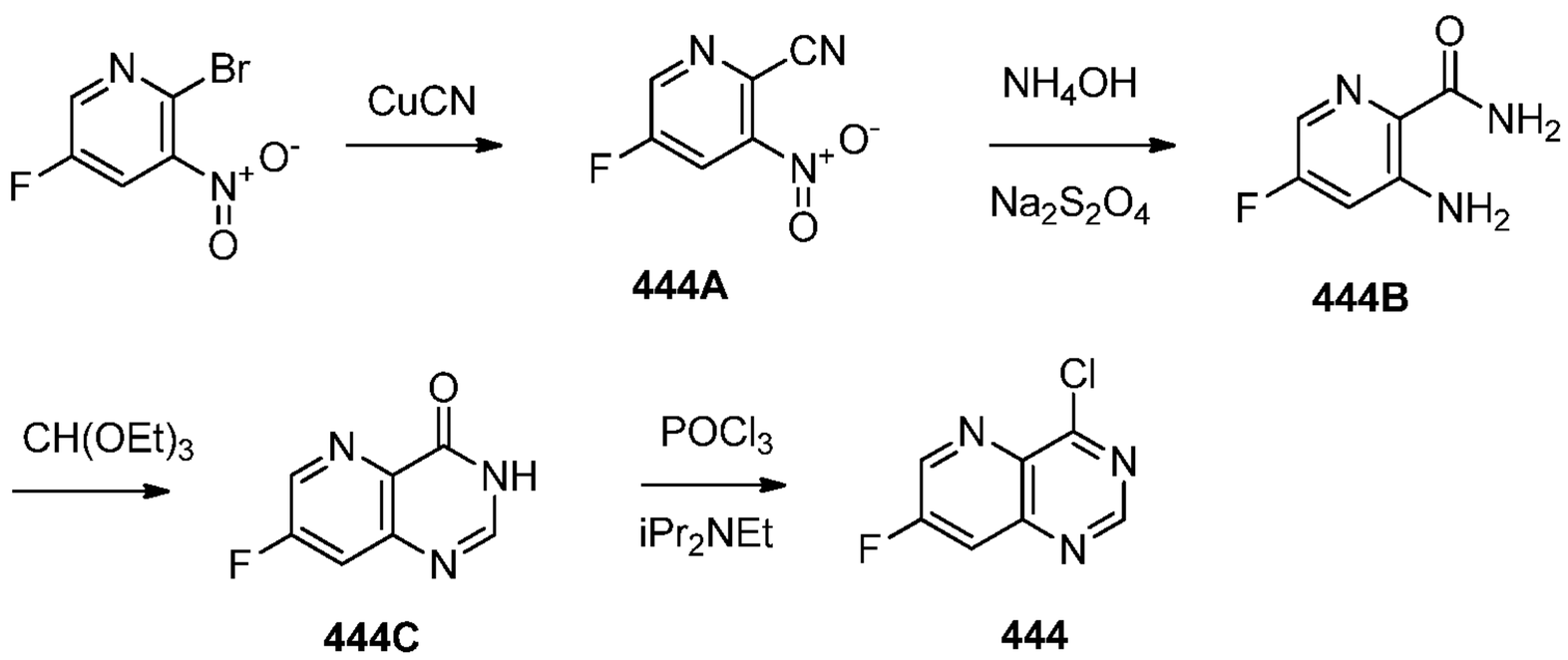
5-Chloro-2-(pent-2-yn-1-yloxy)pyrido[3,4-b]pyrazine (443).



259A **443**

The title compound (0.94 g, 3.81 mmol, 73% yield) as an off-white solid was prepared according to the procedures described for intermediate **259** using 2,5-dichloropyrido[3,4-b]pyrazine (**259A**, 1.04 g, 5.20 mmol) and 2-pentyn-1-ol (0.50 mL, 5.46 mmol). ^1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.18 (t, *J*=7.5 Hz, 3 H), 2.28 (qt, *J*=7.5, 2.2 Hz, 2 H), 5.17 (t, *J*=2.2 Hz, 2 H), 7.66 (d, *J*=5.7 Hz, 1 H), 8.49 (d, *J*=5.7 Hz, 1 H), 8.65 (s, 1 H). LC/MS (ESI^+) *m/z* = 248.2 (M+H).

4-Chloro-7-fluoropyrido[3,2-*d*]pyrimidine(444).



Preparation of 5-fluoro-3-nitropicolinonitrile (444A). Copper (I) cyanide (0.42 g, 4.73 mmol) was added to a solution of 2-bromo-5-fluoro-3-nitropyridine (0.95 g, 4.30 mmol) in DMF (15 mL) and the mixture was heated to 100 °C for 4 h. After cooling to RT, EtOAc (45 mL) was added followed by 9:1 NH_4Cl/NH_4OH (aq, 20 mL). The resulting biphasic mixture was stirred for 10 min, and then the layers were separated. The aqueous layer was extracted with EtOAc (2 x) and then the combined extracts were washed with water (2 x), dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to give an oil. The oil was fused to silica gel and then purified by silica gel chromatography (0-60% EtOAc/heptane gradient) to give the title intermediate **444A** (0.43 g, 2.60 mmol, 60% yield). ^{1}H-NMR (400 MHz, CHLOROFORM-*d*): δ ppm 8.90 (s, 1 H) 8.35 (d, *J*=5.1 Hz, 1 H). LC/MS (ESI^+) *m/z* = 168 $(M+H)^+$.

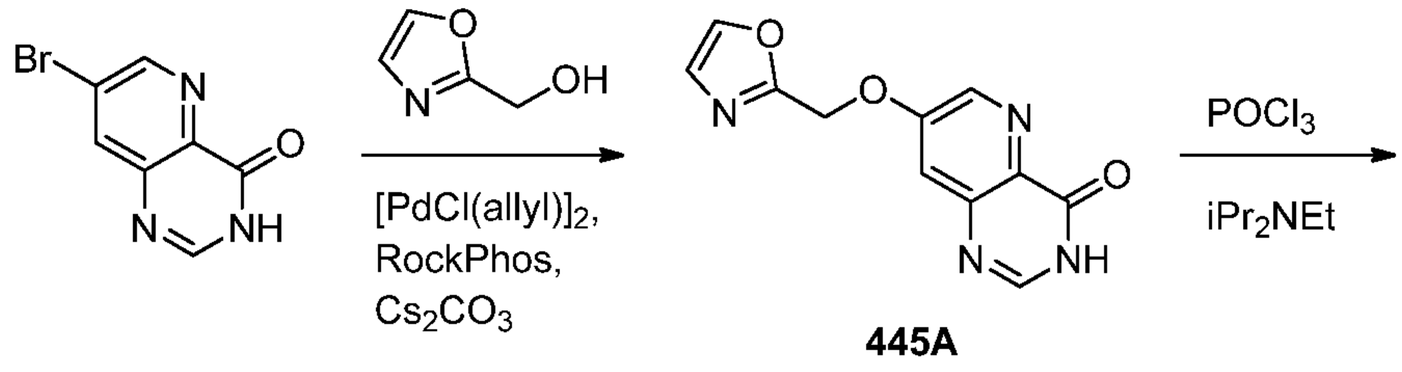
Preparation of 3-amino-5-fluoropicolinamide (444B). Ammonium hydroxide (28% wt., 0.25 mL, 6.42 mmol) was added to a suspension of 5-fluoro-3-nitropicolinonitrile (0.10 g, 0.62 mmol) in water (1.25 mL) and the mixture was stirred for 20 min. $Na_2S_2O_4$ (0.33 g, 1.87 mmol) was added portion wise over 15 min. The resulting brown suspension was stirred for 2 h, then filtered. The brown solid was washed with water three times, then air-dried to give the title intermediate **444B** (56 mg, 0.36 mmol, 58% yield). LC/MS (ESI^+) *m/z* = 156 $(M+H)^+$.

Preparation of 7-fluoropyrido[3,2-*d*]pyrimidin-4(3H)-one (444C). 3-Amino-5-fluoropicolinamide (0.23 g, 1.49 mmol) was heated to reflux in triethyl orthoformate (3.0 mL) for 4 h while distillate was collected in a Dean-Stark trap. The mixture was cooled to RT and the resulting suspension was filtered. The collected solid was washed several times with heptane and then air dried to give the title intermediate **444C** (0.21 g, 1.26 mmol, 85% yield) as a light brown solid. ^{1}H NMR (400MHz, DMSO-d_6) δ ppm 8.81 (d,

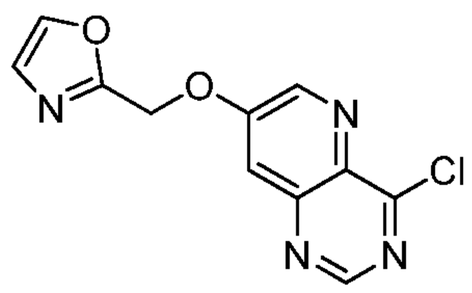
J=2.74 Hz, 1 H) 8.20 (s, 1 H) 8.01 (dd, J=9.49, 2.64 Hz, 1 H). LC/MS (ESI^+) *m/z* = 166 $(M+H)^+$.

Preparation of 4-Chloro-7-fluoropyrido[3,2-*d*]pyrimidine(444). A mixture of 7-fluoropyrido[3,2-*d*]pyrimidin-4(3H)-one (0.20 g, 1.21 mmol), diisopropylethylamine (0.84 mL, 4.84 mmol), and phosphorus oxychloride (0.44 mL, 4.84 mmol) in toluene (3 mL) was heated to 110 °C for 3 h, then cooled to RT. The mixture was then carefully added to water that was being held at 10 °C. This mixture was stirred vigorously for 30 min, and then the product was extracted into EtOAc (3 x). The combined extracts were then dried over anhydrous $_{MgSO4, filtered}$, and concentrated in vacuo to give the title compound (68 mg, 31% yield) as a brown solid. LC/MS (ESI^+) *m/z* = 184 $(M+H)^+$.

2-(((4-Chloropyrido[3,2-*d*]pyrimidin-7-yl)oxy)methyl)oxazole (445).



445A



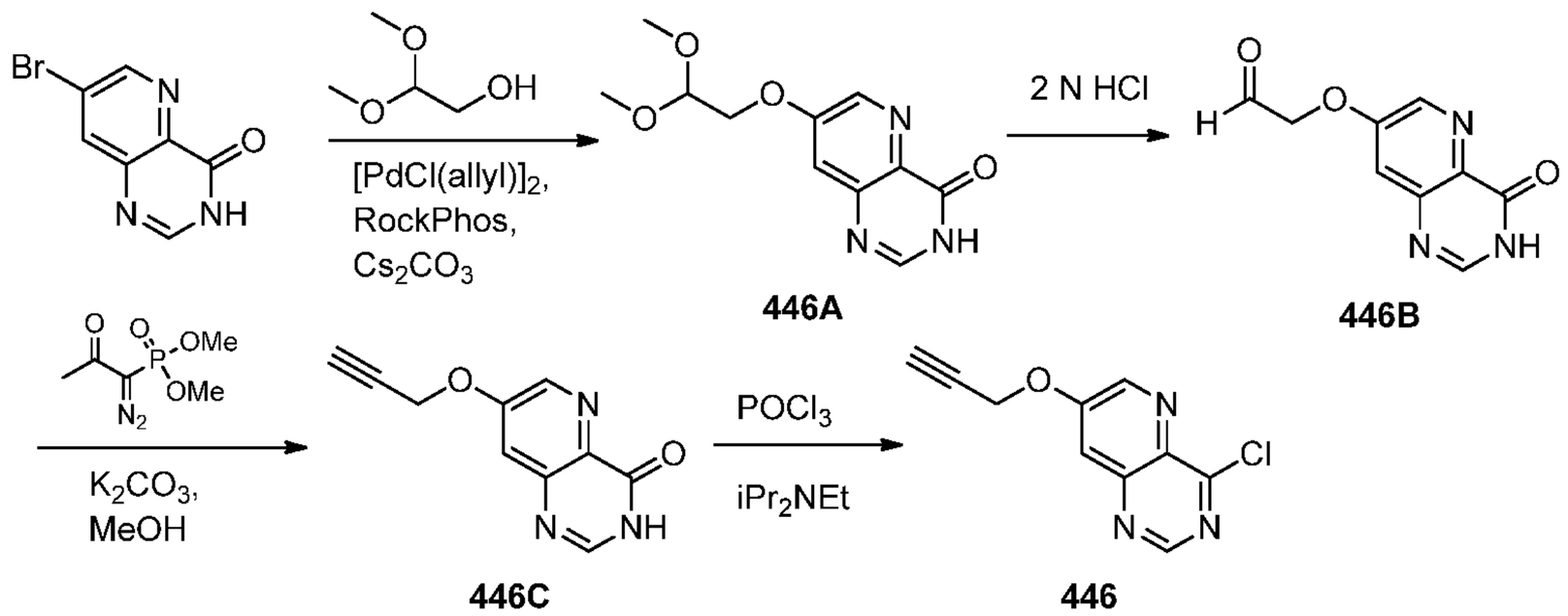
445

Preparation of 7-(oxazol-2-ylmethoxy)pyrido[3,2-*d*]pyrimidin-4(3*H*)-one (445A). To a resealable vial was added 7-bromopyrido[3,2-*d*]pyrimidin-4(3*H*)-one (2.0 g, 8.85 mmol, D-L Chiral Chemicals, LLC), cesium carbonate (8.65 g, 26.5 mmol), 2-(di-*t*-butylphosphono)-3-methoxy-6-methyl-2'-4'-6'-tri-*i*-propyl-1,1'-biphenyl (RockPhos) (0.21 g, 0.44 mmol, Strem Chemicals, Inc.), and allylpalladium(II) chloride dimer (55 mg, 0.15 mmol, Sigma-Aldrich Chemical Company, Inc.). The reaction vessel was carefully evacuated and backfilled with N_2. This was repeated twice. To this mixture was added 1,4-dioxane (10 mL) and 2-oxazolemethanol (2.81 mL, 35.4 mmol, Combi-Blocks, Inc.). Once again, the reaction vessel was carefully evacuated and backfilled with N_2. This was repeated twice. The reaction mixture was heated at 90 °C for 6 h. The mixture was treated with sat NH_4Cl and extracted with 25% iPrOH/$CHCl_3$. The solution needed to be filtered through Celite® filter aid to achieve good extraction. The combined extracts were

dried and concentrated onto silica. Purification by silica gel chromatography (3- 20% MeOH/DCM) afforded an off-white solid that was slurried with 50% EtOAc/heptane and then dried under vacuum to afford the title compound (0.91 g, 42%). MS m/z = 245.0 $(M+H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 5.50 (s, 2 H) 7.31 (s, 1 H) 7.70 (d, *J*=2.74 Hz, 1 H) 8.13 (d, *J*=3.13 Hz, 1 H) 8.21 (s, 1 H) 8.54 (d, *J*=2.74 Hz, 1 H) 12.43 (br s, 1 H).

Preparation of 2-(((4-chloropyrido[3,2-*d*]pyrimidin-7-yl)oxy)methyl)oxazole (445). To a 25 mL round-bottomed flask was added 7-(oxazol-2-ylmethoxy)pyrido[3,2-*d*]pyrimidin-4(3*H*)-one (0.45 g, 1.8 mmol), toluene (10 mL), *N*,*N*-diisopropylethylamine (0.96 mL, 5.5 mmol) and phosphorus oxychloride (1.0 mL, 11 mmol). The solution was heated at 70 °C for 1 h. The reaction mixture was allowed to cool to RT and was pipetted into cold (~10 °C) sat $NaHCO_3$. It was extracted with DCM (2 x) and the combined extracts were dried (Na_2SO_4) and concentrated. The resulting solid was washed with heptane and then dried under vacuum to afford the title compound as a tan solid (0.45 g, 1.7 mmol, 93% yield). MS m/z = 263.1 $(M+H)^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 5.39 (s, 2 H), 7.22 (s, 1 H), 7.75 (s, 1 H), 7.79 (d, *J*=2.7 Hz, 1 H), 8.92 (d, *J*=2.7 Hz, 1 H), 9.05 (s, 1 H).

4-Chloro-7-(prop-2-yn-1-yloxy)pyrido[3,2-d]pyrimidine (446).



Preparation of 7-(2,2-dimethoxyethoxy)pyrido[3,2-d]pyrimidin-4(3H)-one (446A). To a resealable vial was added 7-bromopyrido[3,2-*d*]pyrimidin-4(3*H*)-one (0.50 g, 2.2 mmol, D-L Chiral Chemicals, LLC), cesium carbonate (2.2 g, 6.6 mmol), 2-(di-*t*-butylphosphono)-3-methoxy-6-methyl-2'-4'-6'-tri-*i*-propyl-1,1'-biphenyl (RockPhos) (0.062 g, 0.13 mmol, Strem Chemicals, Inc.) and allylpalladium(II) chloride dimer (0.016 g, 0.044 mmol, Sigma-Aldrich Chemical Company, Inc.). The reaction vessel was carefully evacuated and backfilled with N_2. This was repeated twice. To the mixture was

added 1,4-dioxane (5 mL) followed by glycolaldehyde dimethyl acetal (1.41 g, 13.3 mmol). The reaction mixture was stirred at 90 °C for 2.5 h. After cooling to RT, the solution was treated with sat NH_4Cl and extracted with 25% iPrOH/$CHCl_3$. The solution had to be filtered through Celite® filter aid to prevent emulsion formation during extraction. The combined extracts were dried and concentrated. Purification by silica gel chromatography (0-10% MeOH/DCM) afforded the title compound as a white solid (0.20 g, 36% yield). MS m/z = 252.1 $(M+H)^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 3.37 (s, 6 H), 4.21 (d, *J*=5.1 Hz, 2 H), 4.76 (t, *J*=5.1 Hz, 1 H), 7.57 (d, *J*=2.7 Hz, 1 H), 8.12 (s, 1 H), 8.49 (d, *J*=2.7 Hz, 1 H), 12.40 (br. s., 1 H).

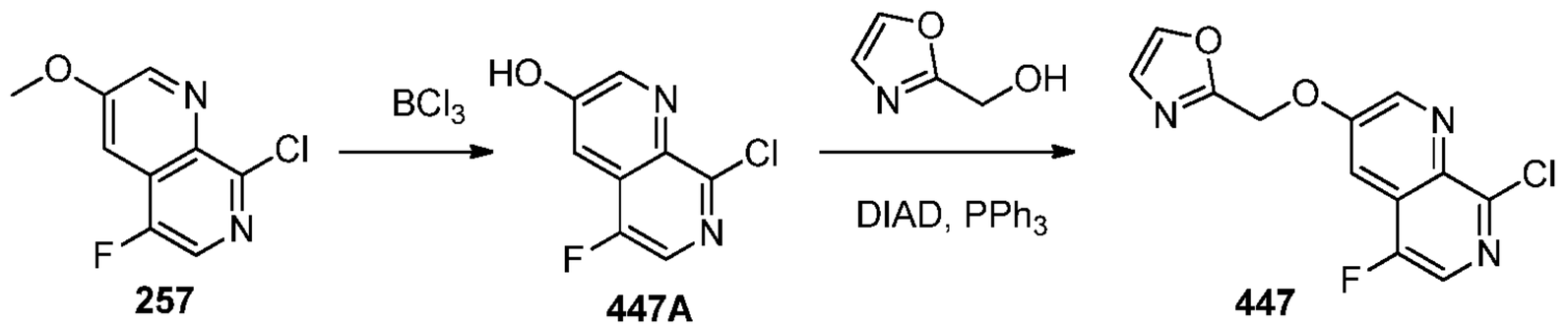
Preparation of 2-((4-oxo-3,4-dihydropyrido[3,2-d]pyrimidin-7-yl)oxy)acetaldehyde (446B). To a resealable vial was added 7-(2,2-dimethoxyethoxy)pyrido[3,2-*d*]pyrimidin-4(3*H*)-one (0.10 g, 0.40 mmol), THF (2 mL) and finally 2 N hydrochloric acid (2.0 mL). The reaction mixture was heated at 60 °C for 2 h. It was allowed to cool to RT and then concentrated to afford the title compound as a brown semi-solid which was carried on directly to the next step. MS m/z = 224.0 $(M+H_2O+H)^+$.

Preparation of 7-(prop-2-yn-1-yloxy)pyrido[3,2-*d*]pyrimidin-4(3*H*)-one (446C). To a 150 mL round bottomed flask was added 2-((4-oxo-3,4-dihydropyrido[3,2-*d*]pyrimidin-7-yl)oxy)acetaldehyde (1.70 g, 8.29 mmol), potassium carbonate (4.58 g, 33.1 mmol) and MeOH (80 mL). To this solution was added dimethyl (1-diazo-2-oxopropyl)phosphonate (2.39 mL, 9.94 mmol, Astatech). The reaction mixture was stirred at RT for 3 h. The solution was poured into saturated $NaHCO_3$ and then the pH was adjusted to 7 with 5 N HCl. The solution was extracted with 25% iPrOH/$CHCl_3$. There was an emulsion present that contained some solid. LC/MS showed this solid to be product so it was filtered and dried under vacuum to afford 0.28 g of product. The combined extracts were dried (Na_2SO_4) and concentrated onto silica. Purification by silica gel chromatography (0-10% MeOH/DCM) afforded 1.07 g (in addition to the 0.28 g solid already isolated) of the title compound as a white solid (1.35 g, 6.71 mmol, 81% yield). MS m/z = 201.9 $(M+H)^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 3.71 (t, *J*=2.3 Hz, 1 H), 5.06 (d, *J*=2.3 Hz, 2 H), 7.58 (d, *J*=2.7 Hz, 1 H), 8.13 (s, 1 H), 8.50 (d, *J*=2.7 Hz, 1 H), 12.43 (br s, 1 H).

Preparation of 4-chloro-7-(prop-2-yn-1-yloxy)pyrido[3,2-d]pyrimidine (446). To a solution of 7-(prop-2-yn-1-yloxy)pyrido[3,2-*d*]pyrimidin-4(3*H*)-one (0.86 g, 4.27 mmol) in toluene (20 mL) was added *N*,*N*-diisopropylethylamine (2.31 mL, 13.3 mmol)

followed by phosphorus oxychloride (1.17 mL, 12.8 mmol, Sigma-Aldrich Chemical Company, Inc.). The reaction mixture was heated at 65 °C for 2.5 h. The solution was allowed to cool to RT and then was slowly pipetted into sat $NaHCO_3$ that had been cooled to 10 °C. The solution was stirred vigorously for 15 min and then was extracted with DCM (2 x). The combined extracts were dried (Na_2SO_4), filtered and concentrated to afford the title compound as an off-white solid (0.86 g, 3.9 mmol, 92% yield). MS m/z = 219.9 $(M+H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 2.66 (t, *J*=2.3 Hz, 1 H), 4.94 (d, *J*=2.3 Hz, 2 H), 7.74 (d, *J*=2.7 Hz, 1 H), 8.88 (d, *J*=2.7 Hz, 1 H), 9.05 (s, 1 H).

2-(((8-Chloro-5-fluoro-1,7-naphthyridin-3-yl)oxy)methyl)oxazole (447).



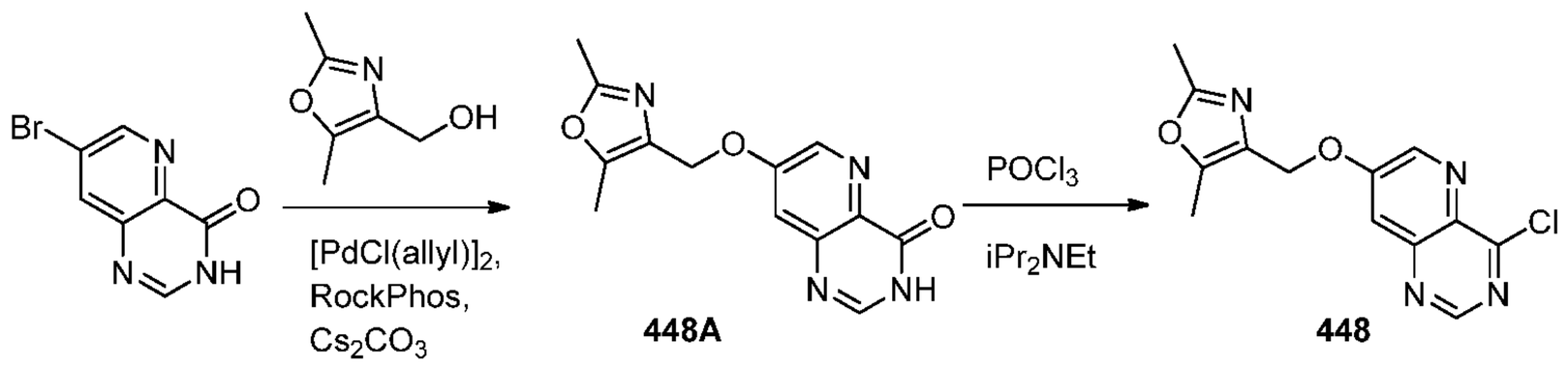
257 **447A** **447**

Boron trichloride (4.99 mL of 1.0 M solution in DCM, 4.99 mmol) was added by syringe over 2 min to a stirring yellow solution of 8-chloro-5-fluoro-3-methoxy-1,7-naphthyridine (212 mg, 0.99 mmol) and tetra-*n*-butylammonium iodide (479 mg, 1.29 mmol) in anhydrous DCM (3.5 mL) under a nitrogen atmosphere at RT. The mixture was stirred at RT for 4 h, then cooled with an ice bath before the careful addition of water. After bubbling ceased with addition of more water drops, the mixture was stirred for 30 min at RT. The mixture was then diluted with DCM and water, then carefully neutralized with portion wise addition of solid sodium bicarbonate. The layers were separated and the aqueous layer was extracted with DCM (3 x 150 mL). The combined extracts were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated in vacuo to give a red oil. This oil was purified by ISCO (12 g Gold silica gel column, 50-100% EtOAc in heptane) to give compound **447A** (123 mg, 62% yield) as a light yellow solid. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 11.72 (br. s., 1 H), 8.83 (d, J=2.7 Hz, 1 H), 8.34 (d, J=1.2 Hz, 1 H), 7.56 (d, J=2.7 Hz, 1 H). MS m/z = 199.0 $(M+H)^+$.

To a 15 mL round-bottomed flask was added 8-chloro-5-fluoro-1,7-naphthyridin-3-ol (Intermediate **447A**) (0.58 g, 2.9 mmol), triphenylphosphine (0.996 g, 3.80 mmol), THF (15 mL), and 2-oxazolemethanol (0.30 mL, 3.8 mmol, Combi-Blocks, Inc.). The solution was cooled to 0 °C and diisopropyl azodicarboxylate (0.75 mL, 3.8 mmol, Sigma-Aldrich Chemical Company, Inc.) was added slowly and then the solution was allowed to warm to RT. After 1 h, the reaction mixture was poured into water and

extracted with EtOAc. The combined extracts were washed with water and brine and then dried (Na_2SO_4) and concentrated onto silica. Purification by silica gel chromatography (0-80% EtOAc/heptane) afforded the title compound (0.68 g, 2.4 mmol, 83% yield). MS m/z = 280.0 $(M+H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 5.40 (s, 2 H), 7.23 (s, 1 H), 7.76 (s, 1 H), 7.80 (d, *J*=2.9 Hz, 1 H), 8.25 (s, 1 H), 8.93 (d, *J*=2.9 Hz, 1 H).

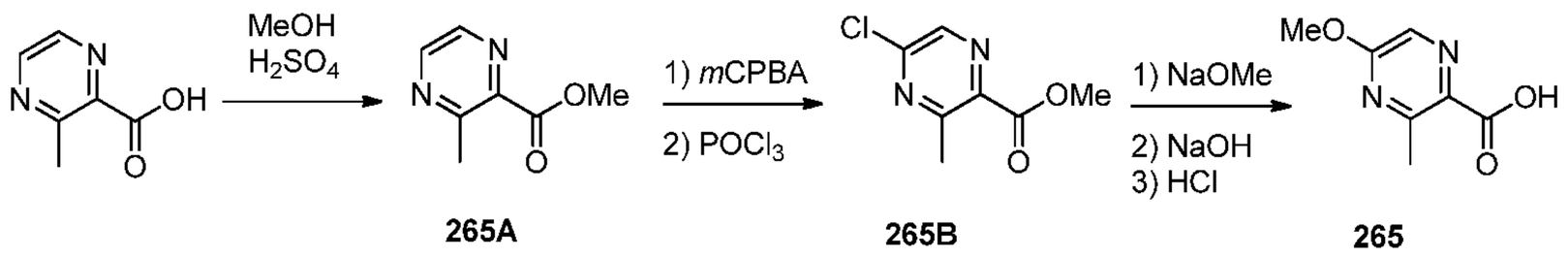
4-(((4-Chloropyrido[3,2-*d*]pyrimidin-7-yl)oxy)methyl)-2,5-dimethyloxazole (448).



Intermediate **448A** (85 mg, 0.31 mmol, 35% yield) as a white solid was prepared according to the procedures described for intermediate **445A**, starting from 7-bromopyrido[3,2-*d*]pyrimidin-4(3*H*)-one (0.20 g, 0.89 mmol) and (2,5-dimethyloxazol-4-yl)methanol (0.450 g, 3.54 mmol, Frontier Scientific, Inc.). MS m/z = 273.2 $(M+H)^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 2.35 (s, 3 H) 2.35 (s, 3 H) 5.12 (s, 2 H) 7.66 (d, *J*=2.74 Hz, 1 H) 8.12 (s, 1 H) 8.48 (d, *J*=2.74 Hz, 1 H) 12.40 (br s, 1 H).

Intermediate **448** as a tan solid (0.057 g, 0.20 mmol, 86% yield) was prepared according to the procedures described for intermediate **445**, starting from 7-((2,5-dimethyloxazol-4-yl)methoxy)pyrido[3,2-*d*]pyrimidin-4(3*H*)-one (**448A**, 62 mg, 0.23 mmol). MS m/z = 290.9 $(M+H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 2.39 (s, 3 H), 2.45 (s, 3 H), 5.08 (s, 2 H), 7.72 (d, *J*=2.7 Hz, 1 H), 8.89 (d, *J*=2.7 Hz, 1 H), 9.04 (s, 1 H).

5-Methoxy-3-methylpyrazine-2-carboxylic acid (265).



Preparation of Compound 265A. In a 2-L flask, 3-methylpyrazine-2-carboxylic acid (Matrix, 19.95 g, 144 mmol) was suspended in MeOH (500 mL). The suspension was cooled in an ice-water bath, and concentrated sulfuric acid (Fluka, 27.3 mL, 506 mmol) was added over a time period of 5 min. The reaction mixture was heated to 80 °C for 5 h. The reaction mixture was concentrated under reduced pressure and the residue was taken up in DCM (750 mL). The excess acid was neutralized carefully with of

aqueous NaOH (5 M, 200 mL). The aqueous layer was separated and extracted with DCM (250 mL). The combined organic layers were combined, dried over $MgSO_4$ and concentrated to afford 16.15 g of methyl 3-methylpyrazine-2-carboxylate (**265A**, 106 mmol, 73%). MS *m/z*=153 $[M+H]^+$.

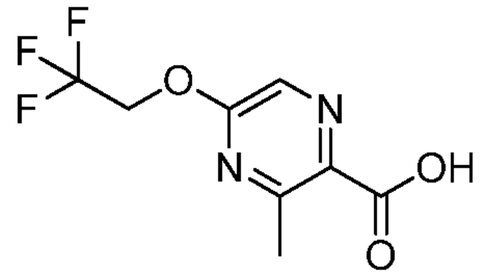
Preparation of Compound 265B. In a 1-L flask, the methyl 3-methylpyrazine-2-carboxylate (265A, 16.08 g, 106 mmol) was suspended in $CHCl_3$ (300 mL). 3-Chlorobenzoperoxoic acid (Aldrich, 24.62 g, 143 mmol) was added. The reaction mixture was heated to 70 °C for 16 h. The reaction mixture was quenched with saturated $NaHCO_3$ (200 mL). The layers were separated, and the aqueous layer was further extracted with DCM (2 x 100 mL). The combined organic layers were dried over $MgSO_4$, and the filtrate was concentrated to afford crude 3-(methoxycarbonyl)-2-methylpyrazine 1-oxide (17.77 g). MS *m/z*=169 $[M+H]^+$.

In a 1-L flask, the crude 3-(methoxycarbonyl)-2-methylpyrazine 1-oxide (17.77 g, 106 mmol) was dissolved in DMF (300 mL). Neat phosphoryl trichloride (29.6 mL, 317 mmol) was added. The reaction mixture was heated to 100 °C. After 1 h, the reaction mixture was concentrated to remove most of the DMF. The flask was cooled in an ice water bath, and 1 M aqueous Na_2CO_3 (300 mL) was added slowly, followed by 80% EtOAc-hexane (400 mL). The mixture was filtered through Celite® filter aid. The resulting filtrate was partitioned and the aqueous phase was extracted further with 80% EtOAc-hexane (2 x 250 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. The material was purified through silica gel using 11% EtOAc-hexane to afford methyl 5-chloro-3-methylpyrazine-2-carboxylate (**265B**, 4.29 g, 23 mmol, 22%). MS *m/z*=187 $[M+H]^+$.

Preparation of Compound 265. A flask was charged with sodium (0.813 g, 35.4 mmol), purged with Argon, and placed in a room temperature water bath. MeOH (47.7 mL, 1179 mmol) was added slowly. After 40 min, methyl 5-chloro-3-methylpyrazine-2-carboxylate (265B, 2.2 g, 11.79 mmol) was added. The vessel was sealed and heated to 45 °C for 1.5 h. Sodium hydroxide (1 M, 12.97 mL, 12.97 mmol) was added and heating was continued for 1.5 h. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in a minimum amount of water (50 mL). The aqueous phase was extracted with Et_2O (15 mL), which was discarded. The aqueous phase was acidified with HCl (5 M, 11 mL, 55 mmol). The mixture was extracted with DCM (3 x 60 mL). The combined organic extracts were dried over $MgSO_4$ and the filtrate was concentrated to afford 5-methoxy-3-methylpyrazine-2-carboxylic acid (**265**, 2.0 g, 100%).

MS *m/z*=169 $[M+H]^+$. ^1H NMR in $CDCl_3$ δ 10.70 (br, 1H), 7.98 (s, 1H), 4.00 (s, 3H), 2.91 (s, 3H).

3-Methyl-5-(2,2,2-trifluoroethoxy)pyrazine-2-carboxylic acid (266).



266

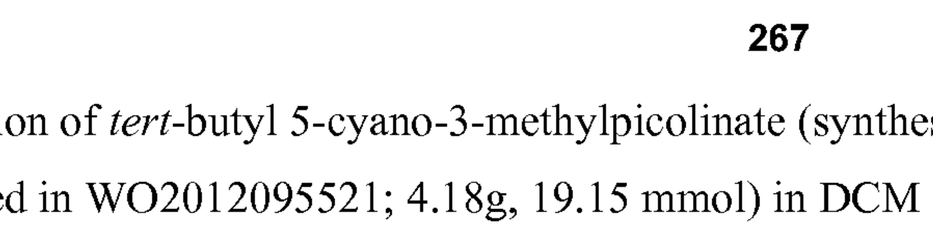
The title compound was synthesized according to Intermediate **265**, using 2,2,2,-trifluoroethanol (Aldrich) to react with Compound **265B**. MS *m/z* = 237 $(M+H)^+$.

5-Cyano-3-methylpicolinic acid (267).

267

To a solution of *tert*-butyl 5-cyano-3-methylpicolinate (synthesized according to procedure described in WO2012095521; 4.18g, 19.15 mmol) in DCM (96 mL) was added TFA (Aldrich, 148 mL, 1915 mmol). The reaction mixture was stirred at RT for 2 h. The reaction mixture was concentrated under reduced pressure and the residue was triturated with EtOAc. The yellow slurry was concentrated under reduced pressure. The residue was triturated with 30 mL of methyl *tert*-butyl ether (30 mL) and of hexanes (50 mL) to yield 5-cyano-3-methylpicolinic acid (2.91 g, 17.95 mmol, 94% yield) as yellow solid. MS *m/z*=163.2 $[M+H]^+$.

5-Chloro-3-methylpicolinic acid (268).



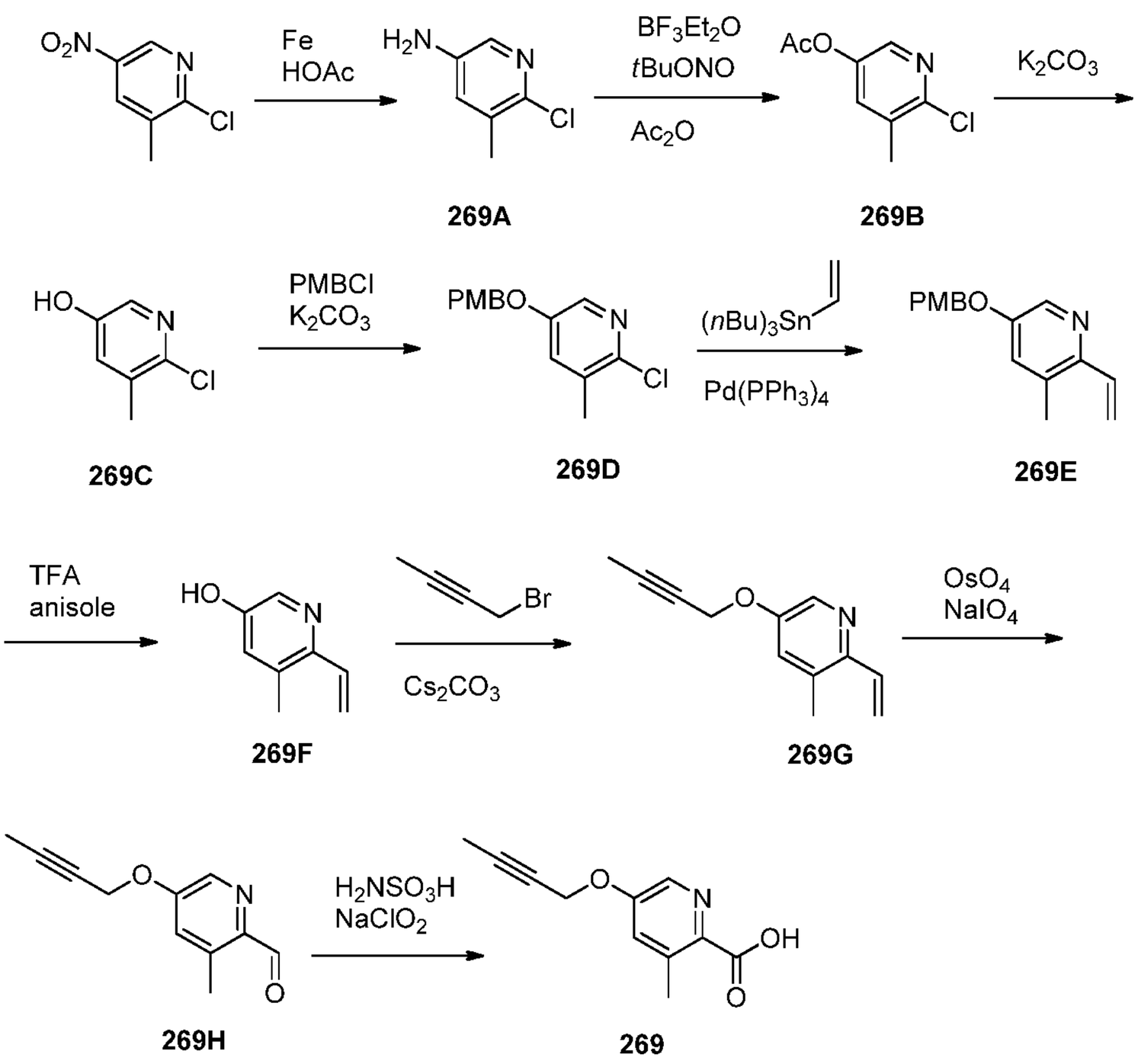
268

A mixture of 2-bromo-5-chloro-3-methylpyridine (45 g, 218 mmol), zinc cyanide (8.30 mL, 131 mmol), tris(dibenzylideneacetone) dipalladium (0) (4.99 g, 5.45 mmol),

and 1,1'-bis(diphenylphosphino)ferrocene (6.04 g, 10.90 mmol) in dimethylacetamide (40 mL) was heated to 110 °C for 4 h. The reaction mixture was cooled to RT, diluted with water and extracted with EtOAc. The organic phase obtained was concentrated under reduced pressure and residue purified by chromatography on silica gel using ISCO eluting with 0-60% EtOAc/hexanes to afford 5-chloro-3-methylpicolinonitrile (25.4 g, 166 mmol, 76 % yield). LC/MS (ESI^+) *m/z* = 153.1 (M+H) .

To a solution of 5-chloro-3-methylpicolinonitrile (24.0 g, 157 mmol) in EtOH (100 mL) was added NaOH (110 mL of 5 N solution, 550 mmol). The resulting mixture was refluxed at 90 °C for 18 h. After cooling to RT, the reaction mixture was concentrated. The residue was diluted with water and the pH of the solution was adjusted to 4 by addition of 5 N HCl. The solid that precipitated was filtered and set aside. The filtrate was extracted with EtOAc (2 x). The aqueous layer was again acidified with 5 N HCl to pH 4 and extracted with EtOAc (2 x). The EtOAc extracts were combined, dried, and concentrated. The solid obtained from all the workup steps were combined and dried in a vacuum oven at 40 °C for 12 h to give 5-chloro-3-methylpicolinic acid (**268**) (24.1 g, 140 mmol, 89% yield). LC/MS (ESI^+) *m/z* = 172.0 $(M+H)^+$. ^1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 11.29 (br. s., 1 H), 8.41 (d, *J*=1.76 Hz, 1 H), 7.73 (d, *J*=1.76 Hz, 1 H), 2.75 (s, 3 H).

5-(But-2-yn-1-yloxy)-3-methylpicolinic acid (269).



Preparation of Compound 269A. Iron powder (9.75 g, 0.17 mol) was added in portions over a period of 2 h to a stirred solution of 2-chloro-3-methyl-5-nitropyridine (10 g, 58.00 mmol, Combi-blocks) in HOAc/water (29 mL : 88 mL). After 3 h, the reaction mixture was filtered through Celite® filter aid and the filter cake was washed with EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with aqueous sodium bicarbonate, brine and dried over Na2SO4. The solvent was removed under reduced pressure to yield 6-chloro-5-methylpyridine-3-amine as a brown solid (**269A**, 8.00 g; 97%). MS m/z = 142.03 $[M+H]^+$. ^{1}H-NMR (300MHz, DMSO-d6): δ 7.54 (d, J=30 Hz, 1H), 6.91-6.90 (dd, J = 0.6 Hz & 2.7 Hz, 1H), 5.39 (s, 2H), 2.17 (s, 3H)

Preparation of Compound 269B. In a 100 mL RBF, boron trifluoride diethyl etherate (1.8 mL, 14.3 mmol, Sigma Aldrich) was added drop wise to a cooled mixture (-15 °C) of 6-chloro-5-methylpyridine-3-amine (269A, 1.0 g, 7.0 mmol) in DME (7.5 mL) and DCM (2.5 mL). Then *tert*-butyl nitrite (850 mg, 8.2 mmol, Sigma-Aldrich) was

added drop wise and the reaction mixture was stirred at -10 °C for 25 min. The reaction mixture was allowed to warm to 0 °C and stirred for additional 20 min. The reaction mixture was diluted with pentane (50 mL) and the tetrafluoroborate diazonium salt was collected by filtration. The salt was dissolved in acetic anhydride (10 mL) and heated at 95 °C for 2 h. The reaction mixture was cooled to ambient temperature and then partitioned between EtOAc (50 mL) and sat. sodium bicarbonate solution (100 mL). The aqueous solution was separated and extracted with EtOAc (2 x 100 mL). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to afford a brown oil. This oil was purified by column chromatography on silica gel, eluting with 5% EtOAc in petroleum ether to give 6-chloro-5-methylpyridine-3-yl acetate as pale yellow oil (**269B**, 780 mg, 62%). MS m/z = 185.02 $[M+H]^{+}$. ^{1}H-NMR (300MHz, DMSO-d_6): δ 8.13 (d, J = 2.4Hz, 1H), 7.72 (d, J= 2.7 Hz 1 H), 2.34(s, 3H), 2.30 (s, 3H).

Preparation of Compound 269C. Potassium carbonate (1.1 g, 8.1 mmol) was added to a stirred solution of 6-chloro-5-methylpyridine-3-yl acetate (**269B**, 750 mg, 4.0 mmol) in MeOH (15 mL) at RT. The reaction mixture was stirred for 1 h at ambient temperature. The reaction mixture was concentrated under reduced pressure and the residue was diluted with minimum amounts of water and neutralized with 1 N HCl (15 mL). After neutralization, the solution was extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated to give 6-chloro-5-methylpyridine-3-ol (**269C**) as an off white solid (500 mg, 89%). MS m/z = 143.01 $[M+H]^{+}$. ^{1}H-NMR (300MHz, DMSO-d_6): δ 10.09 (s, 1H), 7.76 (d, J= 3Hz, 1H), 7.18 (d, J=3.6 Hz, 1H), 2.24 (s, 3H).

Preparation of Compound 269D. A mixture of 6-chloro-5-methylpyridin-3-ol (**269C**, 250 mg, 1.7 mmol), 1-(chloromethyl)-4-methoxybenzene (328 mg, 2.0 mmol, Sigma Aldrich), and potassium carbonate (482 mg, 3.4 mol) in DMF (5 mL) was allowed to stir for 3 h at 60 °C. After completion of the reaction, reaction mixture was cooled to RT and poured into ice cold water (25 mL). The obtained solid was filtered, washed with water (2 x 10 mL) and dried to obtain 2-chloro-5-((4-methoxybenzyl)oxy)-3-methylpyridine as an off white solid (**269D**, 400 mg, 87%). MS m/z = 263.9 $[M+H]^{+}$. ^{1}H-NMR (300MHz, $CDCl_3$): δ 7.96 (d, J = 2.7 Hz, 1H), 7.34 (d, J = 8.7 Hz, 2H), 7.15 (d, J = 3 Hz, 1H), 6.94 - 6.89 (m, 2H), 4.99 (s, 2H), 3.81 (s, 3H), 2.33 (s, 3H).

Preparation of Compound 269E. A 25 mL sealable tube was charged with a mixture of 2-chloro-5-(difluoromethoxy)-3-methylpyridine(**269D**, 330 mg, 1.2 mmol),

toluene (10 mL), and tributyl(vinyl)stannane (447 mg, 1.5 mmol). The reaction mixture was purged with Argon gas for 10 min. Then $Pd(PPh_3)_4$ (144 mg, 0.2 mmol, Alfa-Aesar) was added and the reaction mixture was allowed to stir for 16 h at 100 °C. The reaction mixture was cooled to RT and filtered through Celite® filter aid. The filter cake was washed with EtOAc and concentrated to get a crude residue. The residue was purified by column chromatography using silica and eluting with 5-10% EtOAc in petroleum ether to give 5-((4-methoxybenzyl)oxy)-3-methyl-2-vinylpyridine as an off white solid (**269E**, 250 mg, 65%). MS m/z = 256.1 $[M+H]^+$. ^{1}H-NMR (300MHz, $CDCl_3$): δ 8.20 (d, J = 2.7 Hz, 1H), 7.37-7.33 (m, 2H), 7.02 (d, J = 2.7 Hz, 1H), 6.94-6.87 (m, 3H), 6.21 (dd, J = 1.8 Hz & 16.8 Hz, 1H), 5.39 (dd, J = 2.1 Hz & 10.5 Hz, 1H), 5.01 (s, 2H), 3.81 (s, 3H), 2.33 (s, 3H).

Preparation of 5-methyl-6-vinylpyridin-3-ol (269F). TFA (1.25 mL, 5 times) was added to a stirred solution of 5-((4-methoxybenzyl)oxy)-3-methyl-2-vinylpyridine (**269E**, 250 mg, 9.8 mmol) in anisole (0.5 mL). The reaction mixture was stirred for 2 h at ambient temperature. After completion of the reaction, the mixture was concentrated and quenched with saturated $NaHCO_3$ solution (2 mL). The reaction mixture was extracted with EtOAc (2 x 10 mL) and the combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude residue was triturated with pentane to afford 5-methyl-6-vinylpyridin-3-ol (**269F**) as an off white solid (100 mg, 76%). MS m/z = 136.15 $[M+H]^+$. ^{1}H-NMR (400MHz, $CDCl_3$): δ 9.86 (s, 1H), 7.96 (d, J = 2.8 Hz, 1H), 6.94-6.86 (m, 2H), 6.07 (dd, J = 2.4 Hz, 16.8 Hz, 1H), 5.26 (dd, J = 2.8 Hz, 10.4 Hz, 1H), 2.25 (s, 3H).

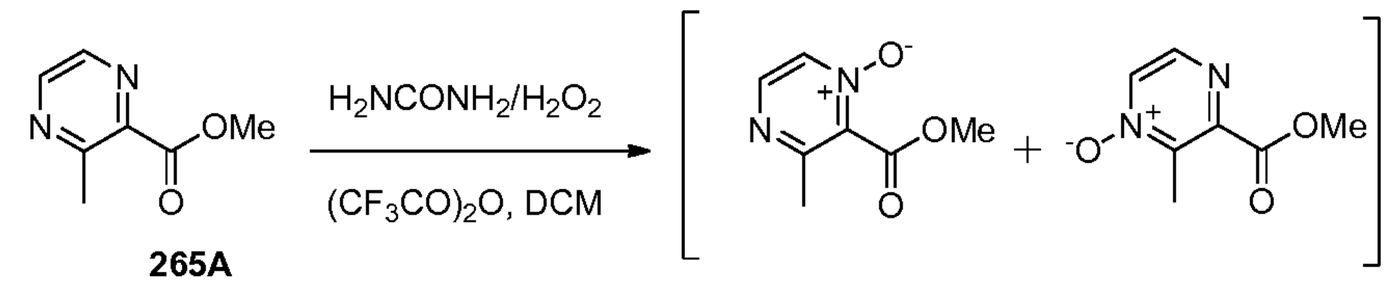
Preparation of 5-(but-2-yn-1-yloxy)-3-methyl-2-vinylpyridine (269G). A mixture of 5-methyl-6-vinylpyridin-3-ol (**269F**, 100 mg, 7.4 mmol), sodium 1-bromobut-2-yne (118 mg, 0.9 mmol, Alfa-Aesar) and cesium carbonate (361 mg, 1.1 mmol) in DMF (2 mL) was stirred for 2 h at 80 °C. After completion of the reaction, reaction mixture was cooled to ambient temperature, poured into ice-cold water (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine, dried over sodium sulfate and concentrated under reduced pressure. The crude residue was purified by column chromatography using silica gel and eluting with 0-10% EtOAc in petroleum ether to give 5-(but-2-yn-1-yloxy)-3-methyl-2-vinylpyridine (**269G**) as an off white solid (85 mg, 61%). MS m/z = 188.3 $[M+H]^+$. ^{1}H-NMR (400MHz, $CDCl_3$): δ 8.21 (d, J = 2.8 Hz, 1H), 7.03 (d, J = 2.4 Hz, 1H), 6.96-6.89 (m, 1H), 6.22 (dd, J = 2.4 Hz & 17.2 Hz,

1H), 5.40 (dd, *J* = 2 Hz & 10.8 Hz, 1H), 4.68-4.67 (m, 2H), 2.35 (s, 3H), 1.85 (t, *J* = 2.4 Hz, 3H).

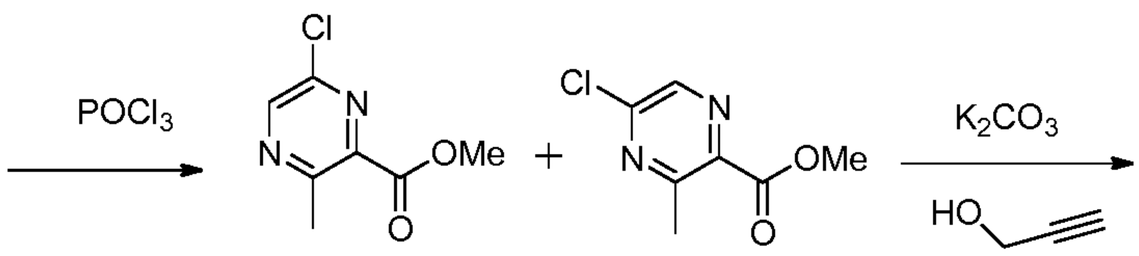
Preparation of 5-(but-2-yn-1-yloxy)-3-methylpicolinaldehyde (269H). OsO_4 (2.5 wt.% sol. in *tert*-butanol) (0.86 mL, 2.7 mmol) was added to a stirred solution of 5-(but-2-yn-1-yloxy)-3-methyl-2-vinylpyridine (5.1 g, 27 mmol) in acetone/ water (100/100 mL) at 0 °C. The reaction mixture was allowed to stir for 30 min at ambient temperature. Then $NaIO_4$ (23.2 g, 108.0 mmol) was added and the reaction mixture was allowed to stir for additional 4 h at ambient temperature. The reaction mixture was diluted with ice cold water (200 mL) and extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel, eluting with 5-10% EtOAc in petroleum ether to give 5-(but-2-yn-1-yloxy)-3-methylpicolinaldehyde (**269H**, 3.6 g, 70%) as an off white solid. MS m/z = 189.9 $[M+H]^+$. ^{1}H-NMR (400MHz, $CDCl_3$): δ 10.10 (s, 1H), 8.37 (d, *J* = 2.8 Hz, 1H), 7.13 (d, *J* = 2.8 Hz, 1H), 4.77 (d, *J* = 2.4 Hz, 2H), 2.67 (s, 3H), 1.86 (t, *J* = 2 Hz, 3H).

Preparation of Compound 269. A stirred solution of 5-(but-2-yn-1-yloxy)-3-methylpicolinaldehyde (**269H**, 3.6 g, 19.0 mmol) in water (216 mL)/ acetone (36 mL) was treated with sulphamic acid (2.5 g, 25.0 mmol) and 85% sodium chlorite (2.7 g, 29.0 mmol). The reaction mixture was allowed to stir for 2 h at ambient temperature. The reaction mixture was extracted with EtOAc (2 x 100 mL). The combined organic layer were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was triturated with *n*-pentane to provide 5-(but-2-yn-1-yloxy)-3-methylpicolinaldehyde (**269**) as an off white solid (3.2 g, 82%). MS m/z = 206.3 $[M+H]^+$. ^{1}H-NMR (400MHz, CD3OD): δ 8.16 (d, *J* = 2.8 Hz, 1H), 7.38 (d, *J* = 2.4 Hz, 1H), 4.84-4.82(m, 2H), 2.63 (s, 3H), 1.83 (t, *J* = 2 Hz, 3H).

3-Methyl-5-(prop-2-yn-1-yloxy)pyrazine-2-carboxylic acid.

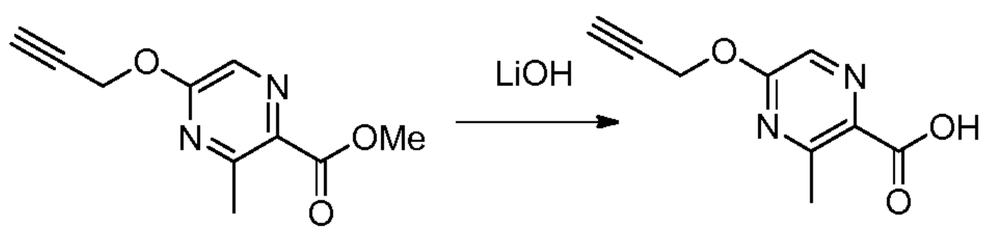


265A



265B1
(major)

265B
(minor)



270A **270**

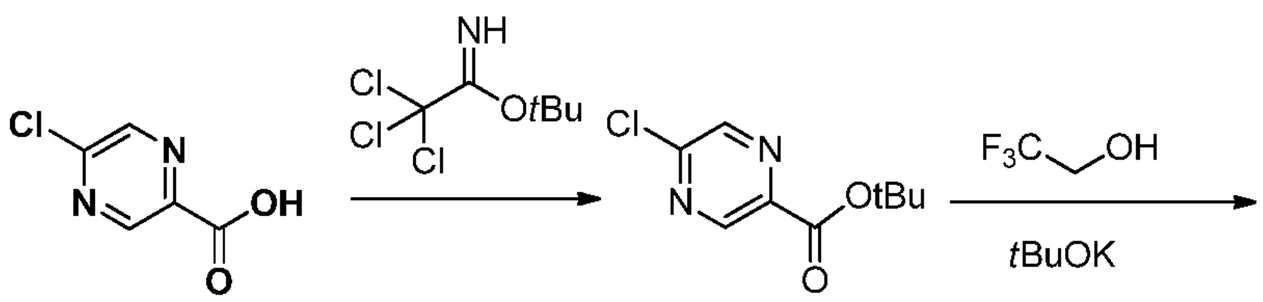
Preparation of Compound 265B. A solution of methyl 3-methylpyrazine-2-carboxylate (265A, 9.1 g, 59.8 mmol) in DCM (100 mL) was cooled to 0 °C was added urea hydrogen peroxide adduct (7.8 g, 83.0 mmol), followed by dropwise addition of trifluoroacetic acid anhydride (10.8 mL, 78.0 mmol). The resulting mixture was stirred at 0 °C for 1 h, and at RT for 18 h, during which LCMS indicated a mixture of two peaks corresponding to MS m/z = 169.0 $[M+H]^+$. The reaction was diluted with DCM and quenched with saturated Na_2SO_3 solution; the aqueous layer was back-extracted with DCM (2 x). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. ISCO purification (20-80% EtOAc/hexanes) afforded a mixture of two regioisomers, containing 3-(methoxycarbonyl)-2-methylpyrazine 1-oxide and 2-(methoxycarbonyl)-3-methylpyrazine 1-oxide (5.2 g, 30.9 mmol, 51.7% yield). The mixture of regioisomers was taken to next step without further purification. MS m/z = 169.0 $[M+H]^+$. A solution of the mixture of 3-(methoxycarbonyl)-2-methylpyrazine 1-oxide and 2-(methoxycarbonyl)-3-methylpyrazine 1-oxide (5.1 g, 15.2 mmol) in toluene (50 mL) was cooled to 0 °C and phosphorus oxychloride (2.8 mL, 30.3 mmol) was added under nitrogen followed by DMF (0.12 mL, 1.52 mmol). The reaction mixture was stirred at RT for 4 h, and heated to 65 °C for 18 h, cooled to RT, diluted with EtOAc and washed

with saturated $NaHCO_3$ solution. The aqueous layer was back-extracted with EtOAc (2 x). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. ISCO purification (0-50% EtOAc/hexanes) with care afforded both isomers: methyl 5-chloro-3-methylpyrazine-2-carboxylate (**265B**, 0.68 g) (minor product) denoted by peak 1 and methyl 6-chloro-3-methylpyrazine-2-carboxylate (**265B1**, 1.50 g) (major product) denoted by peak 2. MS m/z = 187.0 $[M+H]^+$. Peak 1: ^1H NMR (300 MHz, DMSO-d_6) δ 8.73 (s, 1H), 3.91 (s, 3H), 2.71 (s, 3H). Peak 2: ^1H NMR (300 MHz, DMSO-d_6) δ 8.89 (s, 1H), 3.91 (s, 3H), 2.71 (s, 3H).

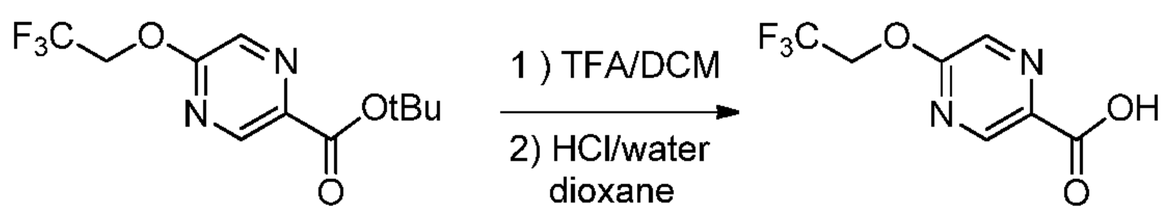
Preparation of compound 270A. To a solution of methyl 5-chloro-3-methylpyrazine-2-carboxylate (**265B**, 750 mg, 4.02 mmol) and propargyl alcohol (356 µL, 6.03 mmol) in 3 mL of DMF was added potassium carbonate (833 mg, 6.03 mmol). After 1 h, about 70% desired conversion was detected by LCMS. Additional propargyl alcohol (356 µL, 6.03 mmol) was added and the reaction was stirred overnight. The reaction was directly loaded to flash column (hexanes /EtOAc = 10:1 to 5:1 to 4:1) to give methyl 3-methyl-5-(prop-2-yn-1-yloxy)pyrazine-2-carboxylate (**270A**, 800 mg, 3.88 mmol, 97% yield) as a white gum. MS m/z = 207.0 $[M+H]^+$. ^1H NMR (300 MHz, CHLOROFORM-d) δ 8.18 (s, 1H), 5.06 (d, *J*=2.48 Hz, 2H), 3.97 (s, 3H), 2.80 (s, 3H), 2.52 (t, *J*=2.41 Hz, 1H).

Preparation of compound 270. A solution of methyl 3-methyl-5-(prop-2-yn-1-yloxy)pyrazine-2-carboxylate (**270A**, 800 mg, 3.88 mmol) in THF (10 mL) was treated with lithium hydroxide hydrate (488 mg, 11.64 mmol) in 10 mL of water and the mixture was stirred at ambient temperature for 3 h. The mixture was treated with 5 M aqueous HCl (2.4 mL), and extracted with DCM (3 x 50 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated to give 3-methyl-5-(prop-2-yn-1-yloxy)pyrazine-2-carboxylic acid (**270**) (380 mg, 1.98 mmol, 51% yield) as a white solid. MS m/z = 193.0 $[M+H]^+$. ^1H NMR (300 MHz, CHLOROFORM-d) δ 8.05 (s, 1H), 5.09 (d, *J*=2.48 Hz, 2H), 2.92 (s, 3H), 2.54 (t, *J*=2.41 Hz, 1H).

5-(2,2,2-Trifluoroethoxy)pyrazine-2-carboxylic acid (272).



272A



272B **272**

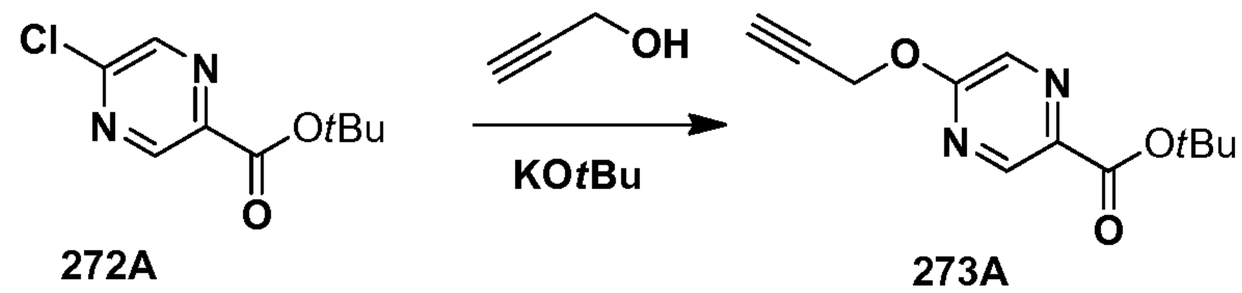
Preparation of *tert*-butyl 5-chloropyrazine-2-carboxylate (272A). A solution of 5-chloropyrazine-2-carboxylic acid (200.0 g, 1.26 mol) in THF (2.5 L) was treated with a solution of *tert*-butyl 2,2,2-trichloroacetimidate (460 mL, 2.57 mol) in cyclohexane (2.5 L). The reaction was stirred at 25 °C for 5 min and then treated with boron trifluoride dimethyl etherate (144.0 mL, 126 mmol). The resulting reaction mixture was stirred at 25 °C for 16 h and then diluted with EtOAc (5.0 L), washed with a saturated aqueous sodium bicarbonate solution (4.0 L) followed by water (5.0 L). The organic layer was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude material was purified by column chromatography (Silica 60-120 mesh, 10% EtOAc in hexanes) to give *tert*-butyl 5-chloropyrazine-2-carboxylate (250 g, 92%) as a colorless oil. MS (ESI, positive ion) m/z: 215.2 $(M+1)^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.01 (d, J = 1.3 Hz, 1H), 8.70 (d, J = 1.3 Hz, 1H), 1.66 (s, 9H).

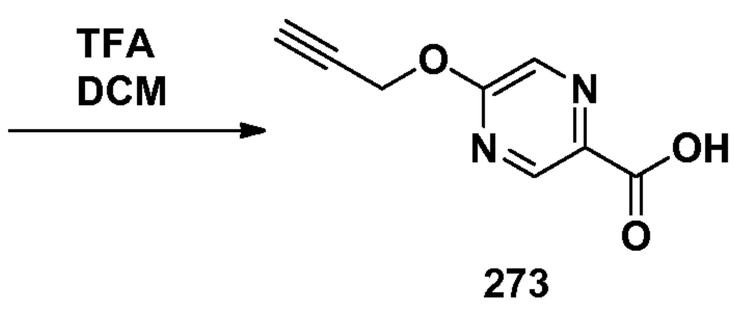
Preparation of *tert*-butyl 5-(2,2,2-trifluoroethoxy)pyrazine-2-carboxylate (272B). To a solution of 2,2,2-trifluoroethanol (2.70 mL, 37.00 mmol) in 30 mL of THF at 0 °C was added potassium *tert*-butoxide (4.47 g, 39.90 mmol) in small portions. The cloudy mixture was stirred at RT for 15 min then cannulated to a solution of *tert*-butyl 5-chloropyrazine-2-carboxylate (6.11 g, 28.50 mmol) in 50 mL of THF at 0 °C. The mixture was stirred at 0 °C for 30 min then quenched with 50 mL of saturated NH_4Cl. It was extracted with 200 mL of EtOAc. The organic layer was washed with 25 mL of brine, dried ($MgSO_4$), filtered, and concentrated. The residue was purified on a silica gel column (5-25% EtOAc in heptane) to afford *tert*-butyl 5-(2,2,2-trifluoroethoxy)pyrazine-2-carboxylate (5.87 g, 21.10 mmol, 74% yield) as an off-white crystalline solid. ^{19}F NMR

(376 MHz, DMSO-d_6) δ -72.16 (s, 1F). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.81 (d, *J*=1.37 Hz, 1H), 8.58 (d, *J*=1.17 Hz, 1H), 5.13 (q, *J*=8.80 Hz, 2H), 1.57 (s, 9H). *m/z* (ESI, +ve ion) 279.1

Preparation of 5-(2,2,2-trifluoroethoxy)pyrazine-2-carboxylic acid (272). At RT, a solution of *tert*-butyl 5-(2,2,2-trifluoroethoxy)pyrazine-2-carboxylate (5.85 g, 21.03 mmol) in 50 mL of DCM was treated with 2,2,2-trifluoroacetic acid (24.14 mL) drop wise. The resulting mixture was stirred at RT for 3 h. The reaction mixture was concentrated under reduced pressure and the crude product was azeotroped with toluene (3 x 5 mL). The crude product was stirred with 5% EtOAc in hexanes (20 mL) for 1 h and filtered. The filtrate was discarded. The white solid thus obtained was washed with hexanes (2 x10 mL) and collected to afford 5-(oxazol-2-ylmethoxy)pyrazine-2-carboxylic acid as a white crystalline solid which was suspended in 10 mL of dioxane and treated with 4 N HCl in dioxane (40 mmol, 10 mL) followed by 5 mL of water. The mixture was stirred for 5 min at RT. It was concentrated to dryness, then azeotroped with toluene (3 x 5 mL) to provide 5-(2,2,2-trifluoroethoxy)pyrazine-2-carboxylic acid (4.41 g, 19.85 mmol, 94% yield) as a white crystalline solid. ^{19}F NMR (377 MHz, DMSO-d_6) δ -72.16. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.48 (br., 1H), 8.86 (d, *J*=1.17 Hz, 1H), 8.60 (d, *J*=1.17 Hz, 1H), 5.15 (q, *J*=9.00 Hz, 2H). *m/z* (ESI, +ve ion) 223.1

5-(Prop-2-yn-1-yloxy)pyrazine-2-carboxylic acid (273)





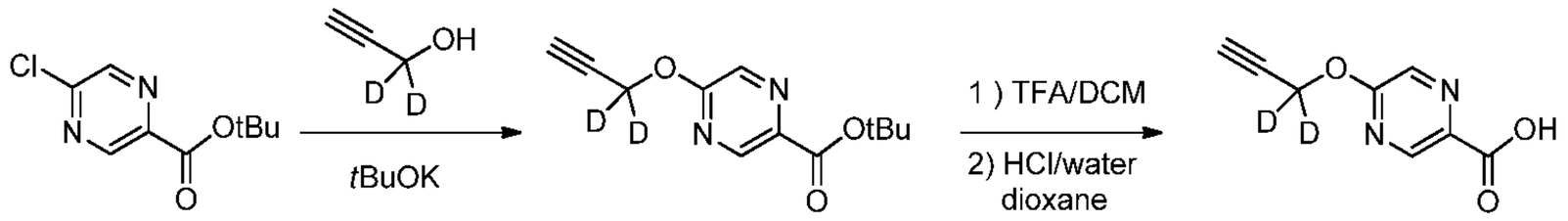
273

Preparation of *tert*-butyl 5-(prop-2-yn-1-yloxy)pyrazine-2-carboxylate. A solution of potassium *tert*-butoxide (**272A**, 78.0 g, 699 mmol) in 1,4-dioxane (2.5 L) was cooled to 0 °C and propargyl alcohol (39.2 g, 699 mmol) was added dropwise. The resulting mixture was allowed to stir for 10 min. A solution of *tert*-butyl 5-chloropyrazine-2-carboxylate (125 g, 582 mmol) in 1,4-dioxane (1.3 L) was added

dropwise to the reaction mixture. The mixture was allowed to slowly warm to ambient temperature and stir for 4 h. The reaction mixture was quenched with sat. aq. NH_4Cl (2.0 L) and stirred for 10 min. The reaction mixture was diluted with EtOAc (3.0 L) and water (2.5 L). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 2 L). The combined organic extract was dried over sodium sulfate, filtered and concentrated under reduced pressure to get the crude product which was purified by column chromatography (silica gel 60-120 mesh, 10% EtOAc in hexanes) to afford *tert*-butyl 5-(prop-2-yn-1-yloxy)pyrazine-2-carboxylate (70 g, 51%) as tan solid. MS (ESI, positive ion) m/z: 235.2 $(M+H)^+$. ^1H NMR (400 MHz, $CDCl_3$) 8.83 (d, J = 1.3 Hz, 1H), 8.35 (d, J = 1.3 Hz, 1H), 5.06 (s, 2H), 2.54 (s, 1H), 1.64 (s, 9H).

Preparation of 5-(prop-2-yn-1-yloxy)pyrazine-2-carboxylic acid (273). A solution of *tert*-butyl 5-(prop-2-yn-1-yloxy)pyrazine-2-carboxylate (140 g, 598 mol) in DCM (480 mL) was cool to 0 °C and TFA (1.4 L) was added dropwise. The reaction mixture was stirred at ambient temperature for 4 h. The reaction mixture was concentrated under reduced pressure to obtain the crude material which was azeotroped with toluene (3 x 1.0 L). The crude material was stirred with 10% EtOAc in hexanes (2.0 L) for 1 h and filtered. The solid was washed with hexane (3.0 L) to provide *tert*-butyl 5-(prop-2-yn-1-yloxy)pyrazine-2-carboxylate (103 g, 97 %) as white solid. MS (ESI, positive ion) m/z: 179.1 $(M+H)^+$. ^1H NMR (400 MHz, DMSO-D_6) δ 13.41 (s, 1H), 8.83 (d, J = 1.3 Hz, 1H), 8.46 (d, J = 1.3 Hz, 1H), 5.11 (d, J = 2.4 Hz, 2H), 3.64 (s, 1H).

5-((1,1-dideuteriumprop-2-yn-1-yl)oxy)pyrazine-2-carboxylic acid (274).

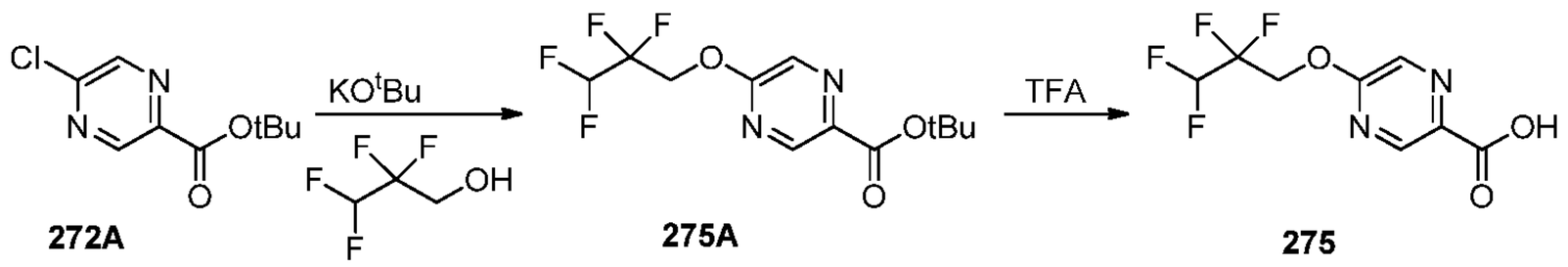


Preparation of *tert*-butyl 5-((1,1-dideuterium-prop-2-yn-1-yl)oxy)pyrazine-2-carboxylate (274A). To a solution of 1,1-dideuterium-prop-2-yn-1-ol (1.81 g, 31.1 mmol) [cat # AM1043, Adesis Inc.] in 30 mL of THF at 0 °C was added potassium *tert*-butoxide (3.77 g, 33.60 mmol) in small portions. The cloudy mixture was stirred at RT for 15 min then cannulated to a solution of *tert*-butyl 5-chloropyrazine-2-carboxylate (5.34 g, 24.88 mmol) in 50 mL of THF at 0 °C. The mixture was stirred at 0 °C for 30 min then treated with 50 mL of saturated NH_4Cl followed by 200 mL of EtOAc. The mixture was transferred to a separatory funnel and the layers were separated. The organic

layer was washed with 25 mL of brine, dried ($MgSO_4$), filtered, and concentrated. The residue was purified on a silica gel column (5-25% EtOAc in heptanes) to afford *tert*-butyl 5-((1,1-dideuterium-prop-2-yn-1-yl)oxy)pyrazine-2-carboxylate (1.40 g, 5.93 mmol, 24% yield) as a colorless viscous oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.81 (d, *J*=1.37 Hz, 1H), 8.46 (d, *J*=1.37 Hz, 1H), 3.63 (s, 1H), 1.57 (s, 9H). *m/z* (ESI, +ve ion) 259.1 $(M+23)^+$.

Preparation of 5-((1,1-dideuteriumprop-2-yn-1-yl)oxy)pyrazine-2-carboxylic acid (274). At RT, a solution of *tert*-butyl 5-((1,1-dideuterium-prop-2-yn-1-yl)oxy)pyrazine-2-carboxylate (1.40 g, 5.93 mmol) in 10 mL of DCM was treated with 2,2,2-trifluoroacetic acid (5.44 mL, 71.1 mmol) drop wise. The resulting mixture was stirred at RT for 4 h. The reaction mixture was concentrated under reduced pressure and the crude product was azeotroped with toluene (2 x 5 mL). The crude product was stirred with 5% EtOAc in hexanes (20 mL) for 1 h and filtered. The filtrate was discarded. The white solid thus obtained was washed with hexanes (2 x10 mL) and collected. ^{19}F-NMR of the white solid indicated the presence of trace amount of 2,2,2-trifluoroacetic acid. The off white solid was suspended in 3 mL of dioxane and treated with 4 N HCl in dioxane (6 mmol, 1.5 mL) followed by 1 mL of water. The mixture was stirred for 5 min at RT. It was concentrated to dryness, then azeotroped with toluene (5 mL) to provide 5-((1,1-dideuteriumprop-2-yn-1-yl)oxy)pyrazine-2-carboxylic acid (1.0 g, 5.55 mmol, 94% yield) as a white crystalline solid. ^{19}F-NMR of the white solid indicated the absence of 2,2,2-trifluoroacetic acid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.36 (br., 1H), 8.84 (d, *J*=1.17 Hz, 1H), 8.47 (d, *J*=1.17 Hz, 1H), 3.63 (s, 1H). *m/z* (ESI, +ve ion) 181.2 $(M+H)^+$.

5-(2,2,3,3-Tetrafluoropropoxy)pyrazine-2-carboxylic acid (275).



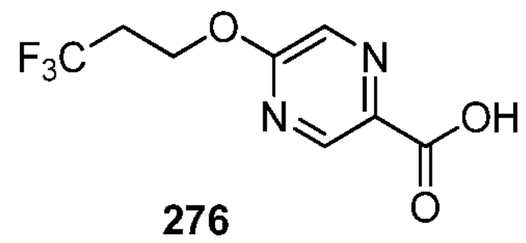
272A **275A** **275**

To a solution of 2,2,3,3-tetrafluoro-1-propanol (1.1 mL, 8.4 mmol) in 5 mL of THF at 0 ºC was added a solution of potassium *tert*-butoxide (1.0 M solution in THF (9.08 mL, 9.08 mmol)) by syringe over 2 min. The orange mixture was stirred at RT for 15 min then cannulated to a solution of *tert*-butyl 5-chloropyrazine-2-carboxylate (**272A**, 1.5 g, 6.99 mmol) in 15 mL of THF at 0 ºC. The mixture was stirred at 0 ºC for 30 min. The reaction was quenched with saturated aqueous NH_4Cl (30 mL) and diluted with EtOAc (100 mL) and water (30 mL). The layers were separated and the organic layer was

washed with brine (25 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography eluting with a gradient of 0-30% EtOAc/heptane to give *tert*-butyl 5-(2,2,3,3-tetrafluoropropoxy)pyrazine-2-carboxylate as a yellow solid (**275A**, 1.88 g, 87%). LC/MS (ESI^+) *m/z* = 333.1 $(M+Na)^+$. ^1H NMR (400 MHz, chloroform-d) δ 8.81 (d, J=1.17 Hz, 1H), 8.41 (d, J=1.17 Hz, 1H), 5.83-6.17 (m, 1H), 4.84 (t, J=12.72 Hz, 2H), 1.65 (s, 9H).

2,2,2-Trifluoroacetic acid (6.66 mL, 87 mmol) was added at RT to a stirring solution of *tert*-butyl 5-(2,2,3,3-tetrafluoropropoxy)pyrazine-2-carboxylate (**275A**, 1.8 g, 5.8 mmol) in DCM (11.6 mL). The pink solution was stirred at RT for 3 h and then concentrated in vacuo. The residue was azeotroped with toluene (2 x 25 mL) to give 5-(2,2,3,3-tetrafluoropropoxy)pyrazine-2-carboxylic acid (**275**) as a white solid (1.38 g, 94%). LC/MS (ESI^+) *m/z* = 255.1 $(M+H)^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 13.44 (br. s., 1H), 8.83 (d, J=1.37 Hz, 1H), 8.53 (d, J=1.17 Hz, 1H), 6.54-6.87 (m, 1H), 5.00 (t, J=14.08 Hz, 2H).

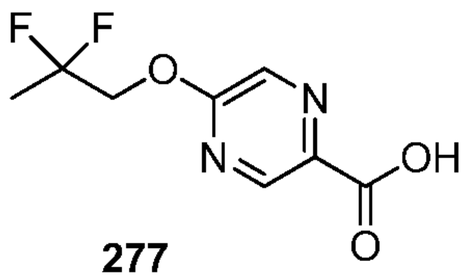
5-(3,3,3-Trifluoropropoxy)pyrazine-2-carboxylic acid (276).



276

The title compound was synthesized according to intermediate **275**, using 3,3,3-trifluoropropan-1-ol to react with *tert*-butyl 5-chloropyrazine-2-carboxylate **272A**. LC/MS (ESI^+) *m/z* = 237.1 $(M+H)^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 13.32 (br. s., 1H), 8.83 (d, J=1.17 Hz, 1H), 8.41 (d, J=1.17 Hz, 1H), 4.63 (t, J=5.97 Hz, 2H), 2.88 (m, 2H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -63.2.

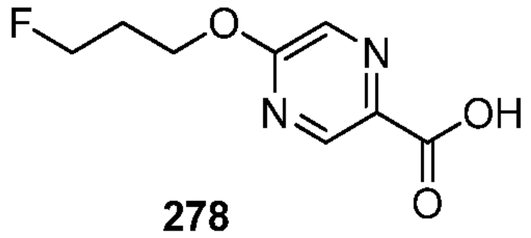
5-(2,2-Difluoropropoxy)pyrazine-2-carboxylic acid (277).



277

The title compound was synthesized according to intermediate **275**, using 3,3,3-trifluoropropan-1-ol to react with *tert*-butyl 5-chloropyrazine-2-carboxylate **272A**. LC/MS (ESI^+) *m/z* = 219.2 $(M+H)^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 13.38 (br. s., 1H), 8.82 (d, J=1.17 Hz, 1H), 8.51 (d, J=0.98 Hz, 1H), 4.70 (t, J=13.20 Hz, 2H), 1.76 (t, J=19.27 Hz, 3H); ^{19}F NMR (376 MHz, DMSO-d_6) δ -97.3.

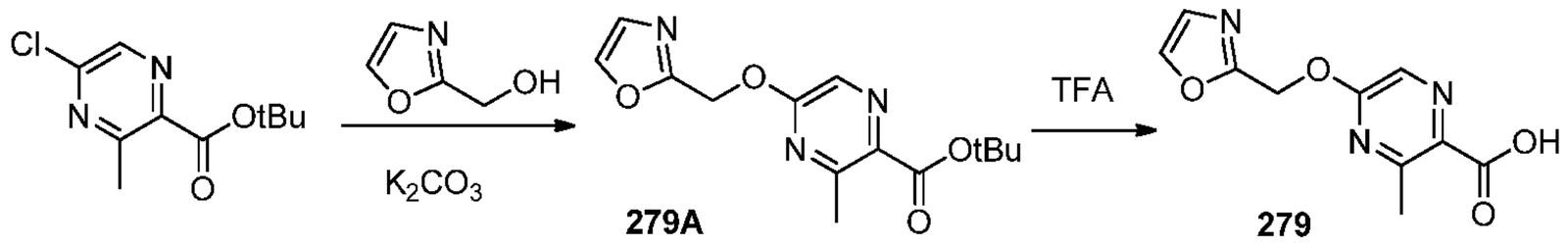
5-(3-Fluoropropoxy)pyrazine-2-carboxylic acid (278).



278

The title compound was synthesized according to intermediate **275**, using 3,3,3-trifluoropropan-1-ol to react with *tert*-butyl 5-chloropyrazine-2-carboxylate **272A**. LC/MS (ESI^+) *m/z* = 201.2 $(M+H)^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.80 (d, J=1.17 Hz, 1H), 8.38 (d, J=1.37 Hz, 1H), 4.67 (t, J=5.87 Hz, 1H), 4.55 (t, J=5.87 Hz, 1H), 4.49 (t, J=6.36 Hz, 2H), 2.08-2.23 (m, 2H); ^{19}F NMR (376 MHz, DMSO-d_6) δ -74.5.

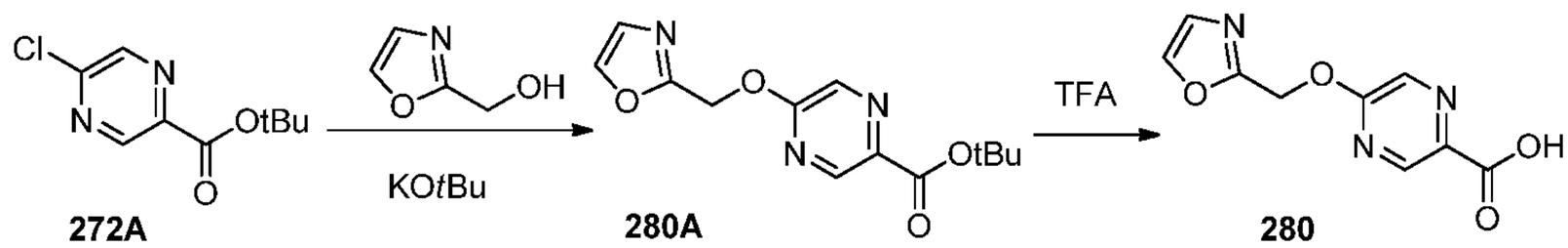
3-Methyl-5-(oxazol-2-ylmethoxy)pyrazine-2-carboxylic acid (279).



279A **279**

To a solution of *tert*-butyl 5-chloro-3-methylpyrazine-2-carboxylate (3.8 g, 16.62 mmol) and oxazol-2-ylmethanol ((Combi-Blocks Inc., 3.29 g, 33.2 mmol) in 3 mL of DMF was added potassium carbonate (4.59 g, 33.2 mmol). The reaction mixture was stirred overnight. The contents were loaded onto a flash column and eluted with a gradient of (hexanes: EtOAc = 5:1 to 2:1) to give *tert*-butyl 3-methyl-5-(oxazol-2-ylmethoxy)pyrazine-2-carboxylate (**279A**, 4.16 g, 14.28 mmol, 86% yield) as a colorless oil. ^1H NMR (300 MHz, CHLOROFORM-d) δ 8.20 (s, 1H), 7.69 (d, *J*=0.88 Hz, 1H), 7.16 (s, 1H), 5.53 (s, 2H), 2.71 (s, 3H), 1.63 (s, 9H). To the ester was added TFA (18.52 mL, 249 mmol) dropwise and the mixture was stirred at RT overnight. The TFA was removed in vacuo. The residue was treated with 15 mL of 1 N aqueous HCl and azeotroped in vacuo to remove the residual TFA (repeated twice). The residue was dried under house vacuum overnight to give 3-methyl-5-(oxazol-2-ylmethoxy)pyrazine-2-carboxylic acid (3.6 g, 15.31 mmol, 92% yield) as a white solid. ^1H NMR (300 MHz, CHLOROFORM-d) δ 8.10 (s, 1H), 7.71 (d, *J*=0.88 Hz, 1H), 7.18 (s, 1H), 5.59 (s, 2H), 2.91 (s, 3H). LC/MS (ESI^+) *m/z* = 236.0 $(M+H)^+$.

5-(Oxazol-2-ylmethoxy)pyrazine-2-carboxylic acid (280).

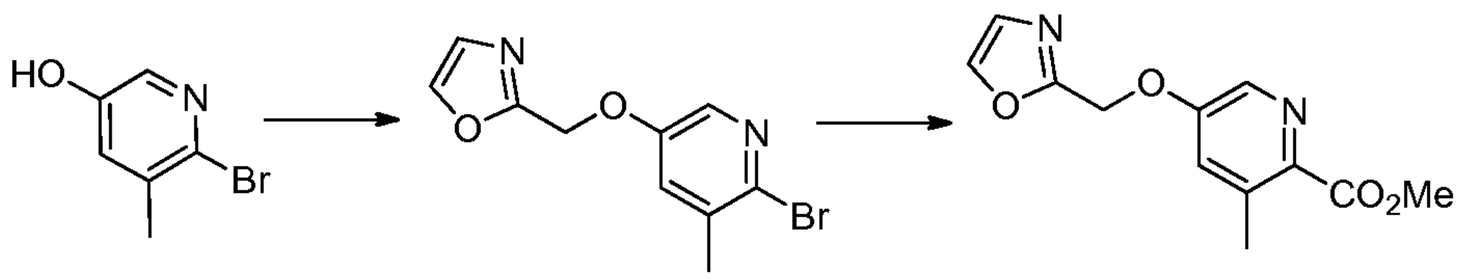


272A **280A** **280**

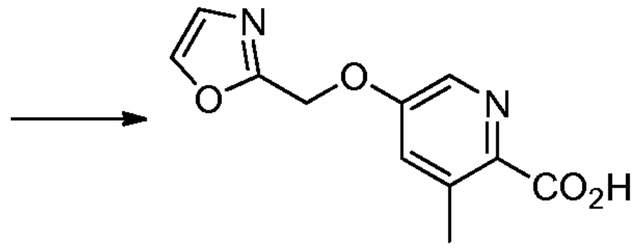
Compound **280A** (3.07 g, 11.07 mmol, 66% yield) as an off white crystalline solid was prepared according to intermediate **272B** starting from **272A** (3.59 g, 16.72 mmol) and oxazol-2-ylmethanol (Combi-Blocks Inc., 1.99 g, 20,07 mmol). LC/MS (ESI^+) *m/z* = 278.1 $(M+H)^+$.

Compound **280** (4.15 g, 18.76 mmol, 99% yield) as an off white crystalline solid was prepared according to intermediate **272** starting from **280A** (5.26 g, 18.97 mmol). ^1H NMR (400 MHz, DMSO-d_6) δ 8.81 (m, 1H), 8.50 (d, *J*=1.37 Hz, 1H), 8.18 (d, *J*=0.78 Hz, 1H), 7.28 (s, 1H), 5.58 (s, 2H), 4.55-5.55 (br., 1H). LC/MS (ESI^+) *m/z* = 222.0 $(M+H)^+$.

3-Methyl-5-(oxazol-2-ylmethoxy)picolinic acid (281).



281A **281B**



281

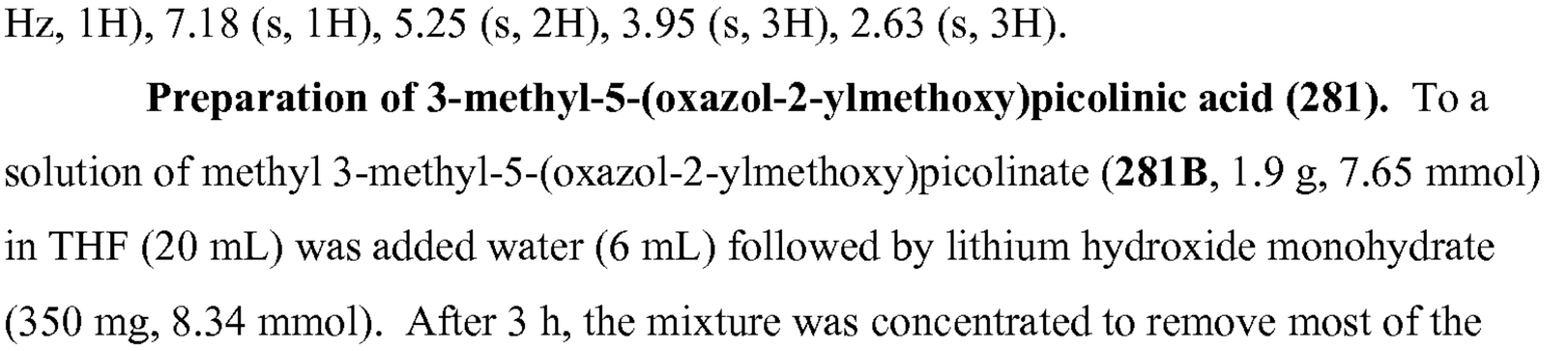
Preparation of 2-(((6-bromo-5-methylpyridin-3-yl)oxy)methyl)oxazole (281A). To a solution of 2-oxazolemethanol (1.12 g, 11.30 mmol, Combi-Blocks Inc.) and triphenylphosphine (3.72 g, 14.18 mmol) in THF (20 mL) was added 2-bromo-5-hydroxy-3-picoline (2.27 g, 12.07 mmol, AOB Chem USA). The mixture was cooled to 0 °C and 1,2-ethoxycarbonyl diazene (2.5 mL, 13.72 mmol) was added slowly. The solution was slowly allowed to warm to RT. After 21 h, diisopropyl azodicarboxylate (1.5 mL, 7.63 mmol) was added to the mixture. About 1.5 h later, a second batch of diisopropyl azodicarboxylate (1.5 mL, 7.63 mmol) was added. The mixture was stirred at RT for an additional 4 h and was diluted with EtOAc (50 mL). The solution was washed with NaOH (0.5 N, 10 mL), water, brine, and then dried over Na_2SO_4 and concentrated. The residue was purified by silica gel chromatography (10-50% EtOAc in DCM) to afford 2-(((6-bromo-5-methylpyrid in-3-yl)oxy)methyl)oxazole (3.8 g, ~80% pure) as a white solid that contained the hydrazine by-product as impurities (based on ^1H-NMR). LCMS (ESI, pos.) 269.0 $(M+1)^+$. ^1H NMR (400 MHz, CHLOROFORM-d) δ 8.02 (d,

J=2.93 Hz, 1H), 7.70 (d, *J*=0.78 Hz, 1H), 7.23 (d, *J*=2.74 Hz, 1H), 7.17 (s, 1H), 5.18 (s, 2H), 2.37 (s, 3H).

Preparation of methyl 3-methyl-5-(oxazol-2-ylmethoxy)picolinate (281B). To a mixture of palladium (II) acetate (63 mg, 0.28 mmol) and 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (327 mg, 0.56 mmol) under N_2 was added 2-(((6-bromo-5-methylpyridin-3-yl)oxy)methyl)oxazole (**281A**, 3.8 g, 11.30 mmol, ~80% pure) in MeOH (50 mL, 1233 mmol) and TEA (18.90 mL, 136 mmol) in a 250 mL pressure tube. The mixture was evacuated-purged with CO gas (balloon) 3-times. The valves were closed and the mixture was heated at 70 °C for 24 h. The mixture was removed from the heater and was filtered through a pad of Celite® filter aid. The Celite® filter aid was washed with EtOAc (3 x 20 mL). The filtrate was concentrated in vacuo and partitioned between EtOAc (60 mL) and saturated $NaHCO_3$ (40 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The crude material was purified by silica gel chromatography using a gradient of 0-5% MeOH in EtOAc. The product was obtained as a white solid (1.9 g, 68% over two steps). LCMS (ESI, pos.) 249.1 $(M+1)^+$. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.33 (d, *J*=2.74 Hz, 1H), 7.71 (s, 1H), 7.23 (d, *J*=2.54 Hz, 1H), 7.18 (s, 1H), 5.25 (s, 2H), 3.95 (s, 3H), 2.63 (s, 3H).

Preparation of 3-methyl-5-(oxazol-2-ylmethoxy)picolinic acid (281). To a solution of methyl 3-methyl-5-(oxazol-2-ylmethoxy)picolinate (**281B**, 1.9 g, 7.65 mmol) in THF (20 mL) was added water (6 mL) followed by lithium hydroxide monohydrate (350 mg, 8.34 mmol). After 3 h, the mixture was concentrated to remove most of the THF. The pH of the aqueous layer was adjusted to 3-4 by HCl (5 N). Solid NaCl was added to saturate the solution. The mixture was extracted with 2% IPA in $CHCl_3$ (5 x 30 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated to give a white solid (1.74 g, 95%). LCMS (ESI, pos.) 235.1 $(M+1)^+$. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.21 (d, *J*=2.35 Hz, 1H), 7.73 (s, 1H), 7.31 (d, *J*=2.15 Hz, 1H), 7.19 (s, 1H), 5.28 (s, 2H), 2.76 (s, 3H).

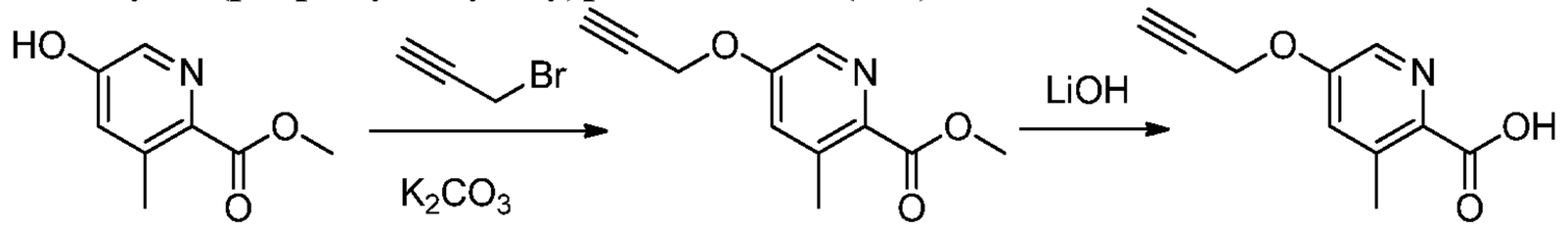
3-Methyl-5-(2,2,2-trifluoroethoxy)picolinic acid (282).



282

To a solution of 5-hydroxy-3-methylpicolinonitrile (0.49 g, 3.63 mmol) in DMF (5 mL) were added cesium carbonate (1.54 g, 4.72 mmol) and 2,2,2-trifluoroethyl trifluoromethanesulfonate (1.01 mL, 4.36 mmol). The resulting suspension was stirred at RT overnight. The reaction mixture was diluted with water and EtOAc. The organic layer was washed with 1 M LiCl solution and brine, dried over $_{MgSO4}$ and concentrating in vacuo. The crude 3-methyl-5-(2,2,2-trifluoroethoxy)picolinonitrile was taken up in EtOH (20 mL) and 1 M NaOH (10.89 mL, 10.89 mmol) was added. The reaction was heated at reflux until the conversion was complete. The mixture was cooled to RT and diluted with ether and water. The organic layer was washed with additional water and the combined aqueous layers were acidified to pH = 1 by the addition of 1 M HCl. The aqueous layer was extracted with DCM twice and the combined organics were washed with brine, dried over $MgSO_4$ and concentrated in vacuo to afford 3-methyl-5-(2,2,2-trifluoroethoxy)picolinic acid (0.75 g, 88% yield). LC/MS (ESI$^-$) *m/z* = 236 $(M+H)^+$. ^{1}H NMR (300 MHz, DMSO-*d*6) δ ppm 2.50 (s, 3 H) 4.94 (q, *J*=8.77 Hz, 2 H) 7.53 (d, *J*=2.63 Hz, 1 H) 8.28 (d, *J*=2.78 Hz, 1 H).

3-Methyl-5-(prop-2-yn-1-yloxy)picolinic acid (283).



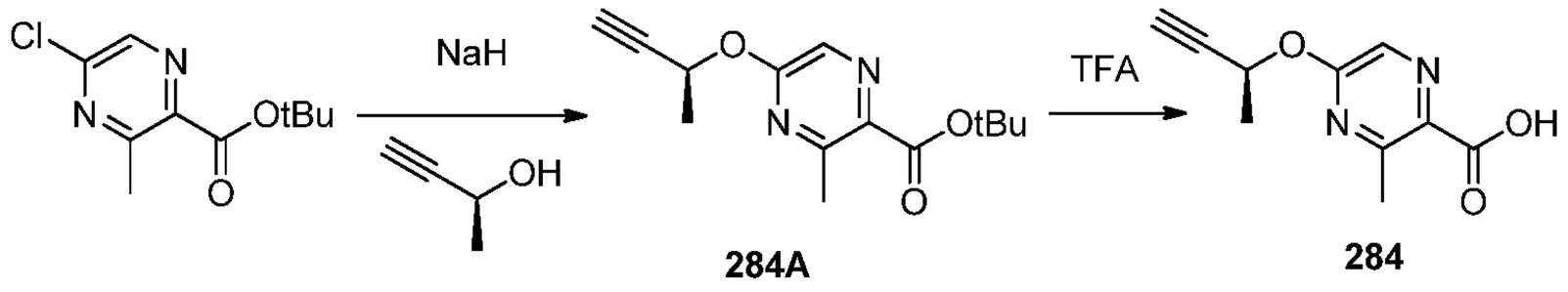
283

To a suspension of methyl 5-hydroxy-3-methylpicolinate (1.00 g, 5.98 mmol) and potassium carbonate (1.24 g, 8.97 mmol) in DMF (25 mL) was added propargyl bromide (80% solution in toluene, 0.80 mL, 7.18 mmol) dropwise at RT. The mixture was heated to 45 °C for 1 h, then diluted with EtOAc and washed with water and brine. The organic solution was dried over Na_2SO_4 and concentrated in vacuo. Purification by silica gel chromatography (40 g, 0-70% EtOAc in hexanes) afforded methyl 3-methyl-5-(prop-2-yn-1-yloxy)picolinate as yellow solid (1.21 g, 99% yield). LC/MS (ESI$^-$) *m/z* = 206 $(M+H)^+$. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 2.58 (t, *J*=2.45 Hz, 1 H) 2.64 (s, 3 H) 3.96 (s, 3 H) 4.79 (d, *J*=2.54 Hz, 2 H) 7.16 (d, *J*=2.54 Hz, 1 H) 8.31 (d, *J*=2.74 Hz, 1 H).

To a suspension of methyl 3-methyl-5-(prop-2-yn-1-yloxy)picolinate (1.21 g, 5.90 mmol) and lithium hydroxide hydrate (0.26 g, 6.19 mmol) was added THF (16 mL) and water (4 mL). The mixture was stirred at RT for 1.5 h, then neutralized with 8.5 mL of 1 N HCl, and diluted with brine and a mixed solvent of i-PrOH:$CHCl_3$ (v/v 1:3). The

aqueous layer was further extracted with the mixed solvent. The organic layer was dried over Na_2SO_4 and concentrated in vacuo to give 3-methyl-5-(prop-2-yn-1-yloxy)picolinic acid (1.10 g, 98% yield) as off-white solid. LC/MS (ESI^-) *m/z* = 192 $(M+H)^+$. ^1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 2.62 (br. s., 1 H) 2.77 (s, 3 H) 4.82 (br. s., 2 H) 7.26 (br. s., 1 H) 8.18 (br. s., 1 H).

(*S*)-5-(But-3-yn-2-yloxy)-3-methylpyrazine-2-carboxylic acid (284).

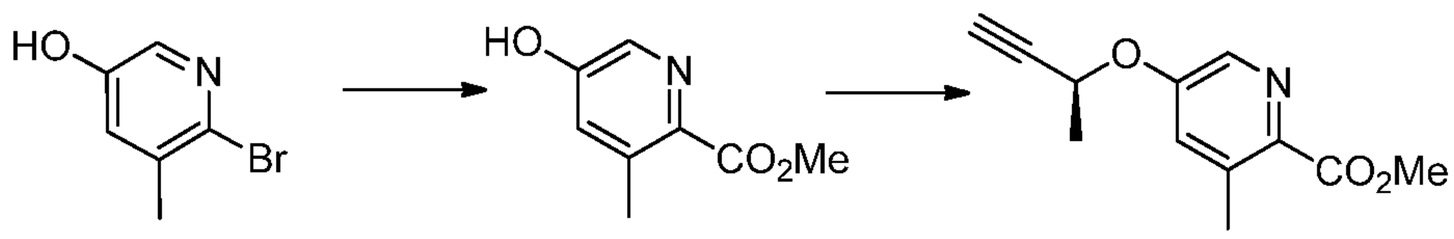


284A 284

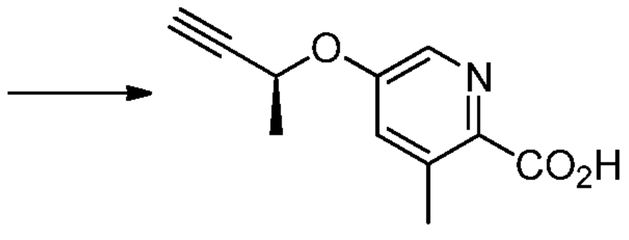
Preparation of (*S*)-*tert*-butyl 5-(but-3-yn-2-yloxy)-3-methylpyrazine-2-carboxylate (284A). To a solution of *tert*-butyl 5-chloro-3-methylpyrazine-2-carboxylate (2.50 g, 10.93 mmol) and (*S*)-3-butyn-2-ol (0.95 mL, 12.03 mmol) in THF (10 mL) at 0 °C was added in portion wise sodium hydride (60% wt. in oil, 0.48 g, 12.03 mmol). The reaction was stirred at 0 °C for 2 h, treated with saturated NH_4Cl solution (100 mL) and extracted with EtOAc (200 mL). The organic solution was concentrated under reduced pressure and the residue was purified via silica gel chromatography (0-10% EtOAc in heptane) to afford (S)-*tert*-butyl 5-(but-3-yn-2-yloxy)-3-methylpyrazine-2-carboxylate (1.25 g, 4.77 mmol, 43% yield) as a colorless oil. LC/MS (ESI^+) *m/z*=285.0 $(M+23)^+$. ^1H NMR (300 MHz, CHLOROFORM-d) δ 8.13 (s, 1H), 5.85 (dq, *J*=2.05, 6.67 Hz, 1H), 2.73 (s, 3H), 2.46 (d, *J*=2.05 Hz, 1H), 1.67 (d, *J*=6.72 Hz, 3H), 1.65 (s, 9H).

Preparation of Compound 284. TFA (20 mL, 269 mmol) was added at RT to a stirring solution of (*S*)-*tert*-butyl 5-(but-3-yn-2-yloxy)-3-methylpyrazine-2-carboxylate (1.85 g, 7.05 mmol) in DCM (20 mL). The reaction mixture was stirred at RT for 4 h and then concentrated in vacuo. The residue was dissolved in 4 N HCl in dioxane (5 mL) and 1 N HCl (10 mL), stirred at RT for 30 min and concentrated in vacuo to give (*S*)-5-(but-3-yn-2-yloxy)-3-methylpyrazine-2-carboxylic acid (1.3 g, 6.30 mmol, 89% yield). LC/MS (ESI^+) *m/z* = 207.2 $(M+H)^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 13.10 (br. s., 1H), 8.22 (s, 1H), 5.80 (dq, *J*=2.05, 6.62 Hz, 1H), 3.56-3.59 (m, 1H), 2.69 (s, 3H), 1.60 (d, *J*=6.65 Hz, 3H).

Preparation of (S)-methyl 5-(but-3-yn-2-yloxy)-3-methylpicolinate (285).



285A **285B**



285

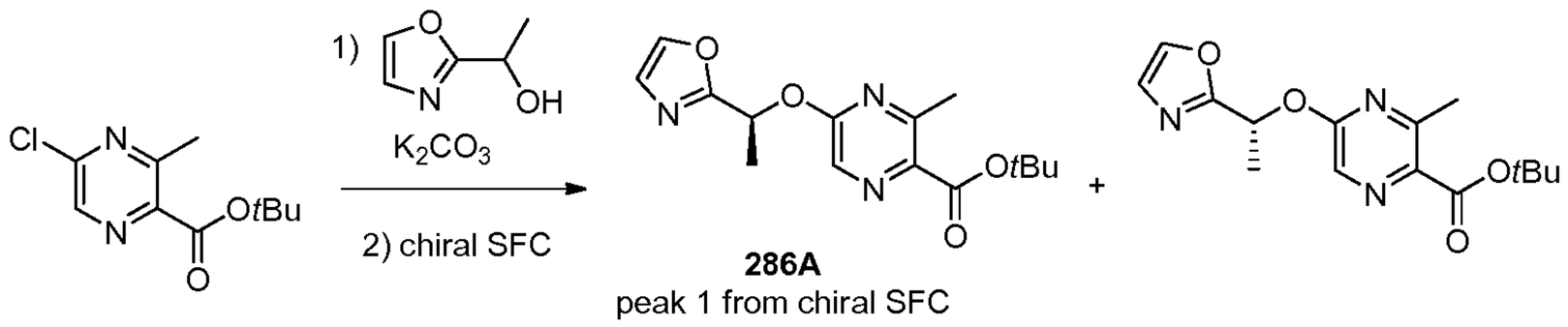
Preparation of methyl 5-hydroxy-3-methylpicolinate (285A). To a mixture of 2-bromo-5-hydroxy-3-picoline (2.18 g, 11.59 mmol), TEA (19.39 mL, 139 mmol), and MeOH (30 mL, 740 mmol) in a 250 mL pressure tube was added 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (335 mg, 0.58 mmol) and palladium (II) acetate (65 mg, 0.29 mmol). The mixture was evacuated-purged with CO gas (balloon) 3-times. The valves were closed and the mixture was heated at 70 °C for 24 h. The mixture was filtered through a pad of Celite® filter aid. The Celite® filter aid was washed with MeOH. The filtrate was concentrated in vacuo and dissolved in DCM (50 mL). The organic solution was washed with saturated $NaHCO_3$ (30 mL). The aqueous layer was saturated with NaCl and extracted with 2% IPA in $CHCl_3$ (3 x 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude was purified by silica gel chromatography using 1-5% MeOH in DCM to give the product as an off-white solid (1.65 g, 85%). LCMS (ESI, pos.) 168.0 $(M+1)^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.57 (br. s., 1H), 8.02 (d, *J*=2.54 Hz, 1H), 7.08 (d, *J*=2.15 Hz, 1H), 3.79 (s, 3H), 2.44 (s, 3H).

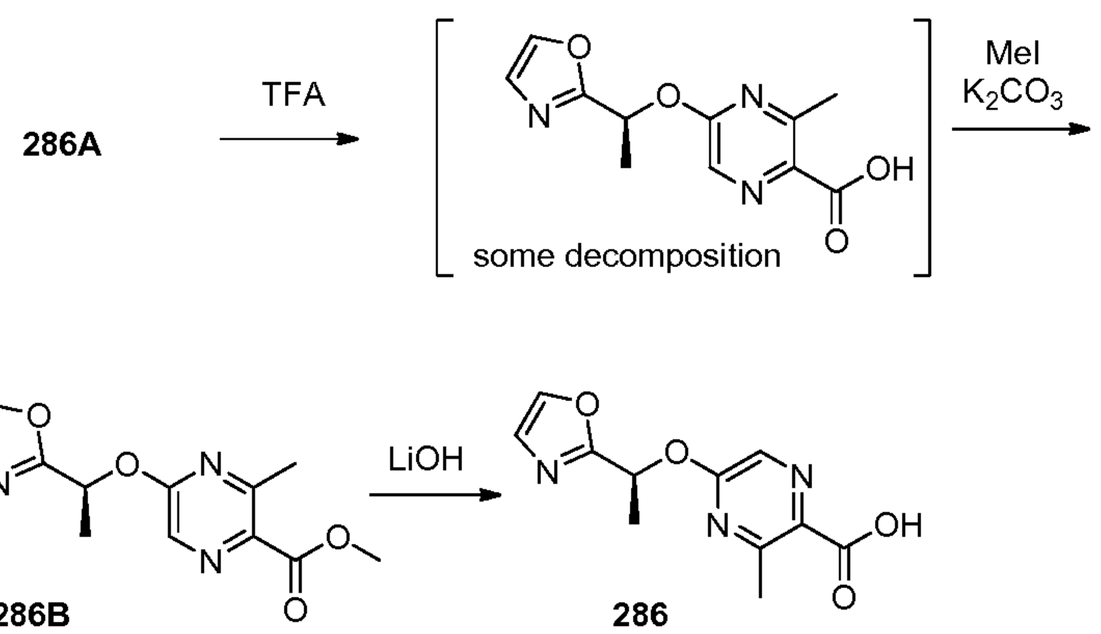
Preparation of (S)-methyl 5-(but-3-yn-2-yloxy)-3-methylpicolinate (285B). To a solution of (*R*)-(+)-3-butyn-2-ol (Sigma-Aldrich, 0.294 mL, 4.19 mmol), triphenylphosphine (1.2 g, 4.58 mmol) and methyl 5-hydroxy-3-methylpicolinate (**285A**, 0.7 g, 4.19 mmol) in THF (20 mL) at 0 °C was added diisopropyl azodicarboxylate (1.0 mL, 5.09 mmol) slowly. The solution was allowed to warm to RT and stirred overnight. About ~1/4 of the theoretical amount of the alcohol, PPh_3, and DIAD were added and the mixture was stirred for additional 1.5 h. The mixture was quenched with MeOH (2 mL)

and concentrated. The residue was purified by silica gel chromatography (10- 50% EtOAc/heptane) to afford (S)-methyl 5-(but-3-yn-2-yloxy)-3-methylpicolinate (1.9 g, 8.67 mmol, 207% yield) as a white foam that was contaminated by the hydrazine by-product. LCMS (ESI, pos.) 220.1 $(M+1)^+$. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.32 (d, *J*=2.74 Hz, 1H), 7.21 (d, *J*=2.54 Hz, 1H), 4.98 (m, 1H, overlapping with DIAD OC-H), 3.96 (s, 3H), 2.64 (s, 3H), 2.54 (d, *J*=1.96 Hz, 1H), 1.71 (d, *J*=6.46 Hz, 4H).

Preparation of (S)-methyl 5-(but-3-yn-2-yloxy)-3-methylpicolinate (285). A mixture of (S)-methyl 5-(but-3-yn-2-yloxy)-3-methylpicolinate prepared above (**285B**, 1.9 g contaminated, theoretical 4.11 mmol) and lithium hydroxide (270 mg, 6.43 mmol) in MeOH (10 mL) and water (10 mL) was stirred at RT for 3 h. The mixture was concentrated to remove most of the MeOH. The aqueous layer was extracted with DCM (3 x10 mL) to remove hydrazine carried from previous step. The aqueous layer was treated with HCl (5 N, 1.5 mL) to bring the pH of the solution to ~3-4. Solid NaCl was added to saturate the solution. The mixture was extracted with 2% IPA in $CHCl_3$ (3 x 10 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated to give a white solid that was still not pure. The solid was dissolved in EtOAc (30 mL) and extracted with saturated $NaHCO_3$ (3 x 10 mL). The combined aqueous layers were acidified with HCl (conc.) until the pH reached ~3. The solution was saturated with NaCl and extracted with 2% IPA in $CHCl_3$ (3 x 10 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated. The resulting solid was suspended in ACN (5 mL) and water (2 mL) and was lyophilized for 48 h to give a white powder (0.78 g, 92% yield over two steps). LCMS (ESI, pos.) 206.0 $(M+1)^+$. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.17 (d, *J*=2.35 Hz, 1H), 7.27 (d, *J*=2.15 Hz, 1H), 4.97 (dq, *J*=1.96, 6.52 Hz, 1H), 4.75 (s, 1H), 2.76 (s, 3H), 2.57 (d, *J*=2.15 Hz, 1H), 1.73 (d, *J*=6.46 Hz, 3H).

(S)-3-Methyl-5-(1-(oxazol-2-yl)ethoxy)pyrazine-2-carboxylic acid (286).





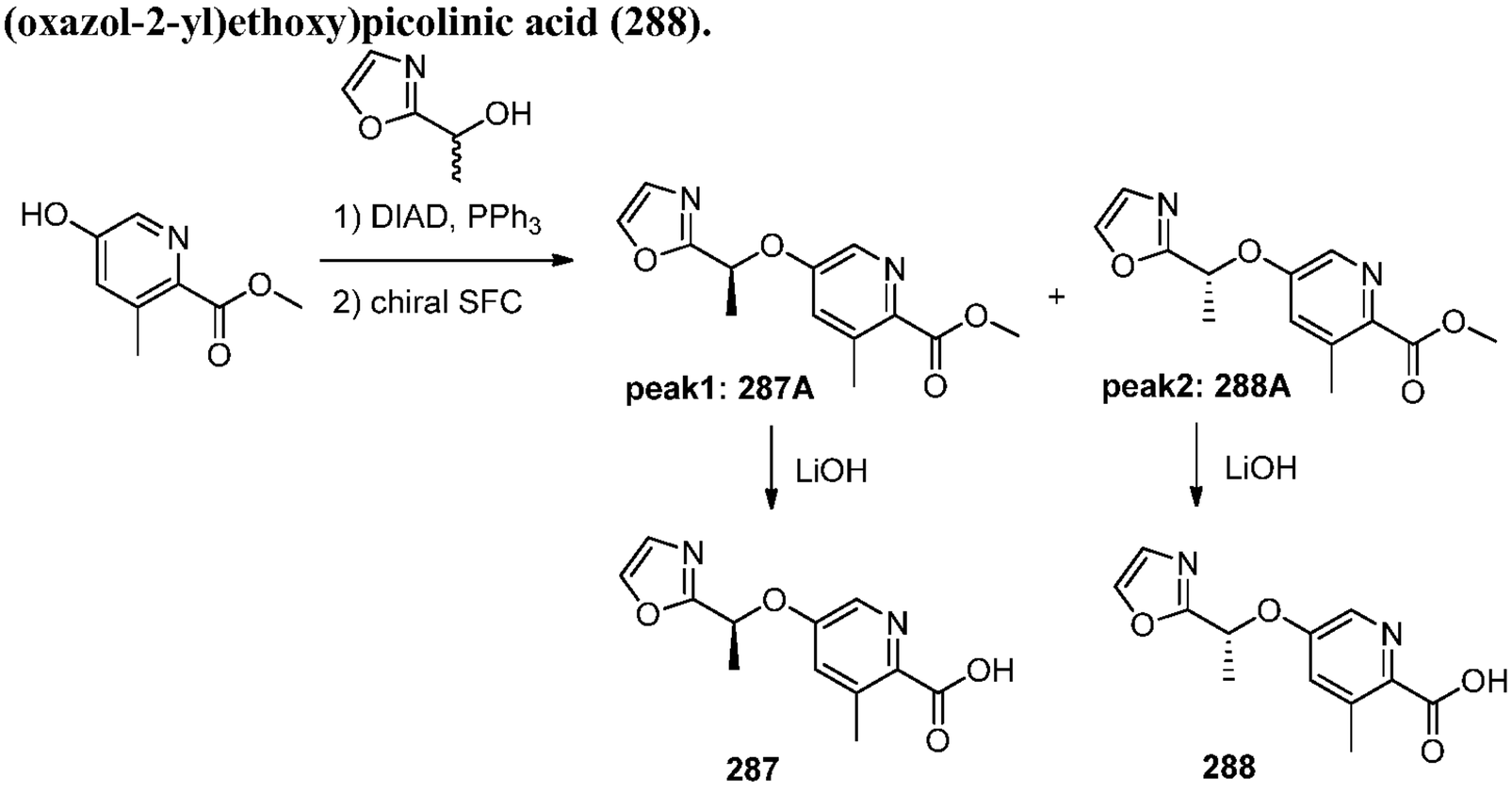
Preparation of Compound 286A. To a solution of *tert*-butyl 5-chloro-3-methylpyrazine-2-carboxylate (7.0 g, 30.6 mmol) and 1-(oxazol-2-yl)ethanol (5.19 g, 45.9 mmol) in 5 mL of DMF was added potassium carbonate (8.46 g, 61.2 mmol). The reaction was stirred overnight. LCMS showed about 10-20% conversion. It was heated at 55 °C for another 24 h. LCMS showed >90% conversion. The reaction was directly loaded onto a silica gel column and eluted with a gradient of (heptane/EtOAc = 5:1 to 4:1 to 2:1) to give *tert*-butyl 3-methyl-5-(1-(oxazol-2-yl)ethoxy)pyrazine-2-carboxylate as a colorless oil. This material (5.5 g) was chromatographed using supercritical CO_2 (additives 10% of 20 mM NH_3 in IPOH) on a AY-H column (30 x 250mm, 5 μm) eluting at a flow rate 100 mL/min (100 bar pressure). The absolute stereochemistry was arbitrarily assigned. The first peak (retention time = 1.0 min) provided (S)-*tert*-butyl 3-methyl-5-(1-(oxazol-2-yl)ethoxy)pyrazine-2-carboxylate (**286A**, 2.25 g, 7.37 mmol, 24% yield). LCMS (ESI^+) m/z = 306 $(M+H)^+$. ^1H NMR (300 MHz, CHLOROFORM-d) δ 8.16 (s, 1H), 7.62 (d, *J*=0.73 Hz, 1H), 7.10 (s, 1H), 6.40 (q, *J*=6.72 Hz, 1H), 2.67 (s, 3H), 1.79 (d, *J*=6.58 Hz, 3H), 1.62 (s, 9H). The second peak (retention time = 3.2 min) provided (R)-*tert*-butyl 3-methyl-5-(1-(oxazol-2-yl)ethoxy)pyrazine-2-carboxylate (2.23 g, 7.30 mmol, 24% yield).

Preparation of Compound 286B. To (S)-*tert*-butyl 3-methyl-5-(1-(oxazol-2-yl)ethoxy)pyrazine-2-carboxylate (**286A**, 2.3 g, 7.53 mmol) was added TFA (8.39 mL,

113 mmol) dropwise and the mixture was stirred at RT overnight. The TFA was removed in vacuo. The residue was treated with 15 mL of 1 N aqueous HCl and azeotroped in vacuo to remove the residual TFA (repeated twice). The residue was dried under house vacuum overnight to give a gum. LCMS showed that the gum not pure (some decomposition). The gum was dissolved in DMF (3 mL), treated with iodomethane (0.56 mL, 9.04 mmol) and potassium carbonate (1.56 g, 11.30 mmol). After stirring overnight, the reaction was diluted with water, extracted with EtOAc, washed with sat. $NaHCO_3$, dried and evaporated to dryness. Flash column (DCM to DCM/EtOAc = 10:1) gave (S)-methyl 3-methyl-5-(1-(oxazol-2-yl)ethoxy)pyrazine-2-carboxylate (**286B**, 540 mg, 2.051 mmol, 27% yield) as a gum. LCMS (ESI^+) m/z = 264.2 $(M+H)^+$. ^1H NMR (300 MHz, CHLOROFORM-d) δ 8.18 (s, 1H), 7.63 (d, *J*=0.73 Hz, 1H), 7.11 (s, 1H), 6.43 (q, *J*=6.72 Hz, 1H), 3.97 (s, 3H), 2.76 (s, 3H), 1.80 (d, *J*=6.72 Hz, 3H).

Preparation of Compound 286. A solution of (S)-methyl 3-methyl-5-(1-(oxazol-2-yl)ethoxy)pyrazine-2-carboxylate (**286B**, 520 mg, 1.97 mmol) in THF (10 mL) was treated with lithium hydroxide hydrate (249 mg, 5.93 mmol) in 50 mL of water and the mixture was stirred at ambient temperature for 3 h. The mixture was treated with 5 M aqueous HCl (1.3 mL), and extracted with DCM (3 x 50 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated to give (S)-3-methyl-5-(1-(oxazol-2-yl)ethoxy)pyrazine-2-carboxylic acid (**286**, 490 mg, 1.97 mmol, 100 % yield) as a white solid. LCMS (ESI^+) m/z = 250.2 $(M+H)^+$. ^1H NMR (300 MHz, CHLOROFORM-d) δ 10.64 (br. s., 1H), 8.05 (s, 1H), 7.64 (d, *J*=0.73 Hz, 1H), 7.12 (d, *J*=0.73 Hz, 1H), 6.46 (q, *J*=6.67 Hz, 1H), 2.87 (s, 3H), 1.82 (d, *J*=6.72 Hz, 3H).

(S)-3-Methyl-5-(1-(oxazol-2-yl)ethoxy)picolinic acid (287) and (R)-3-methyl-5-(1-(oxazol-2-yl)ethoxy)picolinic acid (288).



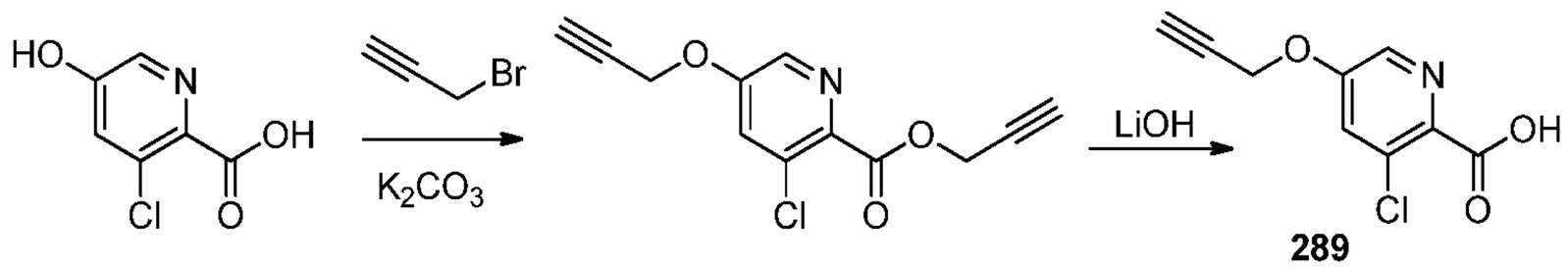
Preparation of Compounds 287A and 288A. To a mixture of methyl 5-hydroxy-3-methylpicolinate (1.66 g, 9.93 mmol), triphenylphosphine (3.91 g, 14.90 mmol), 1-(oxazol-2-yl)ethanol (1.42 g, 11.92 mmol) in THF (40 mL) at 0 °C was added diisopropyl azodicarboxylate (2.93 mL, 14.90 mmol) dropwise. The reaction was gradually warmed to RT and stirred overnight. The mixture was treated with MeOH (2 mL) and concentrated in vacuo. The residue was diluted with EtOAc (50 mL) and washed sequentially with NaOH (0.5 N, 10 mL), water, and brine, then dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel chromatography (10-100% EtOAc in heptane). The mixture of two enantiomers was obtained and chromatographed using supercritical CO_2 (additives 15% of EtOH with 20 mM NH_3) on an AY-H column (150 x 4.6 mm, 5 μm) eluting at a flow rate of 4 mL/min (100 bar pressure). The stereochemistry was assigned arbitrarily. The first peak (retention time = 1.5 min) provided (S)-methyl 3-methyl-5-(1-(oxazol-2-yl)ethoxy)picolinate (**287A**, 1.29 g, 49% yield). LC/MS (ESI$^-$) *m/z* = 263 $(M+H)^+$. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.82 (d, *J*=6.65 Hz, 3 H) 2.59 (s, 3 H) 3.94 (s, 3 H) 5.57 (q, *J*=6.65 Hz, 1 H) 7.11 (s, 1 H) 7.20 (d, *J*=2.54 Hz, 1 H) 7.63 (s, 1 H) 8.28 (d, *J*=2.74 Hz, 1 H). The second peak (retention time = 2.1 min) provided (R)-methyl 3-methyl-5-(1-(oxazol-2-yl)ethoxy)picolinate (**288A**, 1.11 g, 43% yield). LC/MS (ESI$^-$) *m/z* = 263 $(M+H)^+$. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.82 (d, *J*=6.65 Hz, 3 H) 2.59 (s, 3 H) 3.94 (s, 3 H) 5.57 (q, *J*=6.65 Hz, 1 H) 7.11 (s, 1 H) 7.20 (d, *J*=2.54 Hz, 1 H) 7.63 (s, 1 H) 8.28 (d, *J*=2.74 Hz, 1 H).

Preparation of Compound 287. To a suspension of (S)-methyl 3-methyl-5-(1-(oxazol-2-yl)ethoxy)picolinate (**287A**, 1.29 g, 4.92 mmol) and lithium hydroxide hydrate (0.30 g, 7.28 mmol) was added THF (16 mL) and water (4 mL). The mixture was stirred at RT for 1.5 h, then 8.5 mL of 1 N HCl was added and the mixture was diluted with brine and a mixed solvent of i-PrOH:$CHCl_3$ (v/v 1:3). The aqueous layer was further extracted with the mixed solvent. The organic layer was dried over Na_2SO_4 and concentrated in vacuo to afford (S)-3-methyl-5-(1-(oxazol-2-yl)ethoxy)picolinic acid as off-white solid (1.20 g, 98% yield). LC/MS (ESI$^-$) *m/z* = 249 $(M+H)^+$. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.84 (d, *J*=6.65 Hz, 3 H) 2.72 (s, 3 H) 5.51 - 5.67 (m, 1 H) 7.13 (s, 1 H) 7.28 (d, *J*=2.35 Hz, 1 H) 7.66 (s, 1 H) 8.17 (d, *J*=2.54 Hz, 1 H). The acid-proton peak is broad.

Preparation of Compound 288. (R)-3-methyl-5-(1-(oxazol-2-yl)ethoxy)picolinic acid (**288**) (1.20 g, 98% yield) as an off-white solid was synthesized

in a fashion similar to that of intermediate **287**, but starting with (R)-methyl 3-methyl-5-(1-(oxazol-2-yl)ethoxy)picolinate (**288A**, 1.11 g, 4.23 mmol). LC/MS (ESI^-) *m/z* = 249 $(M+H)^+$. ^1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.84 (d, *J*=6.46 Hz, 3 H) 2.72 (s, 3 H) 5.60 (q, *J*=6.52 Hz, 1 H) 7.13 (s, 1 H) 7.28 (d, *J*=1.76 Hz, 1 H) 7.66 (s, 1 H) 8.17 (d, *J*=2.35 Hz, 1 H). The acid-proton peak is broad.

3-Chloro-5-(prop-2-yn-1-yloxy)picolinic acid (289).



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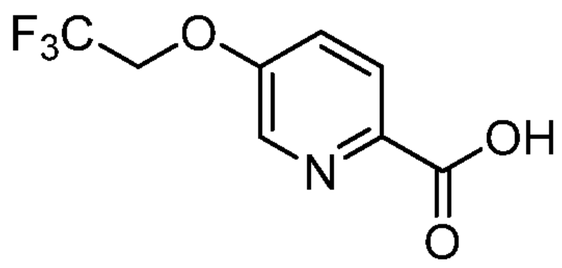
To a suspension of 3-chloro-5-hydroxypicolinic acid (Afferchem, 0.40 g, 2.30 mmol) and potassium carbonate (1.12 g, 8.07 mmol) in DMF (10 mL) was added propargyl bromide (0.56 mL, 5.07 mmol) dropwise at RT. The mixture was heated to 45 °C for 1 h. LCMS showed the reaction was complete. The mixture was diluted with EtOAc and washed with water and brine. The organic solution was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel chromatography: 0-50% EtOAc-Hexane. The product was obtained as yellow solid (0.45 g, 78% yield). LC/MS (ESI^-) *m/z* = 250 $(M+H)^+$. ^1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 2.53 (t, *J*=2.35 Hz, 1 H) 2.63 (t, *J*=2.25 Hz, 1 H) 4.81 (d, *J*=2.15 Hz, 2 H) 4.98 (d, *J*=2.35 Hz, 2 H) 7.41 (d, *J*=2.54 Hz, 1 H) 8.37 (d, *J*=2.54 Hz, 1 H).

To a suspension of prop-2-yn-1-yl 3-chloro-5-(prop-2-yn-1-yloxy)picolinate (0.448 g, 1.795 mmol) and lithium hydroxide monohydrate (0.079 g, 1.884 mmol) was added THF (6 mL) and water (2 mL). The mixture was stirred at RT for 1 h. LCMS showed the reaction was complete. 0.08 mL of 1 N HCl was added and the mixture was concentrated in vacuo. The product was obtained as off-white solid (0.456 g, 100% yield). LC/MS (ESI^-) *m/z* = 212 $(M+H)^+$.

5-(2,2,2-Trifluoroethoxy)picolinic acid (300).

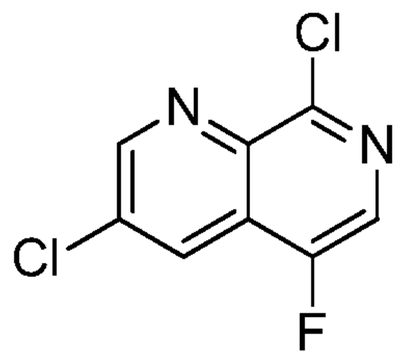


Preparation of ethyl 5-(2,2,2-trifluoroethoxy)picolinate. To a solution of methyl 5-hydroxypicolinate (0.50 g, 3.27 mmol, Frontier Scientific) in DMF (5 mL) were

added cesium carbonate (1.383 g, 4.24 mmol, Aldrich) and 2,2,2-trifluoroethyl ester (0.909 ml, 3.92 mmol) and the resulting suspension was stirred at RT for 1 h. The reaction was diluted with water and EtOAc. The organic layer was washed with 1 M LiCl (aq) solution and brine before drying over magnesium sulfate and concentrating under reduced pressure to afford the crude title compound as a yellow oil, which was used directly in the next step without further purification. M/S *m/z*= 236.0 $[M+H]^+$.

Preparation of Compound 300. The crude material from the previous reaction was taken up in THF (5 mL) and lithium hydroxide (2.0 M of aq. Solution, 4.90 mL, 9.80 mmol) was added. The reaction was stirred at RT for 16 h. The reaction was diluted with water and acidified with 1.0 N HCl (aq.) solution was added until pH = 1. The solution was extracted with DCM and the organic layer was washed with brine, dried over magnesium sulfate and concentrated under reduced pressure to afford the title compound as a white solid. (0.194 g, 0.877 mmol, 26.9 % yield). M/S *m/z*=221.9 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ ppm 5.00 (q, *J*=8.77 Hz, 2 H) 7.66 (dd, *J*=8.77, 2.92 Hz, 1 H) 8.07 (d, *J*=8.77 Hz, 1 H) 8.50 (d, *J*=2.92 Hz, 1 H) 13.00 (br. S., 1 H).

3,8-Dichloro-5-fluoro-1,7-naphthyridine (301).

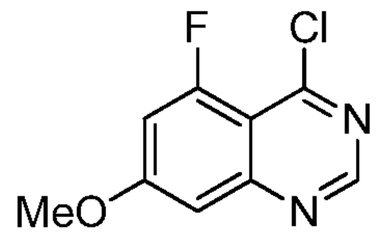


A pressure bottle was charged with 3-chloro-1,7-naphthyridin-8(7*H*)-one (15 g, 83 mmol, Anichem), MeOH (34.6 mL), ACN (173 mL) and 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (30.9 g, 87 mmol), and the mixture was heated at 45 °C for 15 h. Water and EtOAc were added, and the layers were separated. The aqueous portion was extracted twice with EtOAc and once with DCM, and the combined organic layers were dried with anhydrous sodium sulfate, filtered and concentrated. The crude solid was triturated with a minimum amount of EtOAc and filtered. The title intermediate was isolated as an off-white solid (15.34 g, 80%) as a 3:1 mixture of diastereomers.

A vial was charged with 3-chloro-5-fluoro-6-methoxy-6,7-dihydro-1,7-naphthyridin-8(5*H*)-one (7.5 g, 32.5 mmol), ACN (130 mL) and phosphorus oxychloride (9.09 mL, 98 mmol), and the mixture was stirred at 75 °C for 15 hours. The mixture was

concentrated, and the crude material was purified by silica gel chromatography, eluting with 0-50% EtOAc in heptanes, to provide Compound **301** (5.57 g, 25.7 mmol, 79% yield) as a white solid. LC/MS (ESI^+) *m/z* = 217$(M+H)^+$.

4-Chloro-5-fluoro-7-methoxyquinazoline (302).

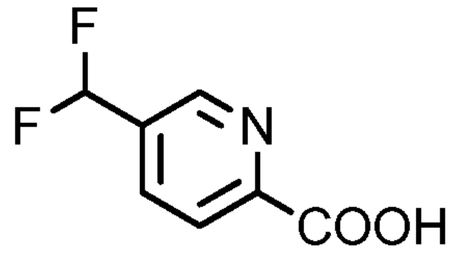


Preparation of 2-amino-6-fluoro-4-methoxybenzonitrile. Ammonia gas was bubbled through a solution of 2,6-difluoro-4-methoxybenzonitrile (1.0 g, 5.91 mmol) in DMSO (11.83 mL) for 10 minutes. The reaction was then sealed and stirred at 90 °C for 24 h. The reaction mixture was cooled to RT and concentrated *in vacuo* to afford a tan residue. The residue was triturated with water, collected be vacuum filtration, and dried *in vacuo* to afford the title intermediate (0.9 g, 5.42 mmol) as a white solid. LC/MS (ESI^+) *m/z* = 167 $(M+H)^+$.

Preparation of 5-fluoro-7-methoxyquinazolin-4-ol. To a mixture of formic acid (11.43 mL, 298 mmol) and sulfuric acid (0.87 mL, 16.25 mmol) was added 2-amino-6-fluoro-4-methoxybenzonitrile (0.9 g, 5.42 mmol) in portions. The reaction mixture was stirred at 100 °C for 1 h, cooled to RT, and poured into 80 mL of an ice-water mixture. The resulting precipitate was collected by vacuum filtration and dried *in vacuo* to provide the title intermediate (0.8 g, 4.12 mmol) as an off-white solid. LC/MS (ESI^+) *m/z* = 195 $(M+H)^+$.

Preparation of 4-chloro-5-fluoro-7-methoxyquinazoline. To a suspension of 5-fluoro-7-methoxyquinazolin-4-ol (0.12 g, 0.64 mmol) in thionyl chloride (1.41 mL, 19.31 mmol) was added *DMF* (0.028 mL, 0.36 mmol). The reaction was stirred at 80 °C for 6 h and concentrated *in vacuo*. The residue was suspended in saturated aqueous sodium bicarbonate and extracted with DCM. The organic layer was concentrated *in vacuo* to generate the title compound (0.13 g, 0.61 mmol) as a yellow solid. LC/MS (ESI^+) *m/z* = 213 $(M+H)^+$.

Difluoromethyl)picolinic acid (303).



Step 1: 5-Formylpicolinonitrile

A suspension of 2-bromo-5-formylpyridine (940 mg, 5.05 mmol) and copper (I) cyanide (233 μL, 7.58 mmol) in DMF (8.4 mL) was stirred at 120°C for 1.5 hours, cooled to RT, and partitioned between water and EtOAc. The solids were removed from the aqueous layer by filtration, and the filtrate was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated. The crude product was purified by silica-gel chromatography, eluting with a gradient of 40%-60% (40% EtOAc in heptane) in heptane, to provide the title compound (236mg, 1.786 mmol) as white solid. LC/MS (ESI^+) *m/z* = 133 $(M+H)^+$.

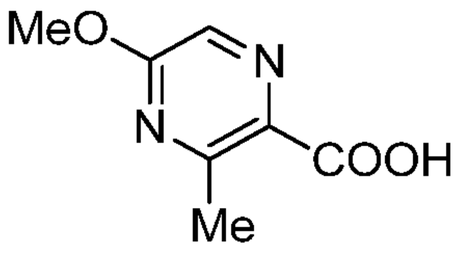
Step 2: 5-(Difluoromethyl)picolinonitrile

To a solution of 5-formylpicolinonitrile (74 mg, 0.560 mmol) in toluene (0.25 mL) was added bis(2-methoxyethyl)aminosulfur trifluoride (0.258 mL, 1.400 mmol), and the reaction was stirred at RT overnight. The reaction mixture was carefully quenched with saturated aqueous sodium bicarbonate, diluted with water, and extracted with DCM. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated. The crude material was purified by silica-gel chromatography, eluting with a gradient of 40% to 60% (40% EtOAc/heptane) in heptane, to provide the title compound (48 mg, 0.311 mmol) as white solid. LC/MS (ESI^+) *m/z* = 155 (M+H).

Step 3: 5-(difluoromethyl)picolinic acid

A suspension of 5-(difluoromethyl) picolinonitrile (48 mg, 0.311 mmol) in 12 N aqueous hydrochloric acid (4.3 mL, 140 mmol) was stirred at 110°C for 1.5 h. After cooling to ambient temperature, the reaction mixture was concentrated and treated with DIPEA (2 mL). The mixture was concentrated and dried *in vacuo* to provide the title compound in quantitative yield. LC/MS (ESI^+) *m/z* = 174 $(M+H)^+$.

5-Methoxy-3-methylpyrazine-2-carboxylic acid (304).



Step 1: Methyl 3-methylpyrazine-2-carboxylate

In a 2-L flask, 3-methylpyrazine-2-carboxylic acid (Matrix, 19.95 g, 144 mmol) was suspended in MeOH (500 mL). The suspension was cooled in an ice-water bath, and concentrated sulfuric acid (Fluka, 27.3 mL, 506 mmol) was added over a time period of 5 min. The reaction mixture was heated to 80 °C for 5 h. The reaction mixture was concentrated under reduced pressure and the residue was taken up in DCM (750 mL). The excess acid was neutralized carefully with of aqueous NaOH (5N or 5M, 200 mL). The aqueous layer was separated and extracted with DCM (250 mL). The combined organic layers were combined, dried over $MgSO_4$ and concentrated to afford 16.15 g of the title compound (106 mmol, 73%). MS *m/z*=153 $[M+H]^+$. Step 2: 3-(Methoxycarbonyl)-2-methylpyrazine 1-oxide

In a 1-L flask, the methyl 3-methylpyrazine-2-carboxylate (step 1, 16.08 g, 106 mmol) was suspended in $CHCl_3$ (300 mL). 3-chlorobenzoperoxoic acid (Aldrich, 24.62 g, 143 mmol) was added. The reaction mixture was heated to 70 °C for 16 h. The reaction mixture was quenched with saturated $NaHCO_3$ (200 mL). The layers were separated, and the aqueous layer was further extracted with DCM (2 x 100 mL). The combined organic layers were dried over $MgSO_4$, and the filtrate was concentrated to afford the title compound. MS *m/z*=169 $[M+H]^+$.

Step 3: Methyl 5-chloro-3-methylpyrazine-2-carboxylate

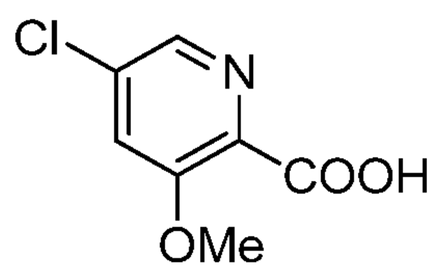
In a 1-L flask, the crude 3-(methoxycarbonyl)-2-methylpyrazine 1-oxide (step 2, 17.77 g, 106 mmol) was dissolved in DMF(300 mL). Neat phosphoryl trichloride (29.6 mL, 317 mmol) was added. The reaction mixture was heated to 100 °C. After 1 h, the reaction mixture was concentrated to remove most of the DMF. The flask was cooled in an ice water bath, and 1 M aqueous Na_2CO_3 (300 mL) was added slowly, followed by 80% EtOAc-hexane (400 mL). The mixture was filtered through Celite® filter aid. The resulting filtrate was partitioned and the aqueous phase was extracted further with 80% EtOAc-hexane (2 x 250 mL). The combimed organic layers were dried over $MgSO_4$ and concentrated. The material was purified through silica gel using 11% EtOAc-hexane to afford the title compound (4.29 g, 23 mmol, 22%). MS *m/z*=187 $[M+H]^+$. ^1H NMR in $CDCl_3$ δ: 8.51 (s, 1H), 4.01 (s, 3H), 2.86 (s, 3H).

Step 4: 5-Methoxy-3-methylpyrazine-2-carboxylic acid

A flask was charged with sodium (0.813 g, 35.4 mmol), purged with Argon. and placed in a room temperature water bath. MeOH (47.7 mL, 1179 mmol) was added

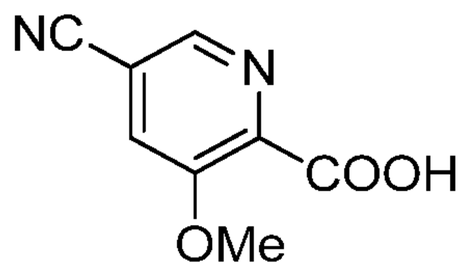
slowly. After 40 min, methyl 5-chloro-3-methylpyrazine-2-carboxylate (step 3, 2.2 g, 11.79 mmol) was added. The vessel was sealed and heated to 45 °C for 1.5 hs. Sodium hydroxide (1M, 12.97 mL, 12.97 mmol) was added and heating was continued for 1.5 hs. The reaction mixture was concentrated unde reduced pressure and the residue was dissolved in a minimum amount of water (50 mL). The aqueous phase was extracted with Et_2O (15 mL), which was discarded. The aqueous phase was acidified with HCl (5M, 11 mL, 55 mmol). The mixture was extracted with DCM (3 x 60 mL). The combined organic extracts were dried over $MgSO_4$ and the filtrate was concentrated to afford the title compound (2.0 g, 100%). MS *m/z*=169 $[M+H]^+$. ^1H NMR in $CDCl_3$ δ: 10.70 (br, 1H), 7.98 (s, 1H), 4.00 (s, 3H), 2.91 (s, 3H).

5-Chloro-3-methoxypicolinic acid (305).



In a 1-L flask, 5-chloro-3-nitropicolinonitrile (Oakwood, 6.67 g, 36.3 mmol) was dissolved in MeOH (185 mL). The solution was cooled to 0 °C, and sodium hydroxide (3 M, 36.3 mL, 109 mmol) was added. The reaction mixture was warmed to RT and stirred overnight. The reaction was concentrated under reduced pressure and the residue was taken up in absolute EtOH (100 mL). NaOH (5 M, 3 equiv, 109 mmol, 22 mL) was added, and the reaction mixture was heated to 100 °C for 1 h. The reaction mixture was concentrated under reduced pressure and the residue was taken up in water (100 mL). The aqueous layer was extracted with Et_2O (30 mL), which was discarded. The aqueous phase was acidified with HCl (5 M, 55 mL), saturated with NaCl, and extracted with EtOAc (5 x 75 mL). The combined organic extracts were dried over $MgSO_4$ and the filtrate was concentrated under reduced pressure. The resulting solid was triturated with Et_2O to afford the title compound (5.63 g, 30 mmol, 83%). MS *m/z*=188 $[M+H]^+$. ^1H NMR in $CDCl_3$ δ: 8.18 (d, 1H, J = 1.8), 7.49 (d, 1H, J = 1.8), 4.03 (s, 3H).

5-Cyano-3-methoxypicolinic acid (306).



Step 1: Methyl 5-chloro-3-methoxypicolinate

In a 350-mL resealable vessel, 5-chloro-3-methoxypicolinic acid (intermediate 14, 7.51 g, 40.0 mmol) was dissolved in MeOH (120 mL). The solution was cooled to 0 °C, and concentrated sulfuric acid (7.57 mL, 140 mmol) was added. The vessel was sealed and heated to 95 °C for 1.5 h. The reaction mixture was cooled to 0 °C, and quenched with Na_2CO_3 (1M, 140 mL). The reaction mixture was concentrated under reduced pressure and the residue was extracted with EtOAc (3 x 100 mL). The combined organics extracts were dried over $MgSO_4$ and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (gradient 20% - 33% EtOAc/hexane) to afford the title compound as a yellow solid (5.59 g, 27.7 mmol, 67%). MS *m/z*=202 $[M+H]^+$. ^1H NMR in $CDCl_3$ δ: 8.24 (d, 1H, J = 1.9), 7.37 (d, 1H, J = 1.9), 3.97 (s, 3H), 3.94 (s, 3H).

Step 2: Methyl 5-cyano-3-methoxypicolinate

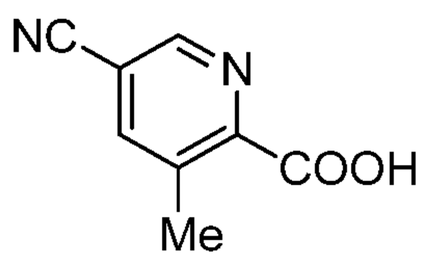
In a 350-mL resealable vessel, Pd_2dba_3 (1.487 g, 1.623 mmol), dicyclohexyl(2',6'-dimethoxy-[1,1'-biphenyl]-2-yl)phosphine (1.444 g, 3.52 mmol), dicyanozinc (3.18 g, 27.1 mmol), and methyl 5-chloro-3-methoxypicolinate (step1 , 5.455 g, 27.1 mmol) were taken up in DMF (80 mL). The reaction mixture was purged with Argon and subsequently heated to 120 °C for 2 h. Upon cooling, the reaction mixture was concentrated under reduced pressure. The residue was filtered through Celite® filter aid, and the filter cake was rinsed with 1% MeOH/DCM. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel chromatography (33-40% EtOAc/hexane) to afford the title compound as a white solid (4.51 g, 23.5 mmol, 87%). , MS *m/z*=193 $[M+H]^+$. ^1H NMR in $CDCl_3$ δ: 8.51 (d, 1H, J = 1.6), 7.55 (d, 1H, J = 1.6), 4.00 (s, 3H), 3.97 (s, 3H).

Step 3: 5-Cyano-3-methoxypicolinic acid

In a 1-L flask, the methyl 5-cyano-3-methoxypicolinate (step 2, 4.51 g, 23.5 mmol) was taken up in THF (74 mL). The suspension was cooled to 0 °C, and sodium hydroxide (1M, 24.64 mL, 24.64 mmol) was added. After 1 h, the reaction was concentrated under reduced pressure. The residue was taken up in 100 mL of water, and

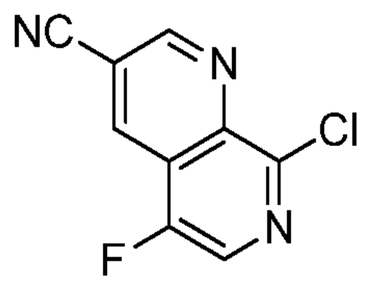
the aqueous phase was extracted with Et_2O (50 mL), which was discarded. The aqueous phase was acidified with HCl (5M, 5.16 mL, 25.8 mmol). The aqueous phase was extracted with DCM(11 x 150 mL). The combined organic extracts were dried over $MgSO_4$ and the filtrate was concentrated under reduced pressure to afford the title compound as a white solid. MS *m/z*=179 $[M+H]^+$. ^1H NMR in $CDCl_3$ δ: 8.48 (d, 1H, J = 1.6), 7.71 (d, 1H, J = 1.6), 4.08 (s, 3H).

5-Cyano-3-methylpicolinic acid (307).



To a solution of *tert*-butyl 5-cyano-3-methylpicolinate (synthesized according to procedure described in WO2012095521; 4.18g, 19.15 mmol) in DCM (96 mL) was added TFA (Aldrich, 148 mL, 1915 mmol). The reaction mixture was stirred at room temperature for 2 hrs. The reaction mixture was concentrated under reduced pressure and the residue was triturated with EtOAc.The yellow slurry was concentrated under reduced pressure. The residue was triturated with 30 mL of methyl tert-butyl ether (30 mL) and hexanes (50 mL) to yield 5-cyano-3-methylpicolinic acid (2.91 g, 17.95 mmol, 94% yield) as yellow solid. MS *m/z*=163.2 $[M+H]^+$.

8-Chloro-5-fluoro-1,7-naphthyridine-3-carbonitrile (308).



Step 1: 3-Chloro-5-fluoro-6-methoxy-6,7-dihydro-1,7-naphthyridin-8(5H)-one

A pressure bottle was charged with 3-chloro-1,7-naphthyridin-8(7H)-one (Anichem, 15 g, 83 mmol), MeOH (34 ml), ACN (173 ml) and 1-(chloromethyl)-4-fluoro-1,4-diazabicyclo[2.2.2]octane-1,4-diium tetrafluoroborate (Aldrich, 30.9 g, 87 mmol). The mixture was heated to 45-50 °C. After 6 hs additional 1-(chloromethyl)-4-fluoro-1,4-diazabicyclo[2.2.2]octane-1,4-diium tetrafluoroborate (2.5 g) was added and heating was continued overnight. Water and EtOAc were added to the cooled reaction mixture and the layers were separated. The aqueous layer was extracted with EtOAc, and

the combined organic layers were dried over $MgSO_4$. The filtrate was concentrated under reduced pressure and the residue was triturated with EtOAc. The solid was filtered off and the title compound (15.34 g, 66.5 mmol, 80% yield) was isolated as a white solid. MS *m/z*=231 $[M+H]^+$.

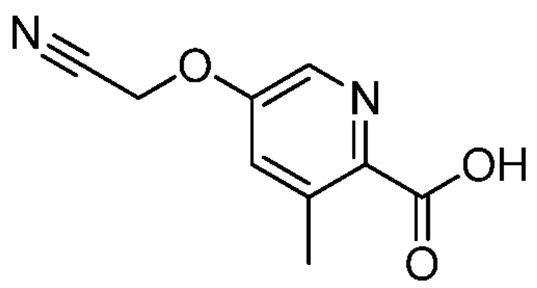
Step 2: 5-Fluoro-6-methoxy-8-oxo-5,6,7,8-tetrahydro-1,7-naphthyridine-3-carbonitrile

A pressure bottle was charged with $Pd(dba)_3$ (Strem, 1.032 g, 1.127 mmol), 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl (Strem 1.157 g, 2.82 mmol), zinc cyanide (Alfa Aesar, 2.482 g, 21.14 mmol), 3-chloro-5-fluoro-6-methoxy-6,7-dihydro-1,7-naphthyridin-8(5H)-one (step 1, 3.25 g, 14.09 mmol) and DMF (70 ml). The bottle was purged with Argon and the reaction mixture was heated to 110 ºC for 1 h. The crude reaction mixture was filtered through a pad of Celite® filter aid and the filtercake was washed with MeOH. The combined filtrates were concentrated under reduced pressure. The residue was triturated with DCM. The solid was filtered off and washed with DCM. The title compound (2.27 g, 10.26 mmol, 73 % yield) was obtained as an off white solid. MS *m/z*=222 $[M+H]^+$.

Step 3: 8-Chloro-5-fluoro-1,7-naphthyridine-3-carbonitrile

A pressure bottle was charged with 5-fluoro-6-methoxy-8-oxo-5,6,7,8-tetrahydro-1,7-naphthyridine-3-carbonitrile (step 3, 2.27 g, 10.26 mmol), ACN (41 ml) and phosphorus oxychloride (Aldrich, 3.35 ml, 35.9 mmol). The bottle was sealed and the reaction mixture was heated to 75 ºC overnight. The reaction mixture was concentrated and the crude material was purified by silica gel chromatography (gradient 0-20% (10 MeOH in DCM)/DCM to afford the title compound (1.2 g, 5.78 mmol, 56% yield) as a white solid. MS *m/z*=208 $[M+H]^+$.

5-(Cyanomethoxy)-3-methylpicolinic acid (309).



Step 1: Methyl 5-(cyanomethoxy)-3-methylpicolinate

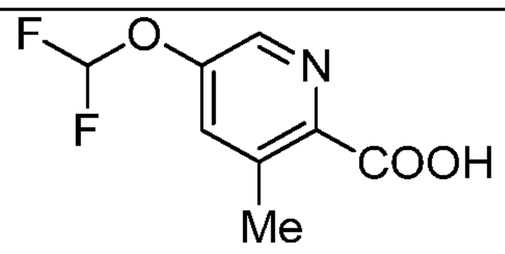
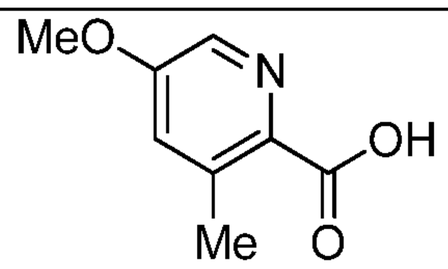
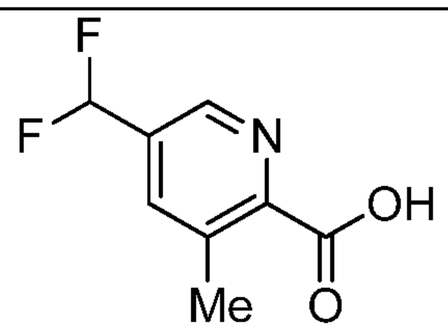
To a suspension of methyl 5-hydroxy-3-methylpicolinate (0.8063 g, 4.82 mmol, step 3 intermediate 38) and cesium carbonate (0.77 ml, 9.65 mmol, Alfa Aesar) in DMF (48.2 mL) was added bromoacetonitrile (0.336 ml, 4.82 mmol, Sigma-Aldrich Chemical

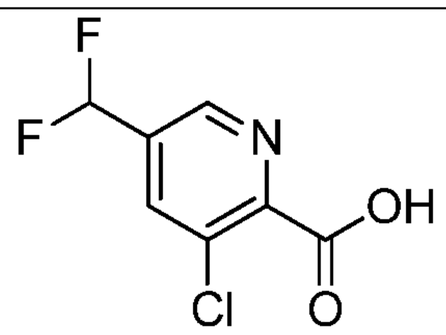
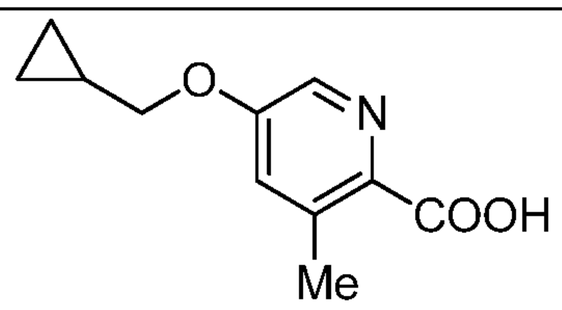
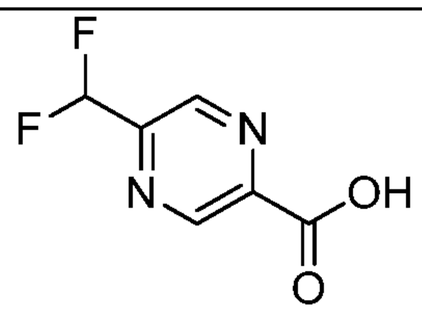
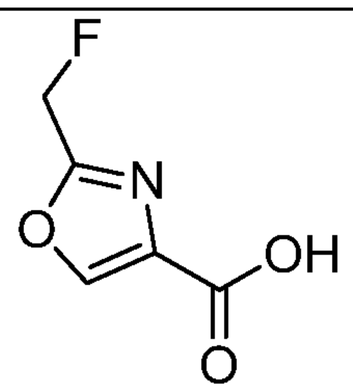
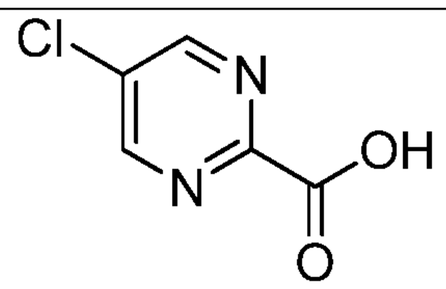
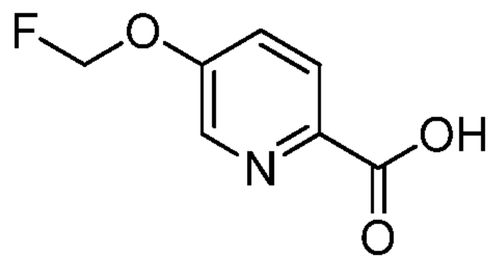
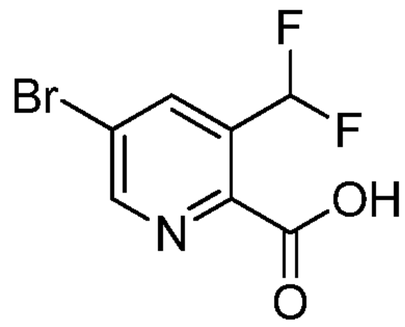
Company, Inc.). The reaction mixture was stirred for 4 h at RT. The reaction mixture was diluted with aqueous, saturated sodium bicarbonate solution and extracted with EtOAc. The organic extract was washed with aqueous, saturated sodium bicarbonate solution, brine and dried over $MgSO_4$. The filtrate was concentrated in vacuo. MS *m/z* = 207.1 $[M+H]^+$. ^1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 2.67 (s, 3 H) 3.98 (s, 3 H) 4.88 (s, 2 H) 7.20 (d, *J*=2.35 Hz, 1 H) 8.32 (br. s., 1 H)

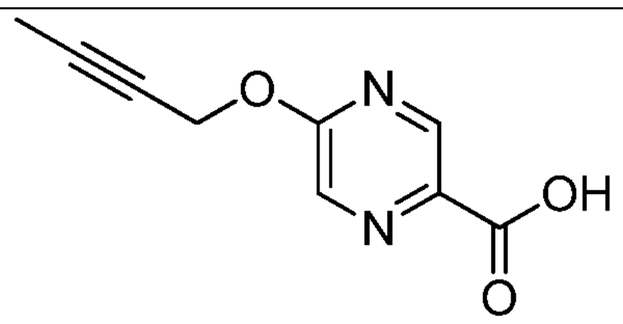
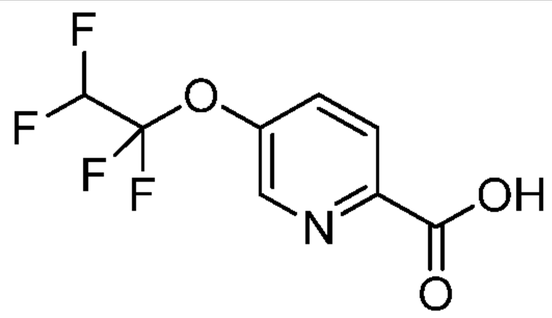
Step 2: 5-(Cyanomethoxy)-3-methylpicolinic acid

To a solution of methyl 5-(cyanomethoxy)-3-methylpicolinate (0.895 g, 4.34 mmol) and sodium iodide (0.354 ml, 8.68 mmol, Sigma-Aldrich Chemical Company, Inc.) in ACN (4.34 ml) was added chlorotrimethylsilane (1.102 ml, 8.68 mmol, Strem Chemicals, Inc.). The reaction mixture was heated to 70 °C and allowed to stir overnight. The reaction mixture was concentrated under reduced pressure and the residue was diluted with water and extracted with EtOAc. The organic extract was washed with water, 10% sodium thiosulfate solution and dried over $MgSO_4$. The filtrate was concentrated in vacuo to give 5-(cyanomethoxy)-3-methylpicolinic acid which was used without further purification. MS *m/z* = 192.9 $[M+H]^+$.

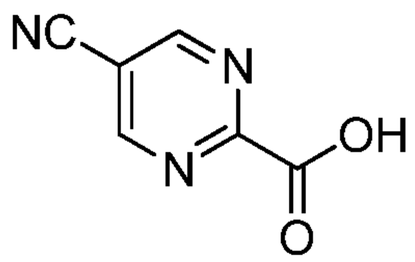
The following carboxylic acid intermediates were synthesized according to existing literature procedures, as listed below:

Intermediate No.	Structure	Literature Reference
310		WO2012095463
311		WO2012095463
312		WO2012095521

313		WO2012095521
314		WO2013061962
315		WO2012138734
316		WO2011069934
317		WO2011044181
318		WO 2011009898
319		WO 2012147763

320		J. Med. Chem. 2013, 56, 3980
321		J. Med. Chem. 2013, 56, 3980

5-Cyanopyrimidine-2-carboxylic acid (322).



Step 1: methyl 5-bromopyrimidine-2-carboxylate

To a solution of 5-bromopyrimidine-2-carboxylic acid (3.22 g, 15.9 mmol) in MeOH (50 mL) at room temperature was added acetyl chloride (4.0 mL, 56.3 mmol). The reaction mixture was heated to reflux for 15 min, cooled to room temperature and concentrated under reduced pressure. The reaction mixture was diluted with saturated $NaHCO_3$ (30 mL) and EtOAc, and transferred to a separatory funnel. The aqueous phase was extracted with EtOAc (4 x) and the combined organic extracts were washed with brine (1 x), dried over $MgSO_4$, filtered, and concentrated to give methyl 5-bromopyrimidine-2-carboxylate (2.30 g, 10.6 mmol, 67% yield) as a white solid. LC/MS (ESI^+) *m/z* = 216.9 (M+H). Calculated for $C_6H_5BrN_2O_2$ 216.0.

Step 2: methyl 5-cyanopyrimidine-2-carboxylate

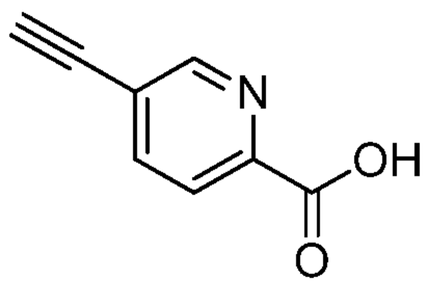
To a mixture of methyl 5-bromopyrimidine-2-carboxylate (2.30 g, 10.6 mmol) and copper (I) cyanide (1.92 g, 21.4 mmol) in a 100 mL round bottom flask was added DMA (21 mL). The reaction mixture was degassed by bubbling nitrogen through the solution for 5 min. The reaction mixture was heated to 110 °C for 2 d and cooled to room temperature. The reaction mixture was diluted with EtOAc and water and filtered through a glass frit (medium). The filtrate was transferred to a separatory funnel. The aqueous phase was extracted with EtOAc (4 x) and the combined organic extracts were washed with brine (1 x), dried over $MgSO_4$, filtered, concentrated to give a yellow oil.

Purification by flash column chromatography on silica gel (80 g, 5% to 50% EtOAc in heptane) gave methyl 5-cyanopyrimidine-2-carboxylate (0.83 g, 5.08 mmol, 48% yield) as a white solid. LC/MS (ESI^+) *m/z* = 164.0 (M+H).

Step 3: 5-cyanopyrimidine-2-carboxylic acid

To a solution of methyl 5-cyanopyrimidine-2-carboxylate (0.11 g, 0.644 mmol) in THF (2.6 mL) at 0 °C was added a solution of lithium hydroxide monohydrate (30 mg, 0.715 mmol) in water (0.5 mL). The reaction mixture was stirred at 0 °C for 20 min and 1 M HCl (0.70 mL) was added. The reaction mixture was concentrated under reduced pressure and dried under high vacuum to give methyl 5-cyanopyrimidine-2-carboxylate (0.11 g, 0.644 mmol) as a white solid that was used without further purification. LC/MS (ESI^+) *m/z* = 148.0 (M-H).

5-Ethynylpicolinic acid (323).



Step 1: Methyl 5-((triethylsilyl)ethynyl)picolinate

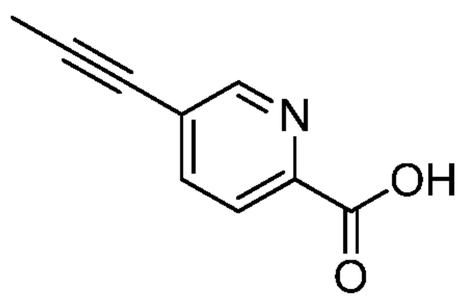
A glass microwave reaction vessel was charged with methyl 5-bromopyridine-2-carboxylate (0.95 mL, 6.94 mmol, Alfa Aesar), (triethylsilyl) acetylene (3.73 mL, 20.81 mmol, Sigma-Aldrich), tetrakis(triphenylphosphine) palladium (0.61 g, 0.527 mmol, Strem Chemicals), TEA (4.82 mL, 34.7 mmol, Sigma-Aldrich Chemical), and copper (I) iodide (198 mg, 1.04 mmol, Sigma-Aldrich). The reaction mixture was stirred and heated in a Biotage Initiator microwave reactor at 70 °C for 30 min. The reaction mixture was filtered through Celite® filter aid and concentrated. The reaction mixture was diluted with saturated NH_4Cl and extracted with EtOAc. The organic extract was washed with water and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was adsorbed onto a plug of silica gel and chromatographed through a silica gel column, eluting with a gradient of 0% to 40% EtOAc in hexane, to provide methyl 5-((triethylsilyl)ethynyl)picolinate (1.68 g, 6.09 mmol, 88% yield). MS *m/z* $[M+H]^+$ = 276.0.

Step 2: 5-Ethynylpicolinic acid

To a solution of methyl 5-((triethylsilyl)ethynyl)picolinate (1.68 g, 6.05 mmol) in THF (12.11 ml) was added TBAF, 1.0M in THF (6.68 ml, 6.68 mmol, Sigma Aldrich).

The reaction was allowed to stir for 6 hours at RT. The reaction was concentrated. The crude product was adsorbed onto a plug of silica gel and chromatographed through silica gel column eluting with a gradient of 10% to 100% EtOAc in hexane followed by 1% HOAc in EtOAc, to afford 5-ethynylpicolinic acid (0.05 g, 0.37 mmol, 6% yield). MS *m/z* $[M+H]^+$ = 147.9.

5-(Prop-1-yn-1-yl)picolinic acid (324).



Step 1: Methyl 5-bromopicolinate

To a suspension of 5-bromopicolinic acid (2.0 g, 9.94 mmol) in MeOH (2 ml)/toluene (20 ml) was added TMS-diazomethane (20M in Et_2O; 5.47 ml, 10.94 mmol, Matrix Scientific) dropwise. The reaction was stirred at room temperature for 3 hours. An additional 0.2 eq (0.99 mL) of TMS-diazomethane was added and the reaction stirred for 1.5 hours. The reaction was concentrated and the brown solid was carried to next step without further work up. MS *m/z* $[M+H]^+$ = 217.9.

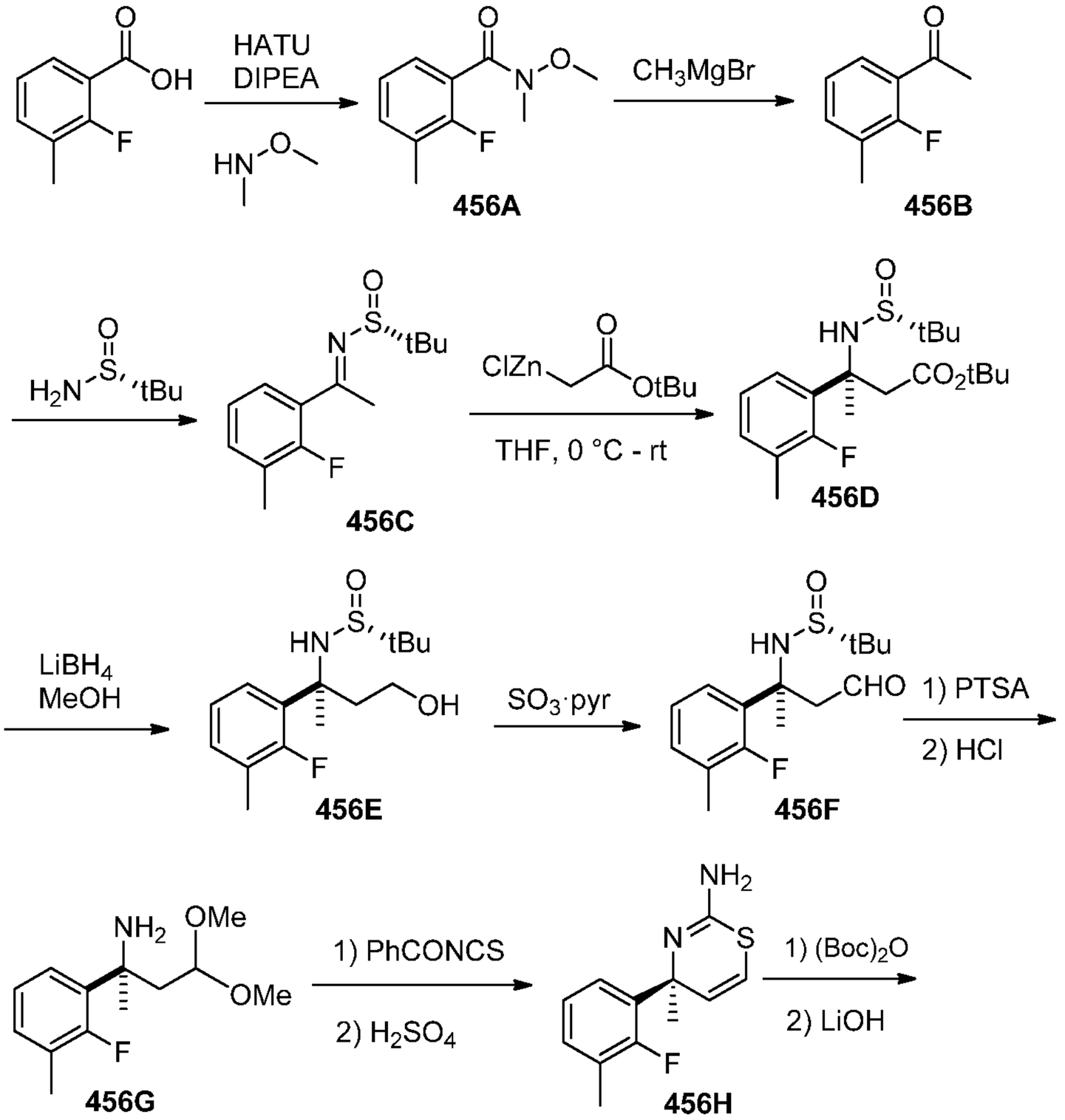
Step 2: Methyl 5-(prop-1-yn-1-yl)picolinate

To a solution of methyl 5-bromopicolinate (0.60g, 2.77 mmol) in toluene (50 mL) was added tributyl(prop-1-yn-1-yl)stannane (1.01 mL, 3.32 mmol, Sigma Aldrich) and tetrakis(triphenylphosphine)palladium (0.04 g, 0.036 mmol, Strem Chemicals, Inc.). The reaction was stirred overnight at 100 °C. The reaction was allowed to cool to RT and concentrated. The residue was adsorbed onto a plug of 10% w/w KF Silica and chromatographed with a silica gel column eluting with a gradient of 10% to 100% EtOAc in hexane, to provide methyl 5-(prop-1-yn-1-yl)picolinate (0.18, 1.05 mmol, 38% yield). MS *m/z* $[M+H]^+$ = 176.0.

Step 3: 5-(Prop-1-yn-1-yl)picolinic acid

To a solution of methyl 5-(prop-1-yn-1-yl)picolinate (0.18 g, 1.05 mmol) in THF (3.48 ml) was added sodium hydroxide 1.0 N solution (1.05 mL, 1.045 mmol, Sigma). The reaction was stirred for 1.5 hours at room temperature. Hydrogen chloride (4.0 M solution in 1,4-dioxane; 0.26 mL, 1.05 mmol, Sigma Aldrich) was added and the reaction stirred for an additional 10 minutes. The reaction was concentrated in vacuo to provide 5-(prop-1-yn-1-yl)picolinic acid as a light yellow solid. The material was used without further purification assuming theoretical yield. MS *m/z* $[M+H]^+$ = 162.1.

(5*S*)-Methyl-3-((tert-butoxycarbonyl)((2-(trimethylsilyl)ethoxy)methyl)amino)-5-(2-fluoro-3-methylphenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylate (456M).



Preparation of 2-fluoro-N-methoxy-N,3-dimethylbenzamide (456A). To a solution of 2-fluoro-3-methylbenzoic acid (240 g, 1.16 mol) in DMF (2.0 L) was added DIPEA (542 mL, 3.12 mol) followed by the addition of HATU (710 g, 1.87 mol) at 0 °C. The reaction mixture was stirred for 10 min at 0 °C and N,O-dimethyl hydroxylamine hydrochloride (167 g, 1.71 mol) was added at 0 °C. The resulting reaction mixture was then stirred for 12 h at RT. The reaction mixture was then quenched with water (3.0 L) and extracted with EtOAc (3 x 5.0 L). The combined organic layera were dried over sodium sulfate and concentrated under reduced pressure. The product thus obtained was purified using silica gel chromatography (30% EtOAc in hexanes) to provide compound **456A** (270 g, 88%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.25 - 7.19 (m, 2H), 7.05 (t, *J* = 3.6 Hz, 1H), 3.53 (s, 3H), 3.32 (s, 3H), 2.29 (s, 3H).

Preparation of 1-(2-fluoro-3-methylphenyl)ethanone (456B). To a solution of compound **456A** (270 g, 1.37 mol) in THF (2.7 L) was added methyl magnesium bromide (3.0 M in Et_2O, 1.82 L, 5.48 mol) drop wise at -78 °C. The resulting mixture was stirred for 1h at -78 °C. The reaction mixture was then quenched with saturated ammonium chloride (5.0 L) and extracted with EtOAc (2 x 5.0 L). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The mixture thus obtained was purified by silica gel chromatography (10% EtOAc in hexanes) to give compound **456B** (200 g, 96%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.68 - 7.64 (m, 1H), 7.37 - 7.34 (m, 1H), 7.09 (t, *J* = 7.0 Hz, 1H), 2.64 (s, 3H), 2.32 (s, 3H).

Preparation of (*R*)-N-(1-(2-fluoro-3-methylphenyl)ethylidene)-2-methylpropane-2-sulfinamide (456C). To a solution of compound **456B** (200.0 g, 1.32 mol) in THF (2.0 L) was added (*R*)-2-methylpropane-2-sulfinamide (239 g, 1.97 mol) followed by addition of titanium tetraethoxide (899 g, 3.94 mol) at RT. The reaction mixture was stirred for 12 h at 70 °C. It was then cooled to RT and quenched with brine (1 L). The precipitates thus obtained were filtered and washed thoroughly with EtOAc (3 x 1.0 L). The layers were separated, and the organic layer was concentrated under reduced pressure to afford the initial mixture which was purified by silica gel chromatography (30% EtOAc in hexanes) to give compound **456C** (230 g, 68%). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.45 (t, *J* = 7.0 Hz, 1H), 7.29 - 7.24 (m, 1H), 7.08 – 7.03 (m, 1H), 2.76 (s, 3H), 2.30 (s, 3H), 1.32 (s, 9H). MS (ESI +ve ion) m/z: [M+1] = 256.2.

Preparation of (3S)-tert-butyl-3-(1,1-dimethylethylsulfinamido)-3-(2-fluoro-3-methylphenyl) butanoate (456D). To a susspension of zinc powder (589 g, 9.01 mol)

in THF (2.5 L) was added TMSCl (92 mL, 721.5 mmol). The reaction mixture was then heated at 60 °C for 45 min. Next, the reaction mixture was cooled to 35 °C, and *t*-butyl bromo acetate (284 mL, 2.25 mol) was added over 6 h (internal temperature did not go above above 45 °C) and the reaction mixture was heated to 55 °C for 60 min. The reaction mixture was then allowed to cool to RT and stand for 30 min. The freshly prepared Zn-reagent was cannulated to a solution of compound **456C** (230 g, 901 mmol) in THF (2.0 L) at 0 °C dropwise. The resulting reaction mixture was stirred for 12 h at RT. It was then quenched with saturated NH_4Cl (3.0 L) and stirred for 2 h (until all the white precipitates were dissolved). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 3.0 L). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to give an orange oil that was purified by silica gel chromatography (25% EtOAc in hexanes) to give compound **456D** (270 g, 81%). ^{1}H NMR: (300 MHz, $CDCl_3$) δ 7.32 - 7.29 (m, 1H), 7.12 - 7.08 (m, 1H), 7.00 - 6.95 (m, 1H), 5.42 (s, 1H), 3.27 - 3.25 (m, 1H), 2.97 - 2.95 (m, 1H), 2.35 (s, 3H), 1.84 (s, 3H), 1.28 (s, 9H), 1.24 (s, 9H). MS (ESI +ve ion) m/z: [M+ 1] = 372.2.

Preparation of (*R*)-N-((S)-2-(2-fluoro-3-methylphenyl)-4-hydroxybutan-2-yl)-2-methyl propane-2-sulfinamide (456E). To a solution of compound **456D** (270 g, 727.2 mmol) in dry THF (2.5 L) was adde $LiBH_4$ (2.0 M solution in THF, 727 mL, 1454 mmol) dropwise at RT. The reaction mixture was stirred for 30 min at RT and was then cooled to 0 °C. MeOH (294 mL) was slowly added. The reaction mixture was then stirred for 12 h at RT and quenched with saturated ammonium chloride (2.5 L). The reaction was then diluted with water and extracted with EtOAc (3 x 2.0 L). The organic layer was dried over sodium sulfate and concentrated under reduced pressure. The material thus obtained was triturated with hexanes (1.0 L) and filtered. The solid was purified by silica gel chromatography (10% EtOAc in hexanes) to give compound **456E** (170 g, 78%). ^{1}H NMR (300 MHz, DMSO) δ 7.31 - 7.28 (m, 1H), 7.19 - 7.17 (m, 1H), 7.04 (t, *J* = 7.6 Hz, 1H), 5.56 (s, 1H), 4.74 – 4.71 (t, *J* = 4.5 Hz, 1H), 3.46 - 3.43 (m, 1H), 3.26 - 3.22 (m, 1H), 2.20 (s, 3H), 2.17 - 2.08 (m, 2H), 1.71 (s, 3H), 1.11 (s, 9H). MS (ESI +ve ion) m/z: [M+ 1] = 302.2.

Preparation of N-((S)-2-(2-fluoro-3-methylphenyl)-4-oxobutan-2-yl)-2-methylpropane-2-sulfinamide (456F). To a solution of compound **456E** (170 g, 564.2 mmol, 1.0 equiv) in DMSO (850 mL) and DCM (1700 mL) at 0 °C was added DIPEA (295 mL, 1692.6 mmol) followed by pyridine sulphur trioxide (135 g, 846.3 mmol). The reaction mixture was then stirred overnight at RT, and then it was treated with water

(2500 mL) and extracted with DCM (3 x 2000 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The product thus obtained was purified by silica gel chromatography (50% EtOAc in hexanes) to give compound **456E** (140 g, 83%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.62 (s, 1H), 7.30-7.20 (m, 1H), 7.06-7.04 (m, 1H), 6.99-6.96 (m, 1H), 4.81 (s, 1H), 3.40 (q, 2H), 2.20 (s, 3H), 1.74 (s, 3H), 1.21 (s, 9H). MS (ESI +ve ion) m/z: [M+1] = 300.2.

Preparation of (S)-2-(2-fluoro-3-methylphenyl)-4,4-dimethoxybutan-2-amine (456G). To a solution of compound **456F** (140 g, 468.6 mmol) in MeOH (700 mL) was added *p*-toluene sulfonic acid monohydrate (4.03 g, 23.38 mmol). The reaction mixture was stirred at 65 °C for 12 h. The solution was then allowed to cool to RT and treated with HCl (4.0 M solution in 1,4-dioxane, 129 mL, 516 mmol) dropwise. The reaction mixture was then stirred at RTfor 3 h. The mixture was concentrated under reduced pressure and the material thus obtained was diluted with EtOAc (2 L) and treated with sat. aq. $NaHCO_3$ (2 L). The layers were separated and the aqueous layer was extracted with EtOAc (2 x 1 L). The combined organic extracts were washed with brine (1 L), dried over magnesium sulfate, filtered and concentrated under reduced pressure to give a light-yellow oil which was purified by silica gel chromatography (50% EtOAc in DCM) gave compound **456G** (90 g, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 - 7.32 (m, 1H), 7.11 - 7.09 (m, 1H), 7.03 - 7.01 (m, 1H), 4.88 - 4.86 (m, 1H), 3.21 (s, 3H), 3.17 (s, 3H) 2.40 - 2.30 (m, 5H), 2.15 - 2.00 (m, 3H). The NH_2 peak was very broad. MS (ESI +ve ion) m/z: [M+1] = 242.2.

Preparation of (S)-4-(2-fluoro-3-methylphenyl)-4-methyl-4H-1,3-thiazin-2-amine (456H). To a stirring solution of compound **456G** (60 g, 249.4 mmol) in THF (600 mL) at 0 °C under nitrogen, was added benzoyl isothiocyanate (36.9 mL, 274.6 mmol) dropwise. The reaction temperature was maintained between 0-5 °C during the addition. The reaction mixture was allowed to stir at 0 °C for 20 min. The solvents were then removed under reduced pressure, and the residue was chilled with an ice bath. Concentrated sulfuric acid (120 mL) was then added dropwise. The resulting solution was stirred for 2 h at 70 °C. The mixture was then cooled to 0 °C and poured onto ice. To the slurry was added EtOAc (5.0 L), and the biphasic solution was chilled to 0 °C and basified to pH ~12 with very slow addition of a 10 M aqueous NaOH solution. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 5 L). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (hexanes :

EtOAc = 4:1) to give compound **456H** (18.0 g, 31% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 - 7.25 (m, 1H), 7.09 - 7.05 (m, 1H), 6.97 (t, *J* = 7.6 Hz, 1H), 6.35 - 6.20 (m, 2H), 2.26 (s, 3H), 1.72 (s, 3H). The NH_2 peak was very broad. MS (ESI +ve ion) m/z: [M+1] = 237.0.

Preparation of (S)-tert-butyl (4-(2-fluoro-3-methylphenyl)-4-methyl-4H-1,3-thiazin-2-yl)carbamate (456I). To a solution of compound **456H** (21 g, 89.6 mmol) in THF (200 mL) was added di-tert-butyl carbonate (42.7 g, 196.2 mmol) and DMAP (0.54 g, 4.4 mmol) at RT. The reaction mixture was then heated at 50 °C for 3 h. The resulting mixture was cooled to RTand treated with water (1 L) and extracted with EtOAc (3 x 1 L). The organic extracts were dried over sodium sulfate and concentrated under reduced pressure. The residue was taken in mixed solvents of THF: MeOH: water (200 mL: 100 mL: 100 mL) and treated with lithium hydroxide monohydrate (11.19 g, 269.0 mmol). The reaction mixture was heated at 50 °C for 40 min. The resulting mixture was then cooled to RT and diluted with water (1 L) and extracted with EtOAc (3 x 1 L). The combined organic layers were dried over sodium sulfate. The resulting mixture was concentrated under reduced pressure, and the product thus obtained was purified by flash chromatography using 10% EtOAc in hexanes to afford compound **456I** (22 g, 73%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15 - 7.10 (m, 2H), 7.01 - 6.96 (m, 1H), 6.24 - 6.17 (m, 2H), 2.27 (s, 3H), 1.80 (s, 3H), 1.53 (s, 9H). NH peak was not observed. MS (ESI +ve ion) m/z: [M+1] = 337.0.

Preparation of (S)-tert-butyl (4-(2-fluoro-3-methylphenyl)-4-methyl-4H-1,3-thiazin-2-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (456J). To a solution of compound **456I** (22 g, 65.4 mmol) in THF (250 mL) was added LiHMDS (1.0 M in THF, 72 mL, 72 mmol) at -78 °C. The reaction mixture was then stirred for 15 min at -78 °C and then treated with SEM chloride (12.0 g, 72.0 mmol). The reaction mixture was slowly warmed to RT and stirred for 3 h at RT. The resulting mixture was quenched with saturated ammonium chloride solution and extracted with EtOAc (3 x 1 L). The organic layers were combined and dried over sodium sulfate. The product thus obtained was purified by flash chromatography using 5% EtOAc in hexanes to afford compound **456J** (25 g, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (t, *J* = 7.7 Hz, 1H), 7.10 (t, *J* = 6.9 Hz, 1H), 7.00 (t, *J* = 7.5 Hz, 1H) 6.29 (d, *J* = 9.3 Hz, 1H), 6.09 (dd, *J* = 3.6 Hz, 9.3 Hz, 1H), 5.30 (d, *J* = 10.4 Hz, 1H), 5.24 (d, *J* = 10.4 Hz, 1H), 3.69 - 3.61 (m, 2H), 2.30 (s, 3H), 1.72 (s, 3H), 1.54 (s, 9H), 0.97 – 0.95 (m, 2H), 0.03 (s, 9H). MS (ESI +ve ion) m/z: [M+1] = 467.2.

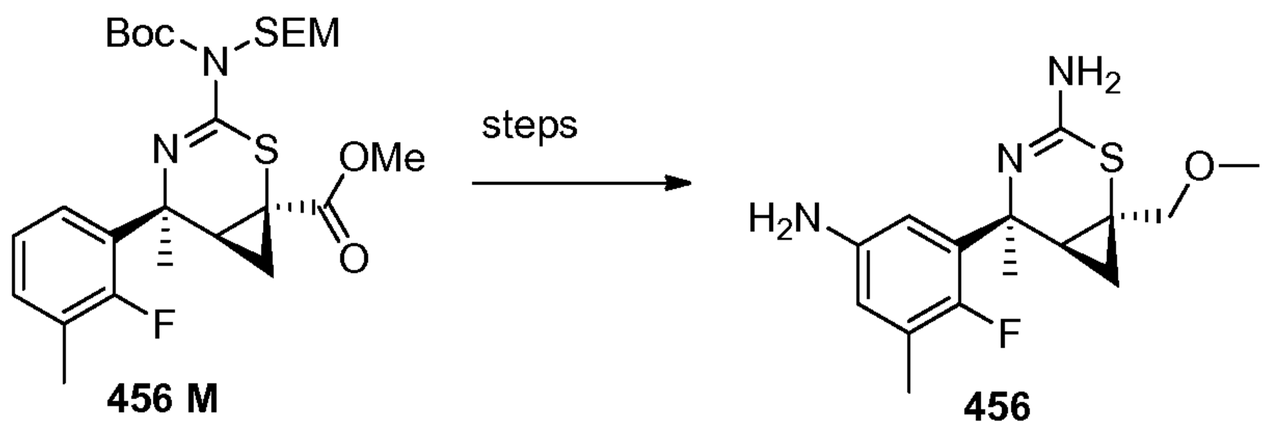
Preparation of (S)-2-((tert-butoxycarbonyl)((2-(trimethylsilyl)ethoxy)methyl)amino)-4-(2-fluoro-3-methylphenyl)-4-methyl-4H-1,3-thiazine-6-carboxylic acid (456K). To a solution of compound **456J** (24.0 g, 51.4 mmol) in THF (250 mL) at -78 °C was added a solution of LDA (2 M in THF, 64.5 mL, 129 mmol) and the reaction mixture was stirred for 20 min at -78 °C. Carbon dioxide gas was purged to the reaction mixture for 5 min and the resulting mixture was warm to RT. The resulting mixture was quenched with sat. NH_4Cl solution (200 mL) and extracted with EtOAc (3 x 500 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The product thus obtained was purified by silica gel chromatography (50% EtOAc in hexanes) to afford compound **456K** (17 g, 65%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 - 7.28 (m, 1H), 7.10 - 7.02 (m, 2H), 6.98 - 6.93 (m, 1H), 5.27 (d, J = 10.6 Hz, 1H), 5.18 (d, J = 10.6 Hz, 1H), 3.68 – 3.64 (m, 2H), 2.27 (s, 3H), 1.72 (s, 3H), 1.51 (s, 9H), 0.99 - 0.89 (m, 2H), 0.03 (s, 9H). -COOH proton was not observed. MS (ESI +ve ion) m/z: [M+1] = 511.2.

Preparation of (S)-methyl-2-((tert-butoxycarbonyl)((2-(trimethylsilyl)ethoxy)methyl)amino)-4-(2-fluoro-3-methylphenyl)-4-methyl-4H-1,3-thiazine-6-carboxylate (456L). To a solution of compound **456K** (17.0 g, 33.3 mmol) in DMF (150 mL) at RT was added potassium carbonate (9.20 g, 66.6 mmol) followed by iodomethane (2.91 mL, 46.6 mmol). After the mixture was stirred for 3 h at RT, it was quenched with water (1 L) and extracted with Et_2O (3 x 500 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The product thus obtained was purified by flash chromatography using 5% EtOAc in hexanes to give compound **456L** (13.0 g, 74%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 - 7.30 (m, 1H), 7.15 - 7.10 (m, 2H), 7.00 (t, J = 7.6 Hz, 1H), 5.31 (d, J = 10.5 Hz, 1H), 5.22 (d, J = 10.5 Hz, 1H), 3.82 (s, 3H), 3.68 – 3.64 (m, 2H), 2.28 (s, 3H), 1.75 (s, 3H), 1.53 (s, 9H), 0.92 – 0.89 (m, 2H), 0.02 (s, 9H). MS (ESI +ve ion) m/z: [M+1] = 525.2.

Preparation of (5S)-methyl-3-((tert-butoxycarbonyl)((2-(trimethylsilyl)ethoxy)methyl)amino)-5-(2-fluoro-3-methylphenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylate (456M). To a solution of trimethylsulfoxonium iodide (6.0 g, 27.3 mmol) in DMSO (100 mL) at RT was added potassium tert-butoxide (3.06 g, 27.3 mmol). The resulting mixture was stirred for 30 min and then it was cannulated to a solution of compound **456L** in THF (150 mL) at RT. The reaction mixture was stirred for 1 h at RT and then it was quenched with sat. NH_4Cl solution, and extracted with DCM (3 x 250 mL). The combined organic layers were dried

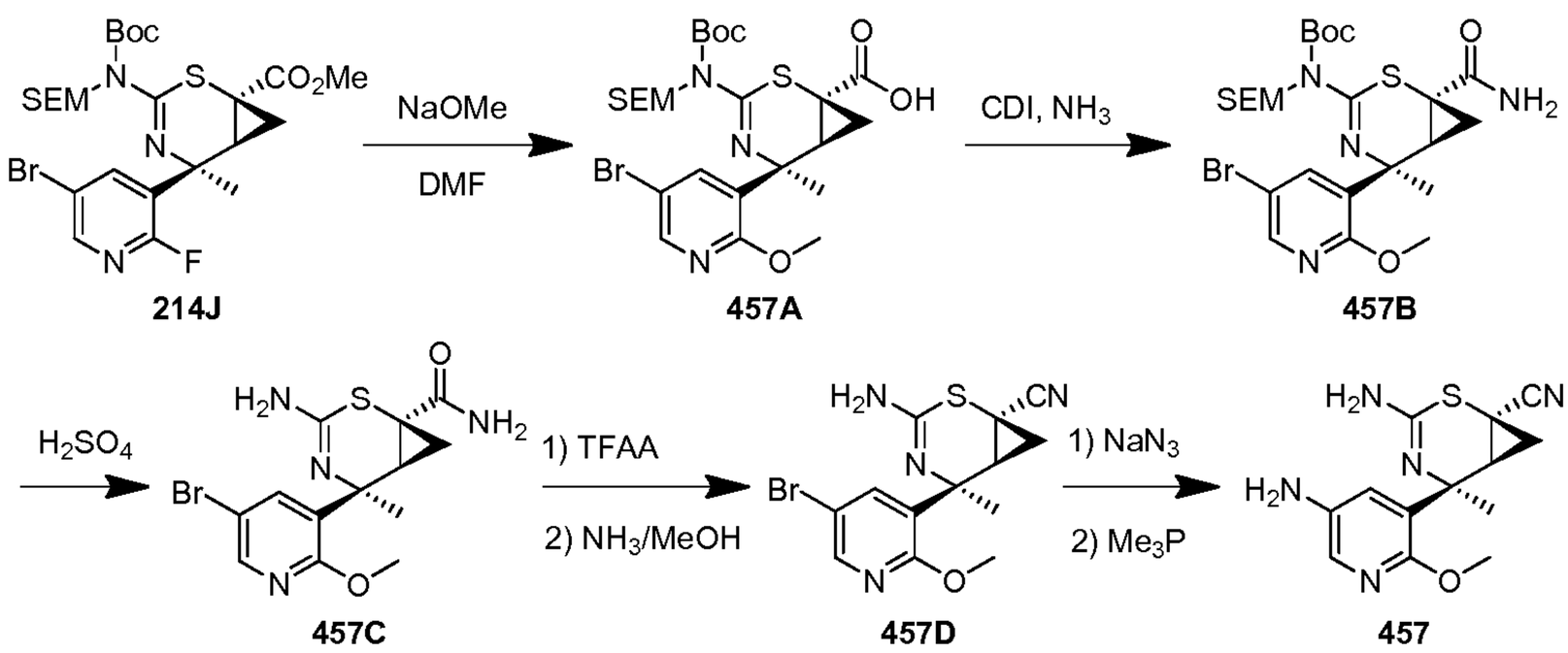
over sodium sulfate and concentrated. The crude product was purified by flash column chromatography using 5% EtOAc in hexanes to afford compound **456M** (7.5 g, 56%). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.45 (m, 1H), 7.15 - 7.11 (m, 1H), 7.03 (t, *J* = 7.6 Hz, 1H), 5.30 (d, *J* = 10.8 Hz, 1H), 5.06 (d, *J* = 10.8 Hz, 1H), 3.83 (s, 3H), 3.71 - 3.67 (m, 2H), 2.71 – 2.67 (m, 1H), 2.32 (s, 3H), 1.77 (s, 3H), 1.54 (s, 9H), 1.26 - 1.22 (m, 2H), 0.98 - 0.94 (m, 2H), 0.02 (s, 9H). MS (ESI +ve ion) m/z: [M+1] = 539.1

(1S,5S,6S)-5-(5-Amino-2-fluoro-3-methylphenyl)-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (456).



The title compound was prepared from **456M** using the procedures described for intermediate **208**. LC/MS (ESI$^-$) *m/z* = 310.0 $(M+H)^+$. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ 6.81 (dd, *J*=3.03, 6.16 Hz, 1H), 6.39 (dd, *J*=2.93, 5.67 Hz, 1H), 3.65 (d, *J*=10.56 Hz, 1H), 3.40 (s, 3H), 3.28-3.35 (m, 1H), 2.20 (d, *J*=2.35 Hz, 3H), 1.76 (dd, *J*=7.24, 9.00 Hz, 1H), 1.68 (d, *J*=1.37 Hz, 3H), 0.87 (dd, *J*=5.87, 9.59 Hz, 1H), 0.72-0.82 (m, 1H).

(1S,5S,6S)-3-Amino-5-(5-amino-2-methoxypyridin-3-yl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carbonitrile (457).



Preparation of (1S,5S,6S)-5-(5-bromo-2-methoxypyridin-3-yl)-3-((*teRT*-butoxycarbonyl)((2-(trimethylsilyl)ethoxy)methyl)amino)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylic acid (457A). To a solution of (1S,5S,6S)-

methyl 5-(5-bromo-2-fluoropyridin-3-yl)-3-((*tert*-butoxycarbonyl)((2-(trimethylsilyl)ethoxy)methyl)amino)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylate (**214J**, 2.80 g, 4.63 mmol) in DMF (10 mL) was added anhydrous sodium methoxide powder (2.50 g, 46.3 mmol) in small portions. The resulting suspension was stirred at RT for 18 h, and then it was diluted with water and acidified to pH 4 with 5 N HCl. The solid that formed was filtered and dried to give the title compound (**457A**, 2.07 g, 3.44 mmol, 74% yield). The product thus obtained was used in next step without further purification. LCMS (ESI^+) *m/z* = 604.2 (M+2H).

Preparation of *tert*-butyl ((1S,5S,6S)-5-(5-bromo-2-methoxypyridin-3-yl)-1-carbamoyl-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (457B). The title compound **457B**, (0.82 g, 1.36 mmol, 82% yield) was prepared according to the procedure described for intermediate **243A** using (1S,5S,6S)-5-(5-bromo-2-methoxypyridin-3-yl)-3-((*tert*-butoxycarbonyl)((2-(trimethylsilyl)ethoxy)methyl)amino)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylic acid, **457A,** (1.00 g, 1.66 mmol) and 1,1'-carbonyldiimidazole (0.40 g, 2.49 mmol). LCMS (ESI^+) *m/z* = 602.1/603.1 (M+H). ^1H NMR (300 MHz, CHLOROFORM-d) δ: 8.12 (d, *J*=2.49 Hz, 1H), 7.87 (d, *J*=2.34 Hz, 1H), 6.57-6.93 (m, 1H), 5.47-5.70 (m, 1H), 5.39 (d, *J*=10.52 Hz, 1H), 5.09 (d, *J*=10.52 Hz, 1H), 3.99-4.03 (m, 3H), 3.66-3.74 (m, 2H), 2.50 (dd, *J*=7.75, 9.65 Hz, 1H), 1.76-1.87 (m, 4H), 1.54-1.58 (m, 9H), 1.01 (ddd, *J*=1.61, 6.94, 9.72 Hz, 2H), 0.78 (dd, *J*=5.12, 7.60 Hz, 1H), -0.07 (s, 9H).

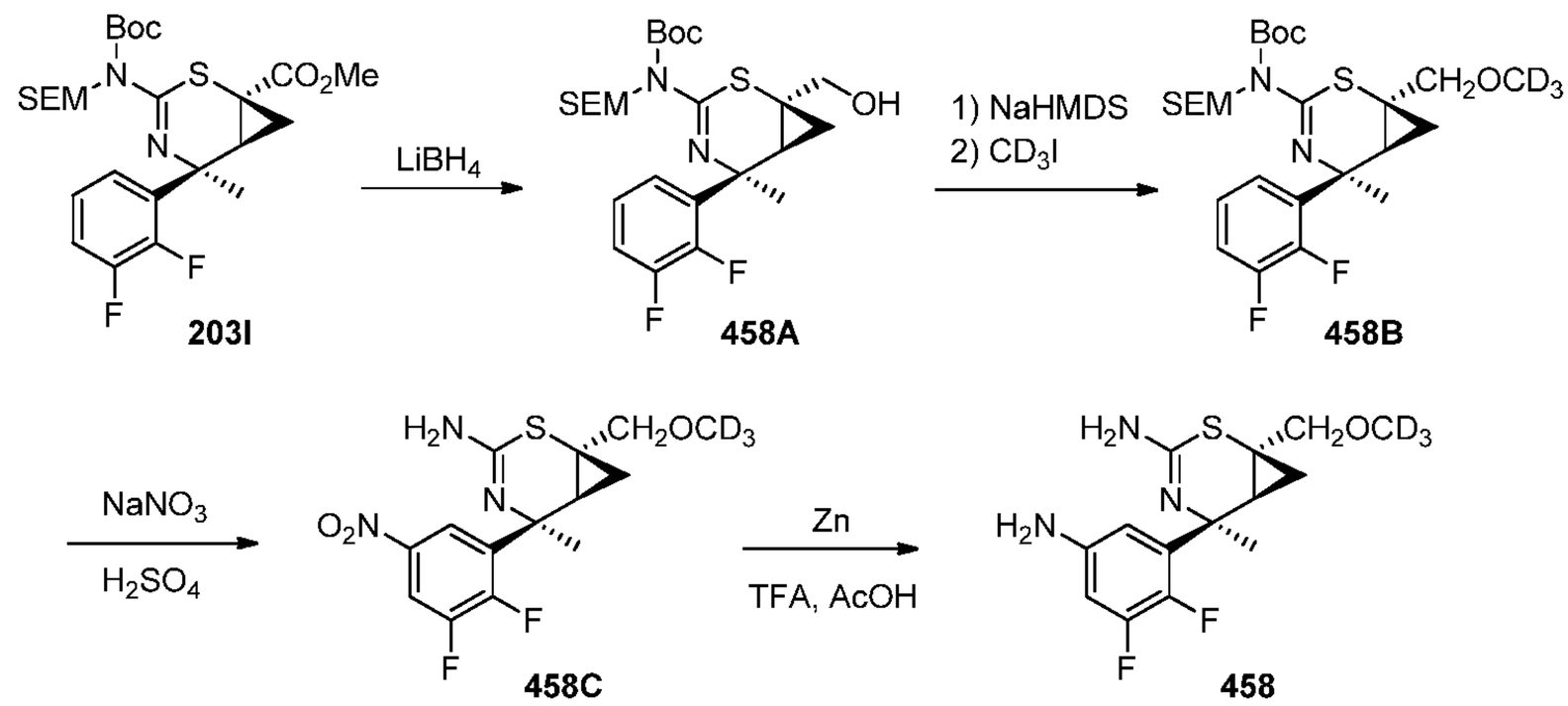
Preparation of (1S,5S,6S)-3-amino-5-(5-bromo-2-methoxypyridin-3-yl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide (457C). The title compound **457C**, (0.50 g, 1.34 mmol, 100% yield) was prepared according to the procedures described for intermediate **218C** using *tert*-butyl ((1S,5S,6S)-5-(5-bromo-2-methoxypyridin-3-yl)-1-carbamoyl-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate, **457B** (0.80 g, 1.33 mmol). LC/MS (ESI^+) *m/z* = 370.0/372.9 (M+H).

Preparation of (1S,5S,6S)-3-amino-5-(5-bromo-2-methoxypyridin-3-yl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carbonitrile (457D). The title compound **457D**, (0.20 g, 0.56 mmol, 42% yield) was prepared according to the procedure described for intermediate **243D** using (1S,5S,6S)-3-amino-5-(5-bromo-2-methoxypyridin-3-yl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide, **457C**, (0.50 g, 1.34 mmol), diisopropylethylamine (1.64 mL, 9.43 mmol), 2,2,2-

trifluoroacetic anhydride (0.75 mL, 5.39 mmol), and 2 M ammonia in MeOH. LCMS (ESI^+) *m/z* = 353.1/355.0 (M+H). ^1H NMR (400 MHz, CHLOROFORM-d) δ: 8.11 (d, *J*=2.15 Hz, 1H), 7.95 (d, *J*=2.35 Hz, 1H), 5.20-4.20 (br.s, 2H), 4.01 (s, 3H), 2.75 (dd, *J*=8.02, 9.98 Hz, 1H), 1.76 (s, 3H), 1.56 (dd, *J*=6.06, 9.98 Hz, 1H), 1.04 (dd, *J*=6.16, 7.92 Hz, 1H).

Preparation of (1S,5S,6S)-3-amino-5-(5-amino-2-methoxypyridin-3-yl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carbonitrile (457). The title compound **457**, (0.05 g, 0.17 mmol, 30% yield) was prepared according to the procedure described for intermediate **218** using (1S,5S,6S)-3-amino-5-(5-bromo-2-methoxypyridin-3-yl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carbonitrile, **457D**, (0.20 g, 0.56 mmol), sodium azide (0.14 g, 2.26 mmol), copper(i) iodide (11 mg, 0.05 mmol), (+)-sodium L-ascorbate (22 mg, 0.11 mmol), (1R,2R)-(-)-N,N''-dimethylcyclohexane-1,2-diamine and 1 M trimethylphosphine solution in THF (1.13 mL, 1.13 mmol). LC/MS (ESI^+) *m/z* = 290.2 (M+H). ^1H NMR (300 MHz, CHLOROFORM-d) δ: 7.56 (d, *J*=2.78 Hz, 1H), 7.24-7.30 (m, 1H), 3.95 (s, 3H), 3.78-4.04 (br.s, 4H), 2.70 (dd, *J*=8.11, 9.87 Hz, 1H), 1.78 (s, 3H), 1.60 (dd, *J*=6.14, 10.08 Hz, 1H), 0.99 (dd, *J*=6.14, 7.89 Hz, 1H).

(1S,5S,6S)-5-(5-Amino-2,3-difluorophenyl)-1-(methoxytrideuteriomethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (458).



Preparation of compound 458A. To a stirred solution of (1S,5S,6S)-methyl 3-((tert-butoxycarbonyl)((2-(trimethylsilyl)ethoxy)methyl)amino)-5-(2,3-difluorophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylate (**203I**, 36 g, 66.3 mmol) in THF (300 mL) at RT was added lithium borohydride (2.0 M in THF, 66.3 mL, 133 mmol). The vessel was then charged with MeOH (21.50 mL, 531 mmol) and gas evolution was evident with the reaction temperature rising to 33 °C. The solution was

stirred for 1 h, cooled to 0 °C, and then it was slowly quenched with 150 mL of 1/2 sat. aqueous NH_4Cl added via addition funnel. The mixture was then extracted twice with 2:1 heptane/EtOAc (500 mL). The combined organic layers were washed with sat. NaCl (2 x 50 mL), 1 M HCl (100 mL), followed again by sat NaCl (2 x 50 mL). The organic layer was dried over $MgSO_4$, filtered, concentrated under reduced pressure, and then purified by silica gel chromatography (0-15% EtOAc/heptane) to afford tert-butyl ((1S,5S,6S)-5-(2,3-difluorophenyl)-1-(hydroxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (**458A**, 27.2 g, 52.8 mmol, 80% yield) as a light colorless oil that crystalized upon setting. LC/MS (ESI^-) *m/z* = 515.2 $(M+H)^+$.

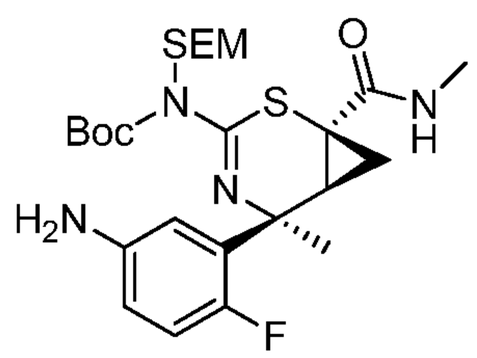
Preparation of compound 458B. To a stirred solution of *tert*-butyl ((1S,5S,6S)-5-(2,3-difluorophenyl)-1-(hydroxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (**458A**, 1.05 g, 2.040 mmol) in THF (10 mL) at 0 °C was added sodium bis(trimethylsilyl)amide (1.0 M in THF, 2.44 mL, 2.44 mmol) dropwise at a rate that did not exceed an internal temp of 6 °C. After 15 min, trideuteriomethyl iodide (0.17 mL, 2.65 mmol) was added. The resulting mixture was warmed to 20 °C and stirred for 18 h. The reaction was then quenched with aq. NH_4Cl (5 mL) and diluted with water (10 mL). The mixture was extracted with 2:1 heptane/EtOAc (50 mL). The organic layer was then washed with 1 M HCl (5 mL) followed by sat. NaCl (2 x 5 mL). The organic layer was then dried over $MgSO_4$. Filtration followed by concentration under reduced pressure afforded tert-butyl ((1S,5S,6S)-5-(2,3-difluorophenyl)-1-(methoxytrideuteriomethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (**458B**, 1.02 g, 1.92 mmol, 94% yield) as a colorless oil. LC/MS (ESI^-) *m/z* = 532.3 $(M+H)^+$.

Preparation of compound 458C. To a 100 mL sigle neck round bottom flask containing tert-butyl ((1S,5S,6S)-5-(2,3-difluorophenyl)-1-(methoxytrideuteriomethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (**458B**, 1.02 g, 1.92 mmol) at 0 °C under nitrogen was added sulfuric acid (3.58 mL, 67.10 mmol). After 15 min, the reaction was removed from the cooling bath, swirled by hand, then allowed to stir at 20 °C for 30 min. The material was chilled to 0 °C and sodium nitrate (0.16 g, 1.92 mmol) was added. The reaction was stirred for 15 min at 0 °C and then more sodium nitrate (0.16 g, 1.92 mmol) was added. The reaction was stirred at 20 °C for 1 h, and then it was added dropwise to a mixture of wet ice (300 mL)/DCM (100 mL). After addition, water (500 mL) was added, and to the rapidly stirred mixture, was added potassium phosphate tribasic (14.25 g, 67.10

mmol) over 30 min periods (pH ~7). The organic layer was separated, and the aqueous layer was extracted with DCM (2 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated under reduced pressure, and then it was purified via silica gel chromatography (40 g) eluting the products with a gradient of 0-30% EtOAc/DCM to afford (1S,5S,6S)-5-(2,3-difluoro-5-nitrophenyl)-1-(methoxytrideuteriomethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (**458C**, 0.48 g, 1.38 mmol, 72% yield) as a yellow crystaline solid. LC/MS (ESI^-) *m/z* = 347.0 $(M+H)^+$. ^1H NMR (400 MHz, CHLOROFORM-d) δ 8.47-8.52 (m, 1H), 7.98 (ddd, *J*=2.93, 6.31, 9.15 Hz, 1H), 4.53 (br. s., 2H), 3.63 (d, *J*=10.56 Hz, 1H), 3.38 (d, *J*=10.56 Hz, 1H), 1.78 (t, *J*=7.73 Hz, 1H), 1.73 (s, 3H), 0.90 (dd, *J*=6.06, 9.19 Hz, 1H), 0.79-0.84 (m, 1H).

Preparation of compound 458. To a stirring solution of (1S,5S,6S)-5-(2,3-difluoro-5-nitrophenyl)-1-(methoxytrideuteriomethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (**458C**, 480 mg, 1.38 mmol) in HOAc (4 mL) and TFA (1 mL) at 20 ºC was added zinc (453 mg, 6.93 mmol) in 2 portions. After 1 h, the suspension was filtered and the metalic residue was extensively washed with DCM (20 mL). The filtrate was then added dropwise to a chilled (0 ºC) mixture of 30% NH_4OH (10 mL) and DCM (10 mL). After separation of the organic and aqueous layers, the aqueous layer was further extracted with DCM (5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to afford (1S,5S,6S)-5-(5-amino-2,3-difluorophenyl)-1-(methoxytrideuteriomethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine as a yellow film. LC/MS (ESI^-) *m/z* = 317.1 $(M+H)^+$.

***tert*-Butyl ((1S,5S,6S)-5-(5-amino-2-fluorophenyl)-5-methyl-1-(methylcarbamoyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (459).**

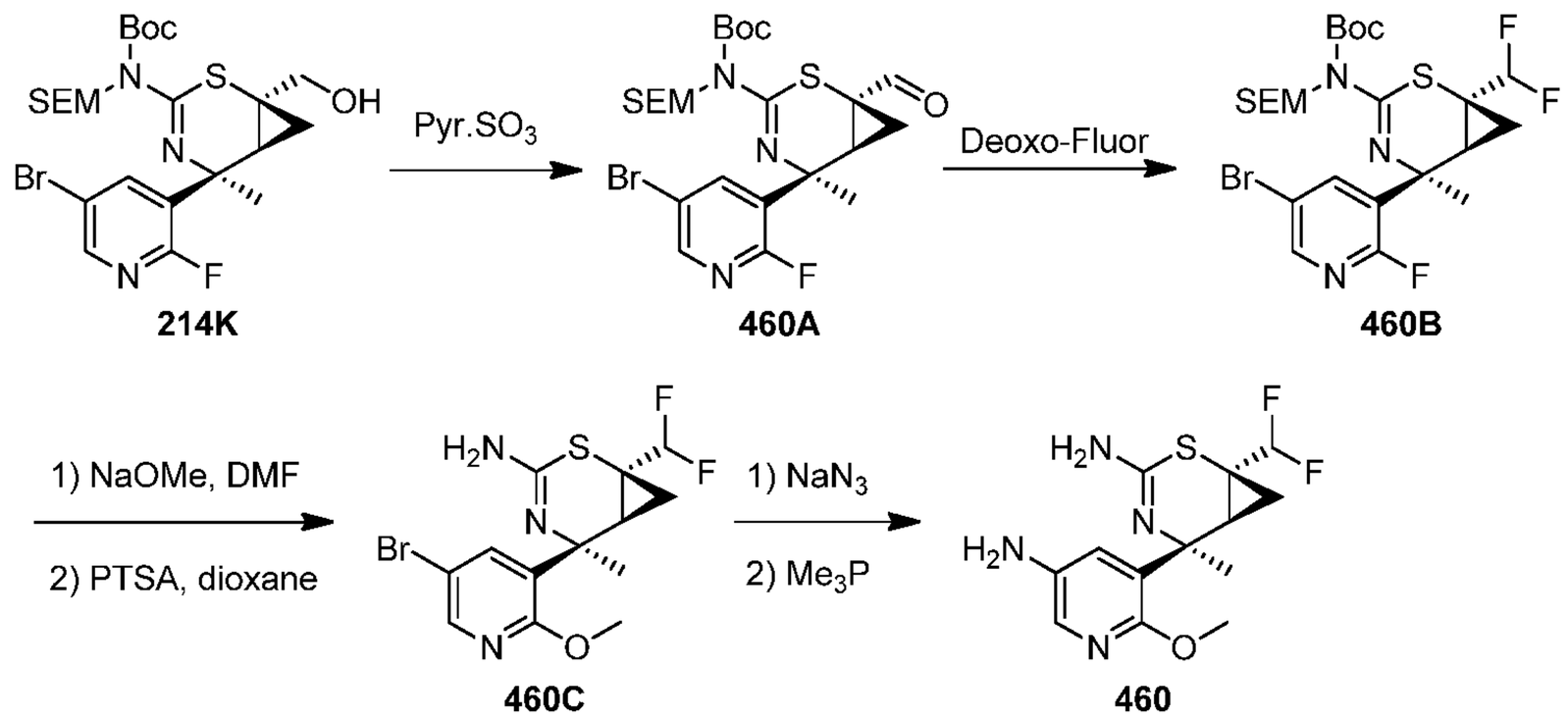


459

The title compound was synthesized according to the procedures described for intermediate **221D**, using methylamine to react with (1S,5S)-5-(5-bromo-2-fluorophenyl)-3-((*tert*-butoxycarbonyl)((2-(trimethylsilyl)ethoxy)methyl)amino)-5-methyl-2-thia-4-

azabicyclo[4.1.0]hept-3-ene-1-carboxylic acid **221A**. LC/MS (ESI^+) *m/z* = 539 $(M+H)^+$. ^1H NMR (400 MHz, CHLOROFORM-d) δ 6.92-7.03 (m, 1H), 6.85 (dd, *J*=8.61, 11.54 Hz, 1H), 6.70 (dd, *J*=2.93, 6.65 Hz, 1H), 6.50 (td, *J*=3.37, 8.51 Hz, 1H), 5.42 (d, *J*=10.56 Hz, 1H), 5.10 (d, *J*=10.76 Hz, 1H), 3.57-3.76 (m, 2H), 3.50 (br. s., 2H), 2.86 (d, *J*=4.69 Hz, 3H), 2.16 (dd, *J*=7.73, 9.29 Hz, 1H), 1.94 (dd, *J*=5.09, 9.59 Hz, 1H), 1.80 (d, *J*=0.78 Hz, 3H), 1.55 (s, 9H), 0.92-1.02 (m, 2H), 0.85 (dd, *J*=5.28, 6.46 Hz, 1H), 0.02 (s, 9H).

(1S,5S,6S)-5-(5-Amino-2-methoxypyridin-3-yl)-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (460).



214K **460A** **460B**

460C **460**

Preparation of *tert*-butyl((1S,5S,6S)-5-(5-bromo-2-fluoropyridin-3-yl)-1-formyl-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (460A). The title compound (7.59 g, 13.21 mmol, 76% yield) was prepared according to the procedure described for intermediate **218A** using *tert*-butyl ((1S,5S,6S)-5-(5-bromo-2-fluoropyridin-3-yl)-1-(hydroxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate, **214K**, (10 g, 17.34 mmol), TEA (12.06 mL, 87 mmol) and pyridine-sulfur trioxide complex (6.90 g, 43.40 mmol). LCMS (ESI^+) *m/z* = 574.1/576.1 (M+H).

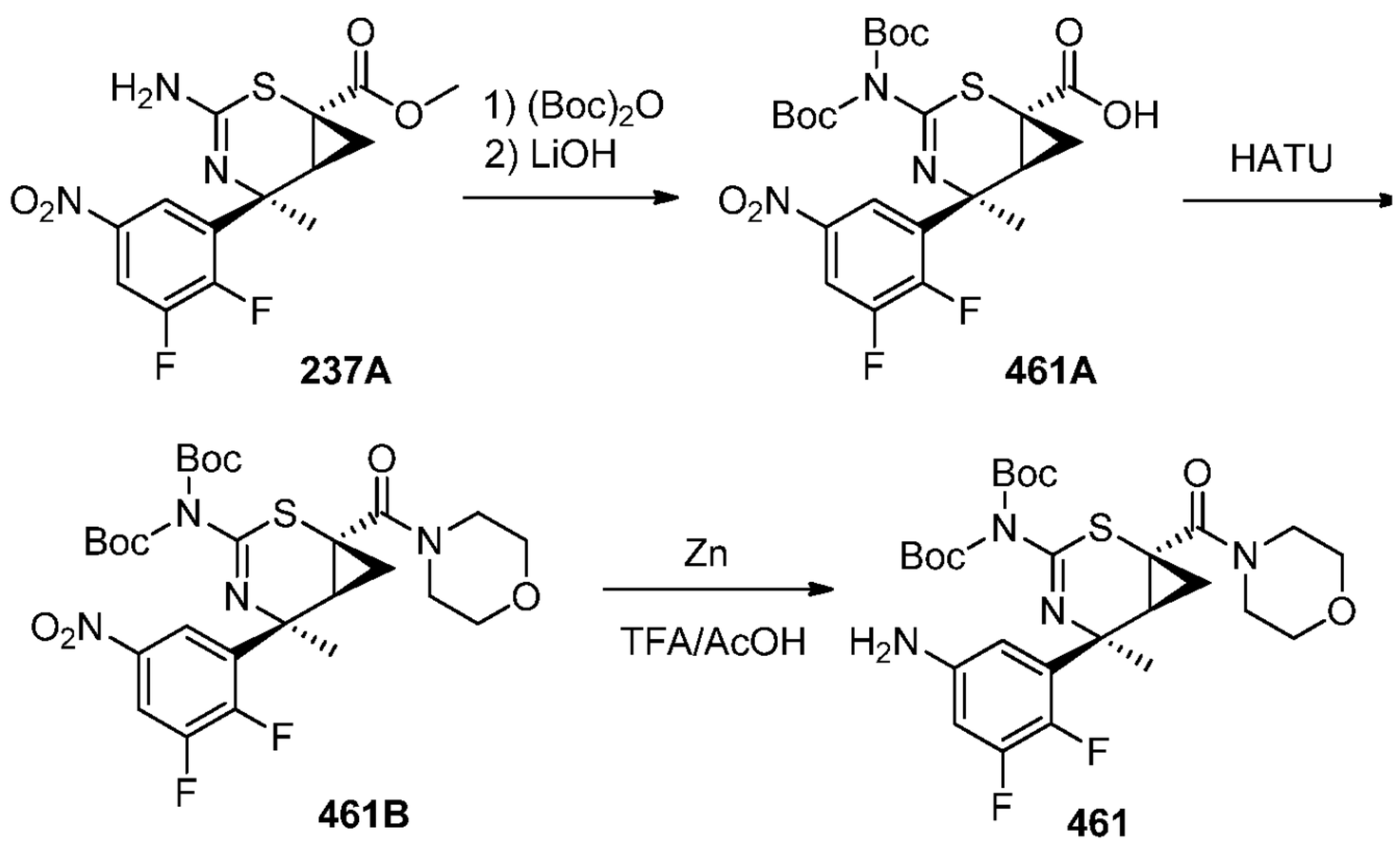
Preparation of *tert*-butyl ((1S,5S,6S)-5-(5-bromo-2-fluoropyridin-3-yl)-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (460B). The title compound (7.43 g, 12.45 mmol, 94% yield) was prepared according to the procedure described for intermediate **218B** using *tert*-butyl ((1S,5S,6S)-5-(5-bromo-2-fluoropyridin-3-yl)-1-formyl-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate (**460A**, 7.59 g, 13.21 mmol) and deoxo-fluor solution (8.51 mL, 46.2 mmol). LCMS

(ESI$^+$) *m/z* = 596.0/598.1 (M+H). ^{1}H NMR (300 MHz, CHLOROFORM-d) δ: 8.16-8.34 (m, 2H), 5.51-6.03 (m, 1H), 5.33 (d, *J*=10.08 Hz, 1H), 5.06 (d, *J*=10.52 Hz, 1H), 3.56-3.83 (m, 2H), 2.18 (t, *J*=8.62 Hz, 1H), 1.76 (s, 3H), 1.55 (s, 9H), 1.13-1.40 (m, 2H), 0.95-1.09 (m, 2H), -0.06 (s, 9H).

Preparation of (1S,5S,6S)-5-(5-bromo-2-methoxypyridin-3-yl)-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (460C). To a solution of *tert*-butyl ((1S,5S,6S)-5-(5-bromo-2-fluoropyridin-3-yl)-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate, **460B**, (4.68 g, 7.84 mmol) in DMF (15 mL) was added sodium methoxide (4.24 g, 78 mmol) portionwise. The suspension was stirred at RT for 30 min, diluted with water and extracted with EtOAc (2 x). The combined organic layers were dried and concentrated under vacuum to afford *tert*-butyl ((1S,5S,6S)-5-(5-bromo-2-methoxypyridin-3-yl)-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-yl)((2-(trimethylsilyl)ethoxy)methyl)carbamate. The product thus obtained in 5 mL of dioxane was treated with *p*-toluenesulfonic acid monohydrate (1.87 g, 9.86 mmol). The reaction was heated to 85 °C for 2 h, and it was then diluted with water and extracted with EtOAc (2 x). The combined organic layers were concentrated, and the residue was purified by flash column chromatography on silica gel (0-5% MeOH in DCM) to afford the title compound (**460C**, 0.55 g, 1.45 mmol, 73% yield). LCMS (ESI$^+$) *m/z* = 378.0/380.1 (M+H).

Preparation of (1S,5S,6S)-5-(5-amino-2-methoxypyridin-3-yl)-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (460). The title compound (0.17 g, 0.54 mmol, 41% yield) was prepared according to the procedure described for **218** using (1S,5S,6S)-5-(5-bromo-2-methoxypyridin-3-yl)-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (**460C**, 0.50 g, 1.32 mmol), sodium azide (0.34 g, 5.3 mmol), (1R,2R)-(-)-N,N''-dimethylcyclohexane-1,2-diamine (0.04 mL, 0.26 mmol), copper(I) iodide (25 mg, 0.13 mmol), and 1 M trimethylphosphine solution in THF (3.97 mL, 3.97 mmol). LC/MS (ESI$^+$) *m/z* = 315.2 (M+H). ^{1}H NMR (300 MHz, CHLOROFORM-d) δ: 7.56 (s, 1H), 7.23 (br. s., 1H), 5.35-5.93 (m, 1H), 3.94 (s, 3H), 3.39 (br. s., 2H), 2.12-2.21 (m, 1H), 1.72-1.84 (m, 3H), 1.53 (s, 2H), 1.29 (d, *J*=13.59 Hz, 1H), 0.70 (br. s., 1H). ^{19}F NMR (377 MHz, DMSO-d_6) δ: -116.63 (d, ^1J=276.2 Hz, 1F), -119.21 (d, ^1J=276.2 Hz, 1F).

(1S,5S,6S)-Methyl 3-(di-*tert*-butoxycarbonyl)amino-5-(2,3-difluoro-5aminophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-(morpholino)methanone (461).



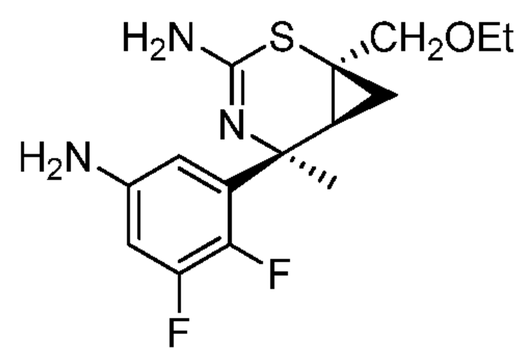
Preparation of compound 461A. To a stirred solution of di-tert-butyl dicarbonate (3.82 g, 17.49 mmol) in THF (15 mL) was added (1S,5S,6S)-methyl 3-amino-5-(2,3-difluoro-5-nitrophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylate (**237A**, 2.5 g, 7.00 mmol) in THF (15 mL) at 20 ºC followed by DMAP (0.02 g, 0.17 mmol). After 30 min, MeOH (5 mL) was added to the mixture followed by an aqueous solution of lithium hydroxide monohydrate (0.88 g, 20.99 mmol) in water (10 mL). The suspension was stirred for 36 h at 20 ºC. The reaction was then partitioned between 1:1 EtOAc/heptane (150 mL) and 0.5 M KH_2PO_4 (50 mL). The organic layer was further washed with brine (2 x 25mL). The organic layer was then dried over $MgSO_4$, and concentrated under reduced pressure to afford (1S,5S,6S)-methyl 3-(di-*tert*-butoxycarbonyl)amino-5-(2,3-difluoro-5-nitrophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylic acid (**461A**, 3.76 g, 6.92 mmol, 99% yield) as white solid. LC/MS (ESI^-) *m/z* = 566.2 $(M+Na)^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.40 (ddd, *J*=2.93, 6.50, 9.54 Hz, 1H), 8.12-8.21 (m, 1H), 3.60-3.66 (m, 1H), 2.29 (t, *J*=7.43 Hz, 1H), 1.63-1.71 (m, 3H), 1.42-1.52 (m, 18H), 1.06 (dd, *J*=3.91, 9.19 Hz, 1H), 0.75 (dd, *J*=4.11, 6.85 Hz, 1H).

Preparation of compound 461B. To a stirred solution of (1S,5S,6S)-methyl 3-(di-*tert*-butoxycarbonyl)amino-5-(2,3-difluoro-5-nitrophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylic acid (**461A**, 270 mg, 0.49 mmol) and diisopropylethylamine (112 μL, 0.646\ mmol) in DMF (2 mL) at 20 ºC was added HATU (246 mg, 0.64 mmol). The resulting solution was stirred for 20 min followed by addition of morpholine (60 μL, 0.69 mmol). Ater 18 h, the reaction was quenched with sat. NH_4Cl

(2 mL) and was then partitioned between 2:1 EtOAc/heptane (30 mL) and water (75 mL). The organic layer was further washed with water (75 mL) and brine (10 mL), dried over $MgSO_4$, and conentrated under reduced pressure. The residue was purified by silica gel chromatography (20-50% EtOAc/heptane) to afford (1S,5S,6S)-methyl 3-(di-*tert*-butoxycarbonyl)amino-5-(2,3-difluoro-5-nitrophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-(morpholino)methanone (**461B**, 300 mg, 0.49 mmol) as a white foam. LC/MS (ESI^-) *m/z* = 636.2 $(M+Na)^+$.

Preparation of compound 461. To a stirred solution of (1S,5S,6S)-methyl 3-(di-*tert*-butoxycarbonyl)amino-5-(2,3-difluoro-5-nitrophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-(morpholino)methanone (**461C**, 300 mg, 0.49 mmol) in glacial HOAc (2 mL) was added zinc (160 mg, 2.44 mmol). After 45 min, the reaction mixture was filtered, and the solid was washed with DCM (30 mL). The filtrate was then chilled to 0 °C, and 30% NH_4OH (5 mL) was slowly added followed by water (50 mL). The organic layer was separated, washed with brine (10 mL), dried over $MgSO_4$, concentrated under reduced pressure, and then purified by silica gel chromatography (0-2.5% MeOH/DCM) to afford (1S,5S,6S)-methyl 3-(di-*tert*-butoxycarbonyl)amino-5-(2,3-difluoro-5aminophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-(morpholino)methanone (**461**, 92 mg, 0.15 mmol, 32% yield) as a colorless film. LC/MS (ESI^-) *m/z* = 605.2 $(M+Na)^+$. ^1H NMR (400 MHz, CHLOROFORM-d) δ 6.62 (br. s., 1H), 6.48 (br. s., 1H), 3.70 (br. s., 8H), 2.43 (t, *J*=8.41 Hz, 1H), 1.81 (s, 3H), 1.51 (s, 18H), 1.33 (dd, *J*=5.58, 9.49 Hz, 1H), 1.13 (t, *J*=6.75 Hz, 1H).

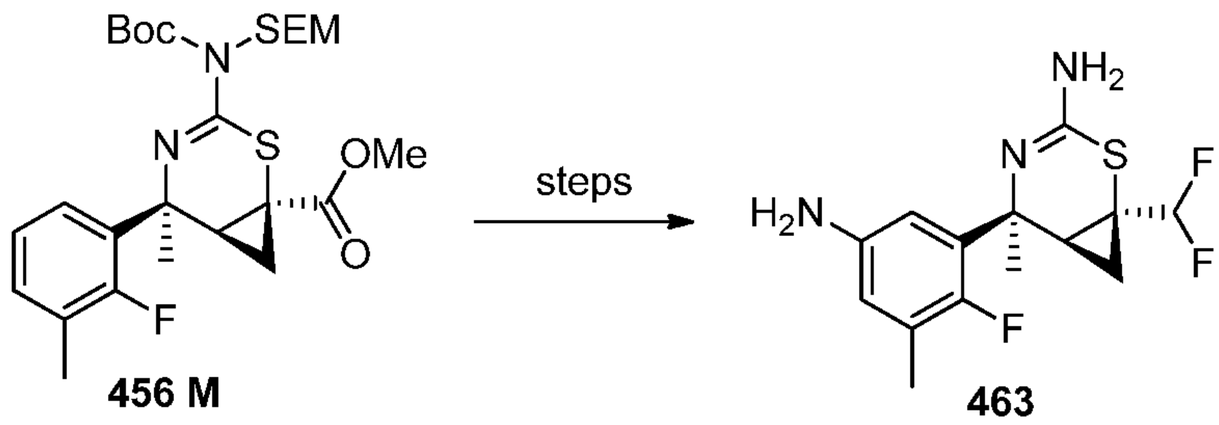
(1S,5S,6S)-5-(5-Amino-2,3-difluorophenyl)-1-(ethoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (462).



462

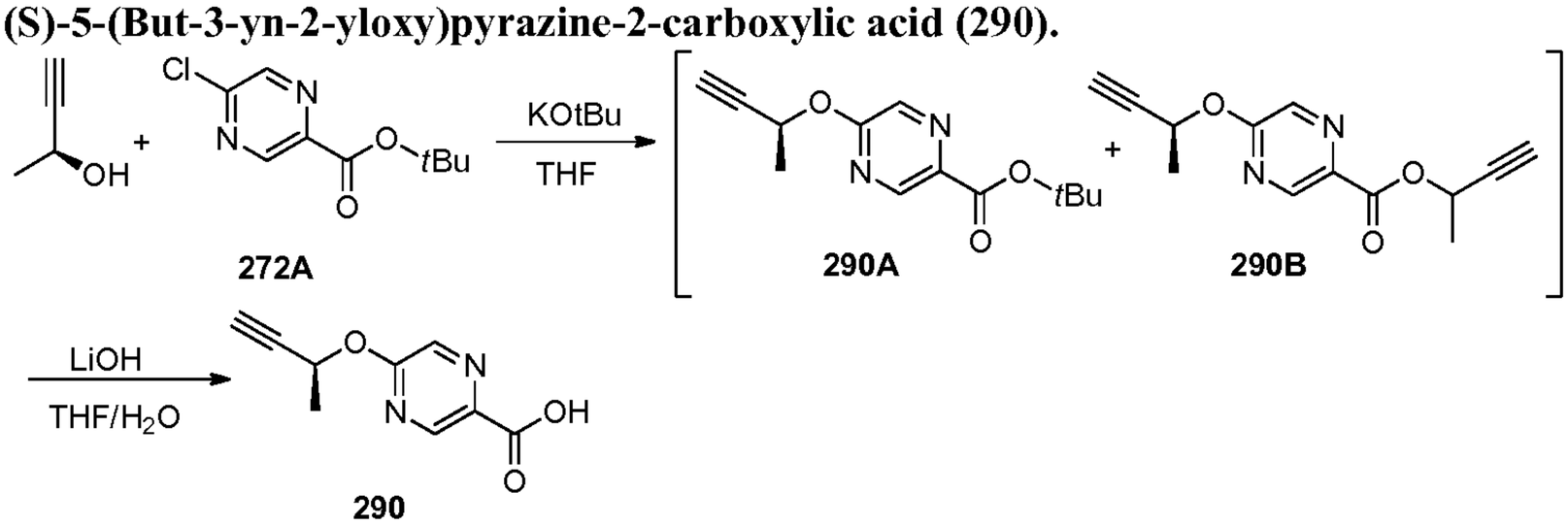
The title compound was prepared in a manner analogous to that described for intermediate **458** with the substitution of iodoethane. LC/MS (ESI^-) *m/z* = 328.1 $(M+H)^+$.

(1S,5S,6S)-5-(5-Amino-2-fluoro-3-methylphenyl)-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (463).



The title compound was prepared from **456 M** using the procedures described for intermediate **211**. LC/MS (ESI$^-$) m/z = 316.0 $(M+H)^+$. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ 6.57-6.64 (m, 1H), 6.39 (dd, *J*=3.03, 5.77 Hz, 1H), 5.48-5.81 (m, 1H), 3.44 (br. s., 2H), 2.20 (d, *J*=2.54 Hz, 3H), 1.93 (dd, *J*=7.34, 9.88 Hz, 1H), 1.73-1.76 (m, 3H), 1.33 (dd, *J*=6.16, 9.88 Hz, 1H), 0.79-0.86 (m, 1H).

(S)-5-(But-3-yn-2-yloxy)pyrazine-2-carboxylic acid (290).

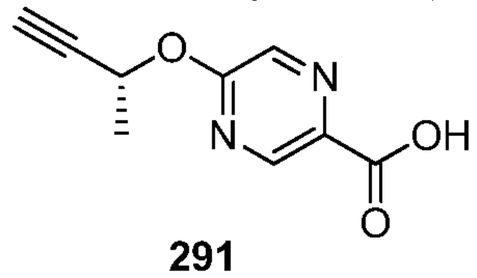


To a solution of (*S*)-(-)-3-butyn-2-ol (Alfa Aesar, 0.91 mL, 11.46 mmol) in THF (15 mL) was added potassium *tert*-butoxide (1.36 g, 12.11 mmol). The resulting solution was stirred at RT for 15 min and then a solution of *tert*-butyl 5-chloropyrazine-2-carboxylate (**272A**, 2.00 g, 9.32 mmol) in THF (20 mL) was added at 0 °C. The mixture was gradually warmed to RT and stirred for 5 h. The reaction was quenched with sat. NH_4Cl, and the mixture was then extracted with EtOAc. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The material thus obtained was purified by silica gel chromatography (0-50% EtOAc in heptane) to provide a mixture of the desired product **290A** and trans-esterification product **290B** as a colorless oil (1.35 g).

A suspension of the above product (1.35 g), lithium hydroxide hydrate (0.46 g, 10.97 mmol), THF (30 mL) and water (10 mL) was heated at 50 °C until the conversion was complete. 1 N HCl (12 mL) was added, and the resulting mixture was extracted with DCM. The organic layer was dried over Na_2SO_4 and concentrated in vacuo to give (*S*)-5-

(but-3-yn-2-yloxy)pyrazine-2-carboxylic acid (**290**) as a white solid (0.96 g, 54% yield over two steps). LC/MS (ESI^+) *m/z* = 193 $(M+H)^+$. ^1H NMR (400 MHz, CHLOROFORM-d) δ 9.01 (d, *J*=1.17 Hz, 1H), 8.20 (d, *J*=0.98 Hz, 1H), 5.83 (dq, *J*=2.05, 6.68 Hz, 1H), 2.49 (d, *J*=2.15 Hz, 1H), 1.71 (d, *J*=6.65 Hz, 3H).

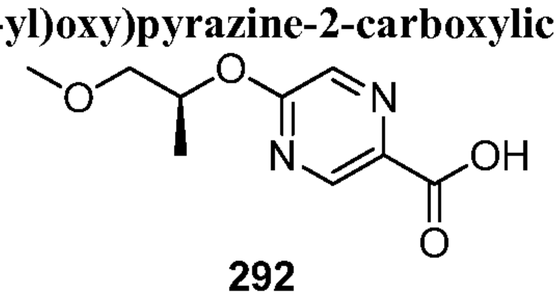
(*R*)-5-(But-3-yn-2-yloxy)pyrazine-2-carboxylic acid (291).



291

The title compound was synthesized according to the procedures described for intermediate **290**, using (*R*)-but-3-yn-2-ol to react with *tert*-butyl 5-chloropyrazine-2-carboxylate **272A**. LC/MS (ESI^+) *m/z* = 193 $(M+H)^+$. ^1H NMR (400 MHz, CHLOROFORM-d) δ 9.01 (d, *J*=1.17 Hz, 1H), 8.21 (d, *J*=1.17 Hz, 1H), 5.83 (dq, *J*=2.05, 6.68 Hz, 1H), 2.50 (d, *J*=1.96 Hz, 1H), 1.71 (d, *J*=6.85 Hz, 3H).

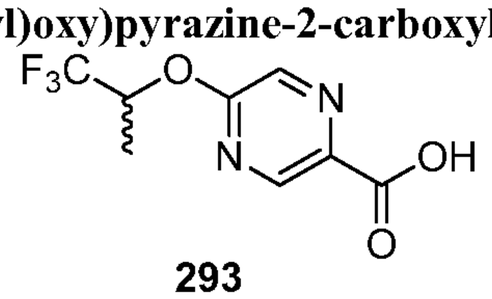
(*S*)-5-((1-Methoxypropan-2-yl)oxy)pyrazine-2-carboxylic acid (292).



292

The title compound was synthesized according to the procedures described for intermediate **290**, using (*S*)-(+)-1-methoxy-2-propanol to react with *tert*-butyl 5-chloropyrazine-2-carboxylate **272A**. LC/MS (ESI^+) *m/z* = 213 $(M+H)^+$. ^1H NMR (400 MHz, CHLOROFORM-d) δ 8.95 (d, *J*=1.37 Hz, 1H), 8.17 (d, *J*=1.37 Hz, 1H), 5.53 (dquin, *J*=3.72, 6.36 Hz, 1H), 3.52-3.68 (m, 2H), 3.40 (s, 3H), 1.39 (d, *J*=6.46 Hz, 3H).

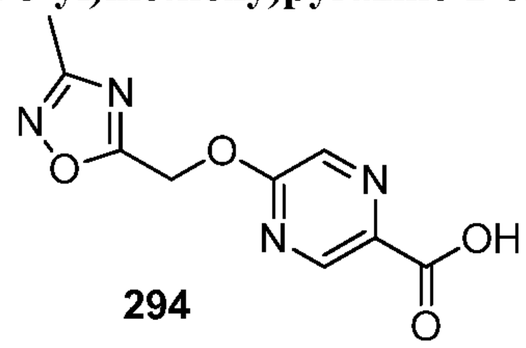
5-((1,1,1-Trifluoropropan-2-yl)oxy)pyrazine-2-carboxylic acid (293).



293

The title compound was synthesized according to the procedures described for intermediate **290**, using 1,1,1-trifluoropropan-2-ol to react with *tert*-butyl 5-chloropyrazine-2-carboxylate **272A**. LC/MS (ESI^+) *m/z* = 237 $(M+H)^+$. ^1H NMR (400 MHz, CHLOROFORM-d) δ 8.85-9.14 (m, 1H), 8.24-8.38 (m, 1H), 5.82 (m, 1H), 1.57 (d, *J*=6.46 Hz, 3H).

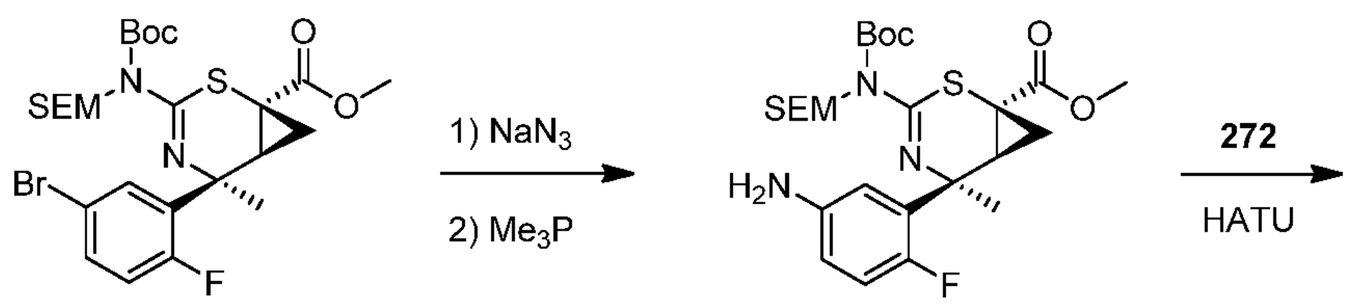
5-((3-Methyl-1,2,4-oxadiazol-5-yl)methoxy)pyrazine-2-carboxylic acid (294).



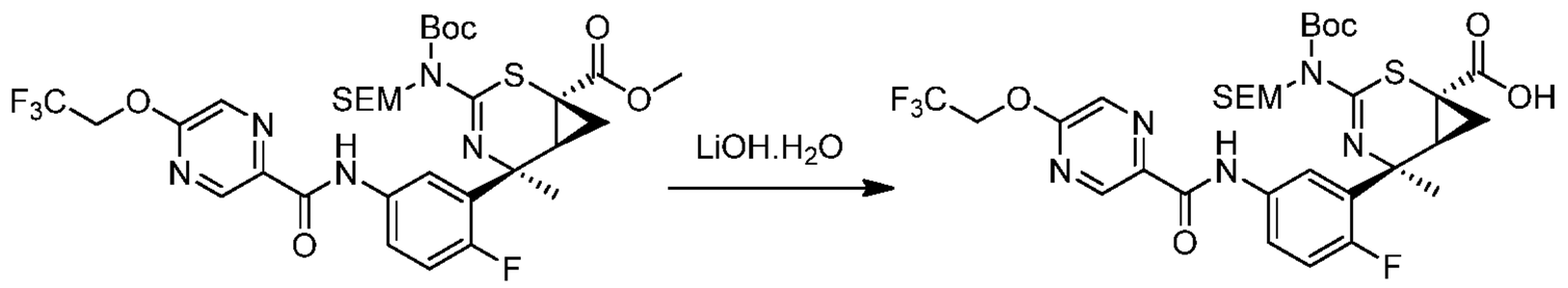
294

The title compound was synthesized according to the procedures described for intermediate **274**, using (3-methyl-1,2,4-oxadiazol-5-yl)methanol to react with *tert*-butyl 5-chloropyrazine-2-carboxylate **272A**. LC/MS (ESI^+) *m/z* = 237 $(M+H)^+$. ^1H NMR (400 MHz, CHLOROFORM-d) δ 8.97 (d, *J*=1.17 Hz, 1H), 8.39 (d, *J*=1.17 Hz, 1H), 5.70 (s, 2H), 2.43 (s, 3H).

(1S,5S,6S)-3-((*tert*-Butoxycarbonyl)((2-(trimethylsilyl)ethoxy)methyl)amino)-5-(2-fluoro-5-(5-(2,2,2-trifluoroethoxy)pyrazine-2-carboxamido)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylic acid (295).



217I **272** **295A**



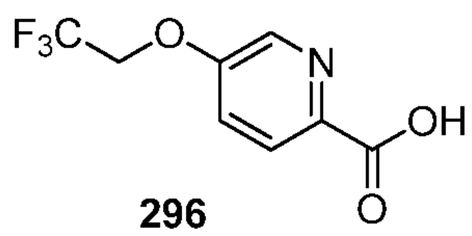
295B **295**

(1S,5S,6S)-Methyl 5-(5-amino-2-fluorophenyl)-3-((*tert*-butoxycarbonyl)((2-(trimethylsilyl)ethoxy)methyl)amino)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylate (295A). The title compound (4.27 g, 7.91 mmol, 93% yield) was prepared according to the procedure described for intermediate **218** using (1S,5S,6S)-methyl 5-(5-bromo-2-fluorophenyl)-3-((*tert*-butoxycarbonyl)((2-(trimethylsilyl)ethoxy)methyl)amino)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylate, **217I**, (5.16 g, 8.55 mmol), sodium azide (2.78 g, 42.7 mmol), copper(i) iodide (0.24 g, 1.282 mmol), (1R,2R)-(-)-N,N"-dimethylcyclohexane-1,2-diamine (0.404 ml, 2.56 mmol), (+)-sodium L-ascorbate (0.508 g, 2.56 mmol) and 1.0 M trimethylphosphine solution in THF (17.10 ml, 17.10 mmol). LCMS (ESI^+) *m/z* = 540.2 (M+H).

(1S,5S,6S)-Methyl 3-((*tert*-butoxycarbonyl)((2-(trimethylsilyl)ethoxy)methyl)amino)-5-(2-fluoro-5-(5-(2,2,2-trifluoroethoxy)pyrazine-2-carboxamido)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylate (295B). To a mixture of (1S,5S,6S)-methyl 5-(5-amino-2-fluorophenyl)-3-((*tert*-butoxycarbonyl)((2-(trimethylsilyl)ethoxy)methyl)amino)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylate, **295A**, (4.27 g, 7.91 mmol), 5-(2,2,2-trifluoroethoxy)pyrazine-2-carboxylic acid, **272**, (2.28 g, 10.28 mmol) in DMF (15 mL) was added TEA (3.30 mL, 23.73 mmol) and HATU (6.02 g, 15.82 mmol). The reaction was stirrred at RT for 2 h and was then diluted with water and extratced with EtOAc (2 x). The organic layers were combined and concentrated, and the product was isolated using silica gel column chromatography (0-20% EtOAc/heptane) to afford the title compound (5.16 g, 6.94 mmol, 88% yield). LCMS (ESI^+) *m/z* = 744.2 (M+H). ^1H NMR (300 MHz, CHLOROFORM-d) δ 9.48 (s, 1H), 9.05 (s, 1H), 8.31 (s, 1H), 7.95-8.02 (m, 1H), 7.73 (dd, *J*=2.63, 6.72 Hz, 1H), 7.14 (dd, *J*=8.99, 11.62 Hz, 1H), 5.34 (d, *J*=10.52 Hz, 1H), 5.10 (d, *J*=10.52 Hz, 1H), 4.89 (q, *J*=8.18 Hz, 2H), 3.82 (s, 3H), 3.67-3.78 (m, 2H), 2.71 (t, *J*=8.70 Hz, 1H), 1.79 (s, 3H), 1.56 (s, 9H), 1.47-1.54 (m, 2H), 1.21-1.36 (m, 1H), 0.94-1.02 (m, 2H), 0.00 (s, 9H). ^{19}F NMR (282 MHz, CHLOROFORM-d) δ -73.61 (s, 3F), -116.70 (s, 1F).

Compound **295** (1.3 g, 1.781 mmol, 96% yield) was prepared according to the procedure for **221A** using (1S,5S,6S)-methyl 3-((*tert*-butoxycarbonyl)((2-(trimethylsilyl)ethoxy)methyl)amino)-5-(2-fluoro-5-(5-(2,2,2-trifluoroethoxy)pyrazine-2-carboxamido)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylate, **295B**, (1.37 g, 1.85 mmol). LCMS (ESI^+) *m/z* = 730.1 (M+H).

5-(2,2,2-Trifluoroethoxy)picolinic acid (296).



296

To a solution of methyl 5-hydroxypicolinate (0.50 g, 3.27 mmol, Frontier Scientific) in DMF (5 mL) were added cesium carbonate (1.38 g, 4.24 mmol) and 2,2,2-trifluoroethyl trifluoromethanesulfonate (0.91 mL, 3.92 mmol), The resulting suspension was stirred at RT for 1 h. The reaction mixture was then diluted with water and EtOAc. The organic layer was washed with brine before drying over magnesium sulfate and concentrating under reduced pressure to afford methyl 5-(2,2,2-trifluoroethoxy)picolinate

as a yellow oil, which was used directly in the next step without further purification. M/S *m/z*= 236.0 $[M+H]^+$.

The methyl 5-(2,2,2-trifluoroethoxy)picolinate from the above reaction was taken up in THF (5 mL) and lithium hydroxide (2.0 M, 4.90 mL, 9.80 mmol) was added. The reaction was stirred at RT for 16 h. The resulting mixture was diluted with water and acidified with 1.0 N HCl (aq) solution until pH = 1 (by pH paper). The solution was extracted with DCM, and the organic layer was washed with brine, dried over magnesium sulfate and concentrated under reduced pressure to afford 5-(2,2,2-Trifluoroethoxy)picolinic acid (**296**) (0.19 g, 0.87 mmol, 27 % yield) as a white solid. M/S *m/z*=221.9 $[M+H]^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 5.00 (q, *J*=8.77 Hz, 2 H) 7.66 (dd, *J*=8.77, 2.92 Hz, 1 H) 8.07 (d, *J*=8.77 Hz, 1 H) 8.50 (d, *J*=2.92 Hz, 1 H) 13.00 (br., 1 H).

General Amide Formation Procedures:

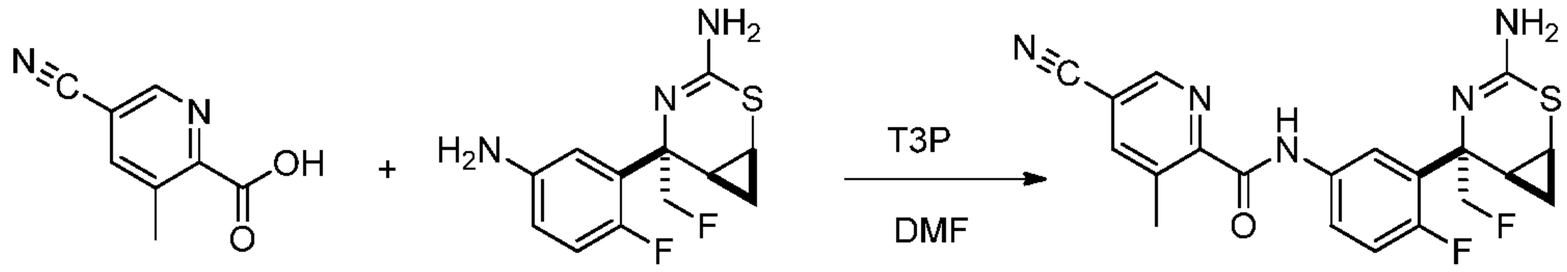
Method A, Method B, Method D, Method F1/2, Method H, and Method J were used to couple an aniline core intermediate to a desired acid as presented herein, to prepare the final compounds of the invention.

General SNAr amination Procedures:

Method C, Method E and Method G were used for the SNAr displacement of the X in ArX intermediate (X = Cl or Br) with a desired aniline core intermediate as presented herein, to prepare the final compounds of the invention.

Method A: Propylphosphonic Anhydride (T3P) procedure in DMF as solvent

Example 3: Synthesis of N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-cyano-3-methylpicolinamide



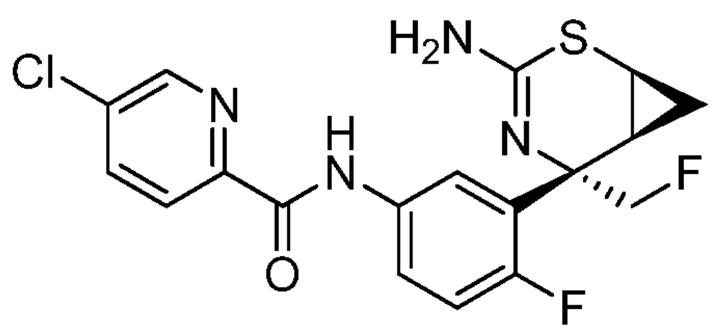
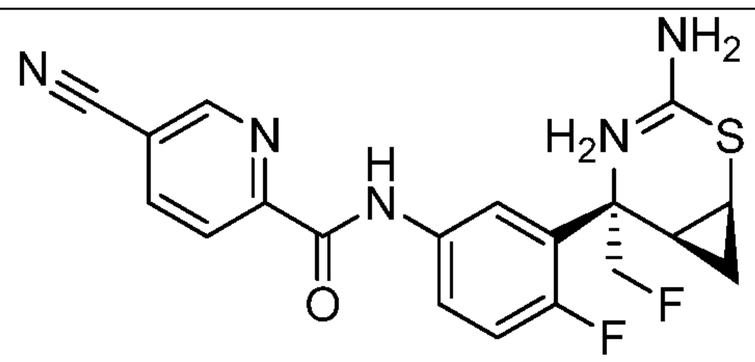
267 **204** **Example 3**

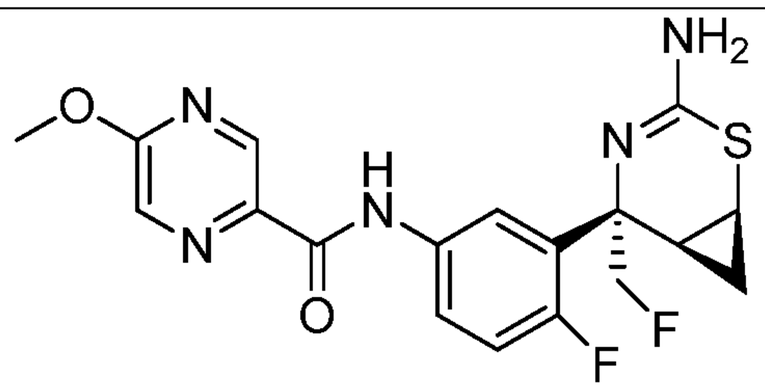
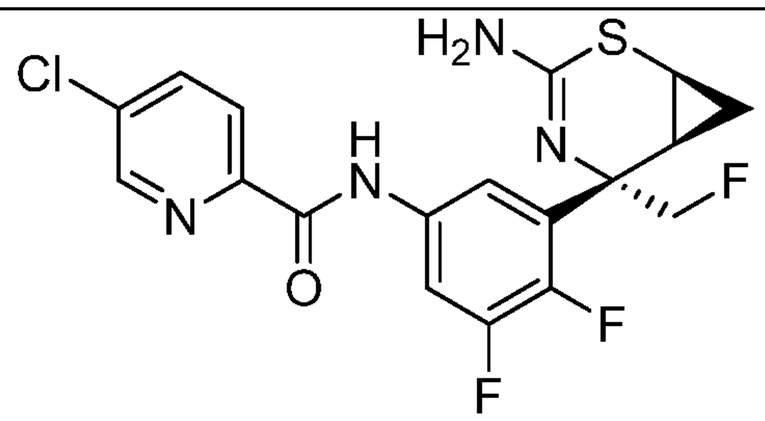
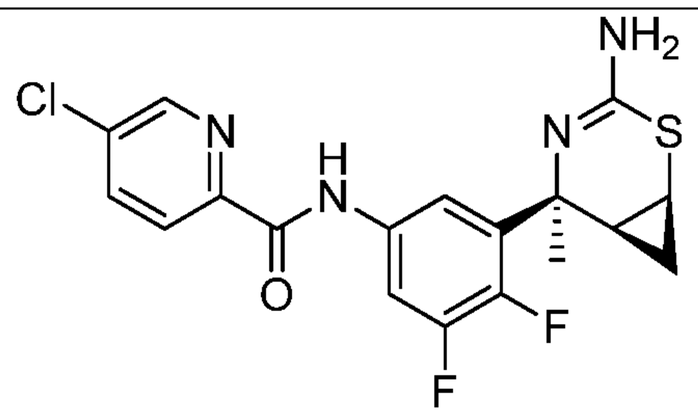
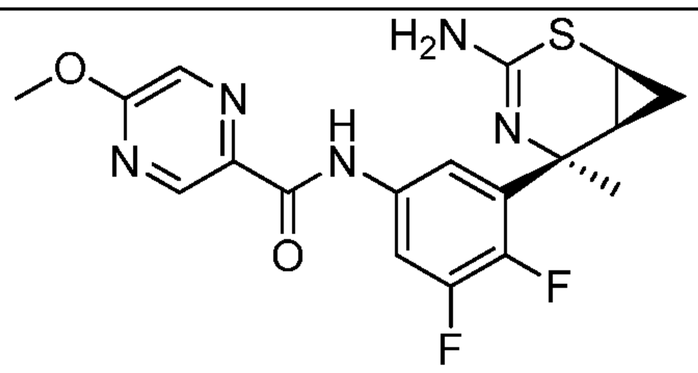
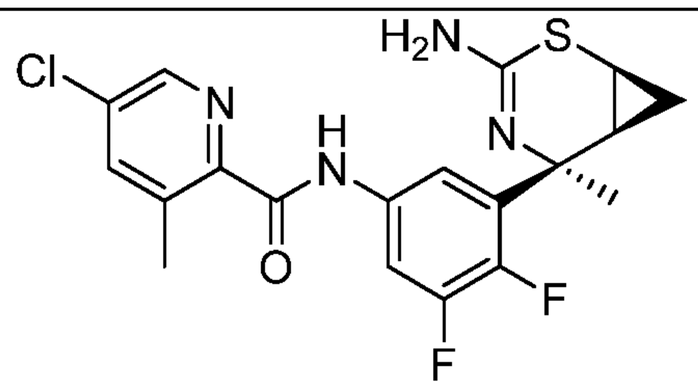
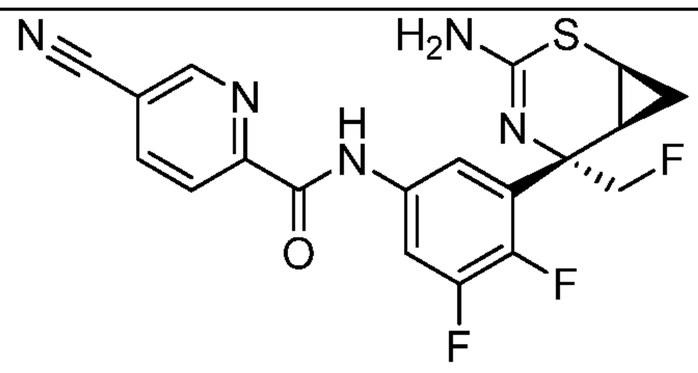
To a solution of (1S,5S,6S)-5-(5-amino-2-fluorophenyl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (intermediate **204**) (72 mg, 0.27 mmol) and 5-cyano-3-methylpicolinic acid (intermediate **267**) (65 mg, 0.40 mmol) in DMF (5 mL) at 0 °C was added propylphosphonic anhydride solution (50 wt.% in EtOAc, 340 μL, 0.53

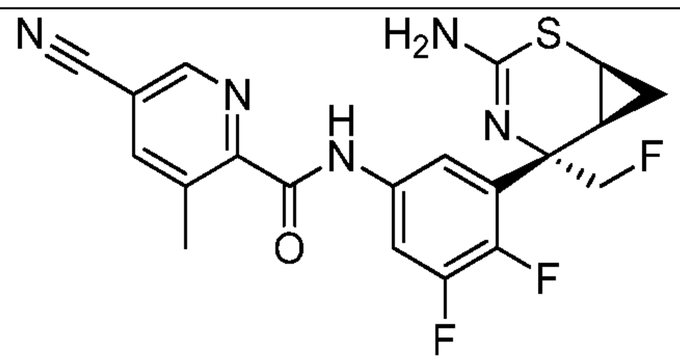
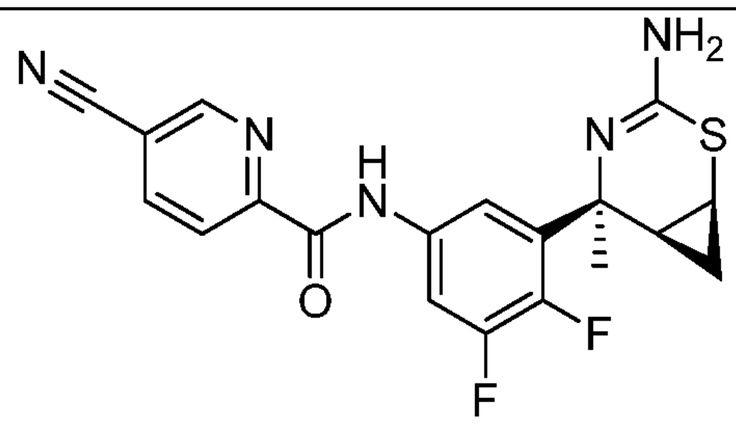
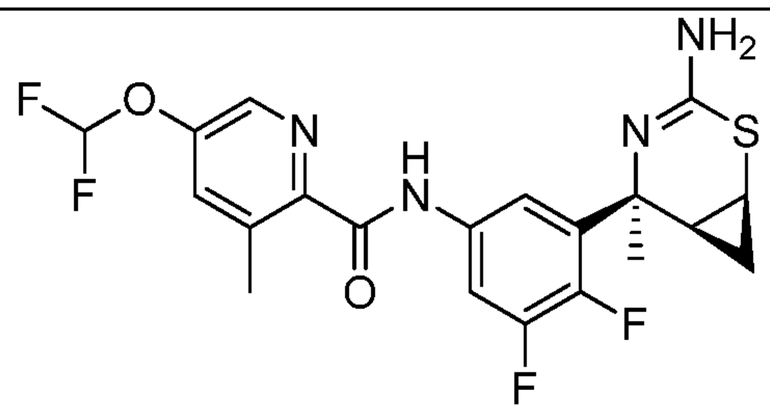
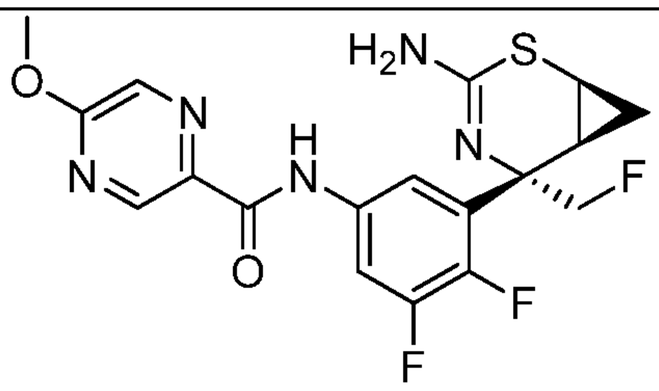
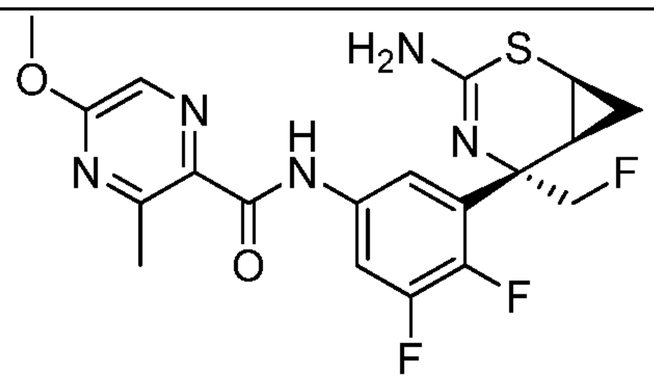
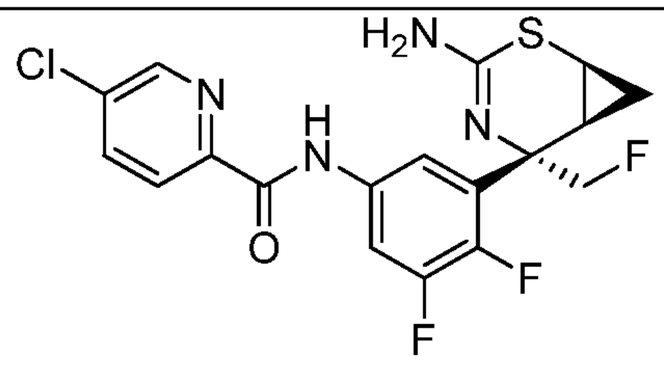
mmol). The reaction was stirred at 0 °C for 30 min. LC/MS showed the presence of the starting aniline (**204**). Another 34 μL of propylphosphonic anhydride solution (50 wt. % in EtOAc) was added. The reaction was stirred at 0 °C for another 30 min. It was quenched with saturated $NaHCO_3$ solution and extracted with DCM (2 x). The combined organic extracts were concentrated. The residue was purified by flash chromatography (12 g ISCO RediSepRf column, 0-60% EtOAc/hexanes) to provide N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-cyano-3-methylpicolinamide (**Example 3**, 72 mg, 0.17 mmol, 65% yield) as a white powder. MS m/z = 414.2 $[M+H]^+$. ^1H NMR (400MHz, CHLOROFORM-d) δ = 10.00 (s, 1 H), 8.69 (d, *J* = 1.4 Hz, 1 H), 8.02 (ddd, *J* = 3.0, 4.1, 8.8 Hz, 1 H), 7.93 (d, *J* = 1.2 Hz, 1 H), 7.62 (dd, *J* = 2.8, 6.7 Hz, 1 H), 7.09 (dd, *J* = 8.8, 11.5 Hz, 1 H), 4.98 - 4.67 (m, 2 H), 4.59 (br. s., 2 H), 2.85 (s, 3 H), 2.34 - 2.25 (m, 1 H), 1.93 (ddt, *J* = 2.1, 6.7, 9.1 Hz, 1 H), 1.11 - 1.02 (m, 1 H), 0.54 (q, *J* = 5.7 Hz, 1 H).

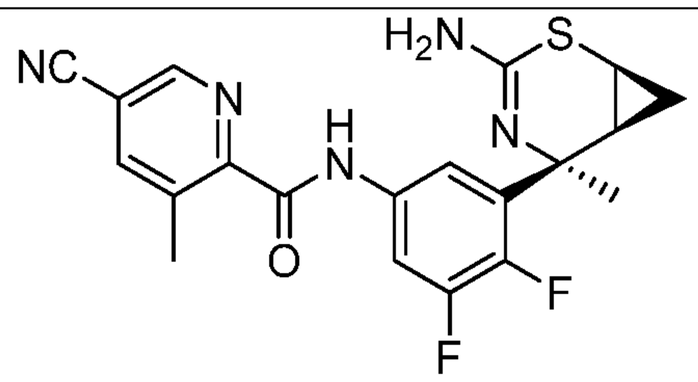
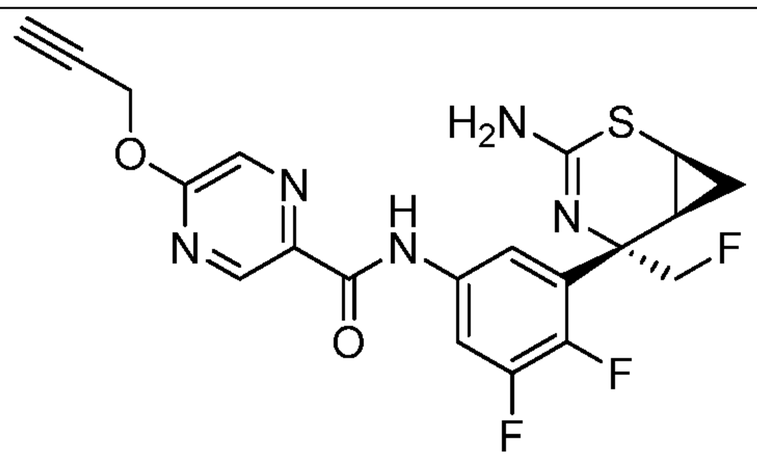
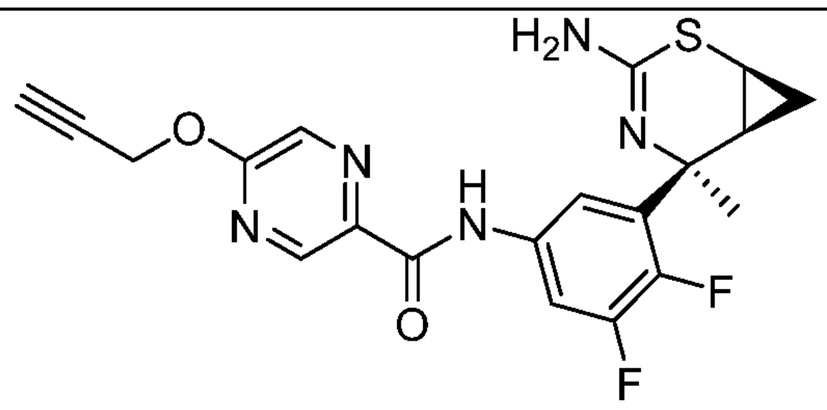
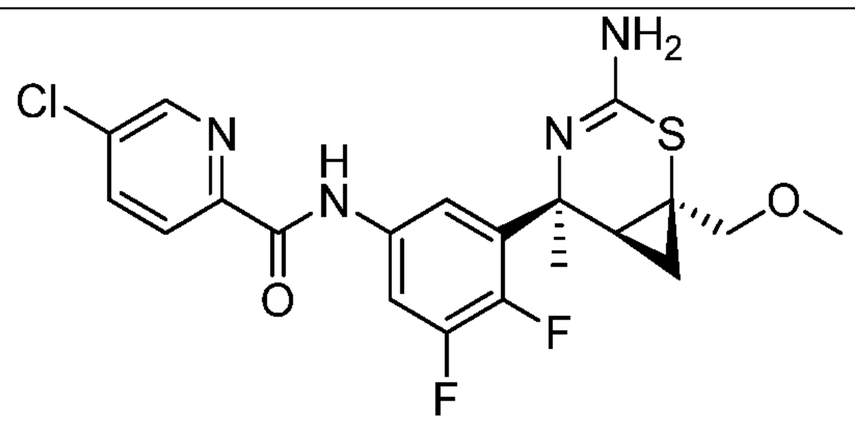
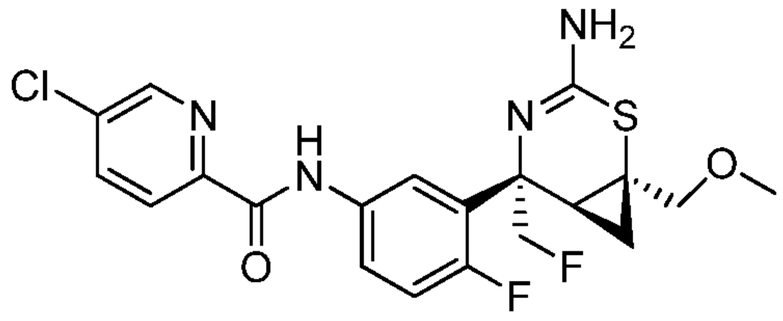
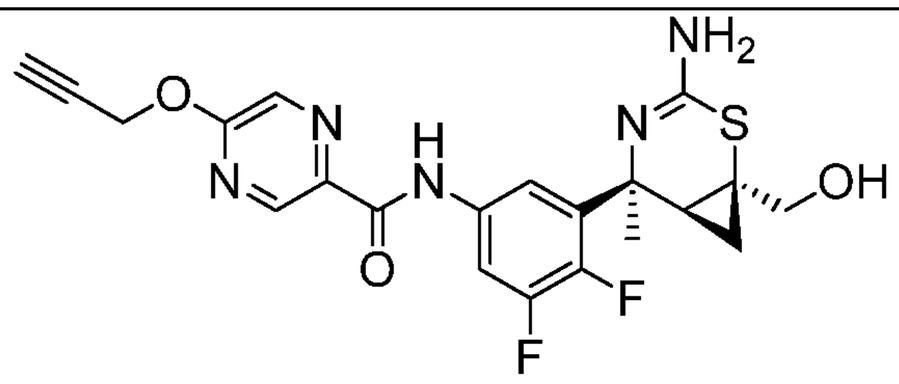
Using procedures analogous or similar to the general amidation **Method A** described above, the appropriate aniline and carboxylic acid intermediates were reacted to provide the 44 examples listed in Table 1 and Table 1'.

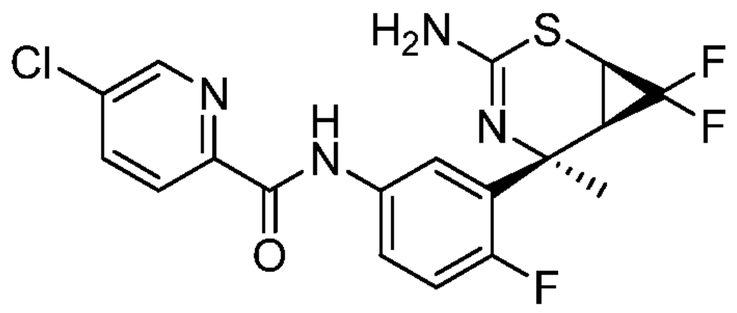
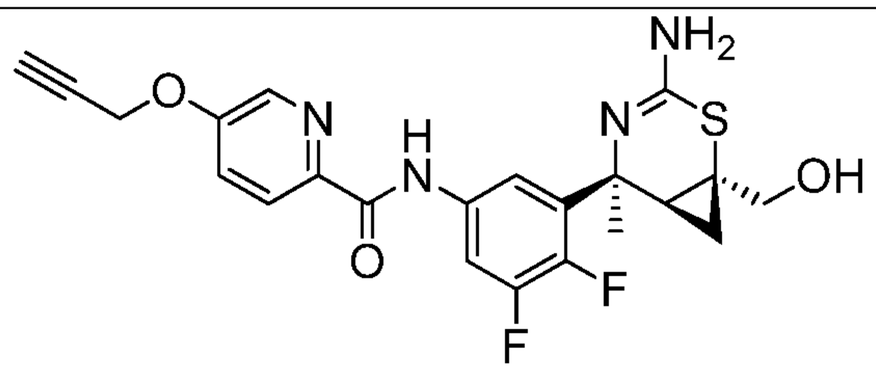
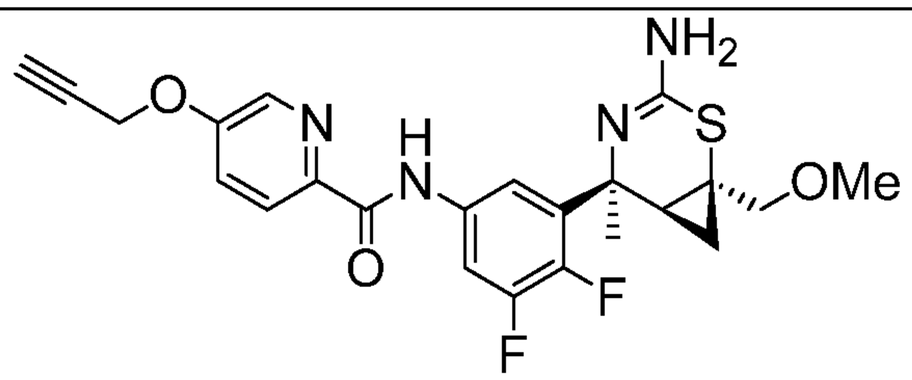
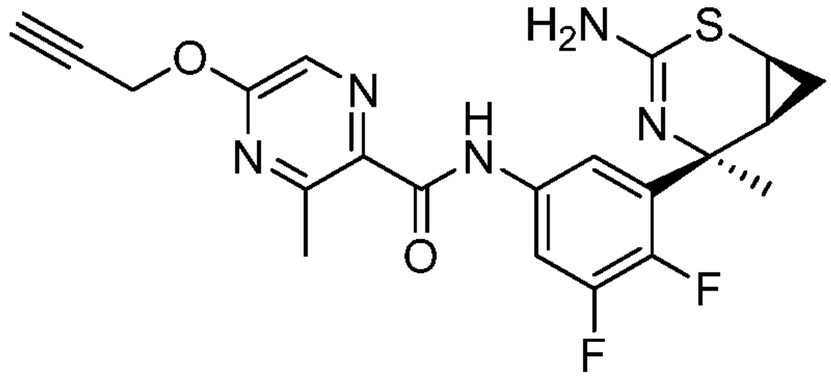
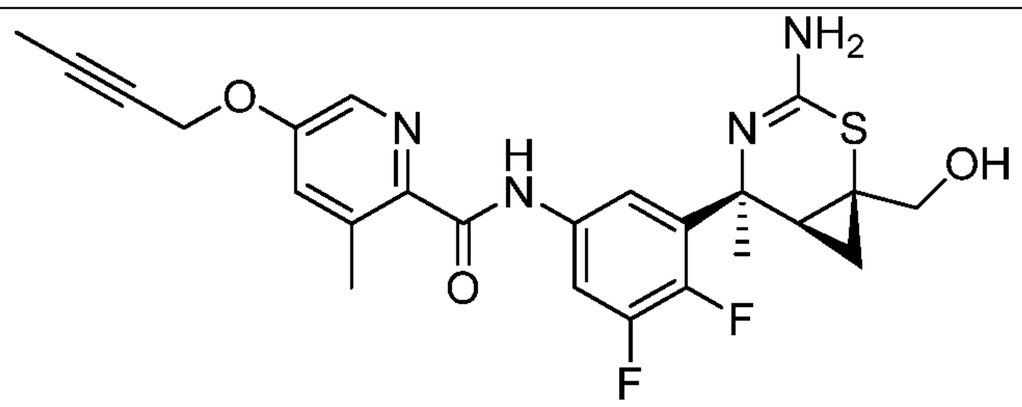
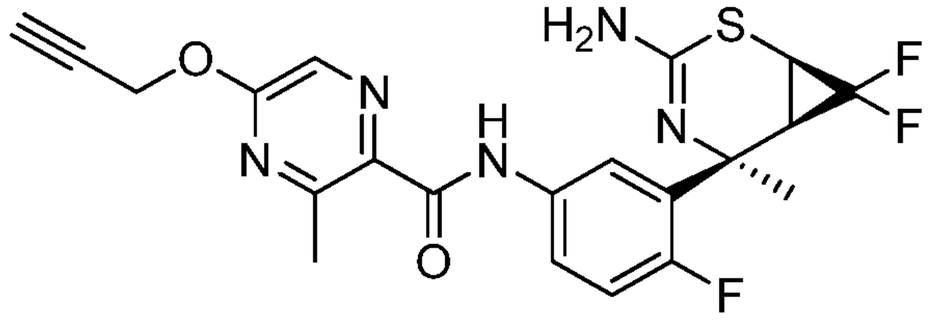
Table 1

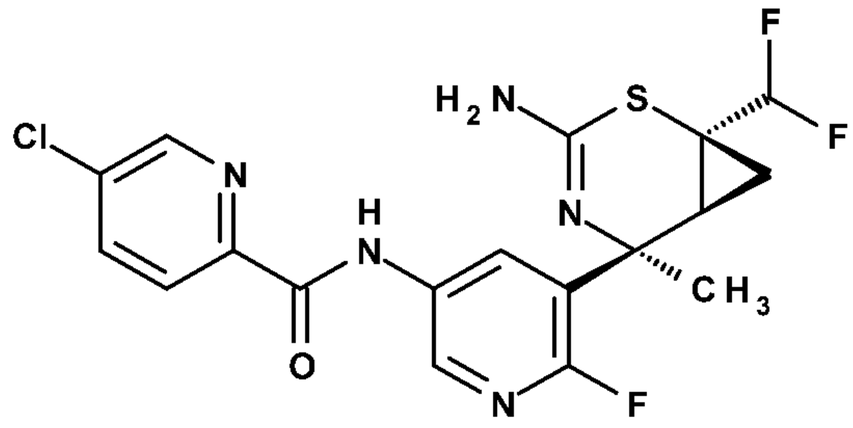
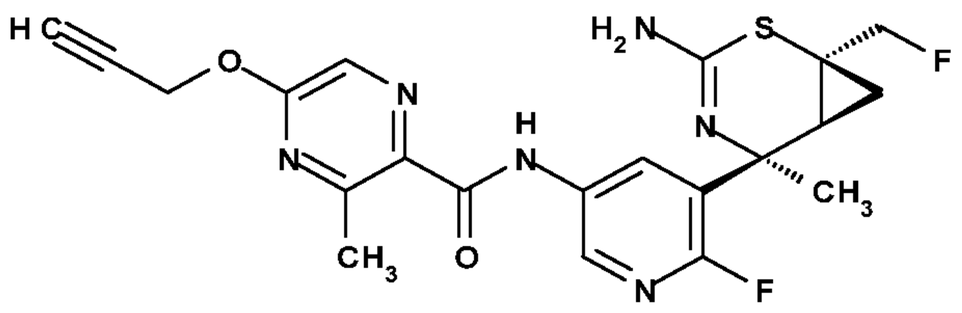
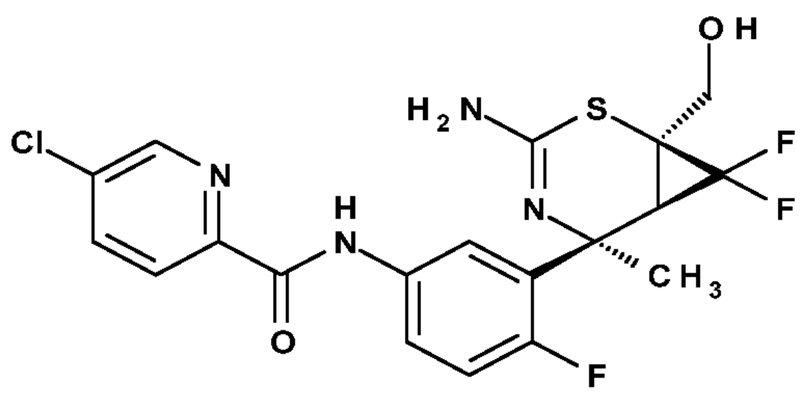
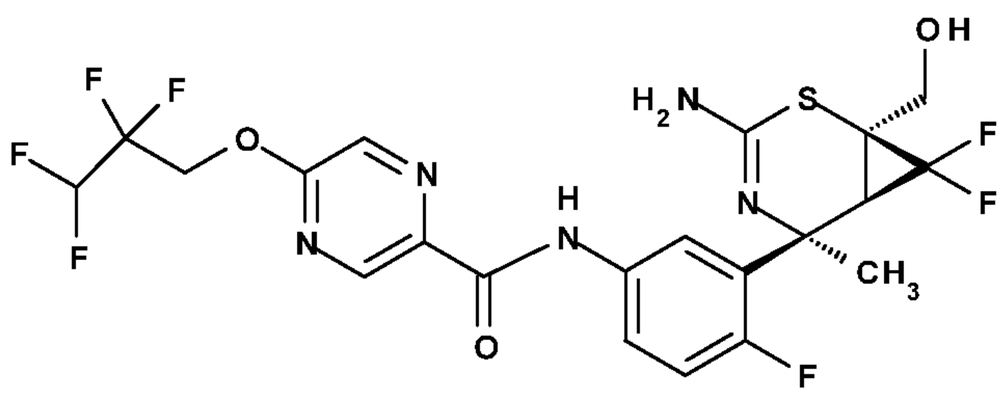
Ex.No.	Chemical Structure	Observed $[M+H]^+$
1		409.1
2		399.9

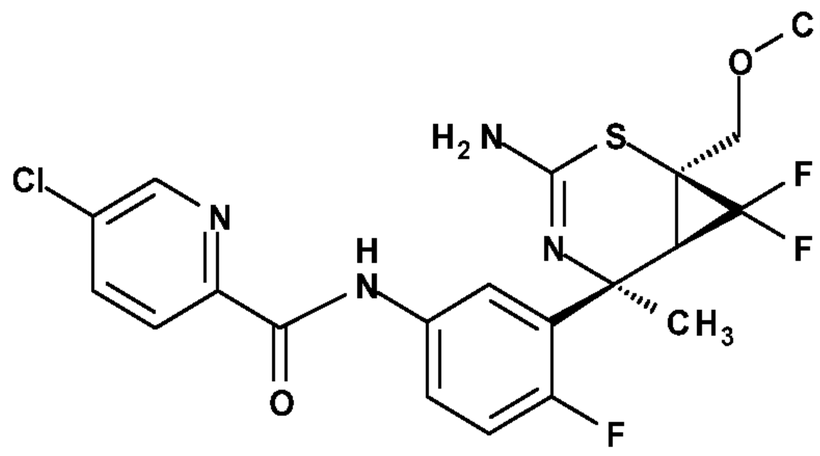
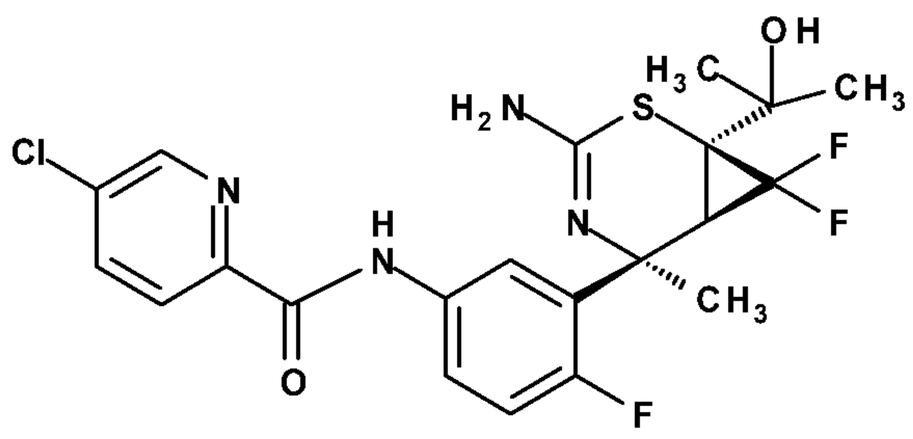
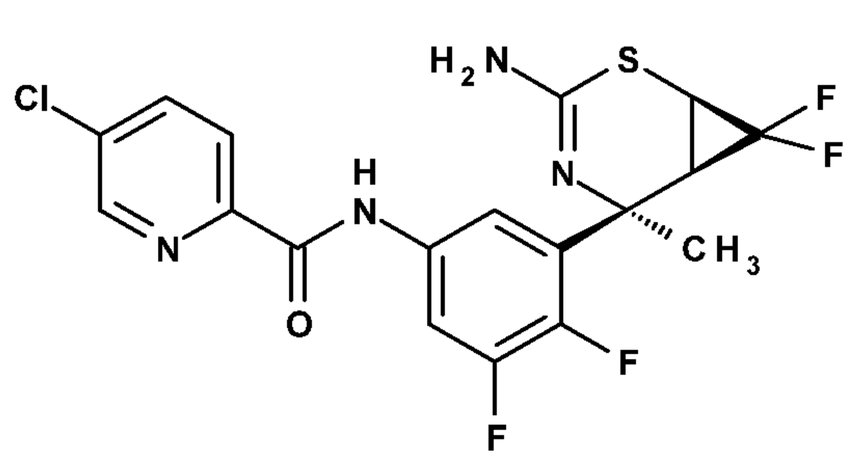
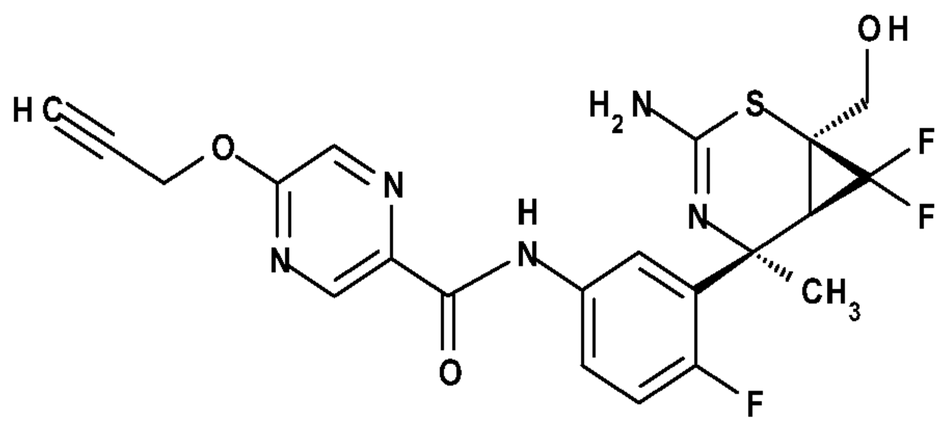
4		406.1
5		427.0
6		409.1
7		406.1
8		423.0
11		418.1

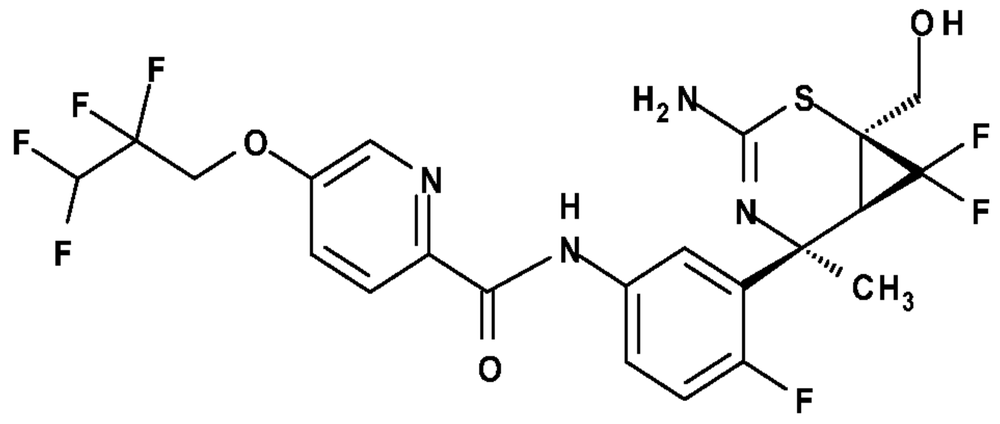
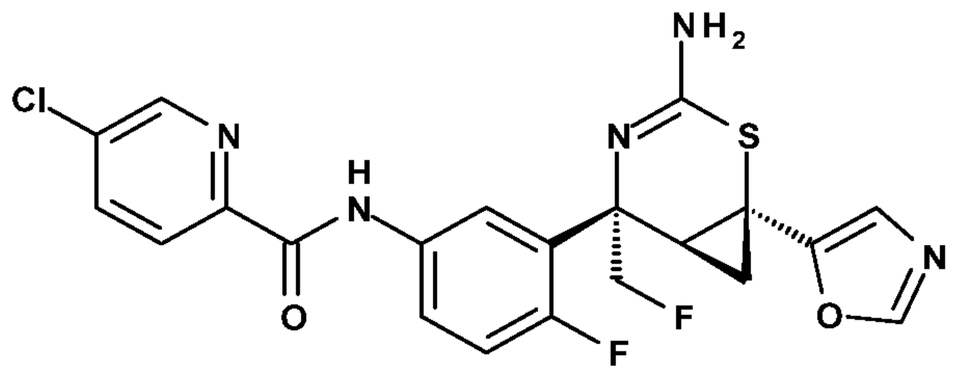
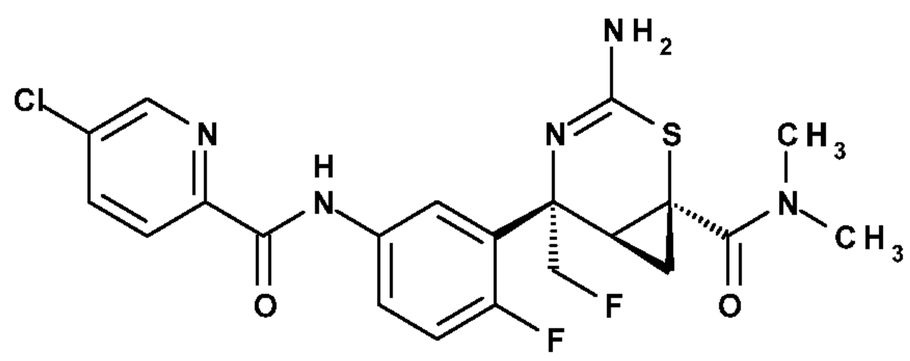
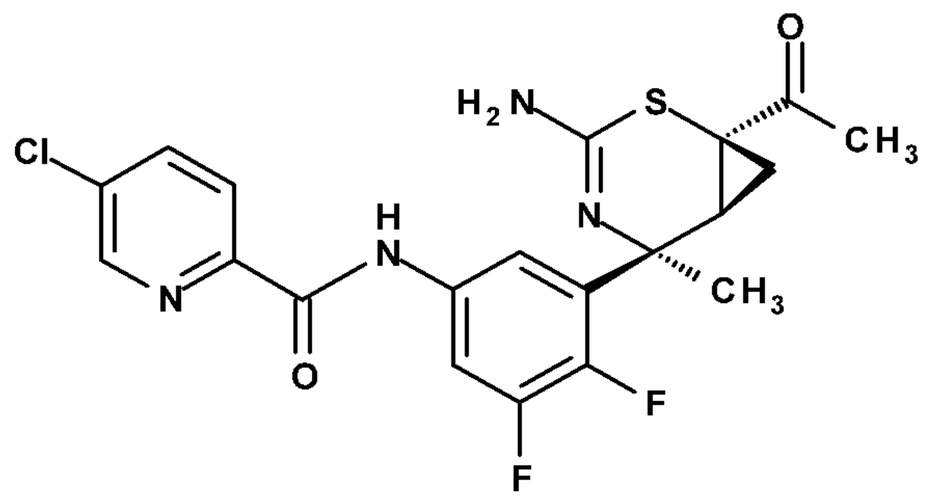
13		432.0
14		400.1
15		455.1
16		424.1
17		438.0
18		427.1

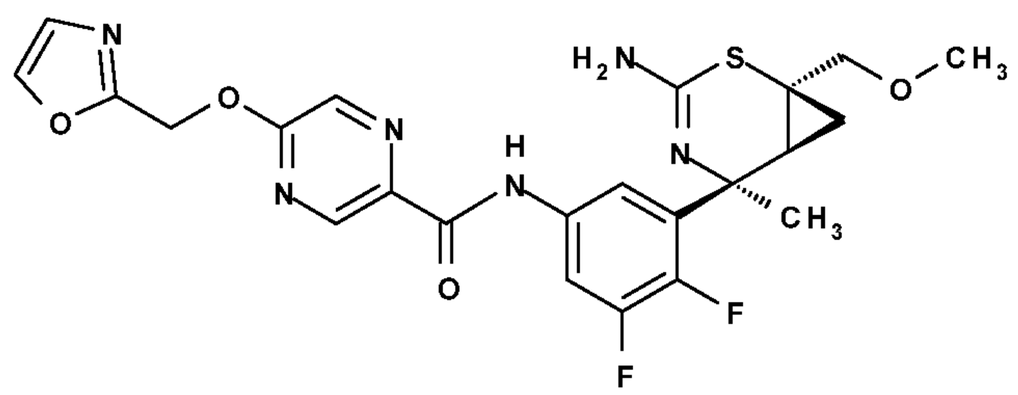
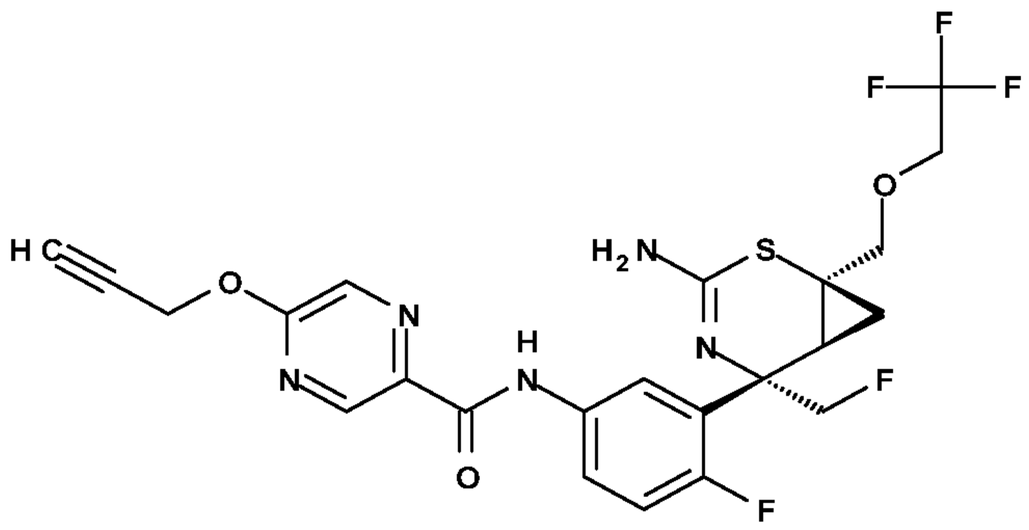
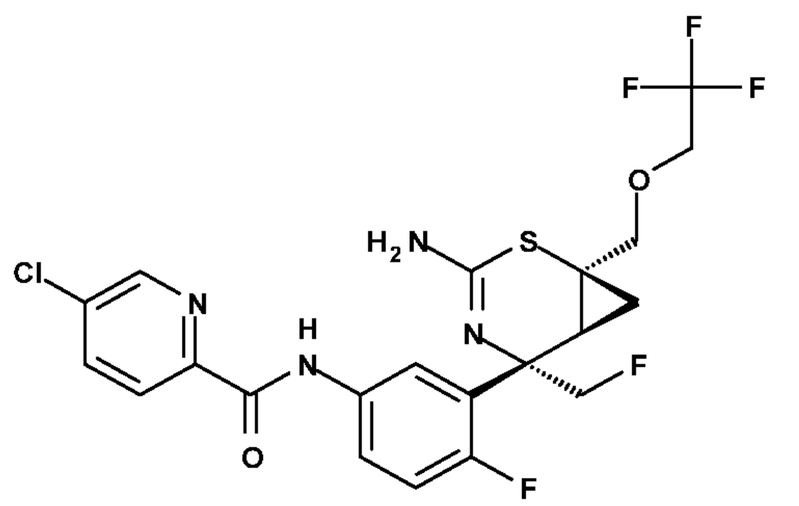
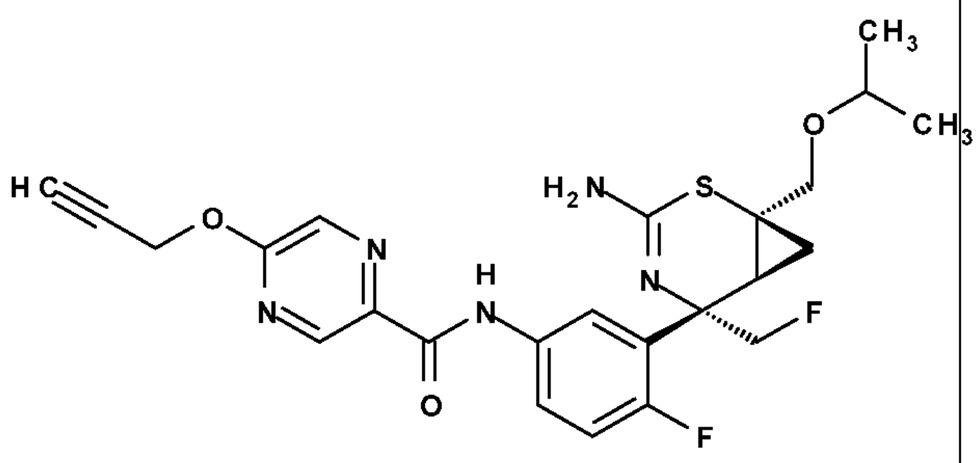
19		414.2
20		448.1
23		430.0
29		453.0
40		453.0
61		460.1

69		427.0
71		459.0
74		473.1
77		444.0
85		487.1
102		462.0

603		459.1
655		442
704		457
708		554

710		471
711		485
748		445.1
749		478.1

751		553.1
785		476
790		480
906		451

910		517
953		542.2
954		521.2
955		502.2

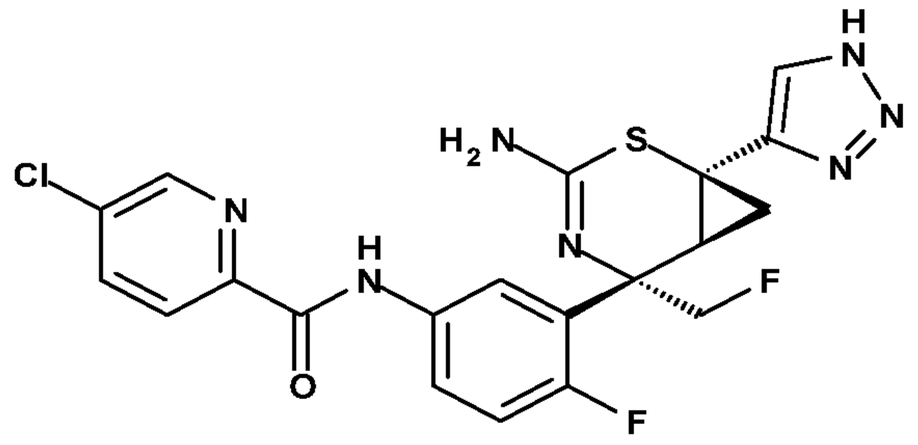
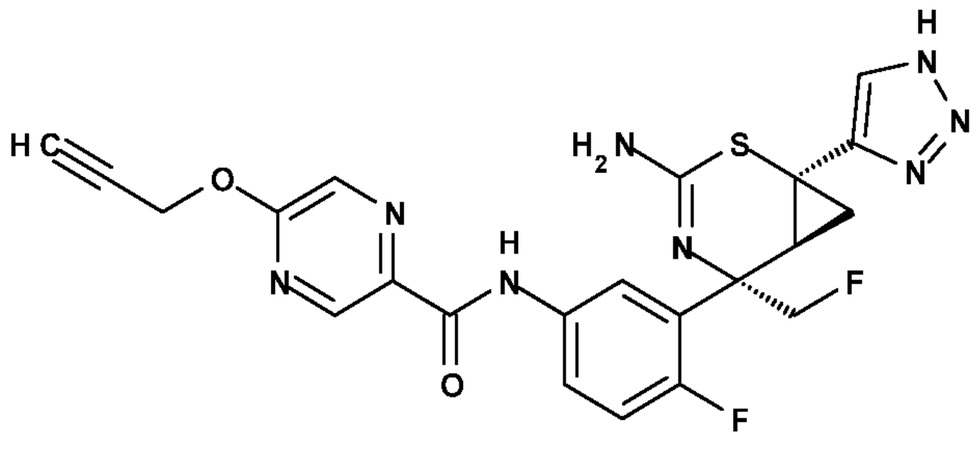
956		476.1
959		497.1

Table 1'

Ex.No.	^{1}H-NMR	Chemical Name
1	^{1}H NMR (400MHz, CHLOROFORM-d) δ = 9.82 (br. s., 1 H), 8.57 - 8.52 (m, 1 H), 8.24 (d, J = 8.4 Hz, 1 H), 8.01 (ddd, J = 2.9, 4.1, 8.8 Hz, 1 H), 7.87 (dd, J = 2.3, 8.4 Hz, 1 H), 7.69 (dd, J = 2.8, 6.7 Hz, 1 H), 7.09 (dd, J = 8.9, 11.6 Hz, 1 H), 4.98 - 4.83 (m, 1 H), 4.82 - 4.67 (m, 1 H), 4.60 (br s, 1 H), 2.30 (ddd, J = 5.1, 7.5, 8.9 Hz, 1 H), 1.93 (ddt, J = 2.0, 6.8, 9.1 Hz, 1 H), 1.60 (br s, 1 H), 1.11 - 1.03 (m, 1 H), 0.55 (q, J = 5.8 Hz, 1 H).	N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide
2	^{1}H NMR (300 MHz, CHLOROFORM-d) δ 9.85 (s, 1H), 8.88 (d, J=1.17 Hz, 1H), 8.42 (d, J=8.04 Hz, 1H), 8.20 (dd, J=1.97, 8.11 Hz, 1H), 7.98-8.07 (m, 1H), 7.73 (dd, J=2.85, 6.80 Hz, 1H), 7.12 (dd, J=8.92, 11.55 Hz, 1H), 4.19-5.32 (m, 4H), 2.25-2.37 (m, 1H), 1.87-2.00 (m, 1H), 1.03-1.15 (m, 1H), 0.56 (q, J=5.89 Hz, 1H).	N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-cyano-2-pyridinecarboxamide
4	^{1}H NMR (400 MHz, CHLOROFORM-d) δ 9.43-9.56 (m, 1H), 9.03 (s, 1H), 8.16 (s, 1H), 7.94-8.05 (m, 1H), 7.68 (dd, J=2.84, 6.75 Hz, 1H), 7.10 (dd, J=8.80, 11.54 Hz, 1H), 4.65-5.00 (m, 2H), 4.08 (s, 3H), 2.23-2.37 (m, 1H), 1.85-2.01 (m, 1H), 1.05-1.18 (m, 1H), 0.48-0.61 (m, 1H)	N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-methoxy-2-pyrazinecarboxamide

5	^{1}H NMR (400 MHz, DMSO-d6) δ ppm 10.80 (s, 1 H) 8.80 (d, J=1.80 Hz, 1 H) 8.22 (dd, J=8.61, 2.35 Hz, 1 H) 8.17 (d, J=8.40 Hz, 1 H) 7.99 (ddd, J=12.37, 6.80, 2.54 Hz, 1 H) 7.89 - 7.93 (m, 1 H) 6.25 (s, 2 H) 4.74 (d, J=47.73 Hz, 2 H) 2.38 - 2.45 (m, 1 H) 1.73 - 1.81 (m, 1 H) 1.06 (ddd, J=8.80, 7.63, 5.28 Hz, 1 H) 0.46 (q, J=5.15 Hz, 1 H)	N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-chloro-2-pyridinecarboxamide
6	^{1}H NMR (400 MHz, CHLOROFORM-d) δ 9.69-9.98 (m, 1H), 8.57 (d, J=2.15 Hz, 1H), 8.25 (d, J=8.41 Hz, 1H), 8.02-8.12 (m, 1H), 7.90 (dd, J=2.35, 8.41 Hz, 1H), 7.37-7.49 (m, 1H), 4.33 (br. s., 2H), 2.21 (dt, J=5.09, 8.31 Hz, 1H), 1.90-2.01 (m, 1H), 1.77 (s, 3H), 0.92 (dd, J=7.43, 14.87 Hz, 1H), 0.63 (q, J=5.87 Hz, 1H)	N-(3-((1S,5S,6S)-3-amino-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-chloro-2-pyridinecarboxamide
7	^{1}H NMR (400 MHz, DMSO-d6) δ ppm 10.56 (s, 1 H), 8.89 (d, J=1.37 Hz, 1 H), 8.41 (d, J=1.17 Hz, 1 H), 7.85 - 7.93 (m, 2 H), 5.91 (s, 2 H), 4.02 (s, 3 H), 2.29 - 2.35 (m, 1 H), 1.67 - 1.74 (m, 1 H), 1.65 (s, 3 H), 0.83 - 0.90 (m, 1 H), 0.48 (q, J=5.15 Hz, 1 H)	N-(3-((1S,5S,6S)-3-amino-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-methoxy-2-pyrazinecarboxamide
8	^{1}H NMR (400 MHz, DMSO-d6) δ ppm 10.65 (s, 1 H), 8.57 (d, J=1.96 Hz, 1 H), 8.02 (d, J=1.56 Hz, 1 H), 7.91 - 7.95 (m, 1 H), 7.68 - 7.73 (m, 1 H), 5.92 (s, 2 H), 2.56 (s, 3 H), 2.29 - 2.36 (m, 1 H), 1.73 (q, J=7.82 Hz, 1 H), 1.64 (s, 3 H), 0.82 - 0.90 (m, 1 H), 0.46 (q, J=5.22 Hz, 1 H)	N-(3-((1S,5S,6S)-3-amino-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-chloro-3-methyl-2-pyridinecarboxamide
11	^{1}H NMR (400 MHz, DMSO-d6) δ ppm 10.96 (s, 1 H) 9.22 (d, J=1.17 Hz, 1 H) 8.60 (dd, J=8.22, 1.96 Hz, 1 H) 8.30 (d, J=8.22 Hz, 1 H) 7.99 (ddd, J=12.18, 6.70, 2.25 Hz, 1 H) 7.91 - 7.96 (m, 1 H) 6.25 (s, 2 H) 4.74 (d, J=47.54 Hz, 2 H) 2.38 - 2.46 (m, 1 H) 1.73 - 1.81 (m, 1 H) 1.06 (td, J=8.07, 5.38 Hz, 1 H) 0.46 (q, J=5.35 Hz, 1 H)	N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-cyano-2-pyridinecarboxamide
13	^{1}H NMR (400 MHz, DMSO-d6) δ ppm 10.87 (s, 1 H) 8.98 (d, J=1.17 Hz, 1 H) 8.40 (d, J=0.78 Hz, 1 H) 7.96 (ddd, J=12.18, 6.80, 2.54 Hz, 1 H) 7.68 - 7.73 (m, 1 H) 6.24 (s, 2 H) 4.73 (d, J=47.54 Hz, 2 H) 2.56 (s, 3 H) 2.37 - 2.44 (m, 1 H) 1.75 (q, J=7.96 Hz, 1 H) 1.04 (td, J=8.22, 5.28 Hz, 1 H) 0.41 (q, J=5.28 Hz, 1 H)	N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-cyano-3-methyl-2-pyridinecarboxamide
14	^{1}H NMR (400 MHz, CHLOROFORM-d) Shift 9.88 (s, 1H), 8.85-8.94 (m, 1H), 8.41-8.48 (m, 1H), 8.17-8.26 (m, 1H), 8.07 (ddd, J=2.84, 6.75, 11.74 Hz, 1H), 7.43 (td, J=2.57, 5.23 Hz, 1H), 2.17-2.30 (m, 1H), 1.92-2.02 (m, 1H), 1.75-1.80 (m, 3H), 0.89-0.98 (m, 1H), 0.62 (q, J=5.87 Hz, 1H)	N-(3-((1S,5S,6S)-3-amino-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-cyano-2-pyridinecarboxamide
15	^{1}H NMR (400 MHz, CHLOROFORM-d) Shift 10.06 (br. s., 1H), 8.32 (s, 1H), 8.01-8.13 (m, 1H), 7.42 (s, 1H), 7.33 (br. s., 1H), 6.42-6.86 (m, 1H), 2.84 (s, 3H), 2.15-2.28 (m, 1H), 1.88-2.01 (m, 1H), 1.77 (s, 3H), 0.85-0.97 (m, 1H), 0.63 (q, J=5.80 Hz, 1H)	N-(3-((1S,5S,6S)-3-amino-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(difluoromethoxy)-3-methyl-2-pyridinecarboxamide

16	^{1}H NMR (400 MHz, DMSO-d6) δ ppm 10.62 (s, 1 H) 8.90 (d, J=0.98 Hz, 1 H) 8.42 (d, J=1.17 Hz, 1 H) 7.96 (ddd, J=12.37, 6.70, 2.45 Hz, 1 H) 7.87 - 7.91 (m, 1 H) 6.23 (s, 2 H) 4.73 (d, J=47.54 Hz, 2 H) 4.03 (s, 3 H) 2.37 - 2.44 (m, 1 H) 1.71 - 1.79 (m, 1 H) 1.02 - 1.09 (m, 1 H) 0.45 (q, J=5.28 Hz, 1 H)	N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-methoxy-2-pyrazinecarboxamide
17	^{1}H NMR (400 MHz, DMSO-d6) δ ppm 10.56 (s, 1 H) 8.24 (s, 1 H) 7.97 (ddd, J=12.42, 6.85, 2.45 Hz, 1 H) 7.72 - 7.76 (m, 1 H) 6.23 (s, 2 H) 4.72 (d, J=47.54 Hz, 2 H) 4.00 (s, 3 H) 2.77 (s, 3 H) 2.37 - 2.44 (m, 1 H) 1.75 (q, J=8.15 Hz, 1 H) 1.01 - 1.08 (m, 1 H) 0.43 (q, J=5.28 Hz, 1 H)	N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-methoxy-3-methyl-2-pyrazinecarboxamide
18	^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 10.87 (s, 1 H) 8.79 (d, J=1.76 Hz, 1 H) 8.12 - 8.24 (m, 2 H) 7.94 - 8.07 (m, 2 H) 6.19 (s, 2 H) 4.73 (dd, J=47.54, 8.61 Hz, 1 H) 4.49 (dd, J=47.73, 8.22 Hz, 1 H) 2.41 - 2.48 (m, 1 H) 1.86 - 1.96 (m, 1 H) 1.04 - 1.15 (m, 1 H) 0.84 (q, J=5.15 Hz, 1 H)	N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-chloropicolinamide
19	^{1}H NMR (400 MHz, CHLOROFORM-d) Shift 10.06 (s, 1H), 8.72 (d, J=1.17 Hz, 1H), 8.07 (ddd, J=2.84, 6.75, 11.74 Hz, 1H), 7.95 (s, 1H), 7.31-7.41 (m, 1H), 2.88 (s, 3H), 2.22 (dt, J=5.09, 8.41 Hz, 1H), 1.95 (td, J=7.09, 8.90 Hz, 1H), 1.76 (s, 3H), 0.84-0.98 (m, 1H), 0.62 (q, J=5.74 Hz, 1H)	N-(3-((1S,5S,6S)-3-amino-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-cyano-3-methyl-2-pyridinecarboxamide
20	^{1}H NMR (400 MHz, DMSO-d6) δ ppm 10.67 (s, 1 H) 8.92 (d, J=1.17 Hz, 1 H) 8.50 (d, J=1.17 Hz, 1 H) 7.97 (ddd, J=12.32, 6.75, 2.64 Hz, 1 H) 7.89 - 7.93 (m, 1 H) 6.24 (s, 2 H) 5.16 (d, J=2.35 Hz, 2 H) 4.74 (d, J=47.34 Hz, 2 H) 3.66 (t, J=2.45 Hz, 1 H) 2.38 - 2.45 (m, 1 H) 1.72 - 1.80 (m, 1 H) 1.06 (ddd, J=8.85, 7.58, 5.09 Hz, 1 H) 0.46 (q, J=5.28 Hz, 1 H)	N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide
23	^{1}H NMR (400 MHz, DMSO-d6) δ ppm 10.60 (s, 1 H) 8.90, (d, J=1.17 Hz, 1 H), 8.48 (d, J=0.98 Hz, 1 H), 7.85 - 7.93 (m, 2 H), 5.92 (br. s., 2 H), 5.14 (d, J=2.35 Hz, 2 H), 3.64 (t, J=2.35 Hz, 1 H), 2.32 (td, J=8.26, 4.99 Hz, 1 H), 1.68 - 1.74 (m, 1 H), 1.65 (s, 3 H), 0.87 (td, J=8.12, 5.28 Hz, 1 H), 0.48 (q, J=5.28 Hz, 1 H)	N-(3-((1S,5S,6S)-3-amino-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide
29	^{1}H NMR (400 MHz, DMSO-d6) δ 10.74 (br., 1H), 8.79 (d, J=1.96 Hz, 1H), 8.14-8.23 (m, 2H), 7.87-7.97 (m, 2H), 6.00 (br., 2H), 3.57 (d, J=10.95 Hz, 1H), 3.34 (m, 1H), 3.33 (s, 3H), 1.58 (m, 1H), 1.66 (s, 3H), 0.90 (m, 1H), 0.65 (m, 1H)	N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-chloro-2-pyridinecarboxamide
40	^{1}H NMR (DMSO-d6) δ: 10.58 (s, 1H), 8.78 (d, J=2.0 Hz, 1H), 8.09-8.24 (m, 2H), 8.02 (d, J=4.9 Hz, 1H), 7.83 (d, J=8.4 Hz, 1H), 7.17 (dd, J=11.7, 8.8 Hz, 1H), 6.25 (s, 2H), 4.57-4.78 (m, 2H), 3.32-3.60 (m, 2H), 3.28 (s, 3H), 1.64 (t, J=8.2 Hz, 1H), 1.04 (dd, J=9.3, 5.4 Hz, 1H), 0.58 (t, J=5.8 Hz, 1H)	N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-(methoxymethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide

61	^{1}H NMR (400 MHz, DMSO-d6) δ 10.62 (s, 1H), 8.92 (d, J=1.37 Hz, 1H), 8.50 (d, J=1.37 Hz, 1H), 7.89-7.98 (m, 2H), 5.95 (s, 2H), 5.16 (d, J=2.35 Hz, 2H), 5.05 (t, J=5.97 Hz, 1H), 3.66 (t, J=2.35 Hz, 1H), 3.55 (dd, J=6.36, 11.64 Hz, 1H), 3.45 (dd, J=5.58, 11.64 Hz, 1H), 1.63 (m, 1H), 1.61 (s, 3H), 0.86 (dd, J=5.09, 9.19 Hz, 1H), 0.57 (t, J=5.77 Hz, 1H).	N-(3-((1S,5S,6S)-3-amino-1-(hydroxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide
69	^{1}H NMR (300MHz, CDCl3) Shift = 9.86 (br. s., 1H), 8.58 (d, J=1.9 Hz, 1H), 8.26 (d, J=7.9 Hz, 1H), 8.06 (ddd, J=2.8, 4.2, 8.9 Hz, 1H), 7.90 (dd, J=2.3, 8.3 Hz, 1H), 7.76 (dd, J=2.8, 6.9 Hz, 1H), 7.12 (dd, J=8.8, 11.8 Hz, 1H), 2.93 (dd, J=8.3, 13.1 Hz, 1H), 2.79 - 2.64 (m, 1H), 1.73 (s, 3H)	N-(3-((1R,5S,6R)-3-amino-7,7-difluoro-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide
71	^{1}H NMR (400 MHz, DMSO-d6) δ 10.56 (br., 1H), 8.45 (d, J=2.54 Hz, 1H), 8.15 (d, J=8.80 Hz, 1H), 7.915 (m, 1H), 7.88 (br., 1H), 7.69 (dd, J=2.64, 8.71 Hz, 1H), 5.97 (br., 2H), 5.00-5.11 (m, 3H), 3.72 (s, 1H), 3.55 (m, 1H), 3.46 (m, 1H), 1.66 (m, 1H), 1.61 (s, 3H), 0.87 (m, 1H), 0.59 (m, 1H).	N-(3-((1S,5S,6S)-3-amino-1-(hydroxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(2-propyn-1-yloxy)-2-pyridinecarboxamide
74	^{1}H NMR (400 MHz, DMSO-d6) δ ppm 10.54 (s, 1 H), 8.43 (d, J=2.74 Hz, 1 H), 8.13 (d, J=8.61 Hz, 1 H), 7.89 - 7.99 (m, 1 H), 7.86 (d, J=5.87 Hz, 1 H), 7.67 (dd, J=8.80, 2.93 Hz, 1 H), 6.00 (br. s., 2 H), 5.04 (d, J=2.35 Hz, 2 H), 3.71 (t, J=2.35 Hz, 1 H), 3.56 (d, J=10.95 Hz, 1 H), 3.36 (d, J=11.15 Hz, 1 H), 3.29 - 3.32 (m, 3 H), 1.56 - 1.68 (m, 4 H), 0.90 (br. s., 1 H), 0.66 (d, J=5.28 Hz, 1 H)	N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(2-propyn-1-yloxy)-2-pyridinecarboxamide
77	^{1}H NMR (400 MHz, DMSO-d6) δ ppm 10.55 (s, 1 H), 8.29 (s, 1 H), 7.91 (ddd, J=12.42, 6.75, 2.54 Hz, 1 H), 7.72 (d, J=5.87 Hz, 1 H), 5.92 (s, 2 H), 5.11 (d, J=2.35 Hz, 2 H), 3.61 (t, J=2.35 Hz, 1 H), 2.75 (s, 3 H) 2.29 - 2.35 (m, 1 H), 1.67 - 1.78 (m, 1 H), 1.64 (s, 3 H), 0.86 (td, J=8.07, 5.38 Hz, 1 H), 0.46 (q, J=5.28 Hz, 1 H)	N-(3-((1S,5S,6S)-3-amino-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-methyl-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide
85	^{1}H NMR (400 MHz, CHLOROFORM-d) Shift 10.10 (s, 1H), 8.17 (d, J=2.54 Hz, 1H), 8.01-8.11 (m, 1H), 7.29 (br. s., 1H), 7.16 (d, J=2.35 Hz, 1H), 4.55-4.82 (m, 2H), 3.59-3.80 (m, 2H), 2.80 (s, 3H), 1.88 (t, J=2.35 Hz, 3H), 1.79-1.86 (m, 1H), 1.73 (s, 3H), 0.84-0.87 (m, 1H), 0.75-0.81 (m, 1H)	N-(3-((1S,5S,6S)-3-amino-1-(hydroxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(2-butyn-1-yloxy)-3-methyl-2-pyridinecarboxamide
102	^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.72 (s, 3 H), 2.55 (s, 1 H), 2.65 - 2.82 (m, 1 H), 2.86 - 3.06 (m, 5 H), 4.58 (br., 2 H), 5.10 (s, 2 H), 7.03 - 7.19 (m, 1 H), 7.55 - 7.74 (m, 1 H), 7.96 - 8.18 (m, 2 H), 9.81 (s, 1 H).	N-(3-((1R,5S,6R)-3-amino-7,7-difluoro-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3-methyl-5-(prop-2-yn-1-yloxy)pyrazine-2-carboxamide

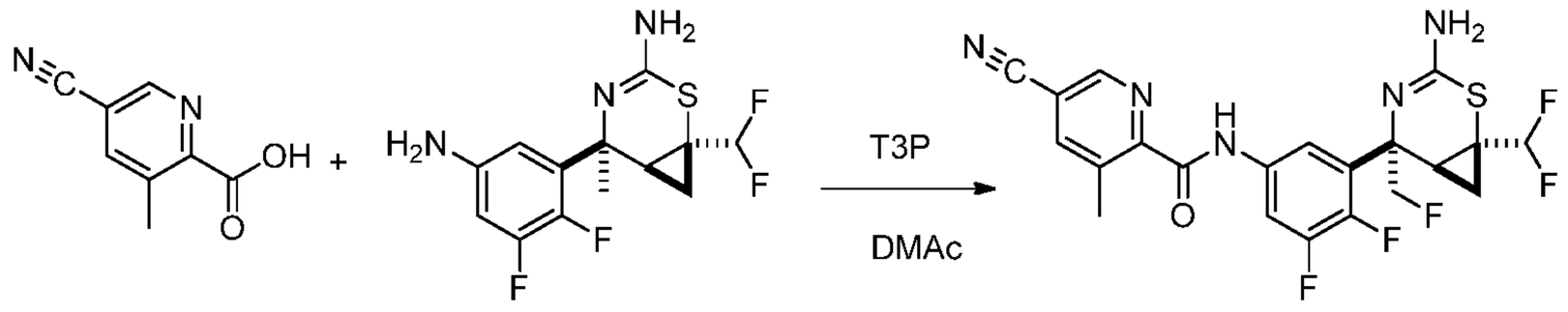
603	^{1}H NMR (300 MHz, CHLOROFORM-d) δ 9.83 (s, 1H), 8.55-8.75 (m, 1H), 8.32 (dd, J=2.70, 8.70 Hz, 1H), 8.09 (s, 1H), 5.11 (d, J=2.34 Hz, 2H), 4.97-5.26 (br. s, 2H), 4.44-4.65 (m, 1H), 4.07-4.43 (m, 1H), 2.98 (s, 3H), 2.56 (t, J=2.41 Hz, 1H), 1.85-2.13 (m, 1H), 1.74 (s, 3H), 1.02 (dd, J=6.14, 9.35 Hz, 1H), 0.84-0.93 (m, 1H).	N-(5-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoro-3-pyridinyl)-3-methyl-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide
655	^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 0.84 (td, J=6.60, 2.84 Hz, 1 H) 1.33 (dd, J=9.88, 6.36 Hz, 1 H) 1.77 (s, 3 H) 1.97 - 2.08 (m, 1 H) 5.47 - 5.86 (m, 1 H) 7.90 (dd, J=8.41, 2.35 Hz, 1 H) 8.23 (d, J=8.22 Hz, 1 H) 8.35 (dd, J=8.61, 2.74 Hz, 1 H) 8.53 - 8.63 (m, 2 H) 9.84 (s, 1 H).	N-(5-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoro-3-pyridinyl)-5-chloro-2-pyridinecarboxamide
704	^{1}H NMR (300MHz, CDCl3) δ = 9.85 (s, 1H), 8.58 (d, J=2.3 Hz, 1H), 8.26 (d, J=9.1 Hz, 1H), 8.03 (ddd, J=2.9, 4.2, 8.8 Hz, 1H), 7.90 (dd, J=2.3, 8.5 Hz, 1H), 7.77 (dd, J=2.8, 6.9 Hz, 1H), 7.12 (dd, J=8.8, 11.7 Hz, 1H), 4.04 - 3.97 (m, 1H), 3.97 - 3.90 (m, 1H), 2.58 - 2.49 (m, 1H), 1.68 (s, 3H)	N-(3-((1S,5S,6R)-3-amino-7,7-difluoro-1-(hydroxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide
708	^{1}H NMR (300MHz, DMSO) δ = 10.48 (s, 1H), 8.91 (d, J=1.3 Hz, 1H), 8.56 (d, J=1.3 Hz, 1H), 8.07 (dd, J=2.7, 7.4 Hz, 1H), 7.83 - 7.73 (m, 1H), 7.19 (dd, J=8.9, 12.0 Hz, 1H), 6.92 - 6.53 (m, 1H), 6.13 (s, 2H), 5.43 (t, J=5.8 Hz, 1H), 5.03 (t, J=14.3 Hz, 2H), 3.82 (br. s., 1H), 3.65 (dd, J=5.2, 10.2 Hz, 1H), 1.52 (s, 3H)	N-(3-((1S,5S,6R)-3-amino-7,7-difluoro-1-(hydroxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(2,2,3,3-tetrafluoropropoxy)-2-pyrazinecarboxamide
710	^{1}H NMR (300MHz, CDCl3) δ = 9.87 (br. s., 1H), 8.58 (s, 1H), 8.26 (d, J=8.3 Hz, 1H), 8.13 - 8.02 (m, 1H), 7.96 - 7.86 (m, 1H), 7.82 - 7.72 (m, 1H), 7.21 - 7.05 (m, 1H), 3.98 (d, J=11.0 Hz, 1H), 3.56 (d, J=10.8 Hz, 1H), 3.42 (s, 3H), 2.44 (d, J=15.9 Hz, 1H), 1.70 (s, 3H)	N-(3-((1S,5S,6R)-3-amino-7,7-difluoro-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide
711	^{1}H NMR (300MHz, CDCl3) δ = 9.85 (s, 1H), 8.62 - 8.53 (m, 1H), 8.27 (d, J=9.1 Hz, 1H), 8.12 - 8.00 (m, 1H), 7.90 (dd, J=2.3, 8.5 Hz, 1H), 7.72 (dd, J=2.8, 7.0 Hz, 1H), 7.13 (dd, J=8.8, 11.6 Hz, 1H), 3.17 - 3.06 (m, 1H), 1.68 (d, J=0.9 Hz, 3H), 1.51 (s, 3H), 1.48 (s, 3H)	N-(3-((1S,5S,6R)-3-amino-7,7-difluoro-1-(1-hydroxy-1-methylethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide
748	^{1}H NMR (300 MHz, CHLOROFORM-d) δ ppm 1.75 (s, 3 H) 2.62 - 2.78 (m, 1 H) 2.90 - 3.02 (m, 1 H) 7.37 - 7.50 (m, 1 H) 7.85 - 7.95 (m, 1 H) 8.11 - 8.20 (m, 1 H) 8.22 - 8.29 (m, 1 H) 8.49 - 8.63 (m, 1 H) 9.77 - 9.96 (m, 1 H)	N-(3-((1R,5S,6R)-3-amino-7,7-difluoro-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-chloro-2-pyridinecarboxamide
749	^{1}H NMR (300 MHz, DMSO-d6) δ ppm 1.52 (br. s., 3 H) 3.63 (br. s., 2 H) 3.82 (br. s., 1 H) 5.13 (br. s., 2 H) 5.42 (br. s., 1 H) 6.12 (br. s., 2 H) 7.03 - 7.28 (m, 1 H) 7.76 (br. s., 1 H) 8.06 (d, J=4.82 Hz, 1 H) 8.47 (s, 1 H) 8.89 (s, 1 H) 10.43 (br. s., 1 H)	N-(3-((1S,5S,6R)-3-amino-7,7-difluoro-1-(hydroxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide

751	^{1}H NMR (300 MHz, DMSO-d6) δ ppm 1.52 (s, 3 H) 2.38 - 2.48 (m, 1 H) 3.65 (dd, J=12.57, 3.22 Hz, 1 H) 3.78 - 3.90 (m, 1 H) 4.85 (t, J=13.52 Hz, 2 H) 5.43 (t, J=5.77 Hz, 1 H) 6.14 (br. s., 2 H) 6.45 - 6.96 (m, 1 H) 7.18 (dd, J=12.06, 8.84 Hz, 1 H) 7.76 (dd, J=8.77, 2.92 Hz, 1 H) 7.81 (dt, J=7.27, 4.26 Hz, 1 H) 8.03 (dd, J=7.31, 2.78 Hz, 1 H) 8.14 (d, J=8.77 Hz, 1 H) 8.49 (d, J=2.63 Hz, 1 H) 10.31 - 10.46 (m, 1 H) 10.39 (s, 1 H)	N-(3-((1S,5S,6R)-3-amino-7,7-difluoro-1-(hydroxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(2,2,3,3-tetrafluoropropoxy)-2-pyridinecarboxamide
785	^{1}H NMR (DMSO-d6) δ: 10.74 (s, 1H), 8.89 (d, J=1.8 Hz, 1H), 8.43 (s, 1H), 8.28-8.33 (m, 1H), 8.22-8.28 (m, 1H), 8.13 (dd, J=7.0, 2.7 Hz, 1H), 7.97 (dt, J=7.3, 4.2 Hz, 1H), 7.31 (dd, J=11.7, 8.8 Hz, 1H), 7.23 (s, 1H), 6.62 (s, 2H), 4.74-5.01 (m, 2H), 2.10-2.18 (m, 1H), 1.74 (dd, J=9.7, 5.6 Hz, 1H), 1.03-1.11 (m, 1H), 1.03-1.11 (m, 1H)	N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-(1,3-oxazol-5-yl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide
790	^{1}H NMR (DMSO-d6) δ: 10.62 (s, 1H), 9.73-10.99 (m, 1H), 8.80 (d, J=1.8 Hz, 1H), 8.19-8.25 (m, 1H), 8.11-8.19 (m, 1H), 7.80-7.91 (m, 2H), 7.22 (dd, J=11.7, 8.8 Hz, 1H), 6.57 (s, 2H), 4.82 (q, J=8.1 Hz, 1H), 4.61-4.75 (m, 1H), 2.97-3.18 (m, 3H), 2.88 (br. s., 3H), 2.04-2.05 (m, 1H), 2.06 (t, J=8.6 Hz, 1H), 1.50 (dd, J=9.5, 5.4 Hz, 1H), 0.69 (t, J=6.2 Hz, 1H).	(1S,5S,6S)-3-amino-5-(5-(((5-chloro-2-pyridinyl)carbonyl)amino)-2-fluorophenyl)-5-(fluoromethyl)-N,N-dimethyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide
906	^{1}H NMR (400 MHz, DMSO-d6) δ 10.79 (s, 1H), 8.79 (s, 1H), 8.15-8.23 (m, 2H), 7.92-8.02 (m, 2H), 6.17 (s, 2H), 2.33-2.41 (m, 1H), 2.11 (s, 3H), 1.74 (dd, J=5.48, 9.78 Hz, 1H), 1.62 (s, 3H), 1.11-1.16 (m, 1H)	N-(3-((1S,5S,6S)-1-acetyl-3-amino-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-chloro-2-pyridinecarboxamide
910	^{1}H NMR (400 MHz, DMSO-d6) δ 10.62 (s, 1H), 8.89 (d, J=1.17 Hz, 1H), 8.54 (d, J=1.17 Hz, 1H), 8.20 (s, 1H), 7.88-7.94 (m, 2H), 7.30 (s, 1H), 5.99 (s, 2H), 5.62 (s, 2H), 3.57 (d, J=10.95 Hz, 1H), 3.36 (d, J=10.95 Hz, 1H), 3.31 (d, J=2.54 Hz, 3H), 1.58-1.65 (m, 4H), 0.90 (dd, J=5.18, 9.10 Hz, 1H), 0.64 (t, J=5.77 Hz, 1H)	N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(1,3-oxazol-2-ylmethoxy)-2-pyrazinecarboxamide
953	^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 0.77 (t, J=6.26 Hz, 1 H) 1.13 (dd, J=9.68, 5.97 Hz, 1 H) 1.80 - 1.88 (m, 1 H) 2.55 (t, J=2.35 Hz, 1 H) 3.60 - 3.84 (m, 2 H) 3.90 (q, J=8.61 Hz, 2 H) 4.57 - 4.97 (m, 3 H) 5.09 (d, J=2.35 Hz, 2 H) 7.09 (dd, J=11.35, 8.80 Hz, 1 H) 7.68 (dd, J=6.65, 2.74 Hz, 1 H) 7.96 (dt, J=8.31, 3.67 Hz, 1 H) 8.20 (d, J=0.98 Hz, 1 H) 9.02 (d, J=0.98 Hz, 1 H) 9.48 (s, 1 H)	N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-((2,2,2-trifluoroethoxy)methyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide
954	^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 0.78 (t, J=6.26 Hz, 1 H) 1.14 (dd, J=9.68, 5.97 Hz, 1 H) 1.26 (br. s., 2 H) 1.83 - 1.89 (m, 1 H) 3.62 - 3.85 (m, 2 H) 3.90 (q, J=8.74 Hz, 2 H) 4.60 - 4.96 (m, 2 H) 7.10 (dd, J=11.54, 8.80 Hz, 1 H) 7.70 (dd, J=6.85, 2.74 Hz, 1 H) 7.88 (dd, J=8.41, 2.35 Hz, 1 H) 7.97 (dt, J=8.75, 3.55 Hz, 1 H) 8.24 (d, J=8.41 Hz, 1 H) 8.56 (d, J=2.15 Hz, 1 H) 9.82 (s, 1 H)	N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-((2,2,2-trifluoroethoxy)methyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide

955	^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 0.75 (t, J=5.97 Hz, 1 H) 1.09 (dd, J=9.49, 5.77 Hz, 1 H) 1.17 (t, J=6.36 Hz, 6 H) 1.75 - 1.81 (m, 1 H) 2.55 (m, 1 H) 3.37 (d, J=10.37 Hz, 1 H) 3.63 (dt, J=12.13, 6.06 Hz, 1 H) 3.71 (d, J=10.37 Hz, 1 H) 4.63 - 4.95 (m, 4 H) 5.08 (d, J=1.96 Hz, 2 H) 7.09 (dd, J=11.44, 9.10 Hz, 1 H) 7.70 (d, J=4.30 Hz, 1 H) 7.93 - 8.05 (m, 1 H) 8.20 (s, 1 H) 9.02 (s, 1 H) 9.49 (br. s., 1 H)	N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-((1-methylethoxy)methyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide
956	^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.14 (t, J=6.36 Hz, 1 H) 1.77 (dd, J=9.59, 5.87 Hz, 1 H) 2.27 (t, J=8.31 Hz, 1 H) 4.68 - 5.07 (m, 2 H) 7.07 - 7.16 (m, 1 H) 7.66 (s, 1 H) 7.77 (d, J=4.11 Hz, 1 H) 7.88 (d, J=8.22 Hz, 1 H) 7.91 - 7.99 (m, 1 H) 8.24 (d, J=8.22 Hz, 1 H) 8.56 (s, 1 H) 9.85 (s, 1 H)	N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-(1H-1,2,3-triazol-4-yl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide
959	^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.13 (t, J=6.36 Hz, 1 H) 1.75 (dd, J=9.39, 5.67 Hz, 1 H) 2.19 - 2.31 (m, 1 H) 2.55 (br. s., 1 H) 4.67 - 5.05 (m, 2 H) 5.09 (d, J=2.15 Hz, 2 H) 7.11 (dd, J=11.25, 9.29 Hz, 1 H) 7.66 (s, 1 H) 7.74 (d, J=4.30 Hz, 1 H) 7.86 - 8.01 (m, 1 H) 8.21 (s, 1 H) 9.03 (s, 1 H) 9.51 (s, 1 H)	N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-(1H-1,2,3-triazol-4-yl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide

Method B: Propylphosphonic Anhydride (T3P) procedure in DMAc as solvent.

Example 94: N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-cyano-3-methylpicolinamide.



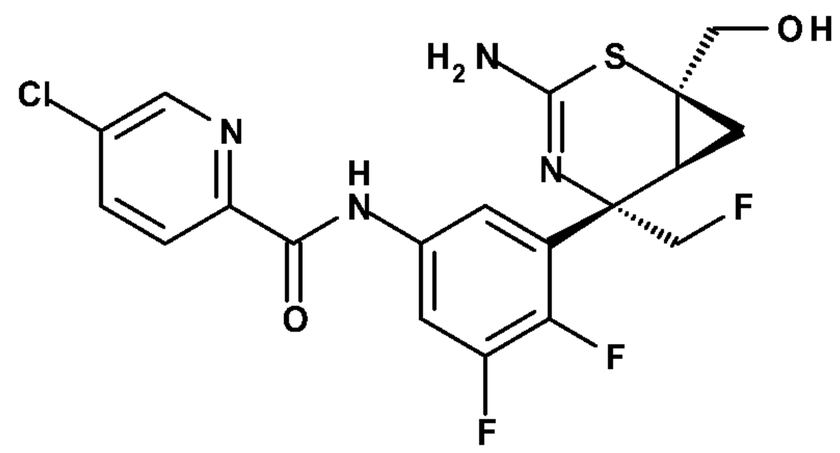
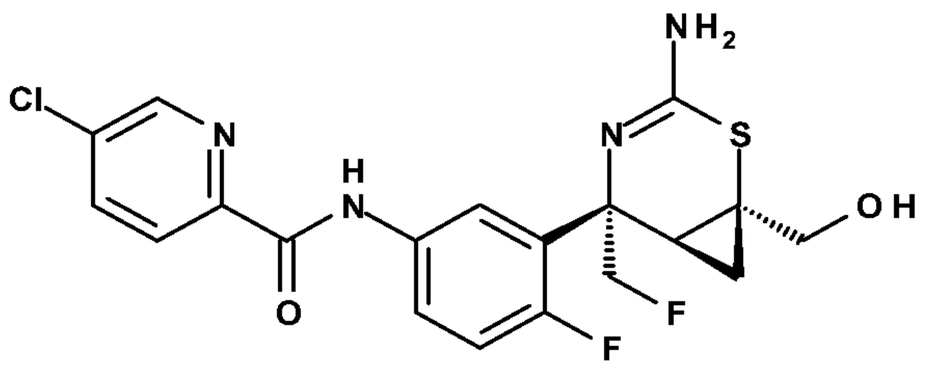
267 **211** **Example 94**

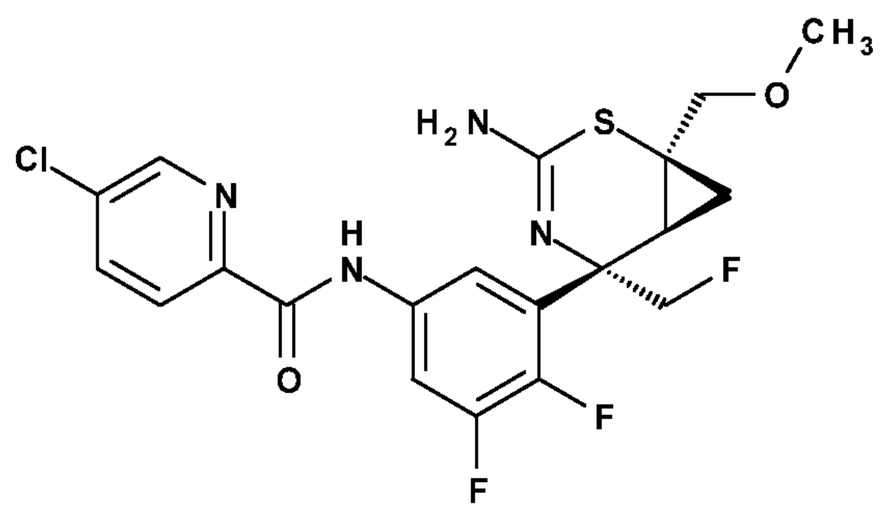
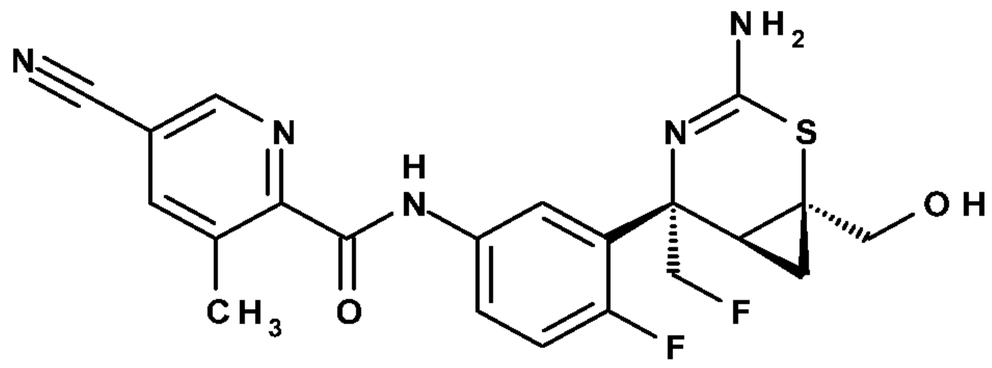
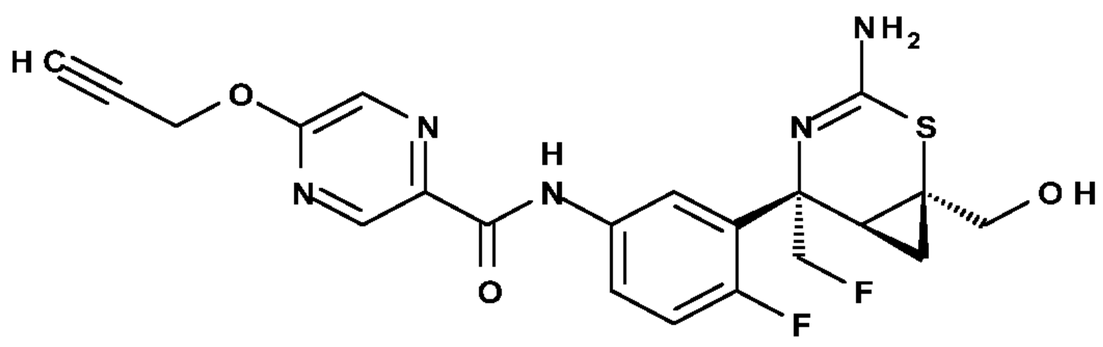
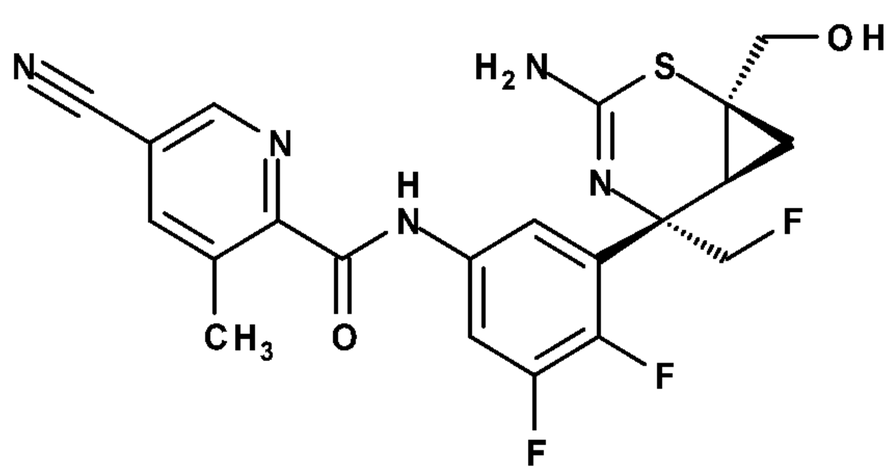
Propylphosphonic anhydride solution (50 wt.% in EtOAc, 279 mg, 0.44 mmol) was added to a stirred solution of (1S,5S,6S)-5-(5-amino-2,3-difluorophenyl)-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-3-amine (Intermediate **211**, 70 mg, 0.22 mmol) and 5-cyano-3-methylpicolinic acid (Intermediate **267**, 46 mg, 0.28 mmol) in DMAc (2 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 0.5 h then RT for 2 h. The reaction mixture was treated with additional 5-cyano-3-methylpicolinic acid (15 mg, 0.09 mmol) followed by T3P (50 wt.% in EtOAc, 100 mg, 0.15 mmol) and stirred at RT for 48 h. It was quenched with sat'd aqueous $NaHCO_3$ and extracted with EtOAc. The organic layer was separated, washed with brine, dried over

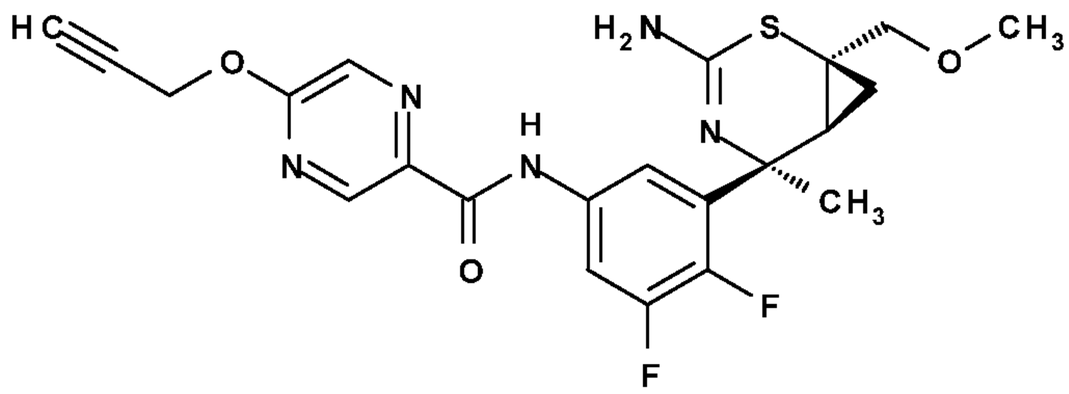
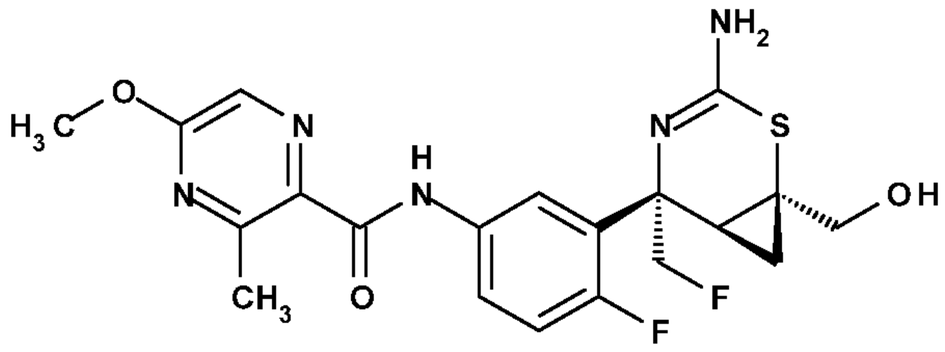
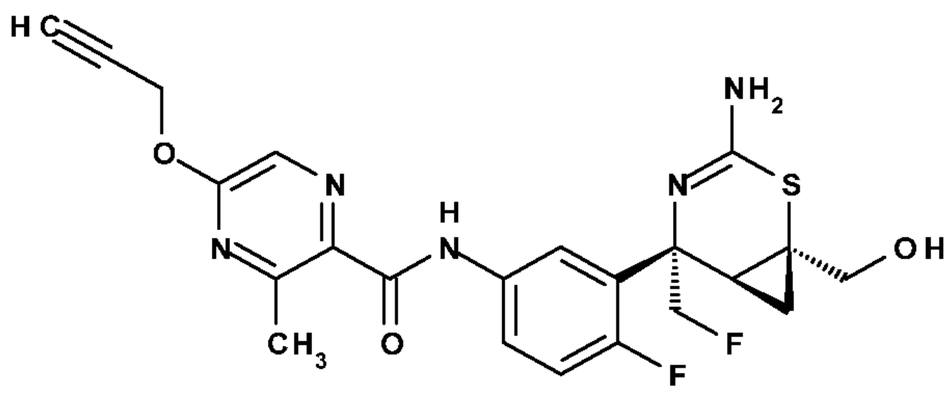
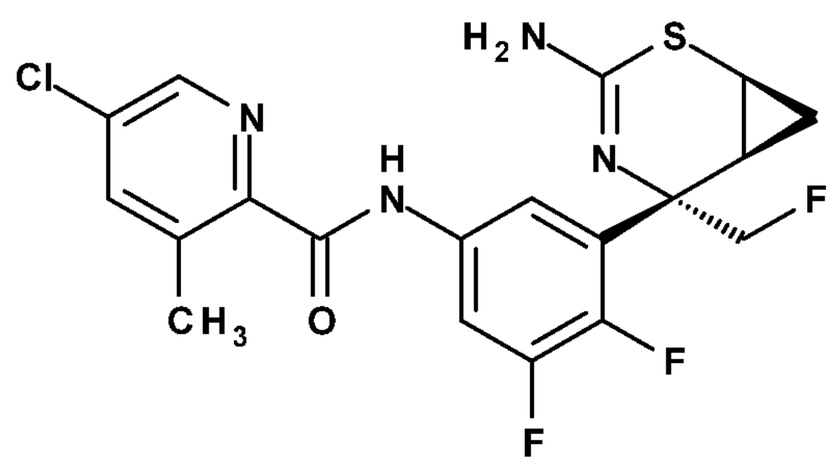
$MgSO_4$, filtered, and concentrated. The resulting crude yellow oil was purified on a silica gel column (35-65% EtOAc in DCM) to afford N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-cyano-3-methylpicolinamide (**Example 94**, 65 mg, 0.14 mmol, 64% yield) as an off-white solid. MS m/z = 464.0 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.86 (br., 1H), 8.99 (d, *J*=1.57 Hz, 1H), 8.41 (d, *J*=1.17 Hz, 1H), 7.94 (ddd, *J*=2.64, 6.75, 12.32 Hz, 1H), 7.62 (m, 1H), 6.31 (br., 2H), 5.81-6.03 (m, 1H), 2.57 (s, 3H), 1.93 (m, 1H), 1.66 (s, 3H), 1.35 (m, 1H), 0.75 (m, 1H). ^{19}F NMR (377 MHz, DMSO-d_6) δ -115.50 (d, ^1J=273.96 Hz, 1F), -118.00 (d, ^1J=273.90 Hz, 1F), -137.95 (d, ^2J=22.56 Hz, 1F), -142.80 (d, ^2J=22.66 Hz, 1F).

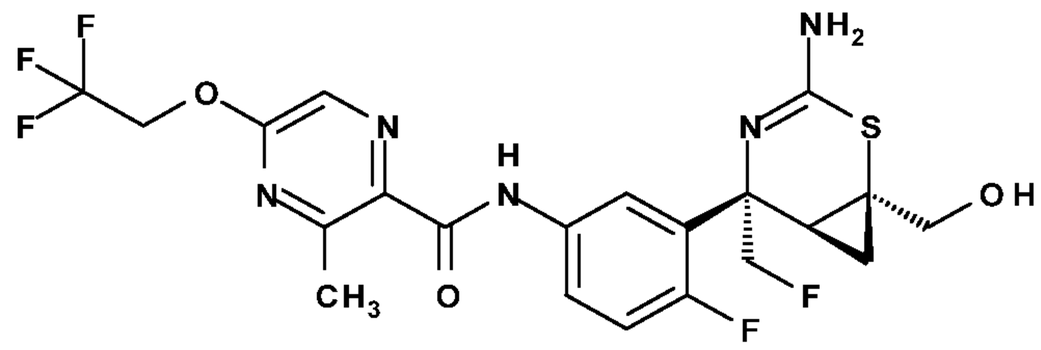
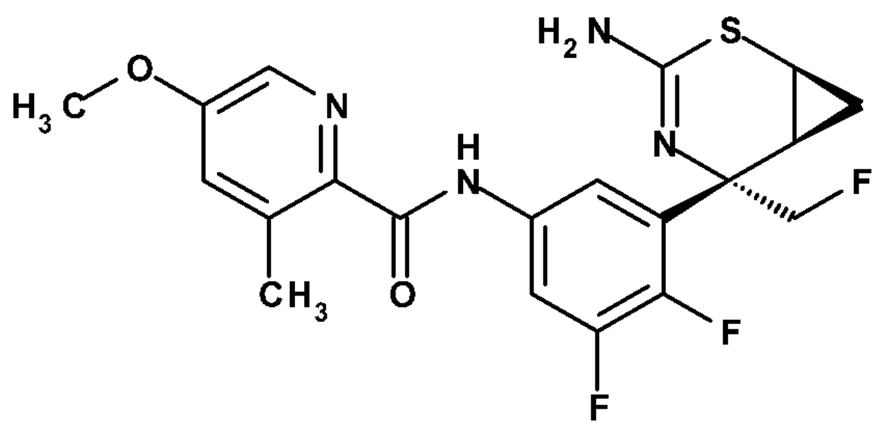
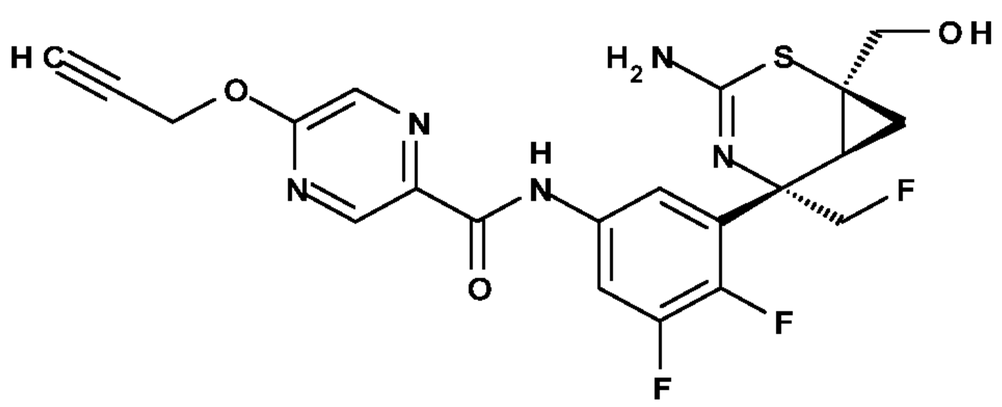
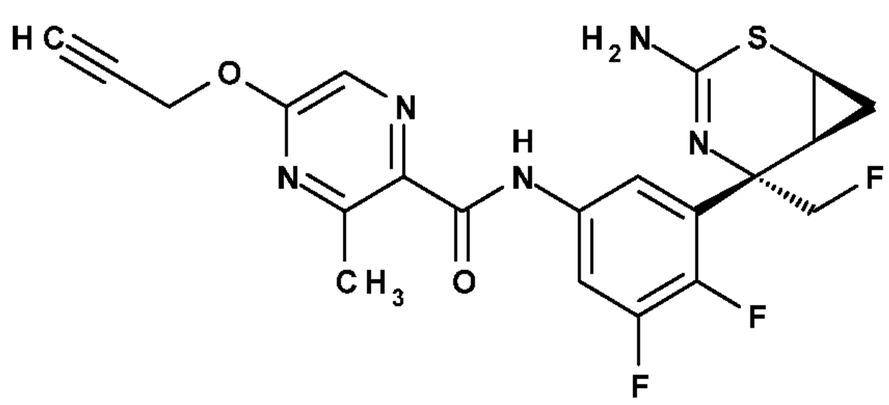
Using procedures analogous or similar to the general amidation **Method B** described above, the appropriate aniline and carboxylic acid intermediates were reacted to provide the 30 examples listed in Table 2 and Table 2'.

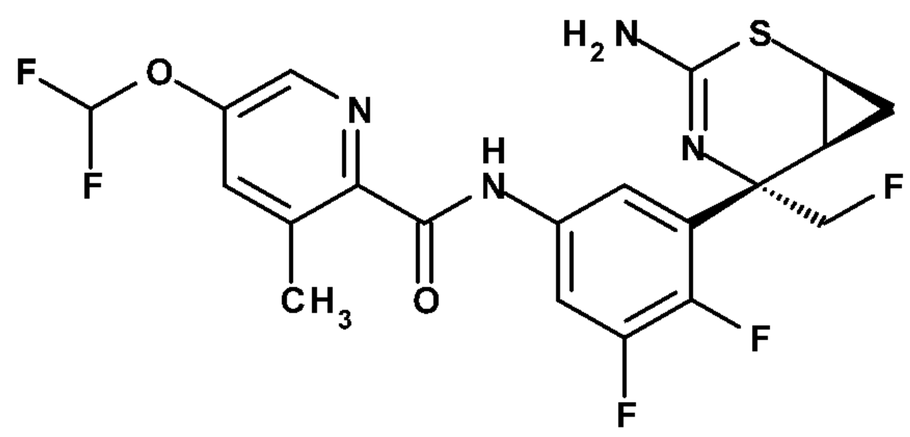
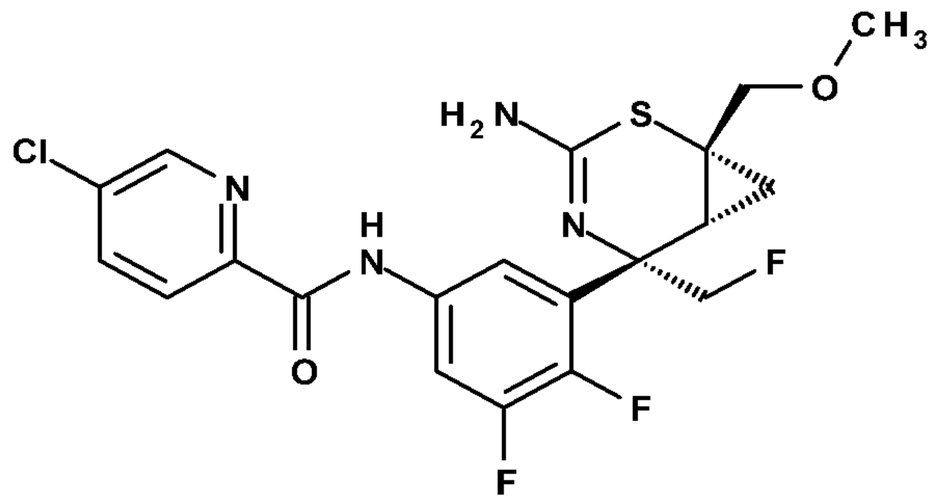
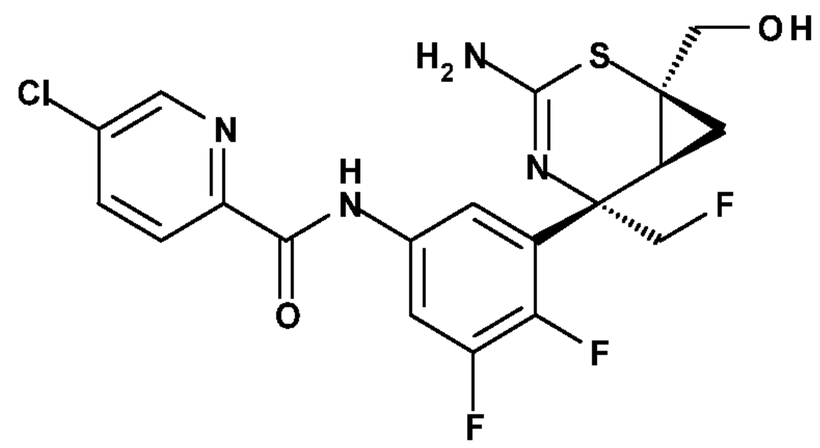
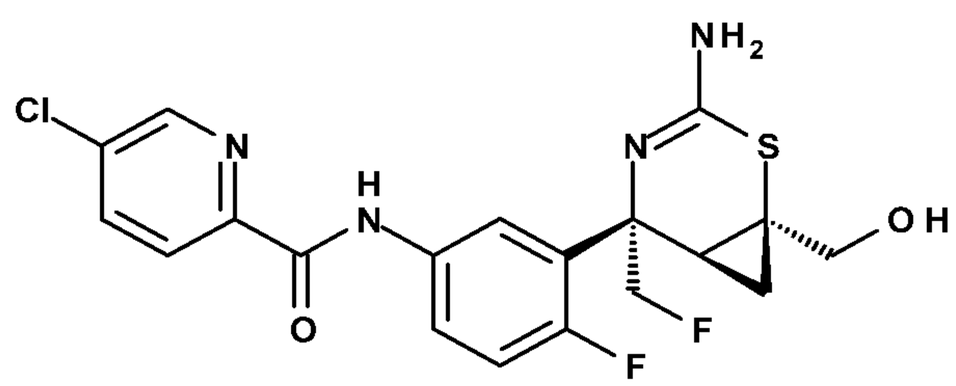
Table 2

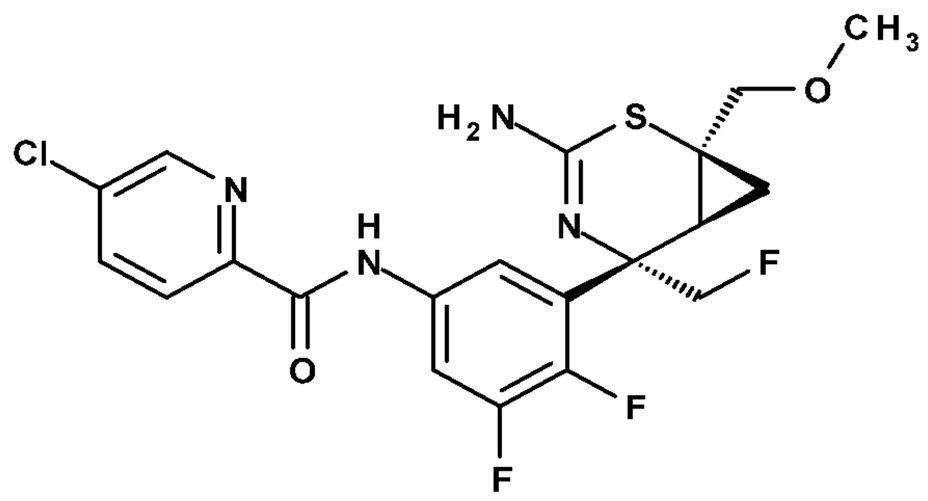
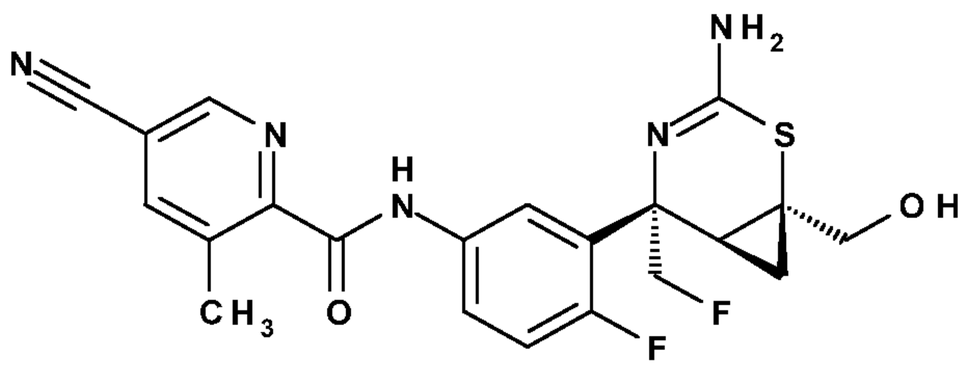
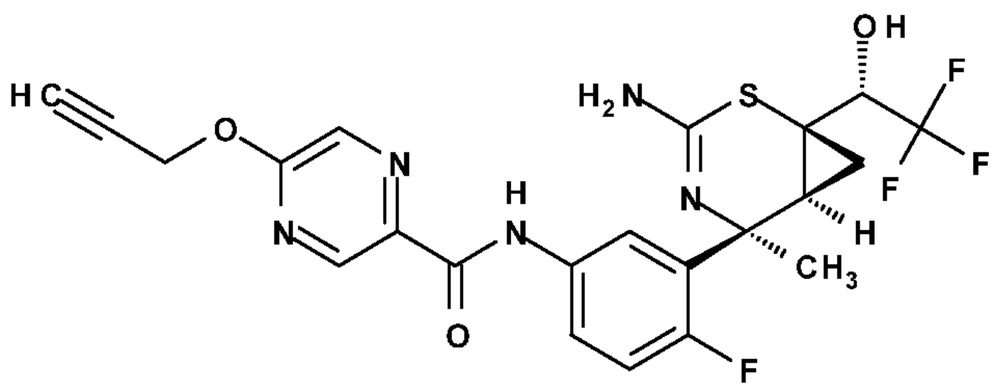
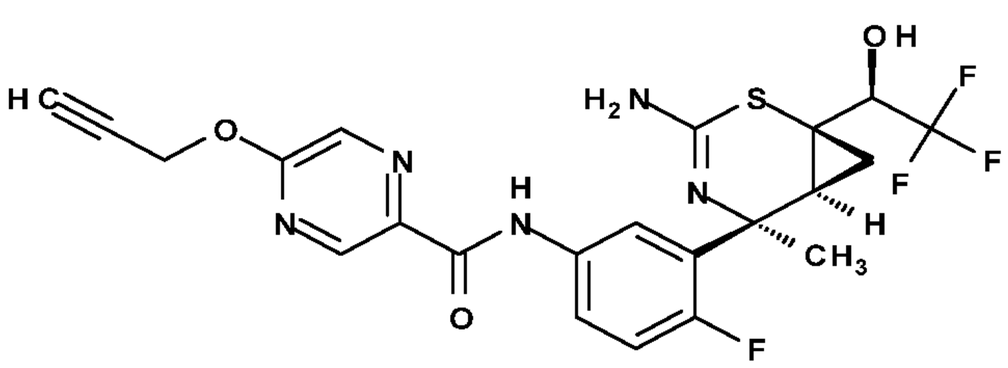
Ex.No.	Chemical Structure	Observed $[M+H]^+$
31		457.1
37		439.1

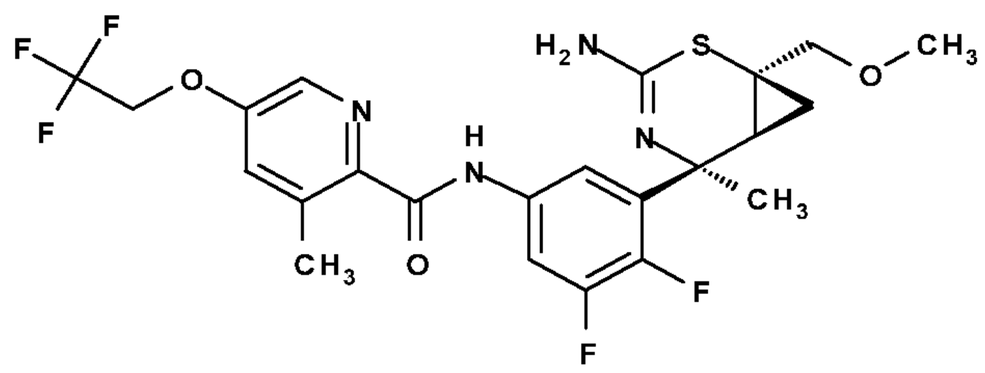
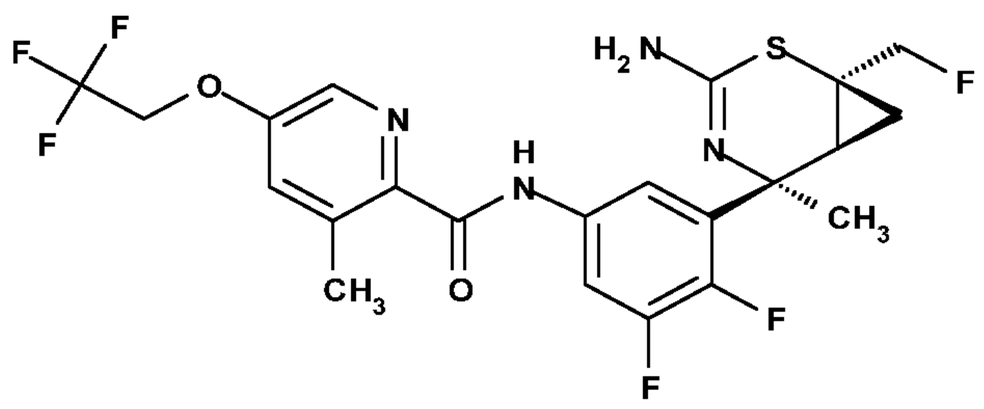
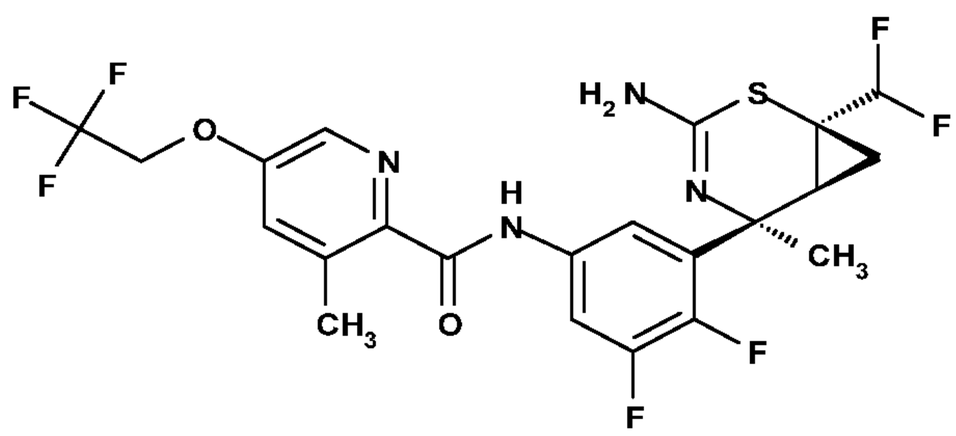
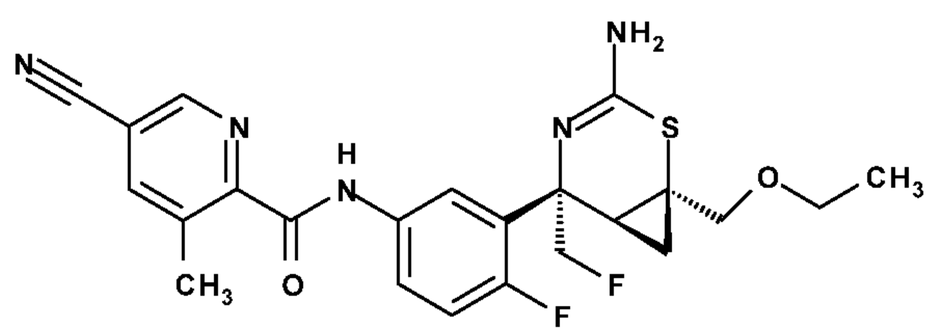
43		471.0
44		444.0
53		460.1
70		462.0

72		474.0
75		450.1
76		474.0
78		441.0

79		518.2
81		437.1
83		478.1
84		462.0

86		473.1
96		471.0
31		457.1
37		439.1

43		471.0
44		444.0
673		510
674		510

675		531
678		519
679		537
715		472.1

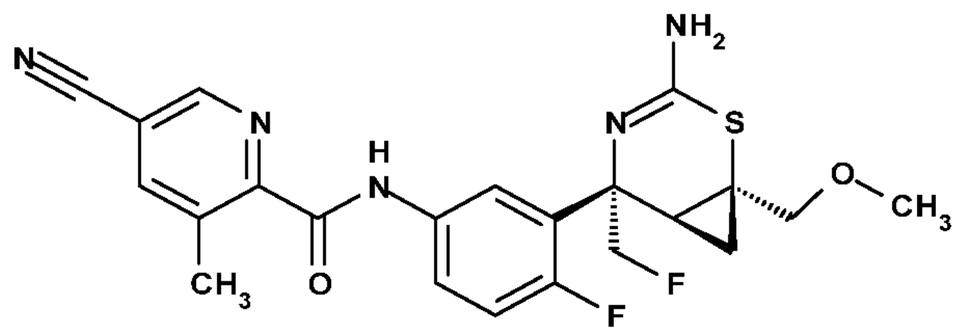
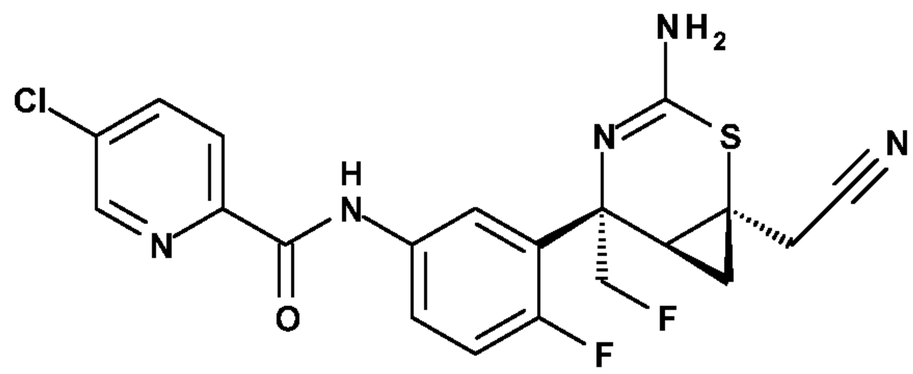
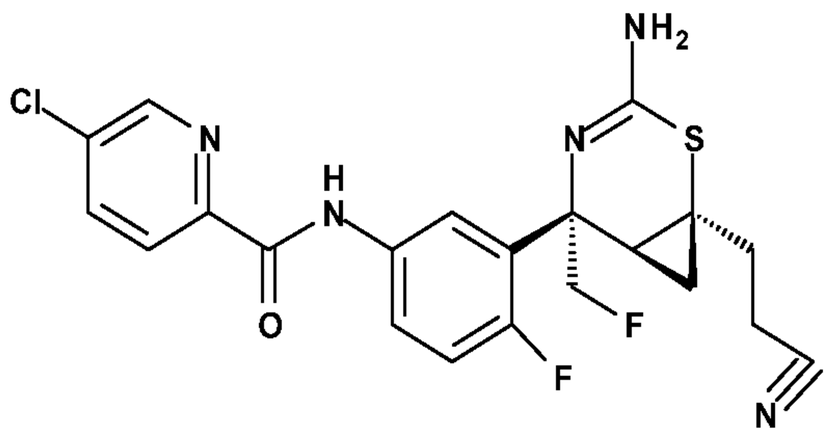
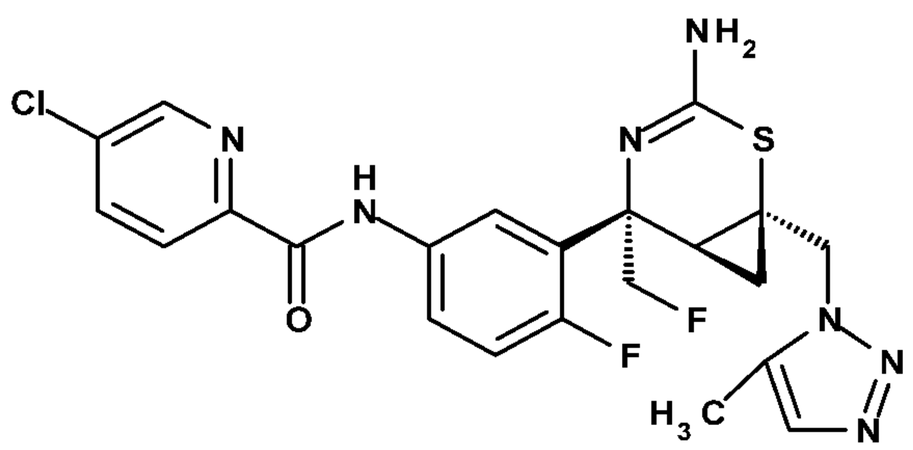
716		458.1
718		448.1
723		462
725		504

Table 2'

Ex.No.	^{1}H-NMR	Chemical Name
31	^{1}H NMR (400 MHz, DMSO-d6) δ ppm 10.79 (s, 1 H) 8.79 (d, J=1.76 Hz, 1 H) 8.21 (dd, J=8.41, 2.35 Hz, 1 H) 8.16 (d, J=8.61 Hz, 1 H) 7.98 (ddd, J=12.23, 6.75, 2.54 Hz, 1 H) 7.89 - 7.93 (m, 1 H) 6.26 (s, 2 H) 5.08 (t, J=5.97 Hz, 1 H) 4.57 - 4.81 (m, 2 H) 3.54 (dd, J=11.74, 6.26 Hz, 1 H) 3.44 (dd, J=11.74, 5.67 Hz, 1 H) 1.61 - 1.67 (m, 1 H) 1.04 (dd, J=9.29, 5.18 Hz, 1 H) 0.57 (t, J=5.77 Hz, 1 H)	N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-(hydroxymethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-chloro-2-pyridinecarboxamide
37	^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 9.80 (br s, 1H), 8.54 (d, J=2.15 Hz, 1H), 8.23 (d, J=8.41 Hz, 1H), 7.94-8.01 (m, 1H), 7.87 (dd, J=8.41, 2.35 Hz, 1H), 7.71 (d, J=4.30 Hz, 1 H), 7.09 (dd, J=11.44, 8.90 Hz, 1H), 4.91 (dd, J=46.95, 8.41 Hz, 1H), 4.77 (s br, 2H), 4.67 (dd, J=47.54, 8.80 Hz, 1H), 3.76 (d, J=11.93 Hz, 1H), 3.60 (d, J=11.74 Hz, 1H), 1.85 (t, J=9.00 Hz, 1H), 1.77 (s br, 1H), 1.08 (dd, J=9.59, 5.87 Hz, 1H), 0.71 (t, J=6.26 Hz, 1H)	N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-(hydroxymethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide
43	^{1}H NMR (400 MHz, DMSO-d6) δ ppm 10.79 (s, 1 H) 8.79 (d, J=1.96 Hz, 1 H) 8.21 (dd, J=8.41, 2.35 Hz, 1 H) 8.16 (d, J=8.22 Hz, 1 H) 7.99 (ddd, J=12.37, 6.80, 2.54 Hz, 1 H) 7.88 - 7.93 (m, 1 H) 6.30 (s, 2 H) 4.60 - 4.78 (m, 2 H) 3.56 (d, J=10.76 Hz, 1 H) 3.35 (d, J=10.95 Hz, 1 H) 3.30 (s, 3 H) 1.63 - 1.69 (m, 1 H) 1.10 (dd, J=9.49, 5.18 Hz, 1 H) 0.64 (t, J=5.87 Hz, 1 H)	N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-(methoxymethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-chloro-2-pyridinecarboxamide
44	^{1}H NMR (400 MHz, DMSO-d6) δ ppm 10.67 (s, 1H), 8.98 (d, J=1.37 Hz, 1H), 8.40 (d, J=1.96 Hz, 1H), 7.90 (dd, J=7.04, 2.74 Hz, 1H), 7.81-7.87 (m, 1H), 7.19 (dd, J=11.93, 8.80 Hz, 1H), 6.22 (s, 2H), 5.06 (t, J=5.87 Hz, 1H), 4.77 (dd, J=26.41, 8.61 Hz, 1H), 4.65 (dd, J=26.41, 9.19 Hz, 1H), 3.54 (dd, J=11.54, 6.26 Hz, 1H), 3.43 (dd, J=11.74, 5.67 Hz, 1H), 2.56 (s, 3H), 1.64 (t, J=7.82 Hz, 1H), 0.98 (dd, J=9.49, 4.99 Hz, 1H), 0.50 (t, J=5.67 Hz, 1H)	N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-(hydroxymethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-cyano-3-methyl-2-pyridinecarboxamide
53	^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 9.48 (s, 1H), 9.02 (d, J=1.37 Hz, 1H), 8.20 (d, J=1.37 Hz, 1H), 7.94-8.01 (m, 1H), 7.68 (dd, J=6.75, 2.64 Hz, 1H), 7.09 (dd, J=11.54, 8.80 Hz, 1H), 5.09 (d, J=2.35 Hz, 2H), 4.91 (dd, J=46.75, 7.82 Hz, 1H), 4.72 (s br, 2H), 4.66 (dd, J=47.73, 8.41 Hz, 1H), 3.76 (d, J=11.74 Hz, 1H), 3.60 (d, J=11.93 Hz, 1H), 2.55 (t, J=2.35 Hz, 1H), 1.84 (t, J=8.80 Hz, 1H), 1.68 (s br, 1H), 1.07 (dd, J=9.68, 5.77 Hz, 1H), 0.71 (t, J=6.26 Hz, 1H)	N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-(hydroxymethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide

70	^{1}H NMR (400 MHz, DMSO-d6) δ ppm 10.87 (s, 1 H) 8.98 (d, J=1.17 Hz, 1 H) 8.40 (d, J=1.17 Hz, 1 H) 7.97 (ddd, J=12.37, 6.80, 2.54 Hz, 1 H) 7.70 - 7.74 (m, 1 H) 6.26 (s, 2 H) 5.08 (t, J=5.97 Hz, 1 H) 4.57 - 4.82 (m, 2 H) 3.53 (dd, J=11.74, 6.26 Hz, 1 H) 3.43 (dd, J=11.74, 5.67 Hz, 1 H) 2.56 (s, 3 H) 1.60 - 1.66 (m, 1 H) 1.02 (dd, J=9.39, 5.09 Hz, 1 H) 0.53 (t, J=5.77 Hz, 1 H)	N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-(hydroxymethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-cyano-3-methyl-2-pyridinecarboxamide
72	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.42-10.79 (m, 1H), 8.90 (d, *J*=1.17 Hz, 1H), 8.48 (d, *J*=1.17 Hz, 1H), 7.70-8.03 (m, 2H), 5.99 (s, 2H), 5.14 (d, *J*=2.35 Hz, 2H), 3.64 (t, *J*=2.45 Hz, 1H), 3.57 (d, *J*=10.95 Hz, 1H), 3.36 (d, *J*=11.15 Hz, 1H), 3.30-3.31 (m, 3H), 1.57-1.70 (m, 4H), 0.90 (dd, *J*=5.28, 9.19 Hz, 1H), 0.65 (t, *J*=5.77 Hz, 1H)	N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide
75	^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 9.76 (s, 1H), 8.00 (dt, J=8.56, 3.64 Hz, 1H), 7.97 (s, 1H), 7.58 (dd, J=6.65, 2.74 Hz, 1H), 7.07 (dd, J=11.54, 9.00 Hz, 1H), 4.91 (dd, J=47.34, 8.22 Hz, 1H), 4.75 (s br, 2H), 4.64 (dd, J=47.14, 8.41 Hz, 1H), 4.04 (s, 3H), 3.75 (d, J=11.93 Hz, 1H), 3.60 (d, J=11.93 Hz, 1H), 2.94 (s, 3H), 1.85 (t, J=8.20 Hz, 1H), 1.72 (s br, 1H), 1.06 (dd, J=9.68, 5.77 Hz, 1H), 0.70 (t, J=6.16 Hz, 1H)	N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-(hydroxymethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-methoxy-3-methyl-2-pyrazinecarboxamide
76	^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 9.75 (s, 1H), 8.05 (s, 1H), 8.01 (dt, J=8.80, 3.50 Hz, 1H), 7.58 (dd, J=6.65, 2.54 Hz, 1H), 7.08 (dd, J=11.54, 8.80 Hz, 1H), 5.08 (d, J=2.35 Hz, 2H), 4.92 (dd, J=47.34, 8.02 Hz, 1H), 4.70 (s br, 2H), 4.64 (dd, J=46.95, 8.61 Hz, 1H), 3.76 (d, J=11.93 Hz, 1H), 3.60 (d, J=11.93 Hz, 1H), 2.95 (s, 3H), 2.53 (t, J=2.35 Hz, 1H), 1.86 (t, J=8.00 Hz, 1H), 1.70 (s br, 1H), 1.06 (dd, J=9.68, 5.77 Hz, 1H), 0.71 (t, J=6.36 Hz, 1H)	N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-(hydroxymethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3-methyl-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide
78	^{1}H NMR (400 MHz, DMSO-d6) δ ppm 10.70 (s, 1 H) 8.57 (d, J=2.15 Hz, 1 H) 8.03 (d, J=1.76 Hz, 1 H) 7.96 (ddd, J=12.42, 6.85, 2.64 Hz, 1 H) 7.69 - 7.73 (m, 1 H) 6.22 (s, 2 H) 4.72 (d, J=47.73 Hz, 2 H) 2.56 (s, 3 H) 2.39 (ddd, J=9.00, 7.63, 5.09 Hz, 1 H) 1.74 (m, J=7.76, 7.76, 7.76 Hz, 1 H) 1.03 (ddd, J=8.80, 7.63, 5.28 Hz, 1 H) 0.41 (q, J=5.15 Hz, 1 H)	N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-chloro-3-methyl-2-pyridinecarboxamide
79	^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 9.73 (s, 1H), 8.13 (s, 1H), 7.97-8.02 (m, 1H), 7.60 (d, J=5.67 Hz, 1H), 7.08 (t, J=10.04 Hz, 1H), 4.85 (q, J=8.40 Hz, 2H), 4.82-4.98 (m, 1H), 4.71 (s br, 2H), 4.65 (dd, J=47.14, 8.61 Hz, 1H), 3.76 (d, J=11.74 Hz, 1H), 3.61 (d, J=11.74 Hz, 1H), 2.95 (s, 3H), 1.85 (t, J=8.12 Hz, 1H), 1.66 (s br, 1H), 1.06 (dd, J=9.59, 5.67 Hz, 1 H), 0.71 (t, J=6.26 Hz, 1H)	N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-(hydroxymethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3-methyl-5-(2,2,2-trifluoroethoxy)-2-pyrazinecarboxamide

81	^{1}H NMR (400 MHz, DMSO-d6) δ ppm 10.51 (s, 1 H) 8.22 (d, J=2.54 Hz, 1 H) 7.98 (ddd, J=12.52, 6.85, 2.54 Hz, 1 H) 7.68 - 7.73 (m, 1 H) 7.41 (d, J=2.54 Hz, 1 H) 6.23 (s, 2 H) 4.71 (d, J=47.73 Hz, 2 H) 3.91 (s, 3 H) 2.62 (s, 3 H) 2.36 - 2.42 (m, 1 H) 1.69 - 1.81 (m, 1 H) 1.00 - 1.07 (m, 1 H) 0.43 (q, J=5.15 Hz, 1 H)	N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-methoxy-3-methyl-2-pyridinecarboxamide
83	^{1}H NMR (400 MHz, DMSO-d6) δ ppm 10.67 (s, 1 H) 8.92 (d, J=1.17 Hz, 1 H) 8.50 (d, J=1.37 Hz, 1 H) 7.97 (ddd, J=12.32, 6.85, 2.74 Hz, 1 H) 7.90 - 7.94 (m, 1 H) 6.26 (s, 2 H) 5.16 (d, J=2.35 Hz, 2 H) 5.09 (t, J=5.87 Hz, 1 H) 4.58 - 4.82 (m, 2 H) 3.66 (t, J=2.35 Hz, 1 H) 3.55 (dd, J=11.74, 6.26 Hz, 1 H) 3.45 (dd, J=11.74, 5.48 Hz, 1 H) 1.62 - 1.68 (m, 1 H) 1.05 (dd, J=9.29, 5.18 Hz, 1 H) 0.58 (t, J=5.67 Hz, 1 H)	N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-(hydroxymethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide
84	^{1}H NMR (400 MHz, DMSO-d6) δ ppm 10.60 (s, 1 H) 8.30 (s, 1 H) 7.97 (ddd, J=12.32, 6.75, 2.25 Hz, 1 H) 7.72 - 7.76 (m, 1 H) 6.23 (s, 2 H) 5.12 (d, J=2.35 Hz, 2 H) 4.73 (d, J=47.54 Hz, 2 H) 3.62 (t, J=2.15 Hz, 1 H) 2.76 (s, 3 H) 2.40 (td, J=8.12, 5.28 Hz, 1 H) 1.75 (q, J=8.28 Hz, 1 H) 1.04 (td, J=8.07, 5.58 Hz, 1 H) 0.43 (q, J=5.28 Hz, 1 H)	N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-methyl-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide
86	^{1}H NMR (400 MHz, DMSO-d6) δ ppm 10.67 (s, 1 H) 8.43 (d, J=2.35 Hz, 1 H) 7.97 (ddd, J=12.42, 6.94, 2.35 Hz, 1 H) 7.71 - 7.75 (m, 2 H) 7.44 (t, J=73.20 Hz, 1 H) 6.23 (s, 2 H) 4.73 (d, J=47.54 Hz, 2 H) 2.60 (s, 3 H) 2.37 - 2.44 (m, 1 H) 1.75 (q, J=8.22 Hz, 1 H) 1.05 (td, J=8.12, 5.48 Hz, 1 H) 0.43 (q, J=5.35 Hz, 1 H)	N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(difluoromethoxy)-3-methyl-2-pyridinecarboxamide
96	^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 9.80 (s, 1 H) 8.54 (d, J=2.15 Hz, 1 H) 8.23 (d, J=8.22 Hz, 1 H) 8.05 (ddd, J=11.59, 6.80, 2.54 Hz, 1 H) 7.89 (dd, J=8.41, 2.15 Hz, 1 H) 7.44 - 7.49 (m, 1 H) 4.56 - 4.91 (m, 2 H) 3.60 (d, J=10.56 Hz, 1 H) 3.50 (d, J=10.76 Hz, 1 H) 3.41 (s, 3 H) 2.03 - 2.09 (m, 1 H) 1.23 - 1.30 (m, 4 H) 1.11 (dd, J=9.49, 6.16 Hz, 1 H)	N-(3-((1R,5S,6R)-3-amino-5-(fluoromethyl)-1-(methoxymethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-chloro-2-pyridinecarboxamide
31	^{1}H NMR (400 MHz, DMSO-d6) δ ppm 10.79 (s, 1 H) 8.79 (d, J=1.76 Hz, 1 H) 8.21 (dd, J=8.41, 2.35 Hz, 1 H) 8.16 (d, J=8.61 Hz, 1 H) 7.98 (ddd, J=12.23, 6.75, 2.54 Hz, 1 H) 7.89 - 7.93 (m, 1 H) 6.26 (s, 2 H) 5.08 (t, J=5.97 Hz, 1 H) 4.57 - 4.81 (m, 2 H) 3.54 (dd, J=11.74, 6.26 Hz, 1 H) 3.44 (dd, J=11.74, 5.67 Hz, 1 H) 1.61 - 1.67 (m, 1 H) 1.04 (dd, J=9.29, 5.18 Hz, 1 H) 0.57 (t, J=5.77 Hz, 1 H)	N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-(hydroxymethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-chloro-2-pyridinecarboxamide

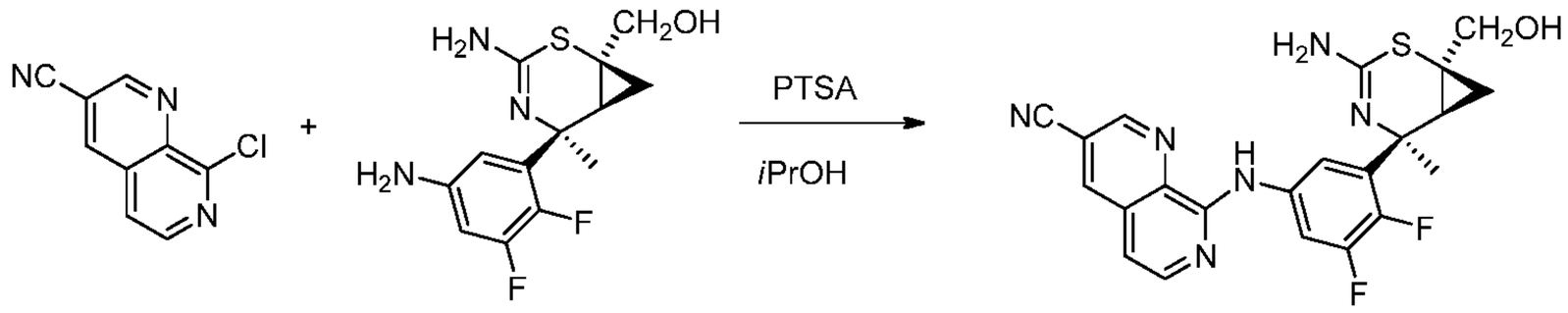
37	^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 9.80 (br s, 1H), 8.54 (d, J=2.15 Hz, 1H), 8.23 (d, J=8.41 Hz, 1H), 7.94-8.01 (m, 1H), 7.87 (dd, J=8.41, 2.35 Hz, 1H), 7.71 (d, J=4.30 Hz, 1 H), 7.09 (dd, J=11.44, 8.90 Hz, 1H), 4.91 (dd, J=46.95, 8.41 Hz, 1H), 4.77 (s br, 2H), 4.67 (dd, J=47.54, 8.80 Hz, 1H), 3.76 (d, J=11.93 Hz, 1H), 3.60 (d, J=11.74 Hz, 1H), 1.85 (t, J=9.00 Hz, 1H), 1.77 (s br, 1H), 1.08 (dd, J=9.59, 5.87 Hz, 1H), 0.71 (t, J=6.26 Hz, 1H)	N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-(hydroxymethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide
43	^{1}H NMR (400 MHz, DMSO-d6) δ ppm 10.79 (s, 1 H) 8.79 (d, J=1.96 Hz, 1 H) 8.21 (dd, J=8.41, 2.35 Hz, 1 H) 8.16 (d, J=8.22 Hz, 1 H) 7.99 (ddd, J=12.37, 6.80, 2.54 Hz, 1 H) 7.88 - 7.93 (m, 1 H) 6.30 (s, 2 H) 4.60 - 4.78 (m, 2 H) 3.56 (d, J=10.76 Hz, 1 H) 3.35 (d, J=10.95 Hz, 1 H) 3.30 (s, 3 H) 1.63 - 1.69 (m, 1 H) 1.10 (dd, J=9.49, 5.18 Hz, 1 H) 0.64 (t, J=5.87 Hz, 1 H)	N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-(methoxymethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-chloro-2-pyridinecarboxamide
44	^{1}H NMR (400 MHz, DMSO-d6) δ ppm 10.67 (s, 1H), 8.98 (d, J=1.37 Hz, 1H), 8.40 (d, J=1.96 Hz, 1H), 7.90 (dd, J=7.04, 2.74 Hz, 1H), 7.81-7.87 (m, 1H), 7.19 (dd, J=11.93, 8.80 Hz, 1H), 6.22 (s, 2H), 5.06 (t, J=5.87 Hz, 1H), 4.77 (dd, J=26.41, 8.61 Hz, 1H), 4.65 (dd, J=26.41, 9.19 Hz, 1H), 3.54 (dd, J=11.54, 6.26 Hz, 1H), 3.43 (dd, J=11.74, 5.67 Hz, 1H), 2.56 (s, 3H), 1.64 (t, J=7.82 Hz, 1H), 0.98 (dd, J=9.49, 4.99 Hz, 1H), 0.50 (t, J=5.67 Hz, 1H)	N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-(hydroxymethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-cyano-3-methyl-2-pyridinecarboxamide
673	^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 0.84 (t, J=6.46 Hz, 1 H) 1.04 - 1.13 (m, 1 H) 1.75 (s, 3 H) 2.00 - 2.08 (m, 1 H) 2.55 (t, J=2.45 Hz, 1 H) 3.23 - 3.64 (m, 3 H) 3.70 (q, J=6.39 Hz, 1 H) 5.08 (d, J=2.35 Hz, 2 H) 7.06 (dd, J=11.54, 8.80 Hz, 1 H) 7.63 (dd, J=6.85, 2.74 Hz, 1 H) 7.75 - 7.86 (m, 1 H) 8.20 (d, J=1.17 Hz, 1 H) 9.01 (d, J=1.17 Hz, 1 H) 9.48 (s, 1 H).	N-(3-((1S,5S,6S)-3-amino-5-methyl-1-((1R)-2,2,2-trifluoro-1-hydroxyethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide
674	^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 0.91 (t, J=6.65 Hz, 1 H) 1.16 - 1.25 (m, 1 H) 1.74 - 1.88 (m, 4 H) 2.55 (t, J=2.35 Hz, 1 H) 3.49 (q, J=6.78 Hz, 1 H) 3.58 - 3.83 (m, 3 H) 5.08 (d, J=2.35 Hz, 2 H) 7.05 (dd, J=11.54, 8.80 Hz, 1 H) 7.59 (dd, J=6.85, 2.74 Hz, 1 H) 7.82 (dt, J=8.46, 3.50 Hz, 1 H) 8.20 (d, J=1.17 Hz, 1 H) 9.01 (d, J=1.17 Hz, 1 H) 9.46 (s, 1 H).	N-(3-((1S,5S,6S)-3-amino-5-methyl-1-((1S)-2,2,2-trifluoro-1-hydroxyethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide
675	^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 0.78 - 0.83 (m, 1 H) 0.89 (dd, J=9.39, 5.87 Hz, 1 H) 1.72 (s, 3 H) 1.77 - 1.85 (m, 1 H) 2.81 (s, 3 H) 3.35 (d, J=10.76 Hz, 1 H) 3.41 (s, 3 H) 3.67 (d, J=10.76 Hz, 1 H) 4.47 (q, J=7.89 Hz, 2 H) 7.15 (d, J=2.35 Hz, 1 H) 7.30 - 7.36 (m, 1 H) 8.09 (ddd, J=12.03, 6.94, 2.74 Hz, 1 H) 8.18 (d, J=2.54 Hz, 1 H) 10.05 (s, 1 H).	N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-methyl-5-(2,2,2-trifluoroethoxy)-2-pyridinecarboxamide

678	^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 0.82 - 0.90 (m, 1 H) 1.00 (dd, J=9.59, 6.06 Hz, 1 H) 1.73 (s, 3 H) 1.87 - 1.95 (m, 1 H) 2.81 (s, 3 H) 4.19 - 4.90 (m, 6 H) 7.15 (d, J=2.54 Hz, 1 H) 7.30 - 7.36 (m, 1 H) 8.05 (ddd, J=11.93, 6.85, 2.74 Hz, 1 H) 8.18 (d, J=2.74 Hz, 1 H) 10.04 (s, 1 H).	N-(3-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-methyl-5-(2,2,2-trifluoroethoxy)-2-pyridinecarboxamide
679	^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 0.80 - 0.88 (m, 1 H) 1.36 (dd, J=9.98, 6.26 Hz, 1 H) 1.79 (s, 3 H) 1.98 (dd, J=9.68, 7.34 Hz, 1 H) 2.80 (s, 3 H) 4.47 (q, J=7.96 Hz, 2 H) 5.49 - 5.86 (m, 1 H) 7.11 - 7.20 (m, 2 H) 8.02 (ddd, J=11.93, 6.85, 2.74 Hz, 1 H) 8.14 (d, J=2.74 Hz, 1 H) 9.97 (s, 1 H).	N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-methyl-5-(2,2,2-trifluoroethoxy)-2-pyridinecarboxamide
715	^{1}H NMR (CHLOROFORM-d) δ: 10.02 (s, 1H), 8.71 (s, 1H), 7.99-8.07 (m, 1H), 7.93 (s, 1H), 7.62 (dd, J=6.6, 2.4 Hz, 1H), 7.10 (dd, J=11.4, 8.9 Hz, 1H), 4.64-4.96 (m, 2H), 3.71 (d, J=10.8 Hz, 1H), 3.50-3.59 (m, 2H), 3.38 (d, J=10.6 Hz, 1H), 2.86 (s, 3H), 1.83 (d, J=7.6 Hz, 1H), 1.22 (t, J=7.0 Hz, 3H), 1.12 (dd, J=9.4, 5.9 Hz, 1H), 0.78 (t, J=6.2 Hz, 1H)	N-(3-((1S,5S,6S)-3-amino-1-(ethoxymethyl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-cyano-3-methyl-2-pyridinecarboxamide
716	^{1}H NMR (CHLOROFORM-d) δ: 10.02 (s, 1H), 8.71 (s, 1H), 7.98-8.08 (m, 1H), 7.93 (s, 1H), 7.63 (dd, J=6.7, 2.7 Hz, 1H), 7.10 (dd, J=11.5, 9.0 Hz, 1H), 4.64-4.96 (m, 2H), 3.64 (d, J=10.6 Hz, 1H), 3.40 (s, 3H), 3.36 (d, J=10.6 Hz, 1H), 2.86 (s, 3H), 1.82 (t, J=8.1 Hz, 1H), 1.09 (dd, J=9.7, 5.8 Hz, 1H), 0.76 (t, J=6.3 Hz, 1H)	N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-(methoxymethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-cyano-3-methyl-2-pyridinecarboxamide
718	^{1}H NMR (CHLOROFORM-d) δ: 9.81 (s, 1H), 8.55 (d, J=2.2 Hz, 1H), 8.23 (d, J=8.2 Hz, 1H), 7.92-7.99 (m, 1H), 7.88 (dd, J=8.3, 2.2 Hz, 1H), 7.70 (dd, J=6.7, 2.6 Hz, 1H), 7.10 (dd, J=11.3, 8.8 Hz, 1H), 4.54-5.03 (m, 3H), 2.76 (s, 2H), 1.88-2.00 (m, 1H), 1.22 (dd, J=9.8, 6.5 Hz, 1H), 0.82 (t, J=6.7 Hz, 1H)	N-(3-((1R,5S,6S)-3-amino-1-(cyanomethyl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide
723	^{1}H NMR (CHLOROFORM-d) δ: 9.84 (s, 1H), 8.56 (d, J=2.0 Hz, 1H), 8.23 (d, J=8.4 Hz, 1H), 7.93-8.01 (m, 1H), 7.88 (dd, J=8.4, 2.3 Hz, 1H), 7.66 (dd, J=6.7, 2.5 Hz, 1H), 7.12 (dd, J=11.2, 8.9 Hz, 1H), 4.60-5.10 (m, 2H), 2.53-2.66 (m, 2H), 1.91-2.00 (m, 1H), 1.84 (dd, J=15.0, 6.6 Hz, 2H), 1.12-1.20 (m, 1H), 0.81 (t, J=6.6 Hz, 1H)	N-(3-((1S,5S,6S)-3-amino-1-(2-cyanoethyl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide

725	^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 9.79 (1 H, s) 8.54 (1 H, d, J=2.35 Hz) 8.22 (1 H, d, J=8.41 Hz) 7.92 - 7.99 (1 H, m) 7.87 (1 H, dd, J=8.41, 2.35 Hz) 7.64 (1 H, dd, J=6.65, 2.74 Hz) 7.47 (1 H, s) 7.10 (1 H, dd, J=11.44, 8.90 Hz) 4.58 - 4.92 (2 H, m) 4.36 - 4.52 (2 H, m) 2.39 (3 H, s) 2.09 - 2.16 (1 H, m) 1.36 (1 H, dd, J=9.78, 6.26 Hz) 1.26 (1 H, s) 0.85 (1 H, t, J=6.65 Hz). MS (ESI, positive ion) m/z: 504 (M+H)	N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-((5-methyl-1H-1,2,3-triazol-1-yl)methyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide

Method C: SNAr in *i*PrOH

Example 54: 8-((3-((1S,5S,6S)-3-amino-1-(hydroxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)amino)-1,7-naphthyridine-3-carbonitrile.

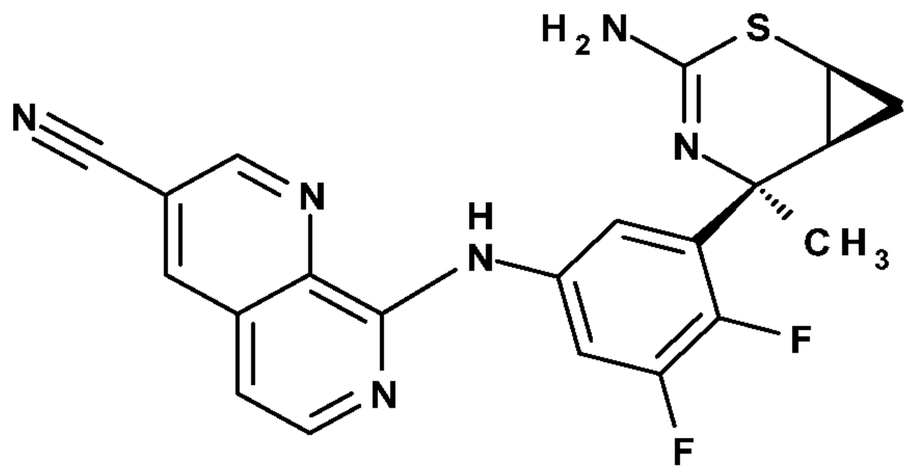
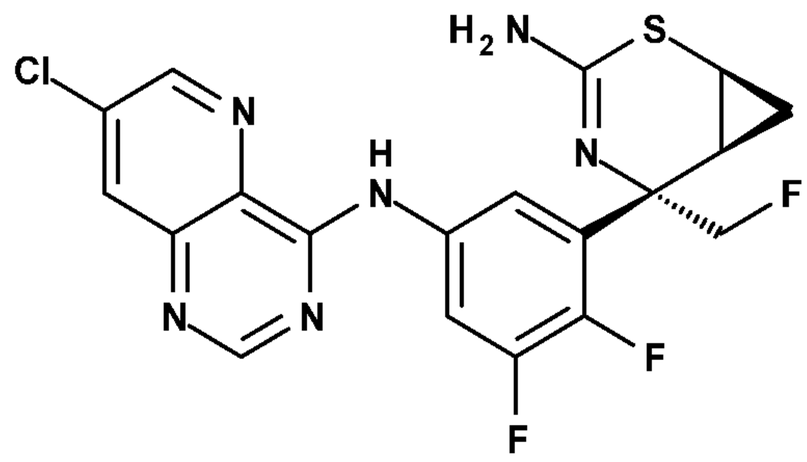
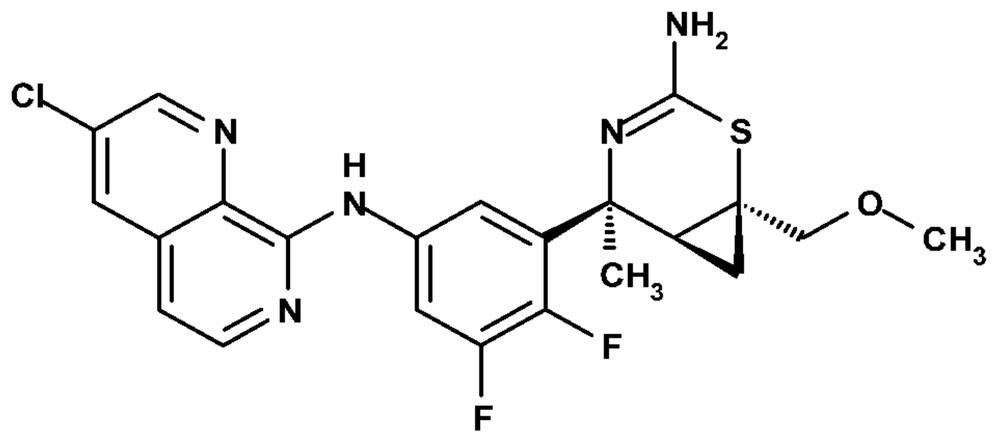


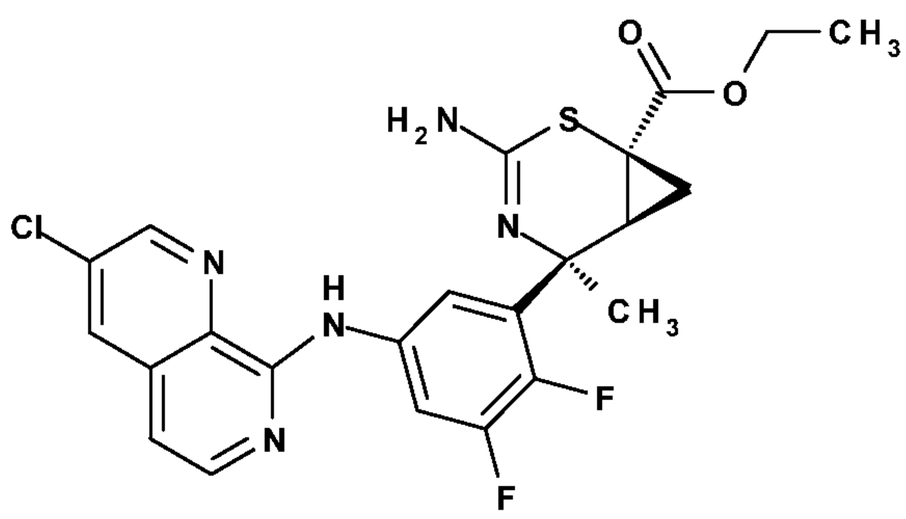
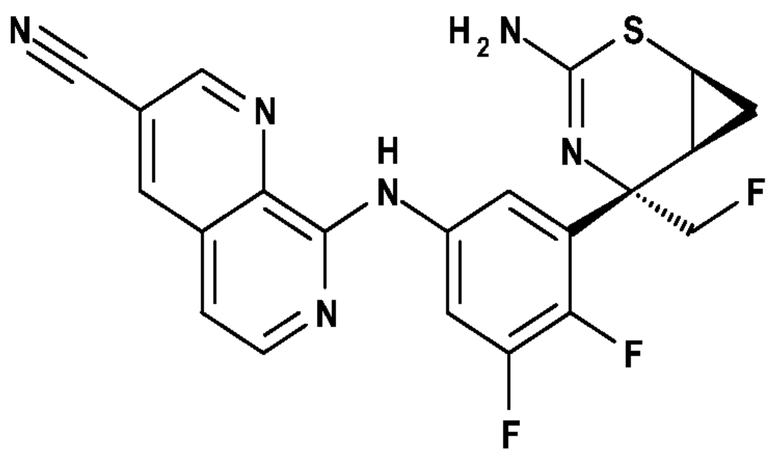
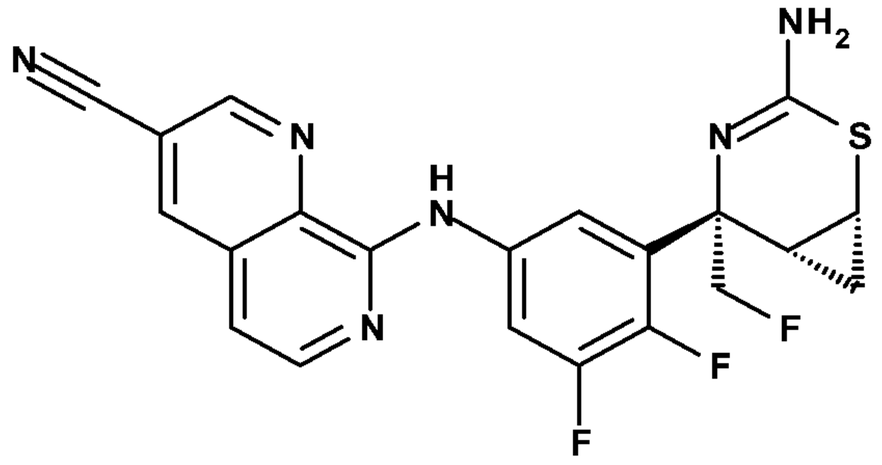
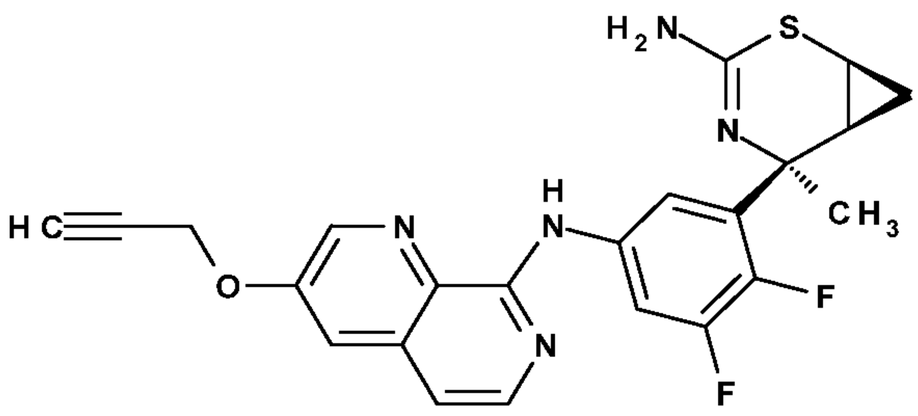
254 **206** **Example 54**

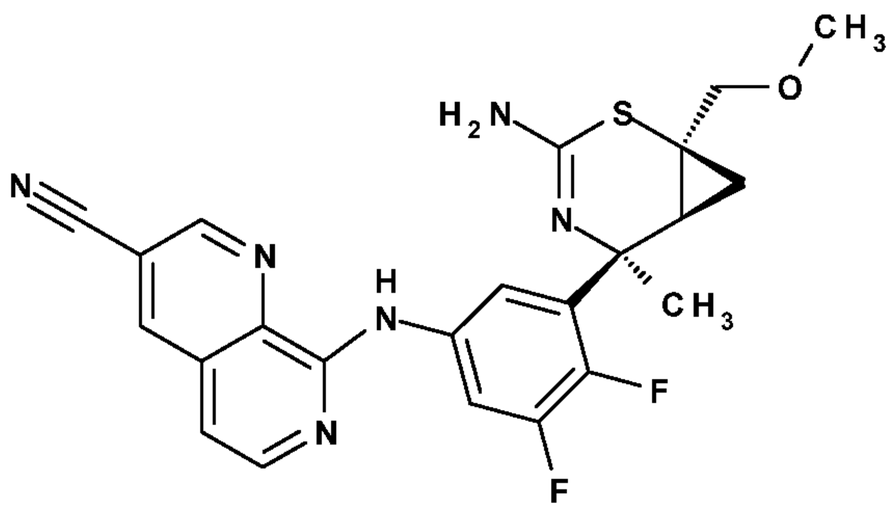
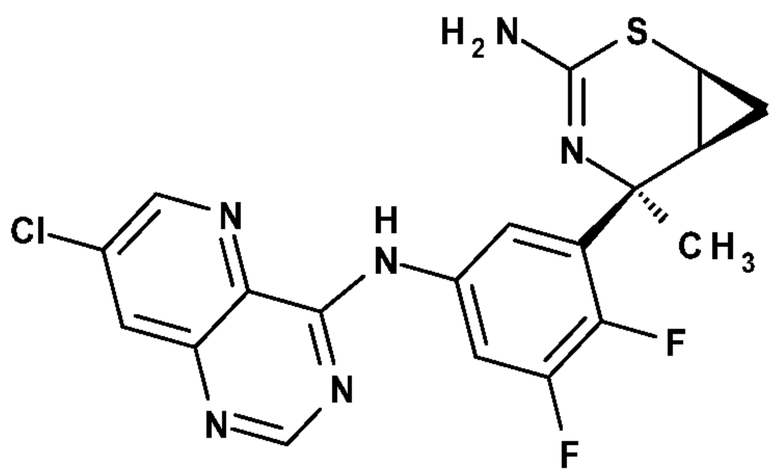
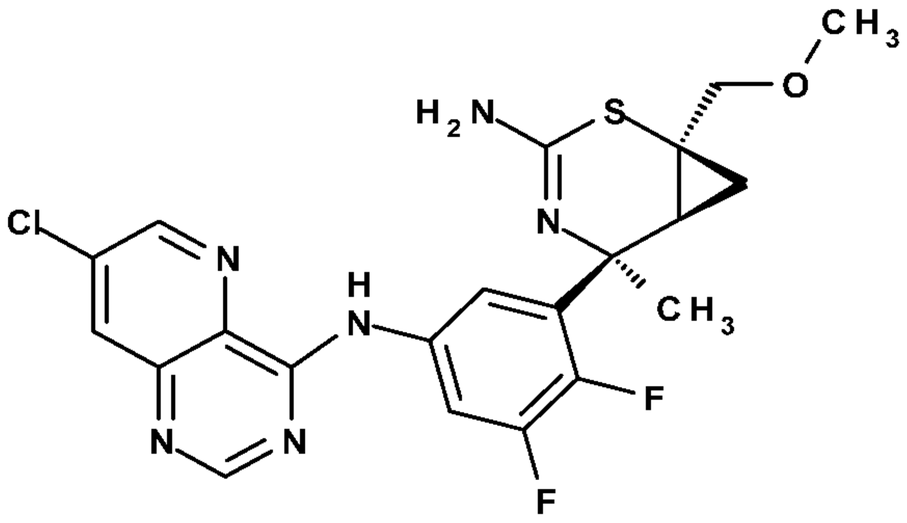
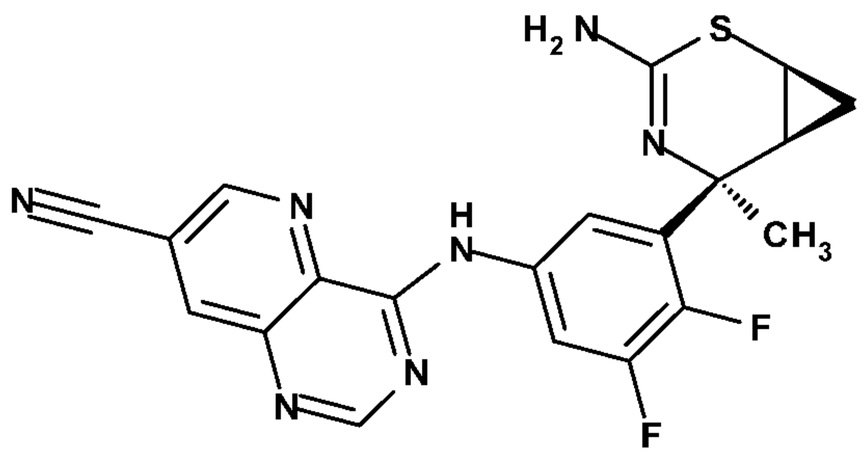
A mixture of ((1S,5S,6S)-3-amino-5-(5-amino-2,3-difluorophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)methanol (Intermediate **206**, 75 mg, 0.25 mmol), 8-chloro-1,7-naphthyridine-3-carbonitrile (Intermediate **254**, 52 mg, 0.27 mmol) and p-toluenesulfonic acid monohydrate (52 mg, 0.27 mmol) in isopropyl alcohol (2.0 mL) was heated to 75 °C in an oil bath for 1 h. The reaction mixture was cooled to RT and partitioned between $CHCl_3$ / iPrOH = 9/1 (40 mL) and sat. $NaHCO_3$ (10 mL). The organic layer was dried over $MgSO_4$, filtered, and then concentrated under reduced pressure to afford a yellow solid. It was purified by silica gel chromatography (12 g) eluting with 35-75% EtOAc in DCM to afford 8-((3-((1S,5S,6S)-3-amino-1-(hydroxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)amino)-1,7-naphthyridine-3-carbonitrile (Example 54, 97 mg, 0.21 mmol, 86% yield) as yellow crystalline solid. MS m/z = 453.2 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.76 (br., 1H), 9.24 (d, *J*=1.76 Hz, 1H), 9.01 (d, *J*=1.76 Hz, 1H), 8.30 (m, 2H), 7.93 (br., 1H), 7.28 (d, *J*=5.87 Hz, 1H), 6.00 (br., 2H), 5.05 (t, *J*=5.58 Hz, 1H), 3.55 (m, 1H), 3.45 (m, 1H), 1.68 (m, 1H), 1.63 (s, 3H), 0.89 (m., 1H), 0.60 (m, 1H). ^{19}F NMR (377 MHz, DMSO-d_6) δ -138.70 (d, *J*=22.59 Hz, 1F), -146.08 (d, *J*=22.59 Hz, 1F).

Using procedures analogous or similar to the general SNAr **Method C** described above, the appropriate aniline and ArX (X = Cl / Br) intermediates were reacted to provide the 195 examples listed in Table 3 and Table 3'.

Table 3

Ex. No.	Chemical Structure	Observed $[M+H]^+$
21		423.0
22		451.0
24		476.1

25		504.0
26		441.0
27		441.0
32		452.0

33		467.1
34		433.0
35		477.0
36		424.1

DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

CECI EST LE TOME 1 DE 2
CONTENANT LES PAGES 1 À 383

NOTE : Pour les tomes additionels, veuillez contacter le Bureau canadien des brevets

JUMBO APPLICATIONS/PATENTS

THIS SECTION OF THE APPLICATION/PATENT CONTAINS MORE THAN ONE VOLUME

THIS IS VOLUME 1 OF 2
CONTAINING PAGES 1 TO 383

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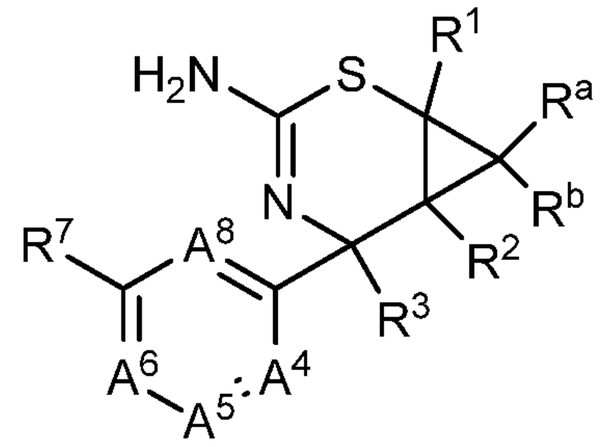
NOM DU FICHIER / FILE NAME :

NOTE POUR LE TOME / VOLUME NOTE:

What is claimed is:

1. A compound of Formula I



I

or a stereoisomer, tautomer, hydrate, solvate or pharmaceutically acceptable salt thereof, wherein

A^4 is CR^4 or N;

A^5 is CR^5 or N;

A^6 is CR^6 or N;

A^8 is CR^8 or N, provided that no more than two of A^4, A^5, A^6 and A^8 is N;

each of R^a and R^b, independently, is H, F, Cl, C_{1-6}-alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, CN, $-CH_2OC_{1-6}$-alkyl, $-OC_{1-6}$-alkyl, $-S(O)_oC_{1-6}$-alkyl, $-NHC_{1-6}$-alkyl or $-C(O)C_{1-6}$-alkyl, wherein each of the C_{1-6}-alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, and C_{1-6}-alkyl portion of $-CH_2OC_{1-6}$-alkyl, $-OC_{1-6}$-alkyl, $-S(O)_oC_{1-6}$-alkyl, $-NHC_{1-6}$-alkyl and $-C(O)C_{1-6}$-alkyl are optionally substituted with 1-4 substituents of F, oxo or OH;

R^1 and either R^a or R^b may optionally join to form a 5-membered saturated ring that includes one S heteroatom;

R^1 is H, F, Cl, C_{1-6}-alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, CN, $-CH_2OC_{1-6}$-alkyl, $-OC_{1-6}$-alkyl, $-S(O)_oC_{1-6}$-alkyl, $-NHC_{1-6}$-alkyl, $-C_{1-6}$-alkylNH$_2$, $-C_{1-6}$-alkylNHC$_{1-6}$-alkyl, $-C_{1-6}$-alkylNHC(O)OC$_{1-6}$-alkyl, $-C_{1-6}$-alkylNHC(O)NHC$_{1-6}$-alkyl, $-C_{1-6}$-alkylNHC(O)C$_{1-6}$-alkyl, $-C(O)NH_2$, $-CH=CHC(O)NH_2$, $-CH=CHC(O)NHC_{1-6}$-alkyl, $-CH=CHC(O)N(C_{1-6}$-alkyl$)_2$, $-CH=CHC(O)NHC_{1-6}$-alkyl-OC_{1-6}-alkyl, $-CH=CHC(O)$-heterocyclyl, $-CH=C(CH_3)C(O)$-heterocyclyl,$-CH=CHC(O)_2H$, $-CH=CHC(O)OC_{1-6}$-alkyl, $-CH=CHCH_2OH$, C_{1-6}-alkyl-$C(O)NHC_{1-6}$-alkyl, C_{1-6}-alkyl-$C(O)N(C_{1-6}$-alkyl$)_2$, $-C(O)C_{1-6}$-alkyl, $-C(O)C_{1-6}$-alkenyl, $-C(O)OH$, $-C(O)OC_1$-C_6alkyl, $-C(O)NHC_{1-6}$-alkyl ,$-C(O)N(C_{1-6}$-alkyl$)_2$, $-C(O)NHC_{3-6}$cycloalkyl, $-C(O)NHOC_{1-6}$-alkyl, $-C(O)N(C_{1-6}$-alkyl$)OC_{1-6}$-alkyl, $-C(O)$-heterocyclyl, $-CH_2$-heteroaryl, or heteroaryl, wherein the heterocyclyl groups of the $-CH=CHC(O)$-heterocyclyl, $-CH=C(CH_3)C(O)$-heterocyclyl, and $-C(O)$-heterocyclyl groups are fully or partially unsaturated 3-, 4-, 5-, 6- or 7-membered monocyclic rings

that include 1 heteroatom selected from N, O, or S if the ring is a 3-membered ring, that include 1 or 2 heteroatoms independently selected from N, O, or S if the ring is a 4- or 5-membered ring, and include 1, 2, or 3 heteroatoms independently selected from N, O, or S if the ring is a 6- or 7-membered ring, wherein the heteroaryl groups of the -CH_2-heteroaryl and heteroaryl groups is a 5- or 6- membered ring that includes 1, 2, 3, or 4 heteroatoms selected from N, O, or S, wherein each of the C_{1-6}-alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, and C_{3-6}cycloalkyl portion of C_{1-6}-alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl ,-CH_2OC_{1-6}-alkyl, -OC_{1-6}-alkyl, -$S(O)_oC_{1-6}$-alkyl, -NHC_{1-6}-alkyl, $C(O)C_{1-6}$-alkyl, -$C(O)C_{1-6}$-alkenyl, -$C(O)NHC_{1-6}$-alkyl ,-$C(O)N(C_{1-6}$-alkyl$)_2$, -$C(O)NHC_{3-6}$cycloalkyl, -CH=CHC(O)NHC_{1-6}-alkyl and C_{1-6}-alkyl-$C(O)NHC_{1-6}$-alkyl groups are optionally substituted with 1-4 substituents of F, CN, methyl, oxo, or OH, and further wherein each of the heterocyclyl groups of the -CH=CHC(O)-heterocyclyl, -$CH=C(CH_3)C(O)$-heterocyclyl, and -C(O)heterocyclyl groups is optionally substituted with 1-4 substituents independently selected from F, methyl, OH, or OCH_3, and further wherein each of the heteroaryl groups of the -CH_2-heteroaryl and heteroaryl groups is optionally substituted with 1-3 substituents independently selected from halo, methyl, or OH;

R^2 is H, F, Cl, C_{1-6}-alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, CN, -CH_2OC_{1-6}-alkyl, -OC_{1-6}-alkyl, -$S(O)_oC_{1-6}$-alkyl, -NHC_{1-6}-alkyl, -$C(O)NH_2$, -CH=CHC(O)NHC_{1-6}-alkyl, -$CH=CHC(O)_2H$, -$CH=CHCH_2OH$, C_{1-6}-alkyl-$C(O)NHC_{1-6}$-alkyl, -$C(O)C_{1-6}$-alkyl or -$C(O)C_{1-6}$-alkenyl, wherein each of the C_{1-6}-alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, and C_{1-6}-alkyl portion of -CH_2OC_{1-6}-alkyl, -OC_{1-6}-alkyl, -$S(O)_oC_{1-6}$-alkyl, -NHC_{1-6}-alkyl, $C(O)C_{1-6}$-alkyl, -$C(O)C_{1-6}$-alkenyl, -CH=CHC(O)NHC_{1-6}-alkyl and C_{1-6}-alkyl-$C(O)NHC_{1-6}$-alkyl, are optionally substituted with 1-4 substituents of F, CN, oxo or OH;

R^3 is C_{1-4}alkyl, CH_2OC_{1-4}alkyl, CH_2OH, C_{1-4}haloalkyl or cyclopropyl, wherein each of the C_{1-4}alkyl, CH_2OC_{1-4}alkyl, C_{1-4}haloalkyl and cyclopropyl is optionally substituted with 1-4 F atoms;

each of R^4, R^5, R^6 and R^8, independently, is H, halo, haloalkyl, haloalkoxyl, C_{1-4}-alkyl, CN, OH, OC_{1-4}-alkyl, $S(O)_oC_{1-4}$-alkyl, NHC_{1-4}-alkyl,$C(O)C_{1-4}$-alkyl, $C(O)OC_{1-4}$-alkyl, or CH_2OH;

R^7 is –NH-R^9 or -NH-C(=O)-R^9;

R^9 is a fully or partially unsaturated 3-, 4-, 5-, 6- or 7-membered monocyclic or 8-, 9- or 10-membered bicyclic ring formed of carbon atoms, said ring optionally including 1-4 heteroatoms if monocyclic or 1-5 heteroatoms if bicyclic, said heteroatoms selected

from O, N or S, wherein the ring is optionally substituted, independently, with 1-5 substituents of R^{10};

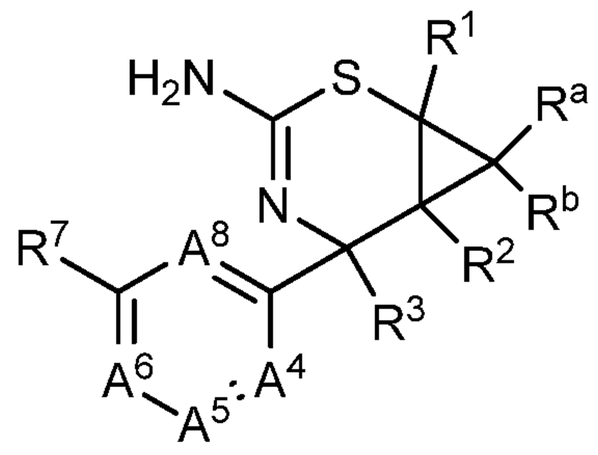
each R^{10}, independently, is H, halo, haloalkyl, CN, OH, NO_2, NH_2, SF_5, acetyl, -$C(O)NHC_{1-6}$-alkyl, -$OCH_2C(O)NHC_{1-6}$-alkyl, -$OCH_2C(O)N(C_{1-6}$-alkyl$)_2$, -OCH_2CH_2-pyrollidinonyl, oxo, cyclopropylmethoxy, 2-propynyloxy, 2-butynyloxy, 3-butynyloxy , 3-pentynyloxy, 2-pentyloxy, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkylamino-, C_{1-6}dialkylamino-, C_{1-6}alkoxyl, -OC_2-C_6alkenyl, C_{1-6}thioalkoxyl, -OCH_2C_{3-6}cycloaklyl, morpholinyl, pyrazolyl, isoxazolyl, dihydropyranyl, pyrrolyl, pyrrolidinyl, tetrahydropyrrolyl, piperazinyl, oxetan-3-yl, imidazo-pyridinyl, dioxolyl, -O-heterocyclyl, or –OCH_2-heteroaryl, wherein the heterocyclyl of the -O-heterocyclyl group is a 3-, 4-, 5-, 6- or 7-membered monocyclic saturated ring that includes 1 heteroatom selected from N, O, or S if the heterocyclyl ring is a 3-membered ring, that includes 1 or 2 heteroatoms independently selected from N, O, or S if the heterocyclyl ring is a 4- or 5-membered ring, and includse 1, 2, or 3 heteroatoms independently selected from N, O, or S if the heterocyclyl ring is a 6- or 7-membered ring wherein the heteroaryl group of the –OCH_2-heteroaryl group is a 5- or 6- membered ring that includes 1, 2, 3, or 4 heteroatoms selected from N, O, or S, and further wherein each of the cyclopropylmethoxy, 2-propynyloxy, 2-butynyloxy, 2-pentyloxy, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkylamino-, C_{1-6}dialkylamino-, C_{1-6}alkoxyl, C_{1-6}thioalkoxyl, , -OCH_2C_{3-6}cycloaklyl, morpholinyl, pyrazolyl, isoxazolyl, dihydropyranyl, pyrrolidinyl, oxetan-3-yl, dioxolyl, or –OCH_2-heteroaryl is optionally substituted independently with 1-5 substituents of F, Cl, Br, CN, NO_2, NH_2, OH, oxo, CF_3, CHF_2, CH_2F, methyl, methoxy, ethyl, ethoxy, CH_2CF_3, CH_2CHF_2, propyl, propoxy, isopropyl, isopropoxy, cyclopropyl, butyl, butoxyl, cyclobutyl, isobutoxy, *tert*-butoxy, isobutyl, sec-butyl, *tert*-butyl, cyclopentyl, cyclohexyl, phenyl, C_{1-3}alkylamino-, C_{1-3}dialkylamino, C_{1-3}thioalkoxyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, thienyl, furyl, pyrrolyl, tetrahydropyranyl, tetrahydropyrrolyl, oxetan-2-yl, or oxetan-3yl; and

the subscript o is selected from 0, 1, or 2.

2. The compound according to Claim 1, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R^1 is a -CH_2-heteroaryl or a heteroaryl and the heteroaryl groups of the -CH_2-heteroaryl and heteroaryl is selected from triazolyl, oxazolyl, or isoxazolyl optionally substituted with 1 or 2 methyl groups.

3. The compound according to Claim 1 or Claim 2, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R^{10} is a -OCH_2-heteroaryl and the heteroaryl group of the -OCH_2-heteroaryl is selected from an oxadiazolyl, thiadiazolyl, oxazolyl, isoxazolyl, thiazolyl, pyridinyl, or pyrimidinyl optionally substituted independently with 1 or 2 F, Cl, Br, or methyl groups.

4. A compound of Formula I



I

or a stereoisomer, tautomer, hydrate, solvate or pharmaceutically acceptable salt thereof, wherein

A^4 is CR^4 or N;

A^5 is CR^5 or N;

A^6 is CR^6 or N;

A^8 is CR^8 or N, provided that no more than two of A^4, A^5, A^6 and A^8 is N;

each of R^a and R^b, independently, is H, F, Cl, C_{1-6}-alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, CN, -CH_2OC_{1-6}-alkyl, -OC_{1-6}-alkyl, -$S(O)_oC_{1-6}$-alkyl, -NHC_{1-6}-alkyl or -$C(O)C_{1-6}$-alkyl, wherein each of the C_{1-6}-alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, and C_{1-6}-alkyl portion of -CH_2OC_{1-6}-alkyl, -OC_{1-6}-alkyl, -$S(O)_oC_{1-6}$-alkyl, -NHC_{1-6}-alkyl and -$C(O)C_{1-6}$-alkyl are optionally substituted with 1-4 substituents of F, oxo or OH;

each of R^1 and R^2, independently, is H, F, Cl, C_{1-6}-alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, CN, -CH_2OC_{1-6}-alkyl, -OC_{1-6}-alkyl, -$S(O)_oC_{1-6}$-alkyl, -NHC_{1-6}-alkyl, -$C(O)NH_2$, -$CH=CHC(O)NHC_{1-6}$-alkyl, -$CH=CHC(O)_2H$, -$CH=CHCH_2OH$, C_{1-6}-alkyl-$C(O)NHC_{1-6}$-alkyl, -$C(O)C_{1-6}$-alkyl or -$C(O)C_{1-6}$-alkenyl, wherein each of the C_{1-6}-alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, and C_{1-6}-alkyl portion of -CH_2OC_{1-6}-alkyl, -OC_{1-6}-alkyl, -$S(O)_oC_{1-6}$-alkyl, -NHC_{1-6}-alkyl, $C(O)C_{1-6}$-alkyl, -$C(O)C_{1-6}$-alkenyl, -$CH=CHC(O)NHC_{1-6}$-alkyl and C_{1-6}-alkyl-$C(O)NHC_{1-6}$-alkyl, are optionally substituted with 1-4 substituents of F, CN, oxo or OH;

R^3 is C_{1-4}alkyl, CH_2OC_{1-4}alkyl, CH_2OH, C_{1-4}haloalkyl or cyclopropyl, wherein each of the C_{1-4}alkyl, CH_2OC_{1-4}alkyl, C_{1-4}haloalkyl and cyclopropyl is optionally substituted with 1-4 F atoms;

each of R^4, R^5, R^6 and R^8, independently, is H, halo, haloalkyl, haloalkoxyl, C_{1-4}-alkyl, CN, OH, OC_{1-4}-alkyl, $S(O)_oC_{1-4}$-alkyl, NHC_{1-4}-alkyl or $C(O)C_{1-4}$-alkyl;

R^7 is –NH-R^9 or -NH-C(=O)-R^9;

R^9 is a fully or partially unsaturated 3-, 4-, 5-, 6- or 7-membered monocyclic or 8-, 9- or 10-membered bicyclic ring formed of carbon atoms, said ring optionally including 1-4 heteroatoms if monocyclic or 1-5 heteroatoms if bicyclic, said heteroatoms selected from O, N or S, wherein the ring is optionally substituted, independently, with 1-5 substituents of R^{10};

each R^{10}, independently, is H, halo, haloalkyl, CN, OH, NO_2, NH_2, SF_5, acetyl, -C(O)$NHCH_3$, oxo, cyclopropylmethoxy, 2-propynyloxy, 2-butynyloxy, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkylamino-, C_{1-6}dialkylamino-, C_{1-6}alkoxyl, C_{1-6}thioalkoxyl, morpholinyl, pyrazolyl, isoxazolyl, dihydropyranyl, pyrrolidinyl, tetrahydropyrrolyl, piperazinyl, oxetan-3-yl, imidazo-pyridinyl or dioxolyl, wherein each of the cyclopropylmethoxy, 2-propynyloxy, 2-butynyloxy, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkylamino-, C_{1-6}dialkylamino-, C_{1-6}alkoxyl, C_{1-6}thioalkoxyl, morpholinyl, pyrazolyl, isoxazolyl, dihydropyranyl, pyrrolidinyl, oxetan-3-yl or dioxolyl, is optionally substituted independently with 1-5 substituents of F, Cl, CN, NO_2, NH_2, OH, oxo, CF_3, CHF_2, CH_2F, methyl, methoxy, ethyl, ethoxy, CH_2CF_3, CH_2CHF_2, propyl, propoxy, isopropyl, isopropoxy, cyclopropyl, butyl, butoxyl, cyclobutyl, isobutoxy, *tert*-butoxy, isobutyl, sec-butyl, *tert*-butyl, cyclopentyl, cyclohexyl, C_{1-3}alkylamino-, C_{1-3}dialkylamino, C_{1-3}thioalkoxyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, thienyl, furyl, pyrrolyl, tetrahydropyranyl, tetrahydropyrrolyl or oxetan-3yl; and

the subscript o is selected from 0, 1, or 2.

5. The compound according to Claim 1 or Claim 4, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein each of R^1 and R^2, independently, is H, F, CH_3, CH_2OCH_3, CH_2F, CHF_2, CF_3, -C(O)NH_2, -CH=CHC(O)NHC_{1-6}alkyl, -CH=CHC$(O)_2$H, -CH=CHCH_2OH or C_{1-6}-alkyl-C(O)NHC_{1-6}-alkyl.

6. The compound according to any one of Claims 1, 4, or 5, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein each of R^a and R^b, independently, is H, F, CH_3, CH_2F, CHF_2 or CF_3.

7. The compound according to any one of Claims 1, 4, 5, or 6, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein each of R^1 and R^2, independently, is H, F, CH_2OCH_3, or CF_3.

8. The compound according to any one of Claims 1, or 4-7, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein each of R^a and R^b, independently, is H or F.

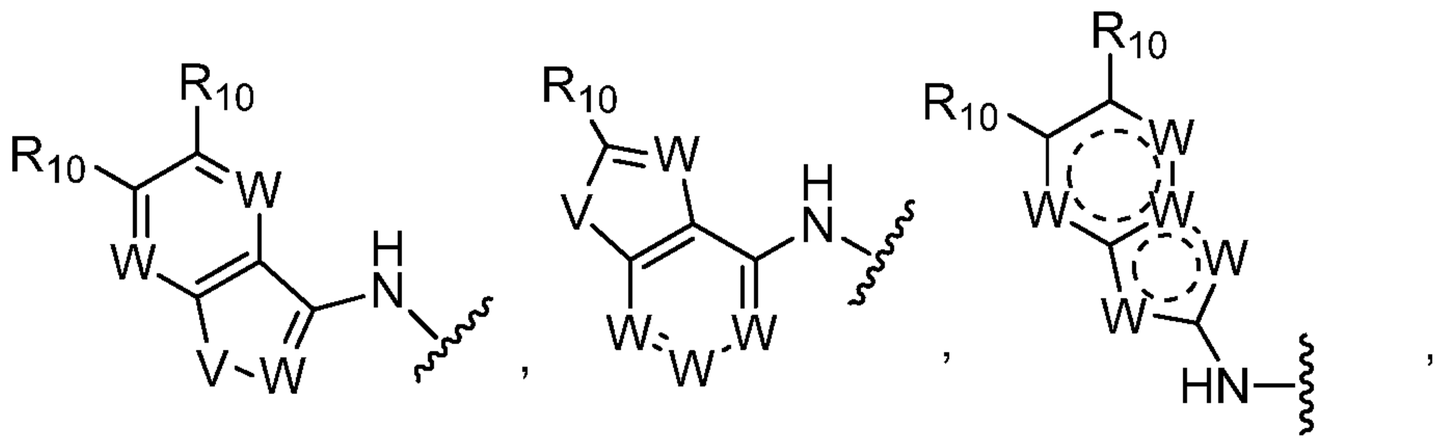
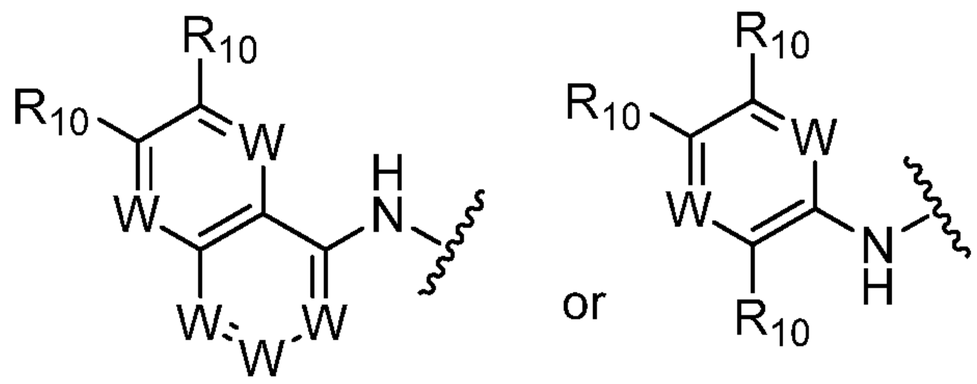
9. The compound according to any one of Claims 1, or 4-8, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein each of R^1 and R^2, independently, is H, F, CH_2OCH_3, or CF_3; and each of R^a and R^b, independently, is H or F.

10. The compound according to any one of Claims 1, or 4-9, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein each of R^1 and R^2 is, independently, H or CH_2OCH_3, and each of R^a and R^b, independently, is H.

11. The compound according to any one of Claims 1, or 4-10, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R^3 is CH_3, CF_3, CH_2F or CHF_2.

12. The compound according to any one of Claims 1 or 4-11, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R^7 is -NH-C(=O)-R^9;

or R^7 is

wherein V is NR^{10}, O or S; and

each W, independently, is CH, CF, CCl, CCH_3 or N.

13. The compound according to any one of Claims 1, 4, or 12, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein

A^4 is CR^4 or N;

A^5 is CR^5 or N;

A^6 is CR^6 or N;

A^8 is CR^8 or N, provided that no more than one of A^4, A^5, A^6 and A^8 is N;

each of R^a and R^b, independently, is H, F, Cl, CF_3, OCF_3, methyl, ethyl, CN, OH, OCH_3, SCH_3, $NHCH_3$, $C(O)CH_3$ or CH_2OCHF_2;

each of R^1 and R^2, independently, is H, F, Cl, CF_3, OCF_3, methyl, ethyl, CN, OH, OCH_3, SCH_3, $NHCH_3$, $C(O)CH_3$, CH_2OCH_3 or CH_2OCHF_2;

R^3 is $C_{1\text{-}4}$alkyl, $C_{1\text{-}4}$haloalkyl, CH_2OH, CH_2OCHF_2 or cyclopropyl; and

each of R^4, R^5, R^6 and R^8, independently, is H, F, Cl, CF_2H, CH_2F, CF_3, OCF_3, methyl, ethyl, CN, OH, OCH_3, SCH_3, $NHCH_3$ or $C(O)CH_3$.

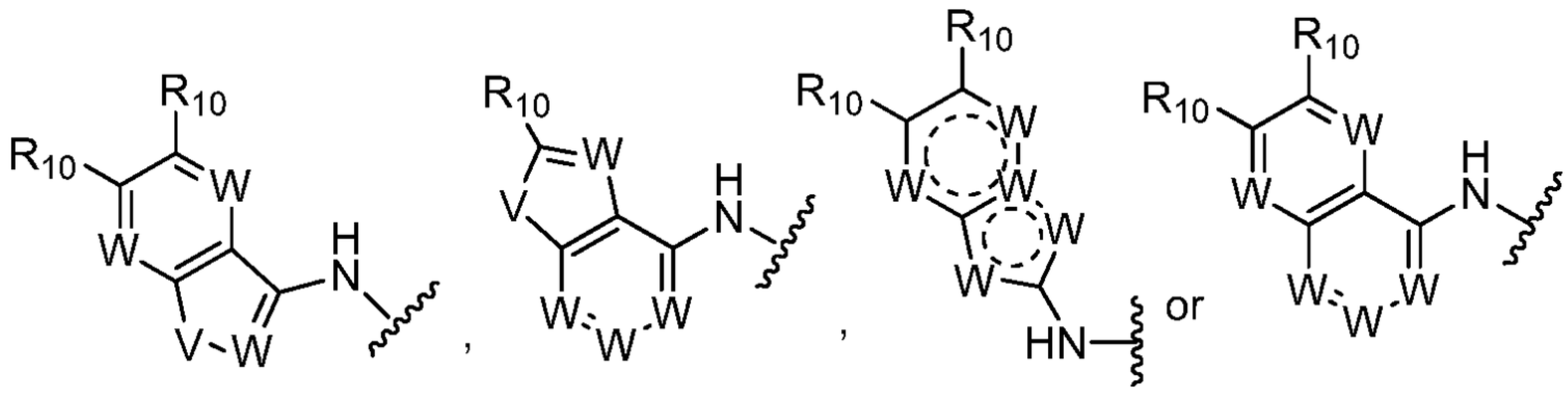
14. The compound according to any one of claims 1, or 4-12, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein

each of R^1 and R^2, independently, is H, F, CH_2OCH_3 or CF_3;

each of R^a and R^b, independently, is H or F;

R^3 is CH_3, CF_3, CH_2F or CHF_2; and

R^7 is -NH-C(=O)-R^9 or

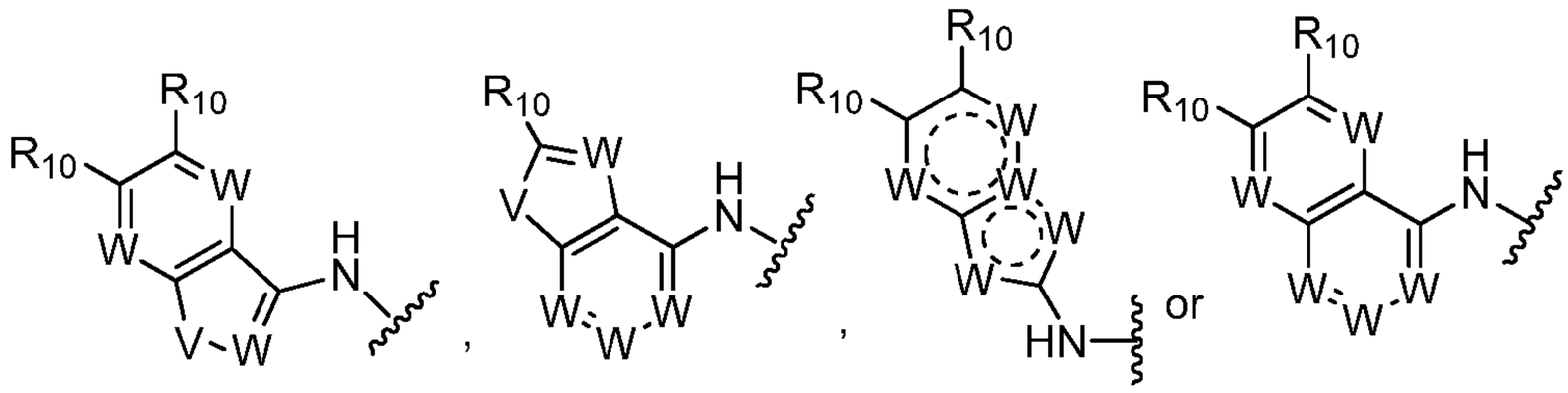


wherein V is NR^{10}, O or S; and

each W, independently, is CH, CF, CCl, CCH_3 or N.

15. The compound according to any one of claims 1, or 4-14, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R^7 is -NH-C(=O)-R^9.

16. The compound according to any one of claims 1, or 4-14, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R^7 is



wherein V is NR^{10}, O or S; and

each W, independently, is CH, CF, CCl, CCH_3 or N.

17. The compound according to any one of claims 1, or 4-16, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein

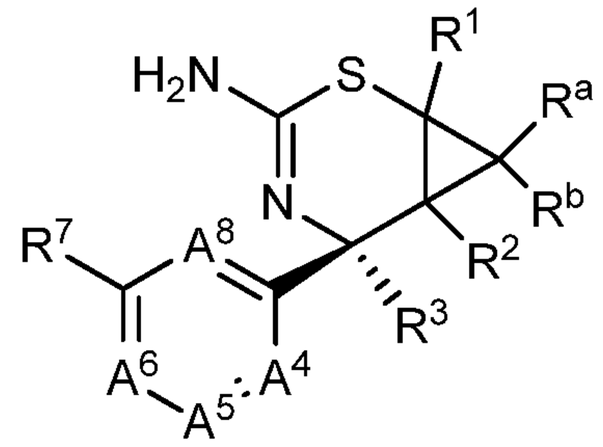
A^4 is CR^4;

A^5 is CR^5 or N;

A^6 is CR^6; and

A^8 is CR^8 or N, provided only one of A^5 and A^8 is N, and wherein each of R^4, R^5, R^6 and R^8, independently, is H, F, Cl, CF_3, CF_2H, CH_2F or CH_3.

18. A compound according to Claim 1 or Claim 4, or a stereoisomer, tautomer, hydrate, solvate or pharmaceutically acceptable salt thereof, of Formula II:



II

wherein

A^4 is CR^4 or N;

A^5 is CR^5 or N;

A^6 is CR^6 or N;

A^8 is CR^8 or N, provided that no more than two of A^4, A^5, A^6 and A^8 is N;

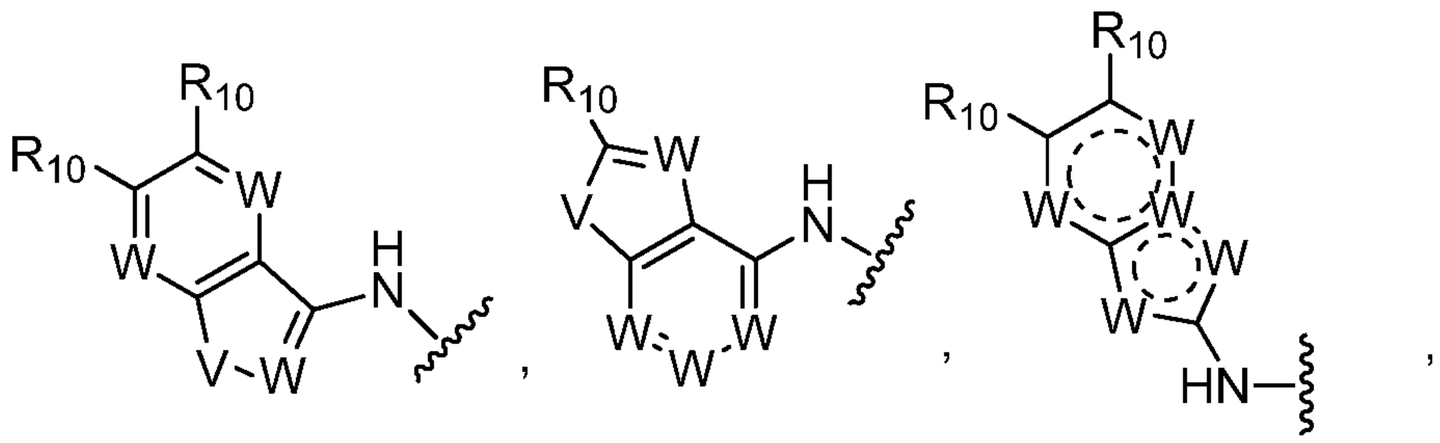
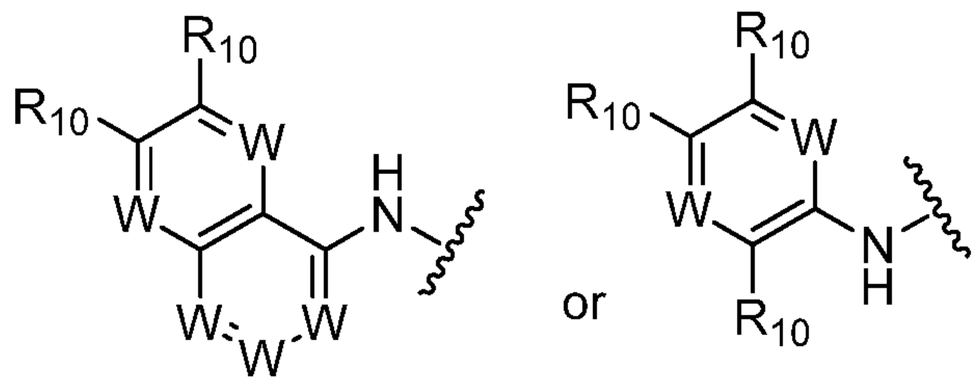
each of R^a and R^b, independently, is H, F, Cl, C_{1-6}-alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, CN, $-CH_2OC_{1-6}$-alkyl, $-OC_{1-6}$-alkyl, $-S(O)_oC_{1-6}$-alkyl, $-NHC_{1-6}$-alkyl or $-C(O)C_{1-6}$-alkyl, wherein each of the C_{1-6}-alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, and C_{1-6}-alkyl portion of $-CH_2OC_{1-6}$-alkyl, $-OC_{1-6}$-alkyl, $-S(O)_oC_{1-6}$-alkyl, $-NHC_{1-6}$-alkyl and $-C(O)C_{1-6}$-alkyl are optionally substituted with 1-4 substituents of F, oxo or OH;

each of R^1 and R^2, independently, is H, F, Cl, C_{1-6}-alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, CN, $-CH_2OC_{1-6}$-alkyl, $-OC_{1-6}$-alkyl, $-S(O)_oC_{1-6}$-alkyl, $-NHC_{1-6}$-alkyl, $-C(O)NH_2$, $-CH=CHC(O)NHC_{1-6}$-alkyl, $-CH=CHC(O)_2H$, $-CH=CHCH_2OH$, C_{1-6}-alkyl-$C(O)NHC_{1-6}$-alkyl, $C(O)C_{1-6}$-alkyl or $-C(O)C_{1-6}$-alkenyl, wherein each of the C_{1-6}-alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, and C_{1-6}-alkyl portion of $-CH_2OC_{1-6}$-alkyl, $-OC_{1-6}$-alkyl, $-S(O)_oC_{1-6}$-alkyl, $-NHC_{1-6}$-alkyl, $C(O)C_{1-6}$-alkyl, $-C(O)C_{1-6}$-alkenyl, $-CH=CHC(O)NHC_{1-6}$-alkyl and C_{1-6}-alkyl-$C(O)NHC_{1-6}$-alkyl, are optionally substituted with 1-4 substituents of F, CN, oxo or OH;

R^3 is C_{1-4}alkyl, CH_2OC_{1-4}alkyl, CH_2OH, C_{1-4}haloalkyl or cyclopropyl, wherein each of the C_{1-4}alkyl, CH_2OC_{1-4}alkyl, C_{1-4}haloalkyl and cyclopropyl is optionally substituted with 1-4 F atoms;

each of R^4, R^5, R^6 and R^8, independently, is H, halo, haloalkyl, haloalkoxyl, C_{1-4}-alkyl, CN, OH, OC_{1-4}-alkyl, $S(O)_oC_{1-4}$-alkyl, NHC_{1-4}-alkyl or $C(O)C_{1-4}$-alkyl;R^7 is -NH-C(=O)-R^9;

or R^7 is

wherein V is NR^{10}, O or S; and

each W, independently, is CH, CF, CCl, CCH_3 or N;

R^9 is a fully or partially unsaturated 3-, 4-, 5-, 6- or 7-membered monocyclic or 8-, 9- or 10-membered bicyclic ring formed of carbon atoms, said ring optionally including 1-4 heteroatoms if monocyclic or 1-5 heteroatoms if bicyclic, said heteroatoms selected from O, N or S, wherein ring is optionally substituted, independently, with 1-5 substituents of R^{10};

each R^{10}, independently, is H, halo, haloalkyl, CN, OH, NO_2, NH_2, SF_5, acetyl, -C(O)$NHCH_3$, oxo, cyclopropylmethoxy, 2-propynyloxy, 2-butynyloxy, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkylamino-, C_{1-6}dialkylamino-, C_{1-6}alkoxyl, C_{1-6}thioalkoxyl, morpholinyl, pyrazolyl, isoxazolyl, dihydropyranyl, pyrrolyl, pyrrolidinyl, tetrahydropyrrolyl, piperazinyl, oxetan-3-yl, imidazo-pyridinyl or dioxolyl, wherein each of the cyclopropylmethoxy, 2-propynyloxy, 2-butynyloxy, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkylamino-, C_{1-6}dialkylamino-, C_{1-6}alkoxyl, C_{1-6}thioalkoxyl, morpholinyl, pyrazolyl, isoxazolyl, dihydropyranyl, pyrrolidinyl, oxetan-3-yl or dioxolyl, is optionally substituted independently with 1-5 substituents of F, Cl, CN, NO_2, NH_2, OH, oxo, CF_3, CHF_2, CH_2F, methyl, methoxy, ethyl, ethoxy, CH_2CF_3, CH_2CHF_2, propyl, propoxy, isopropyl, isopropoxy, cyclopropyl, butyl, butoxyl, cyclobutyl, isobutoxy, tert-butoxy, isobutyl, sec-butyl, *tert*-butyl, cyclopentyl, cyclohexyl, C_{1-3}alkylamino-, C_{1-3}dialkylamino, C_{1-3}thioalkoxyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, thienyl, furyl, pyrrolyl, tetrahydropyranyl, tetrahydropyrrolyl or oxetan-3yl; and

the subscript o is selected from 0, 1, or 2.

19. The compound according to any one of Claims 1, 4 or 18, or a stereoisomer, tautomer or pharmaceutically acceptable salt thereof, wherein

A^4 is CR^4 or N;

A^5 is CR^5 or N;

A^6 is CR^6 or N;

A^8 is CR^8 or N, provided no more than one of A^4, A^5, A^6 and A^8 is N;

each of R^a and R^b, independently, is H, F, CH_3, CH_2F, CHF_2 or CF_3;

each of R^1 and R^2, independently, is H, F, CH_3, CH_2OCH_3, CH_2F, CHF_2 or CF_3;

R^3 is C_{1-4}alkyl, C_{1-4}haloalkyl, CH_2OH, CH_2OCHF_2 or cyclopropyl; and

each of R^4, R^5, R^6 and R^8, independently, is H, F, Cl, CF_2H, CH_2F, CF_3, OCF_3, methyl, ethyl, CN, OH, OCH_3, SCH_3, $NHCH_3$ or $C(O)CH_3$.

20. The compound according to any one of Claims 1, 4-10, 18, or 19, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein

A^4 is CR^4;

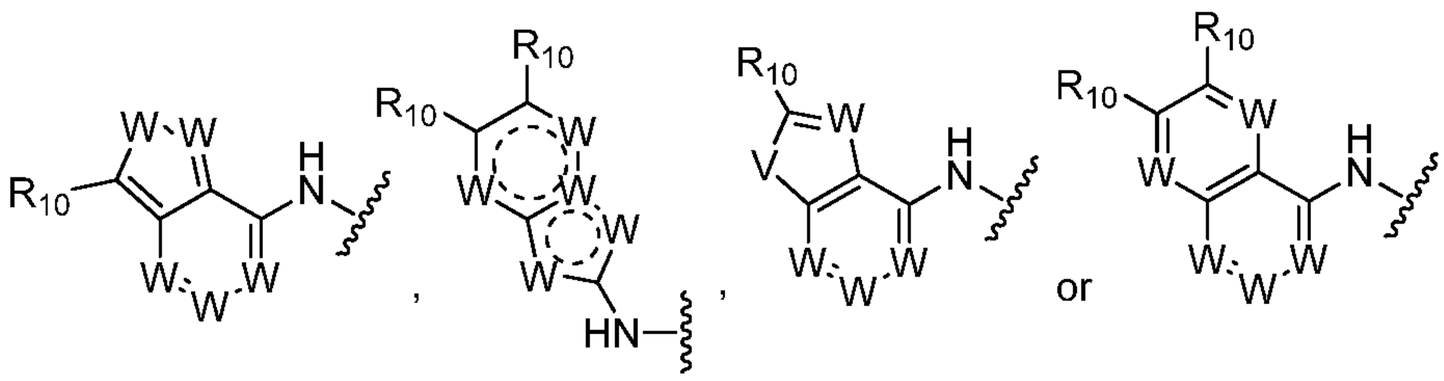
A^5 is CR^5;

A^6 is CR^6; and

A^8 is CR^8; wherein each of R^4, R^5, R^6 and R^8, independently, is H, F, CF_3, CF_2H, CH_2F or CH_3;

R^3 is CH_3, CF_3, CH_2F or CHF_2; and

R^7 is -NH-C(=O)-R^9 or

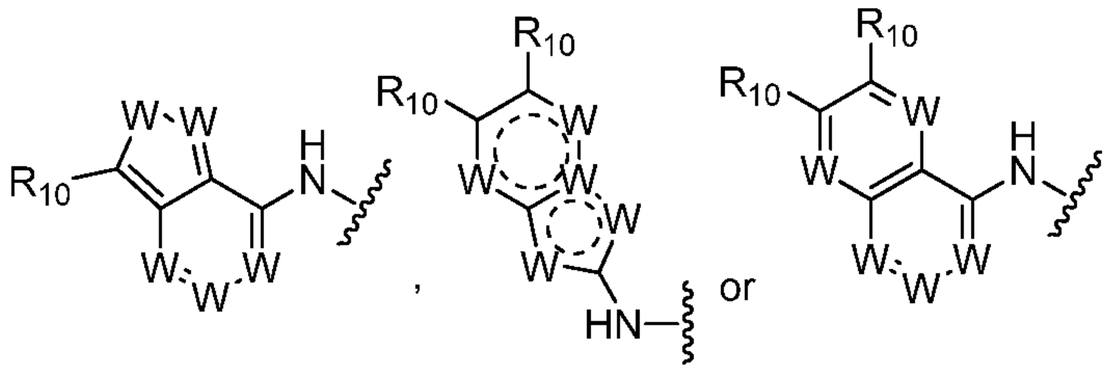


wherein V is NR^{10}, O or S; and

each W, independently, is CH, CF, CCl or N.

21. The compound according to any one of Claims 17-19, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R^7 is -NH-C(=O)-R^9.

22. The compound according to any one of Claims 18-20, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R^7 is

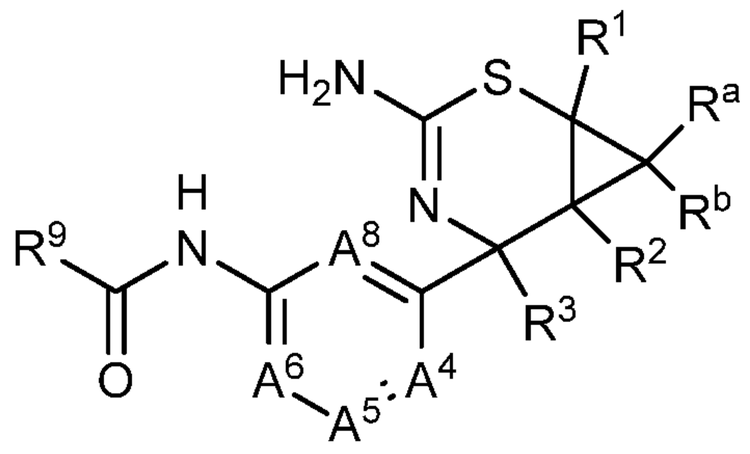


wherein V is NR^{10}, O or S; and

each W, independently, is CH, CF, CCl, CCH_3 or N.

23. The compound according to any one of Claims 18-22, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein each of R^1 and R^2, independently, is H, F, CH_2OCH_3 or CF_3; and each of R^a and R^b, independently, is H or F.

24. The compound according to any one of Claims 1, 4-15, 18, 19, 20, or 21, or a stereoisomer or pharmaceutically acceptable salt thereof, having a Formula I-A



I-A

wherein

A^4 is CR^4 or N;

A^5 is CR^5 or N;

A^6 is CR^6 or N;

A^8 is CR^8 or N, provided that no more than one of A^4, A^5, A^6 and A^8 is N;

each of R^a and R^b, independently, is H, F, Cl, C_{1-6}-alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, CN, $-CH_2OC_{1-6}$-alkyl, $-OC_{1-6}$-alkyl, $-S(O)_oC_{1-6}$-alkyl, $-NHC_{1-6}$-alkyl or $-C(O)C_{1-6}$-alkyl, wherein each of the C_{1-6}-alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, and C_{1-6}-alkyl

portion of -CH_2OC_{1-6}-alkyl, -OC_{1-6}-alkyl, -$S(O)_oC_{1-6}$-alkyl, -NHC_{1-6}-alkyl and -$C(O)C_{1-6}$-alkyl are optionally substituted with 1-4 substituents of F, oxo or OH;

each of R^1 and R^2, independently, is H, F, Cl, C_{1-6}-alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, CN, -CH_2OC_{1-6}-alkyl, -OC_{1-6}-alkyl, -$S(O)_oC_{1-6}$-alkyl, -NHC_{1-6}-alkyl, -$C(O)NH_2$, -$CH=CHC(O)NHC_{1-6}$-alkyl, -$CH=CHC(O)_2H$, -$CH=CHCH_2OH$, C_{1-6}-alkyl-$C(O)NHC_{1-6}$-alkyl, $C(O)C_{1-6}$-alkyl or -$C(O)C_{1-6}$-alkenyl, wherein each of the C_{1-6}-alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, and C_{1-6}-alkyl portion of -CH_2OC_{1-6}-alkyl, -OC_{1-6}-alkyl, -$S(O)_oC_{1-6}$-alkyl, -NHC_{1-6}-alkyl, $C(O)C_{1-6}$-alkyl, -$C(O)C_{1-6}$-alkenyl, -$CH=CHC(O)NHC_{1-6}$-alkyl and C_{1-6}-alkyl-$C(O)NHC_{1-6}$-alkyl, are optionally substituted with 1-4 substituents of F, CN, oxo or OH;

R^3 is C_{1-4}alkyl, CH_2OC_{1-4}alkyl, CH_2OH, C_{1-4}haloalkyl or cyclopropyl, wherein each of the C_{1-4}alkyl, CH_2OC_{1-4}alkyl, C_{1-4}haloalkyl and cyclopropyl is optionally substituted with 1-4 F atoms;

each of R^4, R^5, R^6 and R^8, independently, is H, F, Cl or CH_3;

R^9 is a fully or partially unsaturated 3-, 4-, 5-, 6- or 7-membered monocyclic or 8-, 9- or 10-membered bicyclic ring formed of carbon atoms, said ring optionally including 1-4 heteroatoms if monocyclic or 1-5 heteroatoms if bicyclic, said heteroatoms selected from O, N or S, wherein the ring is optionally substituted, independently, with 1-5 substituents of R^{10};

each R^{10}, independently, is H, halo, haloalkyl, CN, OH, NO_2, NH_2, SF_5, acetyl, -$C(O)NHCH_3$, oxo, cyclopropylmethoxy, 2-propynyloxy, 2-butynyloxy, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkylamino-, C_{1-6}dialkylamino-, C_{1-6}alkoxyl, C_{1-6}thioalkoxyl, morpholinyl, pyrazolyl, isoxazolyl, dihydropyranyl, pyrrolyl, pyrrolidinyl, tetrahydropyrrolyl, piperazinyl, oxetan-3-yl, imidazo-pyridinyl or dioxolyl, wherein each of the cyclopropylmethoxy, 2-propynyloxy, 2-butynyloxy, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkylamino-, C_{1-6}dialkylamino-, C_{1-6}alkoxyl, C_{1-6}thioalkoxyl, morpholinyl, pyrazolyl, isoxazolyl, dihydropyranyl, pyrrolidinyl, oxetan-3-yl or dioxolyl, is optionally substituted independently with 1-5 substituents of F, Cl, CN, NO_2, NH_2, OH, oxo, CF_3, CHF_2, CH_2F, methyl, methoxy, ethyl, ethoxy, CH_2CF_3, CH_2CHF_2, propyl, propoxy, isopropyl, isopropoxy, cyclopropyl, butyl, butoxyl, cyclobutyl, isobutoxy, *tert*-butoxy, isobutyl, sec-butyl, *tert*-butyl, cyclopentyl, cyclohexyl, C_{1-3}alkylamino-, C_{1-3}dialkylamino, C_{1-3}thioalkoxyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, thienyl, furyl, pyrrolyl, tetrahydropyranyl, tetrahydropyrrolyl or oxetan-3yl; and

the subscript o is selected from 0, 1, or 2.

25. The compound according to any one of Claims 1, 4-6, 11-22, or 24, or a stereoisomer, tautomer or pharmaceutically acceptable salt thereof, wherein

A^4 is CR^4;

A^5 is CR^5;

A^6 is CR^6;

A^8 is CR^8; wherein each of R^4, R^5, R^6 and R^8, independently, is H, F, Cl, CF_2H, CH_2F, CF_3, OCF_3, methyl, ethyl, CN, OH, OCH_3, SCH_3, $NHCH_3$ or $C(O)CH_3$;

each of R^a and R^b, independently, is H, F, CH_3, CH_2F, CHF_2 or CF_3;

each of R^1 and R^2, independently, is H, F, CH_3, CH_2OCH_3, CH_2F, CHF_2 or CF_3;

R^3 is CH_3, C_2H_5, CF_2H or CH_2F;

R^9 is a fully or partially unsaturated 3-, 4-, 5-, 6- or 7-membered monocyclic or 8-, 9- or 10-membered bicyclic ring formed of carbon atoms, said ring optionally including 1-4 heteroatoms if monocyclic or 1-5 heteroatoms if bicyclic, said heteroatoms selected from O, N or S, wherein the ring is optionally substituted, independently, with 1-5 substituents of R^{10}; and

each R^{10}, independently, is H, halo, haloalkyl, CN, OH, NO_2, NH_2, SF_5, acetyl, $-C(O)NHCH_3$, oxo, cyclopropylmethoxy, 2-propynyloxy, 2-butynyloxy, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkylamino-, C_{1-6}dialkylamino-, C_{1-6}alkoxyl, C_{1-6}thioalkoxyl, morpholinyl, pyrazolyl, isoxazolyl, dihydropyranyl, pyrrolyl, pyrrolidinyl, tetrahydropyrrolyl, piperazinyl, oxetan-3-yl, imidazo-pyridinyl or dioxolyl, wherein each of the cyclopropylmethoxy, 2-propynyloxy, 2-butynyloxy, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkylamino-, C_{1-6}dialkylamino-, C_{1-6}alkoxyl, C_{1-6}thioalkoxyl, morpholinyl, pyrazolyl, isoxazolyl, dihydropyranyl, pyrrolidinyl, oxetan-3-yl or dioxolyl, is optionally substituted independently with 1-5 substituents of F, Cl, CN, NO_2, NH_2, OH, oxo, CF_3, CHF_2, CH_2F, methyl, methoxy, ethyl, ethoxy, CH_2CF_3, CH_2CHF_2, propyl, propoxy, isopropyl, isopropoxy, cyclopropyl, butyl, butoxyl, cyclobutyl, isobutoxy, *tert*-butoxy, isobutyl, sec-butyl, *tert*-butyl, cyclopentyl, cyclohexyl, C_{1-3}alkylamino-, C_{1-3}dialkylamino, C_{1-3}thioalkoxyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, thienyl, furyl, pyrrolyl, tetrahydropyranyl, tetrahydropyrrolyl or oxetan-3yl.

26. The compound according to any one of Claims 1, 4-21, 24, or 25, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein

A^4 is CR^4 or N;

A^5 is CR^5 or N;

A^6 is CR^6 or N;

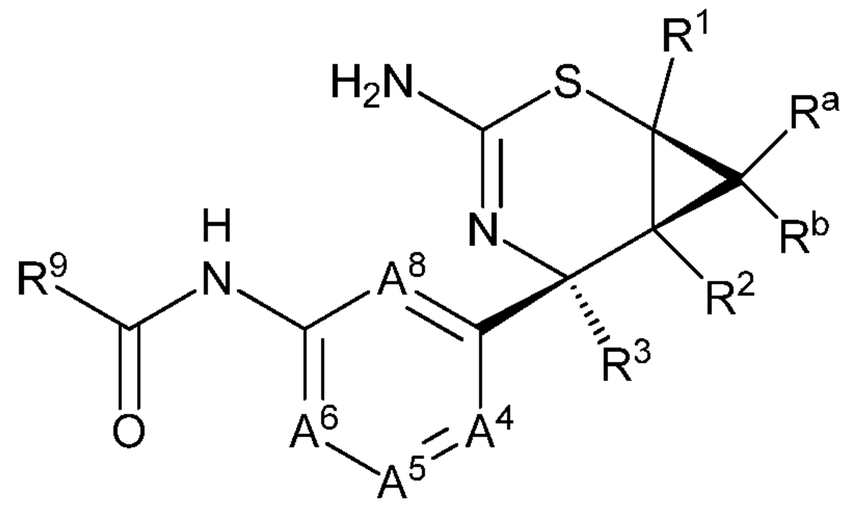
A^8 is CR^8 or N, wherein each of R^4, R^5, R^6 and R^8, independently, is H, F, Cl or CH_3, provided no more than one of A^4, A^5, A^6 and A^8 is N;

each of R^1 and R^2, independently, is H, F, CH_2OCH_3 or CF_3;

each of R^a and R^b, independently, is H or F; and

R^3 is CF_3, CH_3, CF_2H or CH_2F.

27. The compound according to any one of Claims 1, 4-15, 18-21, 24, 25, or 26, or a stereoisomer or pharmaceutically acceptable salt thereof, having a Formula II-A



II-A

wherein

A^4 is CR^4, wherein R^4 is H, F or Cl;

A^5 is CR^5 or N, wherein R^5 is H, F, Cl or CH_3;

A^6 is CH;

A^8 is CR^8 or N, wherein R^8 is H or F,

provided that no more than one of A^5 and A^8 is N;

each of R^1 and R^2, independently, is H, F, CH_2OCH_3 or CF_3;

each of R^a and R^b, independently, is H or F;

R^3 is CH_3, CF_3, CH_2F or CHF_2;

R^9 is a fully unsaturated 5- or 6-membered monocyclic or 8-, 9- or 10-membered bicyclic ring formed of carbon atoms, said ring optionally including 1-4 heteroatoms if monocyclic or 1-5 heteroatoms if bicyclic, said heteroatoms selected from O, N or S, wherein the ring is optionally substituted, independently, with 1-5 substituents of R^{10}; and

each R^{10}, independently, is H, halo, haloalkyl, CN, OH, NO_2, NH_2, SF_5, acetyl, -C(O)$NHCH_3$, oxo, cyclopropylmethoxy, 2-propynyloxy, 2-butynyloxy, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkylamino-, C_{1-6}dialkylamino-, C_{1-6}alkoxyl, C_{1-6}thioalkoxyl, morpholinyl, pyrazolyl, isoxazolyl, dihydropyranyl, pyrrolyl, pyrrolidinyl, tetrahydropyrrolyl, piperazinyl, oxetan-3-yl, imidazo-pyridinyl or dioxolyl, wherein each of the cyclopropylmethoxy, 2-propynyloxy, 2-butynyloxy, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkylamino-, C_{1-6}dialkylamino-, C_{1-6}alkoxyl, C_{1-6}thioalkoxyl, morpholinyl, pyrazolyl, isoxazolyl, dihydropyranyl, pyrrolidinyl, oxetan-3-yl or dioxolyl, is optionally substituted independently with 1-5 substituents of F, Cl, CN, NO_2, NH_2, OH, oxo, CF_3, CHF_2, CH_2F, methyl, methoxy, ethyl, ethoxy, CH_2CF_3, CH_2CHF_2, propyl, propoxy, isopropyl, isopropoxy, cyclopropyl, butyl, butoxyl, cyclobutyl, isobutoxy, *tert*-butoxy, isobutyl, sec-butyl, *tert*-butyl, cyclopentyl, cyclohexyl, C_{1-3}alkylamino-, C_{1-3}dialkylamino, C_{1-3}thioalkoxyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, thienyl, furyl, pyrrolyl, tetrahydropyranyl, tetrahydropyrrolyl or oxetan-3yl.

28. The compound according to Claim 27, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein each of R^a, R^b, R^1 and R^2, independently, is H.

29. The compound according any one of Claims 27 or 28, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R^3 is CH_3, CH_2F or CHF_2.

30. The compound according to any one of Claims 27-29, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R^3 is CH_2F or CHF_2.

31. The compound according to any one of Claims 27-30, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R^3 is CH_2F.

32. The compound according to any one of Claims 27-30, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R^3 is CHF_2.

33. The compound according to any one of Claims 27-32, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein

A^4 is CF or CCl;

A^5 is CH, CF, CH_3 or N;

A^6 is CH; and

A^8 is CH.

34. The compound according to any one of Claims 27-33, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein

A^4 is CF;

A^5 is CH, CF or N;

A^6 is CH; and

A^8 is CH.

35. The compound according to any one of Claims 27-33, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein

A^4 is CCl;

A^5 is CH or CF;

A^6 is CH; and

A^8 is CH.

36. The compound according to any one of Claims 27-35, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein

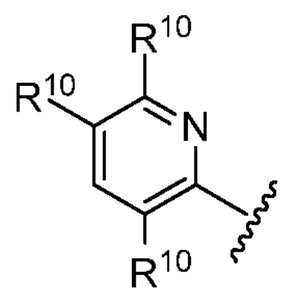
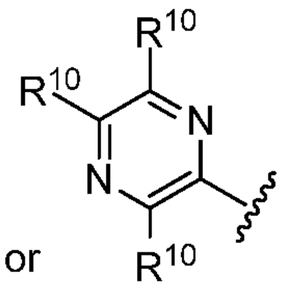
R^9 is a ring selected from phenyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, pyrazolyl, pyrazolo[3,4-c]pyridinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl or thienyl, wherein the ring is optionally substituted with 1-5 substituents of R^{10}; and

each R^{10}, independently, is H, halo, haloalkyl, CN, OH, NO_2, NH_2, SF_5, acetyl, -C(O)$NHCH_3$, oxo, cyclopropylmethoxy, 2-propynyloxy, 2-butynyloxy, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkylamino-, C_{1-6}dialkylamino-, C_{1-6}alkoxyl, C_{1-6}thioalkoxyl, morpholinyl, pyrazolyl, isoxazolyl, dihydropyranyl, pyrrolyl, pyrrolidinyl, tetrahydropyrrolyl, piperazinyl, oxetan-3-yl, imidazo-pyridinyl or dioxolyl, wherein each of the cyclopropylmethoxy, 2-propynyloxy, 2-butynyloxy, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkylamino-, C_{1-6}dialkylamino-, C_{1-6}alkoxyl, C_{1-6}thioalkoxyl, morpholinyl, pyrazolyl, isoxazolyl, dihydropyranyl, pyrrolidinyl, oxetan-3-yl or dioxolyl, is optionally substituted independently with 1-5 substituents of F, Cl, CN, NO_2, NH_2, OH, oxo, CF_3, CHF_2, CH_2F, methyl, methoxy, ethyl, ethoxy, CH_2CF_3, CH_2CHF_2, propyl, propoxy, isopropyl, isopropoxy, cyclopropyl, butyl, butoxyl,

cyclobutyl, isobutoxy, *tert*-butoxy, isobutyl, sec-butyl, *tert*-butyl, cyclopentyl, cyclohexyl, C_{1-3}alkylamino-, C_{1-3}dialkylamino, C_{1-3}thioalkoxyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, thienyl, furyl, pyrrolyl, tetrahydropyranyl, tetrahydropyrrolyl or oxetan-3yl.

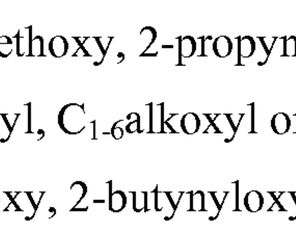
37. The compound according to any one of Claims 27-35, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R^9 is a ring selected from pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, pyrazolyl, pyrazolo[3,4-c]pyridinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl or thienyl, wherein the ring is optionally substituted with 1-5 substituents of R^{10}.

38. The compound according to any one of Claims 27-37 or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R^9 is


or

; and

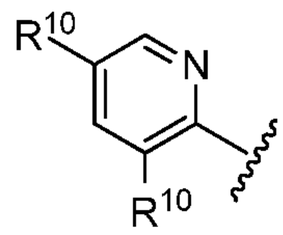
each R^{10}, independently, is H, F, Cl, Br, CF_3, CHF_2, CH_2F, CN, OH, -C(O)NHCH$_3$, cyclopropylmethoxy, 2-propynyloxy, 2-butynyloxy, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkoxyl or C_{1-6}thioalkoxyl, wherein each of the cyclopropylmethoxy, 2-propynyloxy, 2-butynyloxy, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkoxyl and C_{1-6}thioalkoxyl is optionally substituted independently with 1-5 substituents of F, Cl, CN, NO_2, NH_2, OH, oxo, CF_3, CHF_2, CH_2F, methyl, methoxy, ethyl, ethoxy, CH_2CF_3, CH_2CHF_2, propyl, propoxy, isopropyl, isopropoxy, cyclopropyl, butyl, butoxyl, cyclobutyl, isobutoxy, *tert*-butoxy, isobutyl, sec-butyl, *tert*-butyl, C_{1-3}alkylamino-, C_{1-3}dialkylamino, C_{1-3}thioalkoxyl, oxazolyl or thiazolyl.

39. The compound according to any one of Claims 27-38, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R^3 is CHF_2; R^9 is


; and

each R^{10}, independently, is H, F, Cl, Br, CH_3, CHF_2, CH_2F, CN, 2-propynyloxy, 2-butynyloxy or C_{1-2}alkoxyl, wherein the C_{1-2}alkoxyl is optionally substituted independently with 1-5 substituents of F, Cl, methyl, methoxy, ethyl, ethoxy, oxazolyl or thiazolyl.

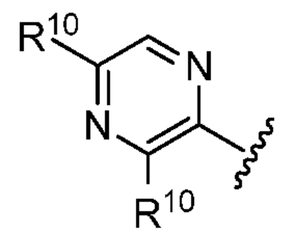
40. The compound according to any one of Claims 27-38, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R^3 is CH_2F; R^9 is



; and

each R^{10}, independently, is H, F, Cl, Br, CH_3, CHF_2, CH_2F, CN, 2-propynyloxy, 2-butynyloxy or C_{1-2}alkoxyl, wherein the C_{1-2}alkoxyl is optionally substituted independently with 1-5 substituents of F, Cl, methyl, methoxy, ethyl, ethoxy, oxazolyl or thiazolyl.

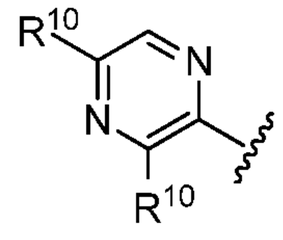
41. The compound according to any one of Claims 27-38, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R^3 is CHF_2; R^9 is



; and

each R^{10}, independently, is H, F, Cl, Br, CH_3, CHF_2, CH_2F, CN, 2-propynyloxy, 2-butynyloxy or C_{1-2}alkoxyl, wherein the C_{1-2}alkoxyl is optionally substituted independently with 1-5 substituents of F, Cl, methyl, methoxy, ethyl, ethoxy, oxazolyl or thiazolyl.

42. The compound according to any one of Claims 27-38, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R^3 is CH_2F; R^9 is

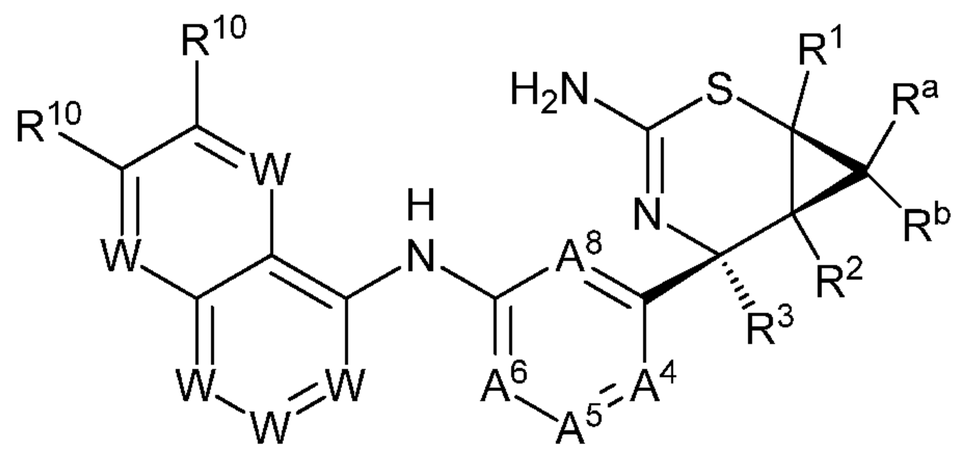


; and

each R^{10}, independently, is H, F, Cl, Br, CH_3, CHF_2, CH_2F, CN, 2-propynyloxy, 2-butynyloxy or C_{1-2}alkoxyl, wherein the C_{1-2}alkoxyl is optionally substituted

independently with 1-5 substituents of F, Cl, methyl, methoxy, ethyl, ethoxy, oxazolyl or thiazolyl.

43. The compound according to any one of Claims 1, 4-14, 16-20, 22, or 23, or a stereoisomer, tautomer, hydrate, solvate or pharmaceutically acceptable salt thereof, having a Formula II-B:



II-B

wherein

A^4 is CR^4, wherein R^4 is H, F or Cl;

A^5 is CR^5 or N, wherein R^5 is H, F, Cl or CH_3;

A^6 is CH;

A^8 is CR^8 or N, wherein R^8 is H or F,

provided that no more than one of A^5 and A^8 is N;

each of R^1 and R^2, independently, is H, F, CH_2OCH_3 or CF_3;

each of R^a and R^b, independently, is H or F;

R^3 is CH_3, CF_3, CH_2F or CHF_2;

R^9 is a fully unsaturated 5- or 6-membered monocyclic or 8-, 9- or 10-membered bicyclic ring formed of carbon atoms, said ring optionally including 1-4 heteroatoms if monocyclic or 1-5 heteroatoms if bicyclic, said heteroatoms selected from O, N or S, wherein the ring is optionally substituted, independently, with 1-5 substituents of R^{10};

each R^{10}, independently, is H, halo, haloalkyl, CN, OH, NO_2, NH_2, SF_5, acetyl, $-C(O)NHCH_3$, oxo, cyclopropylmethoxy, 2-propynyloxy, 2-butynyloxy, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkylamino-, C_{1-6}dialkylamino-, C_{1-6}alkoxyl, C_{1-6}thioalkoxyl, morpholinyl, pyrazolyl, isoxazolyl, dihydropyranyl, pyrrolyl, pyrrolidinyl, tetrahydropyrrolyl, piperazinyl, oxetan-3-yl, imidazo-pyridinyl or dioxolyl, wherein each of the cyclopropylmethoxy, 2-propynyloxy, 2-butynyloxy, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkylamino-, C_{1-6}dialkylamino-, C_{1-6}alkoxyl, C_{1-6}thioalkoxyl, morpholinyl, pyrazolyl, isoxazolyl, dihydropyranyl, pyrrolidinyl, oxetan-3-

yl or dioxolyl, is optionally substituted independently with 1-5 substituents of F, Cl, CN, NO_2, NH_2, OH, oxo, CF_3, CHF_2, CH_2F, methyl, methoxy, ethyl, ethoxy, CH_2CF_3, CH_2CHF_2, propyl, propoxy, isopropyl, isopropoxy, cyclopropyl, butyl, butoxyl, cyclobutyl, isobutoxy, *tert*-butoxy, isobutyl, sec-butyl, *tert*-butyl, cyclopentyl, cyclohexyl, C_{1-3}alkylamino-, C_{1-3}dialkylamino, C_{1-3}thioalkoxyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, thienyl, furyl, pyrrolyl, tetrahydropyranyl, tetrahydropyrrolyl or oxetan-3yl; and

each W, independently, is CH, CF, CCl, CCH_3 or N.

44. The compound according to Claim 43, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein each of R^a, R^b, R^1 and R^2, independently, is H.

45. The compound according any one of Claims 43 or 44, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R^3 is CH_3, CH_2F or CHF_2.

46. The compound according to any one of Claims 43-45, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R^3 is CH_2F or CHF_2.

47. The compound according to any one of Claims 43-46, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein R^3 is CH_2F.

48. The compound according to any one of Claims 43-47, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein

A^4 is CF or CCl;

A^5 is CH, CF, CH_3 or N;

A^6 is CH; and

A^8 is CH.

49. The compound according to any one of Claims 43-47, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein

A^4 is CF;

A^5 is CH, CF or N;

A^6 is CH; and

A^8 is CH.

50. The compound according to any one of Claims 43-47, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein

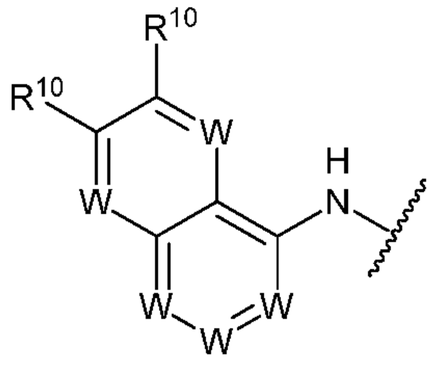
A^4 is CCl;

A^5 is CH, CF, CCl or CCH_3;

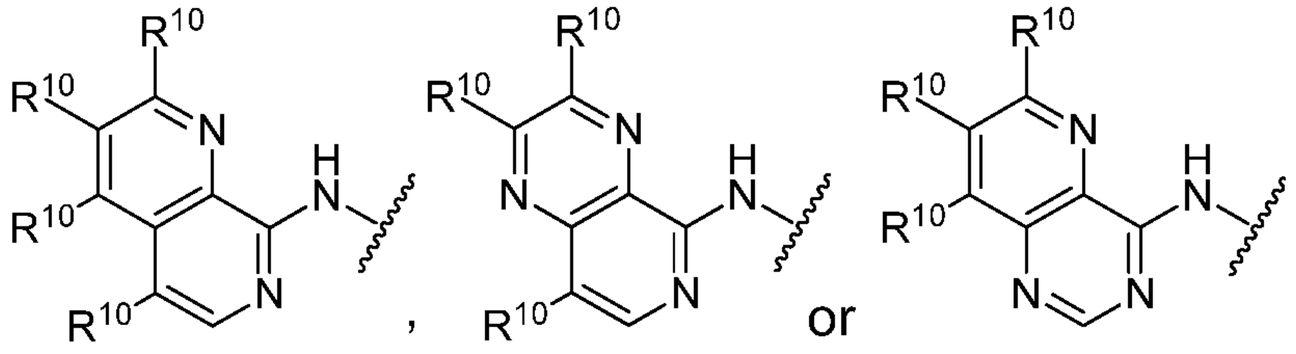
A^6 is CH; and

A^8 is CH.

51. The compound according to any one of Claims 43-50 or a stereoisomer or pharmaceutically acceptable salt thereof, wherein



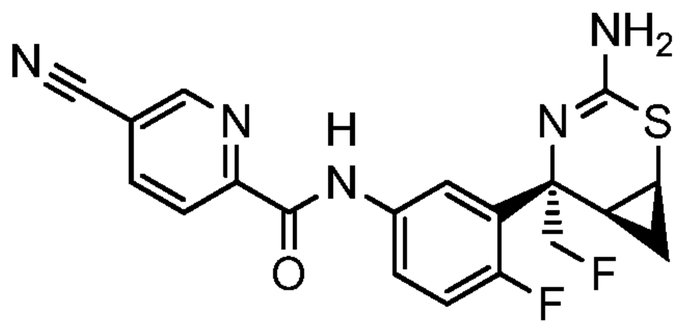
is



, , or ; and

each R^{10}, independently, is H, F, Cl, Br, CH_3, CHF_2, CH_2F, CN, 2-propynyloxy, 2-butynyloxy or C_{1-2}alkoxyl, wherein the C_{1-2}alkoxyl is optionally substituted independently with 1-5 substituents of F, Cl, methyl, methoxy, ethyl, ethoxy, oxazolyl or thiazolyl.

52. The compound of Claim 1 or Claim 4, or a stereoisomer or pharmaceutically acceptable salt thereof, selected from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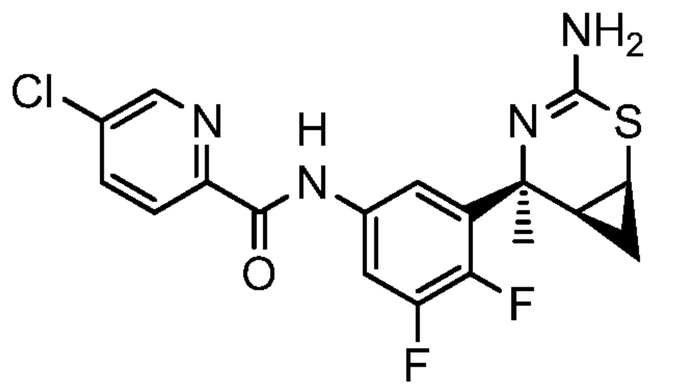
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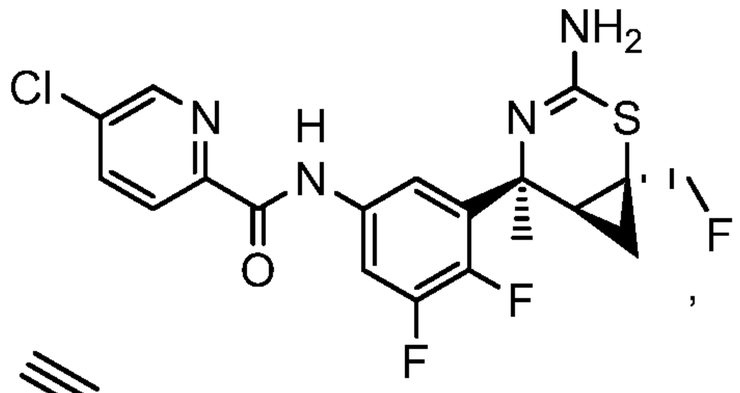
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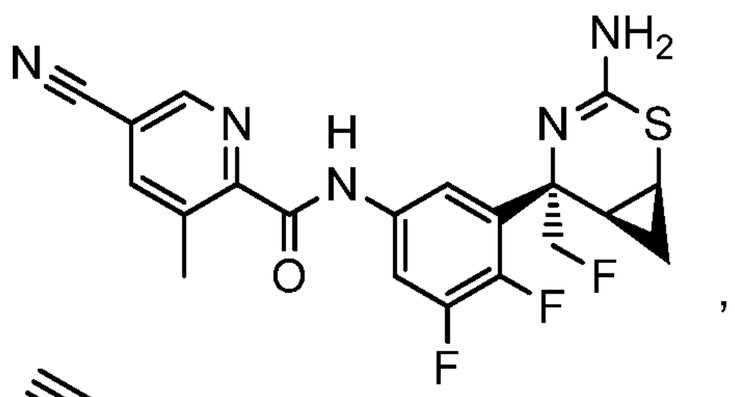
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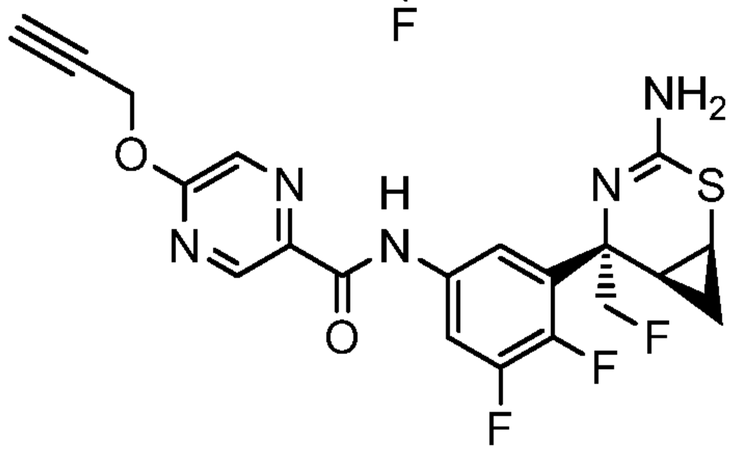
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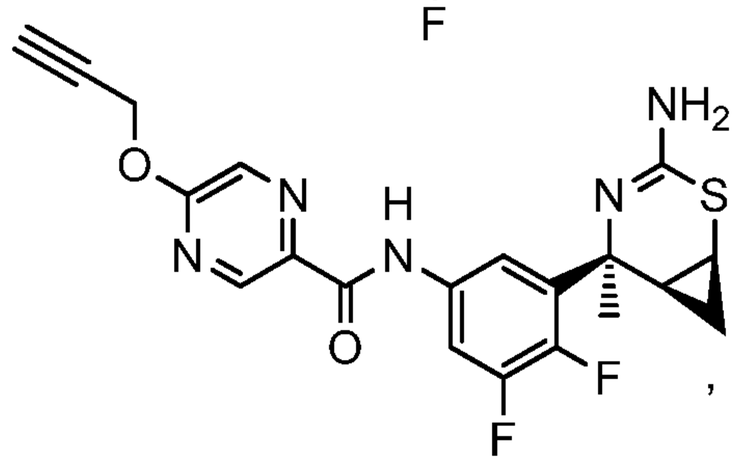
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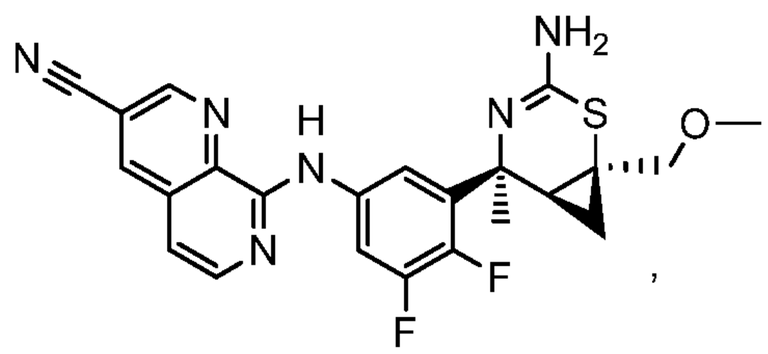
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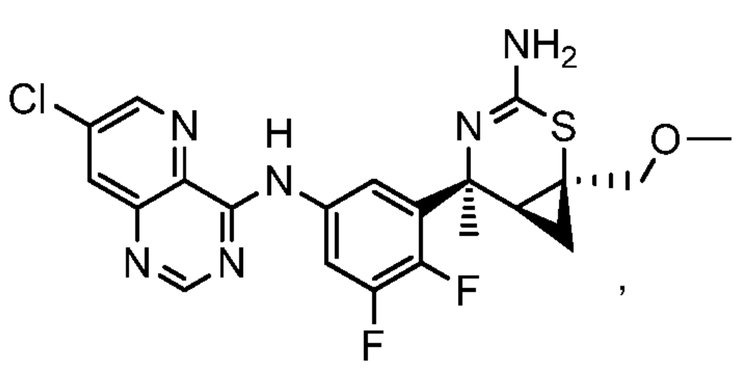
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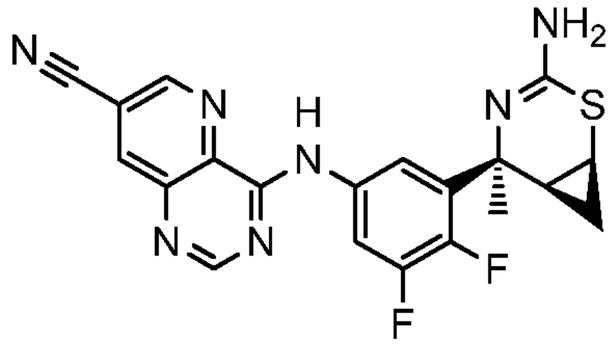
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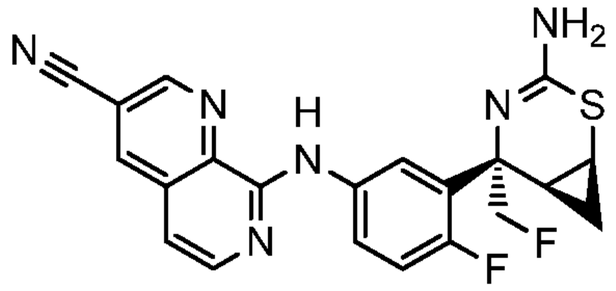
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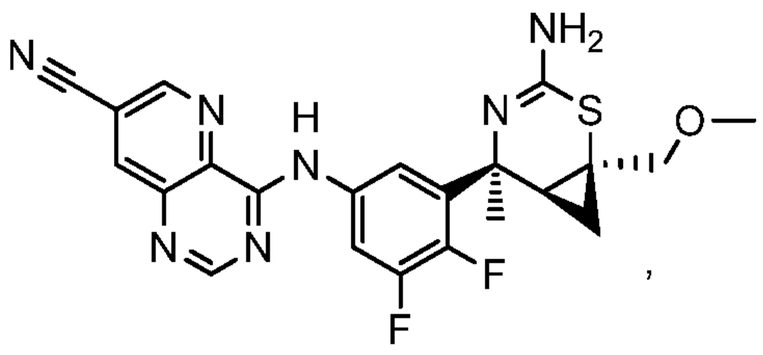
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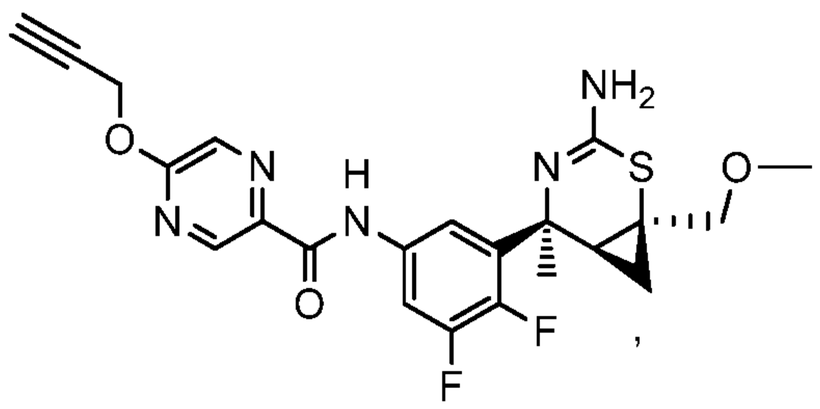
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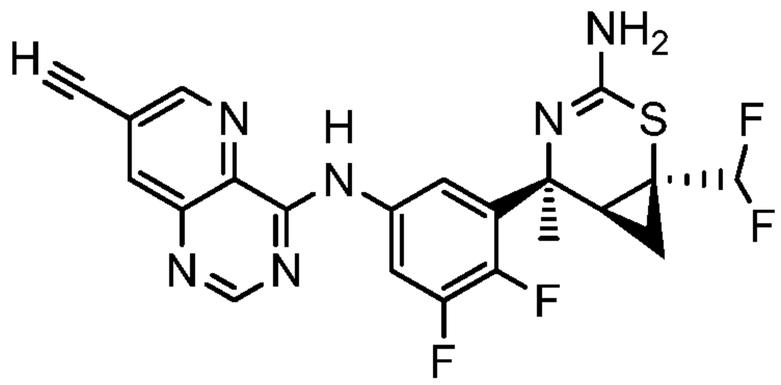

or .

53. The compound of Claim 1 or Claim 4, or a tautomer or pharmaceutically acceptable salt thereof, selected from

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-cyano-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-cyano-3-methyl-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-methoxy-2-pyrazinecarboxamide; and

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-chloro-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-chloro-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-cyano-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-chloro-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-cyano-3-methyl-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

8-((3-((1S,5S,6S)-3-amino-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)amino)-1,7-naphthyridine-3-carbonitrile;

N-(3-((1S,5S,6S)-3-amino-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

8-((3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)amino)-1,7-naphthyridine-3-carbonitrile;

4-((3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)amino)pyrido[3,2-d]pyrimidine-7-carbonitrile;

8-((3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)amino)-1,7-naphthyridine-3-carbonitrile;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-7-chloropyrido[3,2-d]pyrimidin-4-amine;

4-((3-((1S,5S,6S)-3-amino-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)amino)pyrido[3,2-d]pyrimidine-7-carbonitrile;

8-((3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)amino)-1,7-naphthyridine-3-carbonitrile;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-7-chloropyrido[3,2-d]pyrimidin-4-amine;

4-((3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo [4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)amino)pyrido[3,2-d]pyrimidine-7-carbonitrile;

((1S,5S,6S)-3-amino-5-(5-((7-chloropyrido[3,2-d]pyrimidin-4-yl)amino)-2-fluorophenyl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)methanol;

4-((3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)amino)pyrido[3,2-d]pyrimidine-7-carbonitrile;

((1S,5S,6S)-3-amino-5-(fluoromethyl)-5-(2-fluoro-5-((3-(2-propyn-1-yloxy)-1,7-naphthyridin-8-yl)amino)phenyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)methanol;

8-((3-((1S,5S,6S)-3-amino-1-(hydroxymethyl)-5-methyl-2-thia-4-azabicyclo [4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)amino)-1,7-naphthyridine-3-carbonitrile;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-2-(1,3-oxazol-2-ylmethoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo [4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

((1S,5S,6S)-3-amino-5-(2,3-difluoro-5-((2-(2-propyn-1-yloxy)pyrido[3,4-b] pyrazin-5-yl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)methanol;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-methyl-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide; or

4-((3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo [4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)amino)pyrido[3,2-d]pyrimidine-7-carbonitrile.

54. The compound of Claim 1, or a tautomer or pharmaceutically acceptable salt thereof, selected from

N-(5-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoro-3-pyridinyl)-2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-amine;

N-(5-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoro-3-pyridinyl)-2-(1,3-oxazol-2-ylmethoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(5-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoro-3-pyridinyl)-3-methyl-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

8-((5-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoro-3-pyridinyl)amino)-1,7-naphthyridine-3-carbonitrile;

N-(5-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoro-3-pyridinyl)-7-(1,3-oxazol-2-ylmethoxy)pyrido[3,2-d]pyrimidin-4-amine;

N-(5-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoro-3-pyridinyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

N-(5-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoro-3-pyridinyl)-5-(1,3-oxazol-2-ylmethoxy)-2-pyrazinecarboxamide;

((1R,5S,6S)-3-amino-5-(2-fluoro-5-((7-(1,3-oxazol-2-ylmethoxy)pyrido[3,2-d]pyrimidin-4-yl)amino)-3-pyridinyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)acetonitrile;

N-(5-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoro-3-pyridinyl)-5-(2,2,3,3-tetrafluoropropoxy)-2-pyridinecarboxamide;

N-(5-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoro-3-pyridinyl)-5-(2,2,3,3-tetrafluoropropoxy)-2-pyrazinecarboxamide;

N-(5-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-methoxy-3-pyridinyl)-2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-amine;

N-(5-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-methoxy-3-pyridinyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

N-(5-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoro-3-pyridinyl)-2-((~2~H_5_)-2-butyn-1-yloxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-methyl-5-(2,2,2-trifluoroethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-methyl-5-(2,2,2-trifluoroethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-methyl-5-(((1S)-1-methyl-2-propyn-1-yl)oxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-methyl-5-(((1S)-1-methyl-2-propyn-1-yl)oxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-methyl-5-(2,2,2-trifluoroethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3-methyl-5-(((1S)-1-methyl-2-propyn-1-yl)oxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3-methyl-5-(2,2,2-trifluoroethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3-methyl-5-(((1S)-1-methyl-2-propyn-1-yl)oxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-methyl-5-(((1S)-1-methyl-2-propyn-1-yl)oxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3-methyl-5-(2,2,2-trifluoroethoxy)-2-pyrazinecarboxamide;

N-(5-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-methoxy-3-pyridinyl)-5-chloro-2-pyridinecarboxamide;

N-(5-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-methoxy-3-pyridinyl)-7-(2-propyn-1-yloxy)pyrido[3,2-d]pyrimidin-4-amine;

N-(5-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-methoxy-3-pyridinyl)-2-(1,3-oxazol-2-ylmethoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-(1,3-oxazol-4-ylmethoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-methoxy-1,7-naphthyridin-8-amine;

N-(3-((1R,5S,6S)-3-amino-5-methyl-1-(methylsulfonyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-(1,3-oxazol-2-ylmethoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-5-methyl-1-(1-pyrrolidinylcarbonyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-5-methyl-1-(1-pyrrolidinylcarbonyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-5-methyl-1-(1-pyrrolidinylcarbonyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(2,2,2-trifluoroethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1,5-bis(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-2-(2-methoxyethoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-7-fluoropyrido[3,2-d]pyrimidin-4-amine;

N-(5-((1S,5S,6S)-3-amino-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoro-3-pyridinyl)-5-chloro-2-pyridinecarboxamide;

5-((5-((1S,5S,6S)-3-amino-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoro-3-pyridinyl)amino)pyrido[3,4-b]pyrazin-2(1H)-one;

N-(5-((1S,5S,6S)-3-amino-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoro-3-pyridinyl)-2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-amine;

N-(5-((1S,5S,6S)-3-amino-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoro-3-pyridinyl)-2-(1,3-oxazol-2-ylmethoxy)pyrido[3,4-b]pyrazin-5-amine;

8-((5-((1S,5S,6S)-3-amino-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoro-3-pyridinyl)amino)-1,7-naphthyridine-3-carbonitrile;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3-methyl-5-(1,3-oxazol-2-ylmethoxy)-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-methyl-5-(1,3-oxazol-2-ylmethoxy)-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3-methyl-5-(1,3-oxazol-2-ylmethoxy)-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-methyl-5-(1,3-oxazol-2-ylmethoxy)-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-methyl-5-(1,3-oxazol-2-ylmethoxy)-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-methyl-5-(((1S)-1-methyl-2-propyn-1-yl)oxy)-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3-methyl-5-(((1S)-1-methyl-2-propyn-1-yl)oxy)-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3-methyl-5-(((1S)-1-methyl-2-propyn-1-yl)oxy)-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-methyl-5-(((1S)-1-methyl-2-propyn-1-yl)oxy)-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3-methyl-5-(((1S)-1-methyl-2-propyn-1-yl)oxy)-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3-methyl-5-(1,3-oxazol-2-ylmethoxy)-2-pyridinecarboxamide;

N-(5-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoro-3-pyridinyl)-2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-amine;

N-(5-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoro-3-pyridinyl)-2-(1,3-oxazol-2-ylmethoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(5-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoro-3-pyridinyl)-5-chloro-2-pyridinecarboxamide;

8-((5-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoro-3-pyridinyl)amino)-N-(1-methylethyl)-1,7-naphthyridine-3-carboxamide;

8-((5-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoro-3-pyridinyl)amino)-1,7-naphthyridine-3-carbonitrile;

4-((5-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoro-3-pyridinyl)amino)pyrido[3,2-d]pyrimidine-7-carbonitrile;

(1R)-1-((1S,5S,6S)-3-amino-5-(2-fluoro-5-((2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-yl)amino)-3-pyridinyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)-2,2,2-trifluoroethanol;

(1S)-1-((1S,5S,6S)-3-amino-5-(2-fluoro-5-((2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-yl)amino)-3-pyridinyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)-2,2,2-trifluoroethanol;

((1S,5S,6R)-3-amino-7,7-difluoro-5-(2-fluoro-5-((2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-yl)amino)-3-pyridinyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)methanol;

((1S,5S,6S)-3-amino-5-(2-fluoro-5-((2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-yl)amino)-3-pyridinyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)methanol;

((1S,5S,6R)-3-amino-7,7-difluoro-5-(2-fluoro-5-((2-(1,3-oxazol-2-ylmethoxy)pyrido[3,4-b]pyrazin-5-yl)amino)-3-pyridinyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)methanol;

((1S,5S,6R)-3-amino-7,7-difluoro-5-(2-fluoro-5-((7-(1,3-oxazol-2-ylmethoxy)pyrido[3,2-d]pyrimidin-4-yl)amino)-3-pyridinyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)methanol;

(1R)-1-((1S,5S,6S)-3-amino-5-(2-fluoro-5-((7-(2-propyn-1-yloxy)pyrido[3,2-d]pyrimidin-4-yl)amino)-3-pyridinyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)-2,2,2-trifluoroethanol;

(1S)-1-((1S,5S,6S)-3-amino-5-(2-fluoro-5-((7-(2-propyn-1-yloxy)pyrido[3,2-d]pyrimidin-4-yl)amino)-3-pyridinyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)-2,2,2-trifluoroethanol;

(1R)-1-((1S,5S,6S)-3-amino-5-(2-fluoro-5-((7-(1,3-oxazol-2-ylmethoxy)pyrido[3,2-d]pyrimidin-4-yl)amino)-3-pyridinyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)-2,2,2-trifluoroethanol;

(1S)-1-((1S,5S,6S)-3-amino-5-(2-fluoro-5-((7-(1,3-oxazol-2-ylmethoxy)pyrido[3,2-d]pyrimidin-4-yl)amino)-3-pyridinyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)-2,2,2-trifluoroethanol;

((1S,5S,6R)-3-amino-7,7-difluoro-5-(2-fluoro-5-((3-(1,3-oxazol-2-ylmethoxy)-1,7-naphthyridin-8-yl)amino)-3-pyridinyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)methanol;

((1S,5S,6S)-3-amino-5-(2-fluoro-5-((7-(2-propyn-1-yloxy)pyrido[3,2-d]pyrimidin-4-yl)amino)-3-pyridinyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)methanol;

(1R)-1-((1S,5S,6S)-3-amino-5-(2-fluoro-5-((2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-yl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)-2,2,2-trifluoroethanol;

(1S)-1-((1S,5S,6S)-3-amino-5-(2-fluoro-5-((2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-yl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)-2,2,2-trifluoroethanol;

N-(3-((1S,5S,6S)-3-amino-5-methyl-1-((1R)-2,2,2-trifluoro-1-hydroxyethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-5-methyl-1-((1S)-2,2,2-trifluoro-1-hydroxyethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-methyl-5-(2,2,2-trifluoroethoxy)-2-pyridinecarboxamide;

N-(5-((1S,5S,6S)-3-amino-5-methyl-1-((1R)-2,2,2-trifluoro-1-methoxyethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoro-3-pyridinyl)-2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-amine;

N-(5-((1S,5S,6S)-3-amino-5-methyl-1-((1S)-2,2,2-trifluoro-1-methoxyethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoro-3-pyridinyl)-2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-methyl-5-(2,2,2-trifluoroethoxy)-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-methyl-5-(2,2,2-trifluoroethoxy)-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3-methyl-5-(2,2,2-trifluoroethoxy)-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3-methyl-5-(2,2,2-trifluoroethoxy)-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-methyl-5-(2-propyn-1-yloxy)-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3-methyl-5-(2-propyn-1-yloxy)-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-methyl-5-(2-propyn-1-yloxy)-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-methyl-5-(2-propyn-1-yloxy)-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3-methyl-5-(2-propyn-1-yloxy)-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-methyl-5-((1S)-1-(1,3-oxazol-2-yl)ethoxy)-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-methyl-5-((1R)-1-(1,3-oxazol-2-yl)ethoxy)-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3-methyl-5-(2,2,2-trifluoroethoxy)-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3-methyl-5-(2-propyn-1-yloxy)-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-chloro-5-(2-propyn-1-yloxy)-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(2,2,2-trifluoroethoxy)-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-chloro-5-(2,2,2-trifluoroethoxy)-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(2,2,2-trifluoroethoxy)-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(2,2,2-trifluoroethoxy)-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(2,2,2-trifluoroethoxy)-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(2,2,2-trifluoroethoxy)-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(2,2,2-trifluoroethoxy)-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-5-methyl-1-(1-pyrrolidinylcarbonyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(2,2,2-trifluoroethoxy)-2-pyridinecarboxamide;

(1S,5S,6S)-3-amino-5-(2,3-difluoro-5-(((5-(2,2,2-trifluoroethoxy)-2-pyridinyl)carbonyl)amino)phenyl)-N,5-dimethyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-5-(2,3-difluoro-5-(((5-(2,2,2-trifluoroethoxy)-2-pyrazinyl)carbonyl)amino)phenyl)-N,5-dimethyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-5-(2,3-difluoro-5-(((3-methyl-5-(2,2,2-trifluoroethoxy)-2-pyridinyl)carbonyl)amino)phenyl)-N,5-dimethyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

4-((3-((1S,5S,6R)-3-amino-7,7-difluoro-1-(hydroxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)amino)pyrido[3,2-d]pyrimidine-7-carbonitrile;

N-(3-((1S,5S,6R)-3-amino-7,7-difluoro-1-(hydroxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide;

((1S,5S,6R)-3-amino-7,7-difluoro-5-(2-fluoro-5-((2-(1,3-oxazol-2-ylmethoxy)pyrido[3,4-b]pyrazin-5-yl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)methanol;

((1S,5S,6R)-3-amino-7,7-difluoro-5-(2-fluoro-5-((2-(1,3-oxazol-4-ylmethoxy)pyrido[3,4-b]pyrazin-5-yl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)methanol;

((1S,5S,6R)-3-amino-7,7-difluoro-5-(2-fluoro-5-((2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-yl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)methanol;

N-(3-((1S,5S,6R)-3-amino-7,7-difluoro-1-(hydroxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(2,2,3,3-tetrafluoropropoxy)-2-pyrazinecarboxamide;

4-((3-((1S,5S,6R)-3-amino-7,7-difluoro-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)amino)pyrido[3,2-d]pyrimidine-7-carbonitrile;

N-(3-((1S,5S,6R)-3-amino-7,7-difluoro-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide;

N-(3-((1S,5S,6R)-3-amino-7,7-difluoro-1-(1-hydroxy-1-methylethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide;

2-((1S,5S,6R)-3-amino-7,7-difluoro-5-(2-fluoro-5-((2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-yl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)-2-propanol;

(1R)-1-((1S,5S,6R)-3-amino-7,7-difluoro-5-(2-fluoro-5-((2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-yl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)ethanol;

(1S)-1-((1S,5S,6R)-3-amino-7,7-difluoro-5-(2-fluoro-5-((2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-yl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)ethanol;

N-(3-((1S,5S,6S)-3-amino-1-(ethoxymethyl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-cyano-3-methyl-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-(methoxymethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-cyano-3-methyl-2-pyridinecarboxamide;

8-((3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-(methoxymethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)amino)-1,7-naphthyridine-3-carbonitrile;

N-(3-((1R,5S,6S)-3-amino-1-(cyanomethyl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide;

8-((3-((1R,5S,6S)-3-amino-1-(cyanomethyl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)amino)-1,7-naphthyridine-3-carbonitrile;

((1R,5S,6S)-3-amino-5-(fluoromethyl)-5-(2-fluoro-5-((2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-yl)amino)phenyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)acetonitrile;

((1R,5S,6S)-3-amino-5-(fluoromethyl)-5-(2-fluoro-5-((2-(1,3-oxazol-2-ylmethoxy)pyrido[3,4-b]pyrazin-5-yl)amino)phenyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)acetonitrile;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-(1H-1,2,3-triazol-1-ylmethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(2-cyanoethyl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-((4-methyl-1H-1,2,3-triazol-1-yl)methyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-((5-methyl-1H-1,2,3-triazol-1-yl)methyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-(1,3-oxazol-5-ylmethoxy)-1,7-naphthyridin-8-amine;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-(1,3-oxazol-2-ylmethoxy)-1,7-naphthyridin-8-amine;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-(1,3-oxazol-4-ylmethoxy)-1,7-naphthyridin-8-amine;

((8-((3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)amino)-1,7-naphthyridin-3-yl)oxy)acetonitrile;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-(1,2,4-oxadiazol-3-ylmethoxy)-1,7-naphthyridin-8-amine;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-(2,2,3,3-tetrafluoropropoxy)-1,7-naphthyridin-8-amine;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(2,2,3,3-tetrafluoropropoxy)-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-(2-propyn-1-yloxy)-1,7-naphthyridin-8-amine;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(2,2,3,3-tetrafluoropropoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-((5-chloro-1,3-thiazol-2-yl)methoxy)-1,7-naphthyridin-8-amine;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-((4-bromo-1,3-thiazol-2-yl)methoxy)-1,7-naphthyridin-8-amine;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-(1,3-thiazol-2-ylmethoxy)-1,7-naphthyridin-8-amine;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(3,3,3-trifluoropropoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(2,2-difluoropropoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(3-fluoropropoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-((4,4,4-trifluoro-2-butyn-1-yl)oxy)-1,7-naphthyridin-8-amine;

N-(3-((1R,5S,6S)-3-amino-5-methyl-1-(methylsulfonyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-chloro-2-pyridinecarboxamide;

N-(3-((1R,5S,6S)-3-amino-5-methyl-1-(methylsulfonyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(2-propyn-1-yloxy)-2-pyridinecarboxamide;

N-(3-((1R,5S,6S)-3-amino-5-methyl-1-(methylsulfonyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

N-(3-((1R,5S,6S)-3-amino-5-methyl-1-(methylsulfonyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(1,3-oxazol-2-ylmethoxy)-2-pyridinecarboxamide;

N-(3-((1R,5S,6S)-3-amino-5-methyl-1-(methylsulfonyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(1,3-oxazol-2-ylmethoxy)-2-pyrazinecarboxamide;

N-(3-((1R,5S,6S)-3-amino-5-methyl-1-(methylsulfonyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-(1,3-oxazol-2-ylmethoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1R,5S,6R)-3-amino-7,7-difluoro-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-chloro-2-pyridinecarboxamide;

N-(3-((1S,5S,6R)-3-amino-7,7-difluoro-1-(hydroxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

((1S,5S,6R)-3-amino-7,7-difluoro-5-(2-fluoro-5-((7-(1,3-oxazol-2-ylmethoxy)pyrido[3,2-d]pyrimidin-4-yl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)methanol;

N-(3-((1S,5S,6R)-3-amino-7,7-difluoro-1-(hydroxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(2,2,3,3-tetrafluoropropoxy)-2-pyridinecarboxamide;

N-(3-((4S,4aR,7aS)-2-amino-4-(fluoromethyl)-4,4a,4b,5-tetrahydrothieno[3',4':2,3]cyclopropa[1,2-e][1,3]thiazin-4-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide;

N-(3-((4S,4aS,7aR)-2-amino-4-(fluoromethyl)-4,4a,4b,5-tetrahydrothieno[3',4':2,3]cyclopropa[1,2-e][1,3]thiazin-4-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide;

N-(3-((4S,4aS,7aR)-2-amino-4-(fluoromethyl)-4,4a,4b,5-tetrahydrothieno[3',4':2,3]cyclopropa[1,2-e][1,3]thiazin-4-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3-chloropyrido[2,3-d]pyridazin-8-amine;

ethyl (2E)-3-((1R,5S,6S)-3-amino-5-(5-(((5-chloro-2-pyridinyl)carbonyl)amino)-2-fluorophenyl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)-2-propenoate;

N-(3-((1R,5S,6S)-3-amino-5-(fluoromethyl)-1-((1E)-3-hydroxy-1-propen-1-yl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide;

(2E)-3-((1R,5S,6S)-3-amino-5-(5-(((5-chloro-2-pyridinyl)carbonyl)amino)-2-fluorophenyl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)-2-propenoic acid;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-(3-hydroxypropyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide;

N-(3-((1R,5S,6S)-3-amino-1-((1E)-3-amino-3-oxo-1-propen-1-yl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide;

N-(3-((1R,5S,6S)-3-amino-5-(fluoromethyl)-1-((1E)-3-(methylamino)-3-oxo-1-propen-1-yl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide;

N-(3-((1R,5S,6S)-3-amino-1-((1E)-3-(dimethylamino)-3-oxo-1-propen-1-yl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-7-(1,3-oxazol-2-ylmethoxy)pyrido[3,2-d]pyrimidin-4-amine;

N-(3-((1R,5S,6S)-3-amino-5-(fluoromethyl)-1-((1E)-3-(4-morpholinyl)-3-oxo-1-propen-1-yl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(3-(dimethylamino)-3-oxopropyl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide;

N-(3-((1R,5S,6S)-3-amino-5-(fluoromethyl)-1-((1E)-3-(3-methoxy-1-azetidinyl)-3-oxo-1-propen-1-yl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide;

N-(3-((1R,5S,6S)-3-amino-5-(fluoromethyl)-1-((1E)-3-((2-methoxyethyl)amino)-3-oxo-1-propen-1-yl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide;

(2E)-3-((1R,5S,6S)-3-amino-5-(fluoromethyl)-5-(2-fluoro-5-((2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-yl)amino)phenyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)-N,N-dimethyl-2-propenamide;

(2E)-3-((1R,5S,6S)-3-amino-5-(fluoromethyl)-5-(2-fluoro-5-((2-(1,3-oxazol-2-ylmethoxy)pyrido[3,4-b]pyrazin-5-yl)amino)phenyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)-N,N-dimethyl-2-propenamide;

(2E)-3-((1R,5S,6S)-3-amino-5-(fluoromethyl)-5-(2-fluoro-5-((3-(1,3-oxazol-2-ylmethoxy)-1,7-naphthyridin-8-yl)amino)phenyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)-N,N-dimethyl-2-propenamide;

(2E)-3-((1R,5S,6S)-3-amino-5-(5-((3-(2-butyn-1-yloxy)-1,7-naphthyridin-8-yl)amino)-2-fluorophenyl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)-N,N-dimethyl-2-propenamide;

N-(3-((1R,5S,6S)-3-amino-1-((1E)-3-(3,3-difluoro-1-azetidinyl)-3-oxo-1-propen-1-yl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide;

N-(3-((1R,5S,6S)-3-amino-1-((1E)-3-(3,3-difluoro-1-azetidinyl)-3-oxo-1-propen-1-yl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1R,5S,6S)-3-amino-1-((1E)-3-(dimethylamino)-3-oxo-1-propen-1-yl)-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

(2E)-3-((1R,5S,6S)-3-amino-5-(fluoromethyl)-5-(2-fluoro-5-((7-(1,3-oxazol-2-ylmethoxy)pyrido[3,2-d]pyrimidin-4-yl)amino)phenyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)-N,N-dimethyl-2-propenamide;

(2E)-3-((1R,5S,6S)-3-amino-5-(fluoromethyl)-5-(2-fluoro-5-((7-(2-propyn-1-yloxy)pyrido[3,2-d]pyrimidin-4-yl)amino)phenyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)-N,N-dimethyl-2-propenamide;

N-(3-((1R,5S,6S)-3-amino-5-(fluoromethyl)-1-((1Z)-2-methyl-3-(4-morpholinyl)-3-oxo-1-propen-1-yl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide;

N-(3-((1R,5S,6S)-3-amino-5-(fluoromethyl)-1-((1E)-2-methyl-3-(4-morpholinyl)-3-oxo-1-propen-1-yl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide;

(1S,5S,6S)-3-amino-5-(fluoromethyl)-5-(2-fluoro-5-((2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-yl)amino)phenyl)-N,N-dimethyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-(1,3-oxazol-5-yl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-(1,3-oxazol-5-yl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-(1,3-oxazol-5-yl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-7-(2-propyn-1-yloxy)pyrido[3,2-d]pyrimidin-4-amine;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-(1,3-oxazol-5-yl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(1,3-oxazol-2-ylmethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-(4-methyl-1,3-oxazol-5-yl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-(1,3-oxazol-5-yl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-(3-isoxazolyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-(4-methyl-1,3-oxazol-5-yl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-(4-methyl-1,3-oxazol-5-yl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-7-(2-propyn-1-yloxy)pyrido[3,2-d]pyrimidin-4-amine;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-(4-methyl-1,3-oxazol-5-yl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(2-propyn-1-yloxy)-2-pyridinecarboxamide;

(1S,5S,6S)-3-amino-5-(5-(((5-chloro-2-pyridinyl)carbonyl)amino)-2-fluorophenyl)-5-(fluoromethyl)-N,N-dimethyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-N-cyclopropyl-5-(2-fluoro-5-((7-(2-propyn-1-yloxy)pyrido[3,2-d]pyrimidin-4-yl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-5-(5-(((5-chloro-2-pyridinyl)carbonyl)amino)-2-fluorophenyl)-N-cyclopropyl-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-(3-isoxazolyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(2-propyn-1-yloxy)-2-pyridinecarboxamide;

(1S,5S,6S)-3-amino-N-cyclopropyl-5-(2-fluoro-5-((2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-yl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-N-cyclopropyl-5-(2-fluoro-5-(((5-(2-propyn-1-yloxy)-2-pyrazinyl)carbonyl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-N-cyclopropyl-5-(2-fluoro-5-((2-(1,3-oxazol-2-ylmethoxy)pyrido[3,4-b]pyrazin-5-yl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-N-tert-butyl-5-(5-(((5-chloro-2-pyridinyl)carbonyl)amino)-2-fluorophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-N-tert-butyl-5-(2-fluoro-5-(((5-(2-propyn-1-yloxy)-2-pyrazinyl)carbonyl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-N-cyclopropyl-5-(2-fluoro-5-(((5-(1,3-oxazol-2-ylmethoxy)-2-pyrazinyl)carbonyl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-N-cyclopropyl-5-(2-fluoro-5-(((5-(2,2,2-trifluoroethoxy)-2-pyrazinyl)carbonyl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

4-((3-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)amino)pyrido[3,2-d]pyrimidine-7-carbonitrile;

N-(3-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-(1,3-oxazol-2-ylmethoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-methyl-5-(1,3-oxazol-2-ylmethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-chloro-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-7-(1,3-oxazol-2-ylmethoxy)pyrido[3,2-d]pyrimidin-4-amine;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-7-(1,3-oxazol-2-ylmethoxy)pyrido[3,2-d]pyrimidin-4-amine;

N-(3-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(1,3-oxazol-2-ylmethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-7-(1,3-oxazol-2-ylmethoxy)pyrido[3,2-d]pyrimidin-4-amine;

N-(3-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-7-(2-propyn-1-yloxy)pyrido[3,2-d]pyrimidin-4-amine;

N-(3-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(2,2,2-trifluoroethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(2,2,2-trifluoroethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-2-(1,3-oxazol-2-ylmethoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-7-(2-propyn-1-yloxy)pyrido[3,2-d]pyrimidin-4-amine;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-7-(2-propyn-1-yloxy)pyrido[3,2-d]pyrimidin-4-amine;

N-(3-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-2-(1,3-oxazol-2-ylmethoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(2,2,2-trifluoroethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-2-(((1S)-1-methyl-2-propyn-1-yl)oxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-2-((5-methyl-1,2,4-oxadiazol-3-yl)methoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3-methyl-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3-methyl-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(2,2,2-trifluoroethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3-methyl-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3-methyl-5-(1,3-oxazol-2-ylmethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3-methyl-5-(1,3-oxazol-2-ylmethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-3-methyl-5-(1,3-oxazol-2-ylmethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(1,1-dideuterium-prop-2-yn-1-yloxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(1,1-dideuterium-prop-2-yn-1-yloxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxy)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(1,1-dideuterium-prop-2-yn-1-yloxy)pyrazine-2-carboxamide;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-(1,3-oxazol-2-ylmethoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-(1,3-oxazol-4-ylmethoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(5-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoro-3-pyridinyl)-7-chloropyrido[3,2-d]pyrimidin-4-amine;

N-(5-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoro-3-pyridinyl)-3-methyl-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

4-((5-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoro-3-pyridinyl)amino)pyrido[3,2-d]pyrimidine-7-carbonitrile;

8-((5-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoro-3-pyridinyl)amino)-1,7-naphthyridine-3-carbonitrile;

N-(5-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoro-3-pyridinyl)-2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-amine;

N-(5-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoro-3-pyridinyl)-2-(1,3-oxazol-2-ylmethoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(5-((1S,5S,6S)-3-amino-5-methyl-1-(((~2~H_3_)methyloxy)methyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoro-3-pyridinyl)-3-methyl-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

N-(5-((1S,5S,6S)-3-amino-5-methyl-1-(((~2~H_3_)methyloxy)methyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoro-3-pyridinyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

N-(5-((1S,5S,6S)-3-amino-5-methyl-1-(((~2~H_3_)methyloxy)methyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoro-3-pyridinyl)-7-chloropyrido[3,2-d]pyrimidin-4-amine;

N-(5-((1S,5S,6S)-3-amino-5-methyl-1-(((~2~H_3_)methyloxy)methyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoro-3-pyridinyl)-2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-amine;

N-(5-((1S,5S,6S)-3-amino-5-methyl-1-(((~2~H_3_)methyloxy)methyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoro-3-pyridinyl)-2-((1,1-~2~H_2_)-2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-amine;

methyl (1S,5S,6S)-3-amino-5-(5-(((5-chloro-2-pyridinyl)carbonyl)amino)-2-fluoro-3-(methoxycarbonyl)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylate;

methyl (1S,5S,6S)-3-amino-5-(2-fluoro-3-(methoxycarbonyl)-5-((2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-yl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylate;

methyl 3-((1S,5S,6S)-3-amino-1-(hydroxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-2-fluoro-5-((2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-yl)amino)benzoate;

N-(3-((1S,5S,6S)-3-amino-1-(hydroxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluoro-5-(hydroxymethyl)phenyl)-5-chloro-2-pyridinecarboxamide;

N-(5-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoro-3-pyridinyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-methyl-5-(1,3-oxazol-2-ylmethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-methyl-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-methyl-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-methyl-5-(1,3-oxazol-2-ylmethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-methyl-5-((1S)-1-(1,3-oxazol-2-yl)ethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1,5-bis(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-2-(2-butyn-1-yloxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-(1,3-oxazol-2-ylmethoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-(1,3-oxazol-4-ylmethoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-(2-butyn-1-yloxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-(2-butyn-1-yloxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-((2-methyl-1,3-oxazol-4-yl)methoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-(3-fluoropropoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-(2,2-difluoropropoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-((3-fluoro-2-pyridinyl)methoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-((4-methyl-2-pyrimidinyl)methoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-(1,3-thiazol-4-ylmethoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-(1-methylethoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-((5-methyl-1,3,4-oxadiazol-2-yl)methoxy)pyrido[3,4-b]pyrazin-5-amine;

2-((5-((3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)amino)pyrido[3,4-b]pyrazin-2-yl)oxy)-N,N-dimethylacetamide;

N-(3-((1S,5S,6S)-3-amino-1,5-bis(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-2-(((1S)-1-methyl-2-propyn-1-yl)oxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1,5-bis(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-2-((3-methyl-1,2,4-oxadiazol-5-yl)methoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-(2-pyrimidinylmethoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-((3-methyl-1,2,4-oxadiazol-5-yl)methoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-((5-methyl-1,2,4-oxadiazol-3-yl)methoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-(2-pyrimidinylmethoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-((5-methyl-1,2,4-oxadiazol-3-yl)methoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-((2,5-dimethyl-1,3-oxazol-4-yl)methoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-((3-methyl-1,2,4-oxadiazol-5-yl)methoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-((5-methyl-1,3-oxazol-2-yl)methoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-((5-methyl-1,3,4-thiadiazol-2-yl)methoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-(((1S)-1-methyl-2-propyn-1-yl)oxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-((1R)-1-(1,3-oxazol-2-yl)ethoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-((1S)-1-(1,3-oxazol-2-yl)ethoxy)pyrido[3,4-b]pyrazin-5-amine;

1-(2-((5-((3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)amino)pyrido[3,4-b]pyrazin-2-yl)oxy)ethyl)-2-pyrrolidinone;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-((1S)-2-methoxy-1-methylethoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-methoxypyrido[3,4-b]pyrazin-5-amine;

5-((3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)amino)pyrido[3,4-b]pyrazin-2(1H)-one;

N-(3-((1S,5S,6S)-3-amino-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-7-methoxypyrido[3,2-d]pyrimidin-4-amine;

methyl (1S,5S,6S)-3-amino-5-(5-(((5-chloro-2-pyridinyl)carbonyl)amino)-2,3-difluorophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylate;

(1S,5S,6S)-3-amino-5-(5-(((5-chloro-2-pyridinyl)carbonyl)amino)-2,3-difluorophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylic acid;

N-(3-((1S,5S,6S)-3-amino-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-methoxypyrido[3,4-b]pyrazin-5-amine;

(1S,5S,6S)-3-amino-5-(5-((7-chloropyrido[3,2-d]pyrimidin-4-yl)amino)-2,3-difluorophenyl)-N-methoxy-N,5-dimethyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

1-((1S,5S,6S)-3-amino-5-(5-((7-chloropyrido[3,2-d]pyrimidin-4-yl)amino)-2,3-difluorophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)ethanone;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-(2-butyn-1-yloxy)-1,7-naphthyridin-8-amine;

4-((3-((1S,5S,6S)-1-acetyl-3-amino-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)amino)pyrido[3,2-d]pyrimidine-7-carbonitrile;

(1S,5S,6S)-3-amino-5-(5-(((5-chloro-2-pyridinyl)carbonyl)amino)-2,3-difluorophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

N-(3-((1S,5S,6S)-1-acetyl-3-amino-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-chloro-2-pyridinecarboxamide;

4-((3-((1S,5S,6S)-3-amino-1-(1-hydroxyethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)amino)pyrido[3,2-d]pyrimidine-7-carbonitrile;

4-((3-((1R,2S,6S)-4-amino-6-((R)-1-hydroxyethyl)-2-methyl-3-azabicyclo[4.1.0]hept-3-en-2-yl)-4,5-difluorophenyl)amino)pyrido[3,2-d]pyrimidine-7-carbonitrile;

4-((3-((1S,5S,6S)-3-amino-1-(1-hydroxy-1-methylethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)amino)pyrido[3,2-d]pyrimidine-7-carbonitrile;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(1,3-oxazol-2-ylmethoxy)-2-pyrazinecarboxamide;

(1S,5S,6S)-3-amino-5-(2,3-difluoro-5-((2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-yl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-5-(2,3-difluoro-5-((2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-yl)amino)phenyl)-N,N,5-trimethyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-5-(2,3-difluoro-5-(((5-(2-propyn-1-yloxy)-2-pyrazinyl)carbonyl)amino)phenyl)-N,N,5-trimethyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-5-(2,3-difluoro-5-(((5-(2-propyn-1-yloxy)-2-pyrazinyl)carbonyl)amino)phenyl)-N,5-dimethyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-5-(2,3-difluoro-5-((2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-yl)amino)phenyl)-N,5-dimethyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-5-(2,3-difluoro-5-((2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-yl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carbonitrile;

(1S,5S,6S)-3-amino-5-(2,3-difluoro-5-((7-(2-propyn-1-yloxy)pyrido[3,2-d]pyrimidin-4-yl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-5-(2,3-difluoro-5-((7-(1,3-oxazol-2-ylmethoxy)pyrido[3,2-d]pyrimidin-4-yl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-5-(2,3-difluoro-5-(((5-(2-propyn-1-yloxy)-2-pyrazinyl)carbonyl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-5-(5-((2-(2-butyn-1-yloxy)pyrido[3,4-b]pyrazin-5-yl)amino)-2,3-difluorophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-5-(2,3-difluoro-5-((7-(2-propyn-1-yloxy)pyrido[3,2-d]pyrimidin-4-yl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carbonitrile;

(1S,5S,6S)-3-amino-5-(2,3-difluoro-5-(((5-(2,2,3,3-tetrafluoropropoxy)-2-pyrazinyl)carbonyl)amino)phenyl)-N,N,5-trimethyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-5-(2,3-difluoro-5-((7-(1,3-oxazol-2-ylmethoxy)pyrido[3,2-d]pyrimidin-4-yl)amino)phenyl)-N,N,5-trimethyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

N-(3-((1S,5S,6S)-3-amino-1-cyano-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

(1S,5S,6S)-3-amino-5-(2,3-difluoro-5-((2-(((1S)-1-methyl-2-propyn-1-yl)oxy)pyrido[3,4-b]pyrazin-5-yl)amino)phenyl)-N,N,5-trimethyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-5-(2,3-difluoro-5-(((5-(2,2,2-trifluoroethoxy)-2-pyrazinyl)carbonyl)amino)phenyl)-N,N,5-trimethyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

N-(3-((1S,5S,6S)-3-amino-1-cyano-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

(1S,5S,6S)-3-amino-5-(2-fluoro-5-((7-(2-propyn-1-yloxy)pyrido[3,2-d]pyrimidin-4-yl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carbonitrile;

N-(3-((1S,5S,6S)-3-amino-1-cyano-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide;

(1S,5S,6S)-3-amino-5-(5-(((5-chloro-2-pyridinyl)carbonyl)amino)-2,3-difluorophenyl)-N,N,5-trimethyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-5-(2,3-difluoro-5-((2-(((1S)-1-methyl-2-propyn-1-yl)oxy)pyrido[3,4-b]pyrazin-5-yl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carbonitrile;

N-(3-((1S,5S,6S)-3-amino-1-cyano-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-chloro-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-5-methyl-1-(1-pyrrolidinylcarbonyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-7-(2-propyn-1-yloxy)pyrido[3,2-d]pyrimidin-4-amine;

N-(3-((1S,5S,6S)-3-amino-5-methyl-1-(1-pyrrolidinylcarbonyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-5-methyl-1-(1-pyrrolidinylcarbonyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-chloro-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-5-methyl-1-(1-pyrrolidinylcarbonyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-7-(1,3-oxazol-2-ylmethoxy)pyrido[3,2-d]pyrimidin-4-amine;

N-(3-((1S,5S,6S)-3-amino-5-methyl-1-(1-pyrrolidinylcarbonyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-(((1S)-1-methyl-2-propyn-1-yl)oxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-5-methyl-1-(1-pyrrolidinylcarbonyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-2-((1S)-1-(1,3-oxazol-2-yl)ethoxy)pyrido[3,4-b]pyrazin-5-amine;

(1S,5S,6S)-3-amino-5-(2,3-difluoro-5-((2-((1S)-1-(1,3-oxazol-2-yl)ethoxy)pyrido[3,4-b]pyrazin-5-yl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carbonitrile;

N-(3-((1S,5S,6S)-3-amino-1-cyano-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(2,2,2-trifluoroethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-7-(2-propyn-1-yloxy)pyrido[3,2-d]pyrimidin-4-amine;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-(methoxymethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-7-(2-propyn-1-yloxy)pyrido[3,2-d]pyrimidin-4-amine;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-7-(2-propyn-1-yloxy)pyrido[3,2-d]pyrimidin-4-amine;

N-(5-((1S,5S,6S)-3-amino-1-(fluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-fluoro-3-pyridinyl)-7-(2-propyn-1-yloxy)pyrido[3,2-d]pyrimidin-4-amine;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-7-(2-propyn-1-yloxy)pyrido[3,2-d]pyrimidin-4-amine;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-7-(2-methoxyethoxy)pyrido[3,2-d]pyrimidin-4-amine;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-(methoxymethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-7-(2-methoxyethoxy)pyrido[3,2-d]pyrimidin-4-amine;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-7-((2,5-dimethyl-1,3-oxazol-4-yl)methoxy)pyrido[3,2-d]pyrimidin-4-amine;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-fluoro-3-(1,3-oxazol-2-ylmethoxy)-1,7-naphthyridin-8-amine;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-fluoro-3-(1,3-oxazol-2-ylmethoxy)-1,7-naphthyridin-8-amine;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-fluoro-3-(2-propyn-1-yloxy)-1,7-naphthyridin-8-amine;

(2E)-3-((1R,5S,6S)-3-amino-5-(fluoromethyl)-5-(2-fluoro-5-((2-(2-pentyn-1-yloxy)pyrido[3,4-b]pyrazin-5-yl)amino)phenyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)-N,N-dimethyl-2-propenamide;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-((2,2,2-trifluoroethoxy)methyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-((2,2,2-trifluoroethoxy)methyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-((1-methylethoxy)methyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-(1H-1,2,3-triazol-4-yl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-chloro-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-(1H-1,2,3-triazol-4-yl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-2-(1,3-oxazol-2-ylmethoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-(1-propyn-1-yl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-2-(1,3-oxazol-2-ylmethoxy)pyrido[3,4-b]pyrazin-5-amine;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-(1H-1,2,3-triazol-4-yl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-1-(1H-1,2,3-triazol-4-yl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-amine;

4-((3-((1R,5S,6S)-3-amino-7,7-difluoro-1-(hydroxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)amino)pyrido[3,2-d]pyrimidine-7-carbonitrile; or

N-(3-((4S,4aR,7aS)-2-amino-4-(fluoromethyl)-4a,4b,5,7-tetrahydro-4H-thieno[3',4':2,3]cyclopropa[1,2-e][1,3]thiazin-4-yl)-4-fluorophenyl)-5-chloropicolinamide.

55. The compound of Claim 1, or a tautomer or pharmaceutically acceptable salt thereof, selected from

(1S,5S,6S)-3-amino-5-(2,3-difluoro-5-(((5-(2,2,3,3-tetrafluoropropoxy)-2-pyrazinyl)carbonyl)amino)phenyl)-N,5-dimethyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

N-(5-((1S,5S,6S)-3-amino-1-cyano-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-methoxy-3-pyridinyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(((1S)-1-methyl-2-propyn-1-yl)oxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(((1S)-1-methyl-2-propyn-1-yl)oxy)-2-pyrazinecarboxamide;

(1S,5S,6S)-3-amino-5-(2,3-difluoro-5-(((5-(((1S)-1-methyl-2-propyn-1-yl)oxy)-2-pyrazinyl)carbonyl)amino)phenyl)-N,5-dimethyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-((1R)-2,2,2-trifluoro-1-methylethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-((1S)-2,2,2-trifluoro-1-methylethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-5-methyl-1-((trideuteriummethyloxy)methyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-((1S)-2-methoxy-1-methylethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-((1S)-2-methoxy-1-methylethoxy)-2-pyrazinecarboxamide;

(1S,5S,6S)-3-amino-5-(2-fluoro-5-(((5-(2,2,2-trifluoroethoxy)-2-pyrazinyl)carbonyl)amino)phenyl)-5-methyl-N-(2,2,2-trifluoroethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-5-(2-fluoro-5-(((5-(2,2,2-trifluoroethoxy)-2-pyrazinyl)carbonyl)amino)phenyl)-N,5-dimethyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-N-((1S)-1,2-dimethylpropyl)-5-(2-fluoro-5-(((5-(2,2,2-trifluoroethoxy)-2-pyrazinyl)carbonyl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

methyl (1S,5S,6S)-3-amino-5-(2,3-difluoro-5-(((5-(2-propyn-1-yloxy)-2-pyrazinyl)carbonyl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxylate;

(1S,5S,6S)-3-amino-5-(2-fluoro-5-(((5-(2,2,2-trifluoroethoxy)-2-pyrazinyl)carbonyl)amino)phenyl)-5-methyl-N-(1-methylethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-N-ethyl-5-(2-fluoro-5-(((5-(2,2,2-trifluoroethoxy)-2-pyrazinyl)carbonyl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-5-(2-fluoro-5-(((5-(((1S)-1-methyl-2-propyn-1-yl)oxy)-2-pyrazinyl)carbonyl)amino)phenyl)-N,5-dimethyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-5-(2-fluoro-5-((2-(2-propyn-1-yloxy)pyrido[3,4-b]pyrazin-5-yl)amino)phenyl)-N,5-dimethyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

tert-butyl (((1S,5S,6S)-3-amino-5-(2,3-difluoro-5-(((5-(2-propyn-1-yloxy)-2-pyrazinyl)carbonyl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-1-yl)methyl)carbamate;

N-(3-((1S,5S,6S)-3-amino-1-(aminomethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

(1S,5S,6S)-3-amino-N-((1R)-2,2-difluorocyclopropyl)-5-(2-fluoro-5-(((5-(2,2,2-trifluoroethoxy)-2-pyrazinyl)carbonyl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-N-((1S)-2,2-difluorocyclopropyl)-5-(2-fluoro-5-(((5-(2,2,2-trifluoroethoxy)-2-pyrazinyl)carbonyl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-N-(2-fluoro-1,1-dimethylethyl)-5-(2-fluoro-5-(((5-(2,2,2-trifluoroethoxy)-2-pyrazinyl)carbonyl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-5-(2-fluoro-5-(((5-(2,2,2-trifluoroethoxy)-2-pyrazinyl)carbonyl)amino)phenyl)-N-methoxy-N,5-dimethyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-5-(5-(((5-chloro-2-pyridinyl)carbonyl)amino)-2-fluorophenyl)-N,5-dimethyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-N-tert-butyl-5-(5-(((5-cyano-2-pyridinyl)carbonyl)amino)-2-fluorophenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-5-(2-fluoro-5-(((5-(2-propyn-1-yloxy)-2-pyrazinyl)carbonyl)amino)phenyl)-N,5-dimethyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(((1R)-1-methyl-2-propyn-1-yl)oxy)-2-pyrazinecarboxamide;

N-(5-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-methoxy-3-pyridinyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

N-(5-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-6-methoxy-3-pyridinyl)-5-chloro-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(((3R)-3-fluoro-1-pyrrolidinyl)carbonyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(2,2,2-trifluoroethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(((3S)-3-fluoro-1-pyrrolidinyl)carbonyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(2,2,2-trifluoroethoxy)-2-pyrazinecarboxamide;

(1S,5S,6S)-3-amino-N-cyclopropyl-5-(2-fluoro-5-(((5-(((1S)-1-methyl-2-propyn-1-yl)oxy)-2-pyrazinyl)carbonyl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-N-tert-butyl-5-(2-fluoro-5-(((5-(((1S)-1-methyl-2-propyn-1-yl)oxy)-2-pyrazinyl)carbonyl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-((1S)-2,2,2-trifluoro-1-methylethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-((1R)-2,2,2-trifluoro-1-methylethoxy)-2-pyrazinecarboxamide;

(1S,5S,6S)-3-amino-N-((1R)-1,2-dimethylpropyl)-5-(2-fluoro-5-(((5-(2,2,2-trifluoroethoxy)-2-pyrazinyl)carbonyl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

N-(3-((1S,5S,6S)-3-amino-5-methyl-1-(4-morpholinylcarbonyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(2,2,2-trifluoroethoxy)-2-pyrazinecarboxamide;

(1S,5S,6S)-3-amino-N-(2,2-difluoroethyl)-5-(2-fluoro-5-(((5-(2,2,2-trifluoroethoxy)-2-pyrazinyl)carbonyl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-5-(2-fluoro-5-(((5-(2,2,2-trifluoroethoxy)-2-pyrazinyl)carbonyl)amino)phenyl)-N,N,5-trimethyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-N-cyclopropyl-5-(2-fluoro-5-(((5-((1S)-2-methoxy-1-methylethoxy)-2-pyrazinyl)carbonyl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-N-tert-butyl-5-(2-fluoro-5-(((5-(2,2,2-trifluoroethoxy)-2-pyrazinyl)carbonyl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-N-tert-butyl-5-(2-fluoro-5-(((5-((1S)-2-methoxy-1-methylethoxy)-2-pyrazinyl)carbonyl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

N-(3-((1S,5S,6S)-3-amino-5-methyl-1-(4-morpholinylcarbonyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-5-methyl-1-(4-morpholinylcarbonyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

(1S,5S,6S)-3-amino-N-(2-fluoro-1,1-dimethylethyl)-5-(2-fluoro-5-(((5-(2-propyn-1-yloxy)-2-pyrazinyl)carbonyl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-chloro-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-((3-methyl-1,2,4-oxadiazol-5-yl)methoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(((1S)-1-methyl-2-propyn-1-yl)oxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-cyano-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-((1S)-2-methoxy-1-methylethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-cyano-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(((1S)-1-methyl-2-propyn-1-yl)oxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-cyano-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(2,2,2-trifluoroethoxy)-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-((5-methyl-1,2,4-oxadiazol-3-yl)methoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-((3-methyl-1,2,4-oxadiazol-5-yl)methoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-cyano-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-methyl-5-(2,2,2-trifluoroethoxy)-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-cyano-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-3-methyl-5-(2-propyn-1-yloxy)-2-pyridinecarboxamide;

(1S,5S,6S)-3-amino-N-ethyl-5-(2-fluoro-5-(((5-(2-propyn-1-yloxy)-2-pyrazinyl)carbonyl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-5-(5-(((5-cyano-2-pyridinyl)carbonyl)amino)-2-fluorophenyl)-N-(2-fluoro-1,1-dimethylethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-N-(2-fluoro-1,1-dimethylethyl)-5-(2-fluoro-5-(((5-(((1S)-1-methyl-2-propyn-1-yl)oxy)-2-pyrazinyl)carbonyl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(cyclobutylmethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(cyclopropylmethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(3-oxetanylmethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(((2R)-2-methoxypropyl)oxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(((2S)-2-methoxypropyl)oxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-((1S)-2-methoxy-1-methylethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(2,2-difluoroethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-((3,3-difluorocyclobutyl)methoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-oxo-4,5-dihydro-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(2-methylpropoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-((2R)-2-oxetanylmethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-((2S)-2-oxetanylmethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-((2-methyl-2-propen-1-yl)oxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-((3-methyl-5-isoxazolyl)methoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-((5-methyl-3-isoxazolyl)methoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(benzyloxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(1,3-thiazol-2-ylmethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(((1R)-2,2-difluorocyclopropyl)methoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(((1S)-2,2-difluorocyclopropyl)methoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(2-propen-1-yloxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-((5-methyl-1,3,4-oxadiazol-2-yl)methoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-ethoxy-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-((3-methyl-1,2,4-oxadiazol-5-yl)methoxy)-2-pyrazinecarboxamide;

(1S,5S,6S)-3-amino-N-(2-fluoroethyl)-5-(2-fluoro-5-(((5-(2,2,2-trifluoroethoxy)-2-pyrazinyl)carbonyl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-5-(2-fluoro-5-(((5-(2,2,2-trifluoroethoxy)-2-pyrazinyl)carbonyl)amino)phenyl)-5-methyl-N-(1-methylcyclopropyl)-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

N-(3-((1S,5S,6S)-1-((acetylamino)methyl)-3-amino-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluoro-5-methylphenyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluoro-5-methylphenyl)-5-((3-methyl-1,2,4-oxadiazol-5-yl)methoxy)-2-pyrazinecarboxamide;

(1S,5S,6S)-3-amino-N-((1R)-2,2-difluoro-1-methylethyl)-5-(2-fluoro-5-(((5-(2,2,2-trifluoroethoxy)-2-pyrazinyl)carbonyl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

(1S,5S,6S)-3-amino-N-((1S)-2,2-difluoro-1-methylethyl)-5-(2-fluoro-5-(((5-(2,2,2-trifluoroethoxy)-2-pyrazinyl)carbonyl)amino)phenyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-ene-1-carboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(ethoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(2-propyn-1-yloxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(3-pentyn-1-yloxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(3-butyn-1-yloxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-((1-methylcyclopropyl)methoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-((3-methyl-3-oxetanyl)methoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(((1R)-1-methyl-2-propen-1-yl)oxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(((1S)-1-methyl-2-propen-1-yl)oxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(2-fluoroethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(cyclopropylmethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(cyclobutylmethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(3-oxetanylmethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(2-methylpropoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(2,2-difluoroethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-((2R)-2-oxetanylmethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-((2S)-2-oxetanylmethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(3-pentyn-1-yloxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(3-butyn-1-yloxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-((1-methylcyclopropyl)methoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-((3-methyl-3-oxetanyl)methoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(((1R)-1-methyl-2-propen-1-yl)oxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(((1S)-1-methyl-2-propen-1-yl)oxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(2-fluoroethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluoro-5-methylphenyl)-5-(2,2,2-trifluoroethoxy)-2-pyrazinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluoro-5-methylphenyl)-5-chloro-2-pyridinecarboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluorophenyl)-5-(oxetan-3-yloxy)pyrazine-2-carboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(oxetan-3-yloxy)pyrazine-2-carboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(neopentyloxy)pyrazine-2-carboxamide;

N-(3-((1S,5S,6S)-1-acetyl-3-amino-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-(prop-2-yn-1-yloxy)pyrazine-2-carboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(methoxymethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluoro-5-methylphenyl)-5-(oxazol-2-ylmethoxy)pyrazine-2-carboxamide;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluoro-5-methylphenyl)-5-(prop-2-yn-1-yloxy)pyrazine-2-carboxamide;

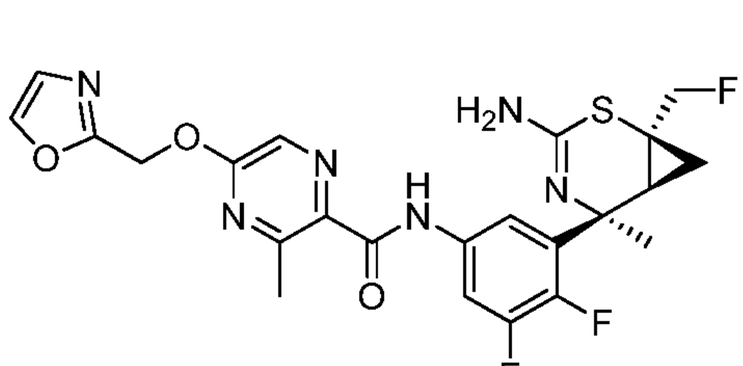
N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluoro-5-methylphenyl)-5-(2,2,2-trifluoroethoxy)pyrazine-2-carboxamide;

N-(3-((1S,5S,6S)-3-amino-5-(fluoromethyl)-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4,5-difluorophenyl)-5-chloropicolinamide ;

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluoro-5-methylphenyl)-5-(oxazol-2-ylmethoxy)pyrazine-2-carboxamide; or

N-(3-((1S,5S,6S)-3-amino-1-(difluoromethyl)-5-methyl-2-thia-4-azabicyclo[4.1.0]hept-3-en-5-yl)-4-fluoro-5-methylphenyl)-5-((3-methyl-1,2,4-oxadiazol-5-yl)methoxy)pyrazine-2-carboxamide.

56. The compound of Claim 1, or a stereoisomer or pharmaceutically acceptable salt thereof, selected from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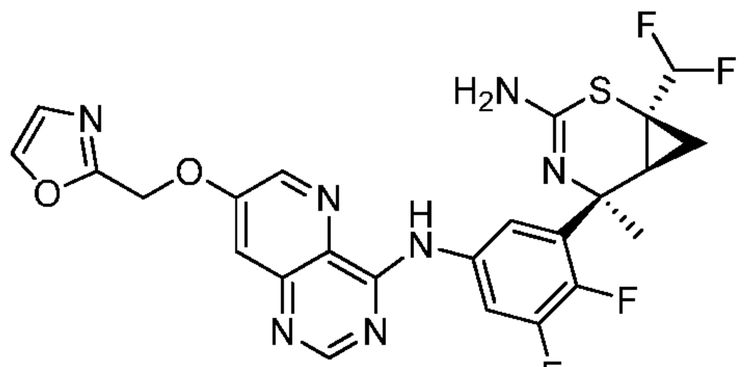
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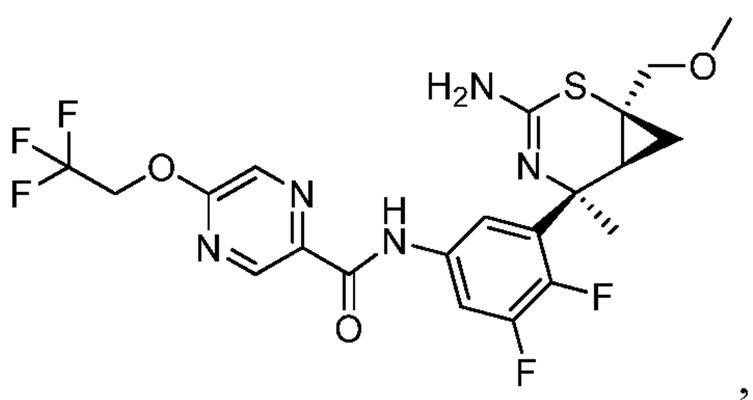
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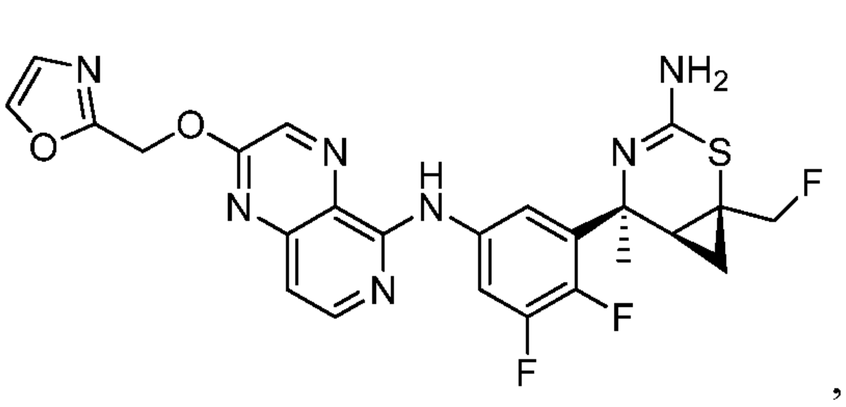
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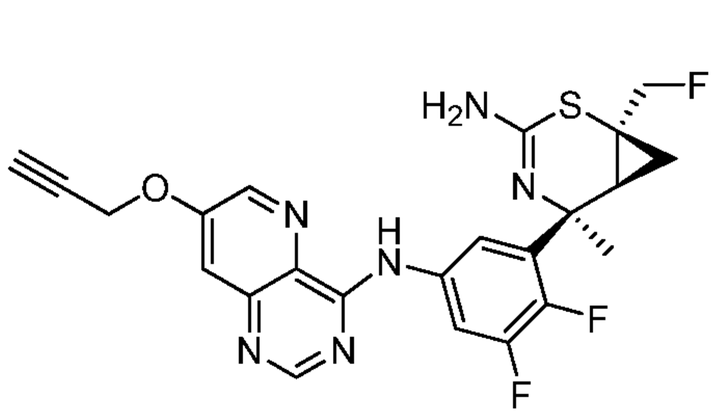
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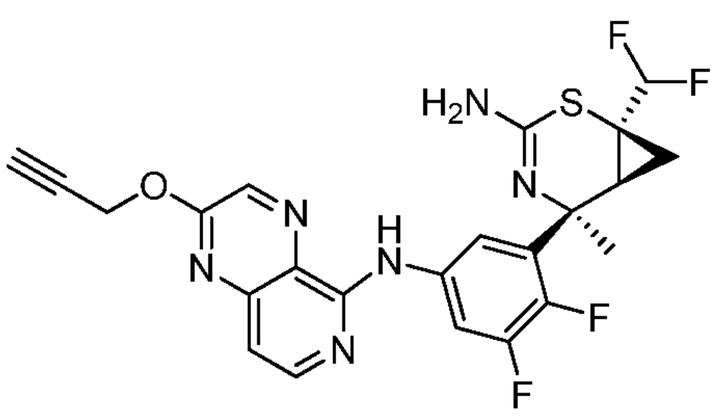
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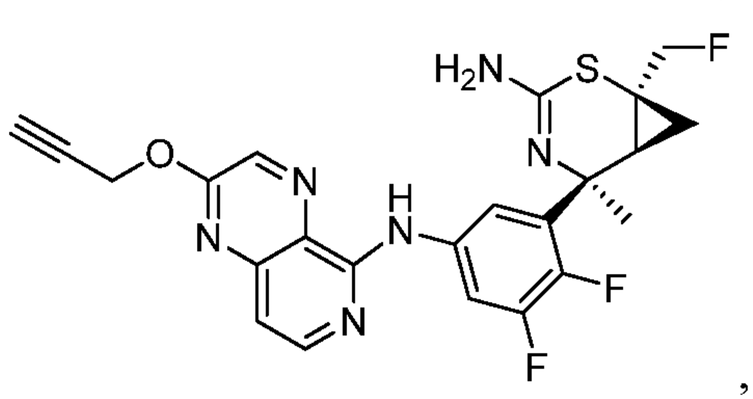
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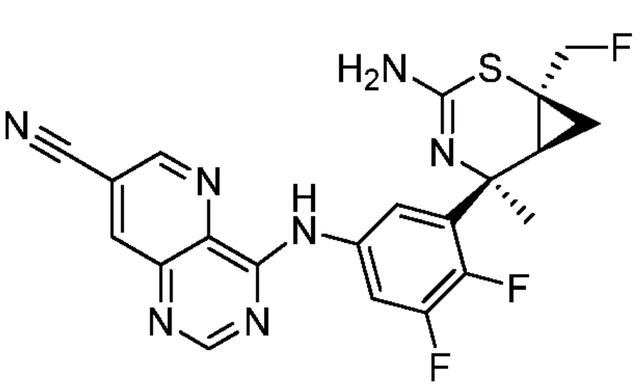
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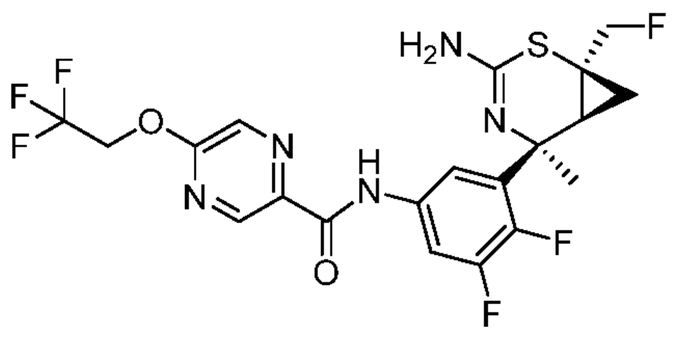
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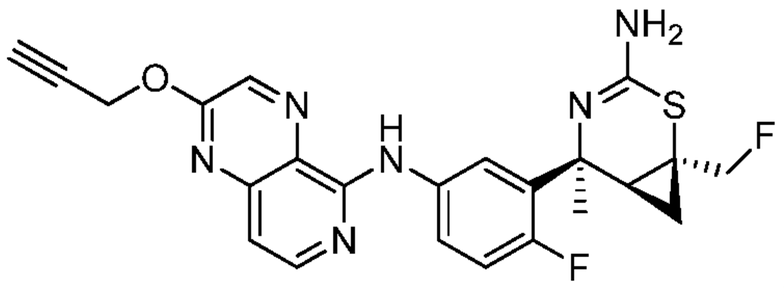
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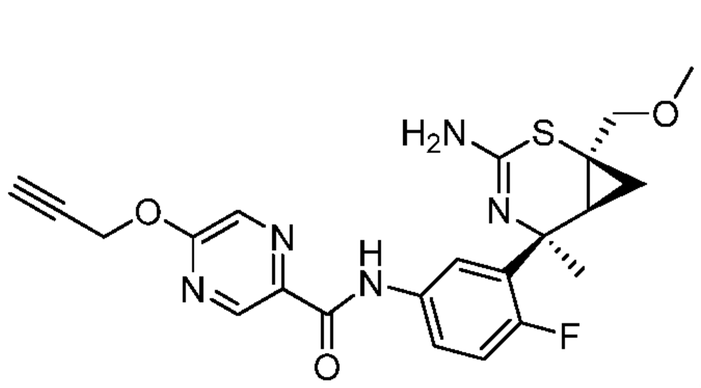
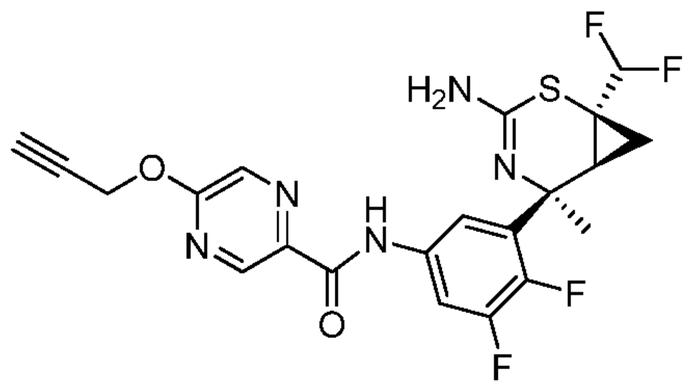
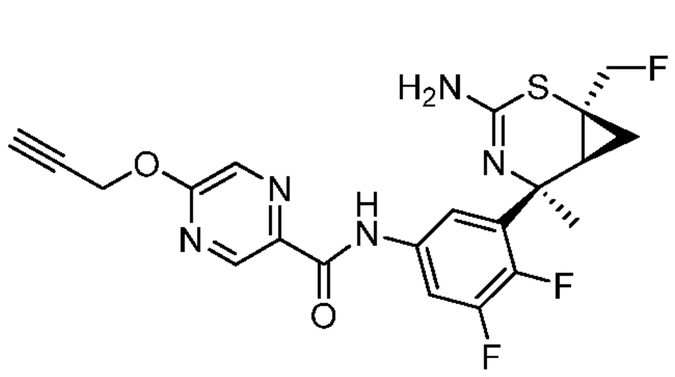
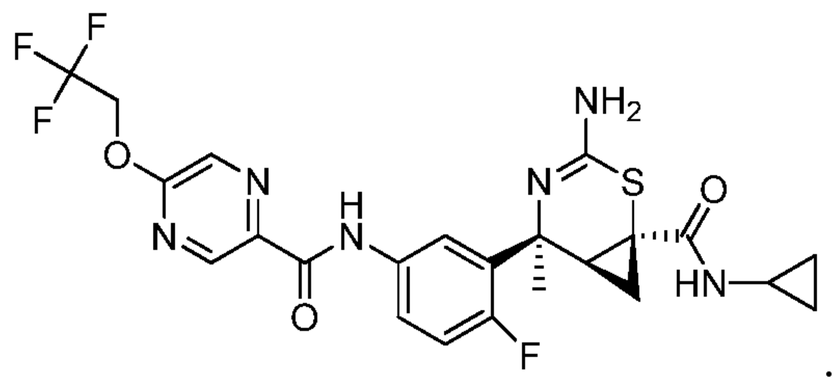



, or 
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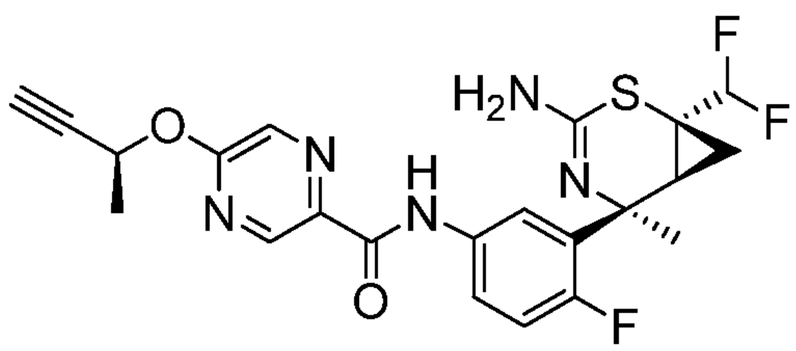
57. The compound of Claim 1, or a stereoisomer or pharmaceutically acceptable salt thereof, selected from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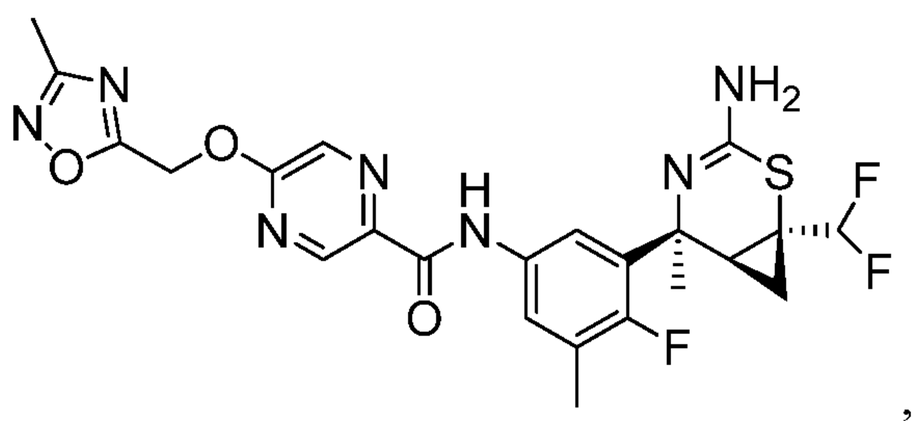
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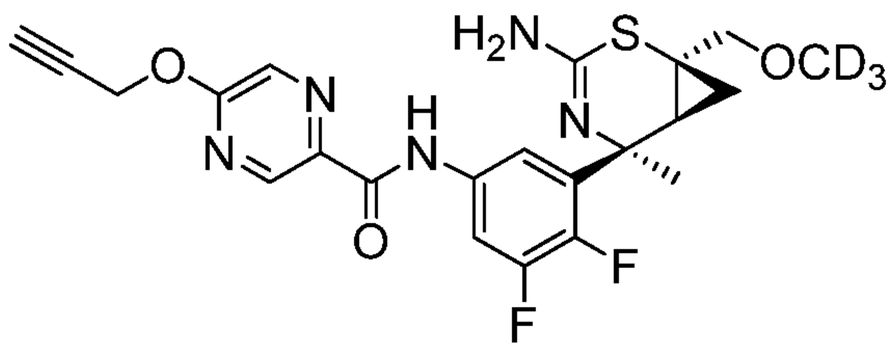
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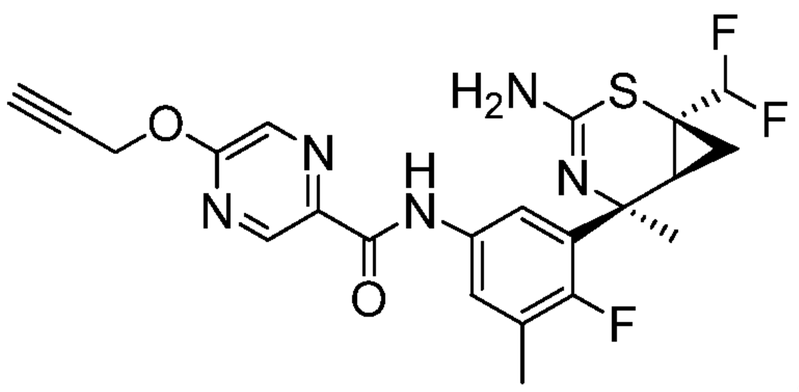

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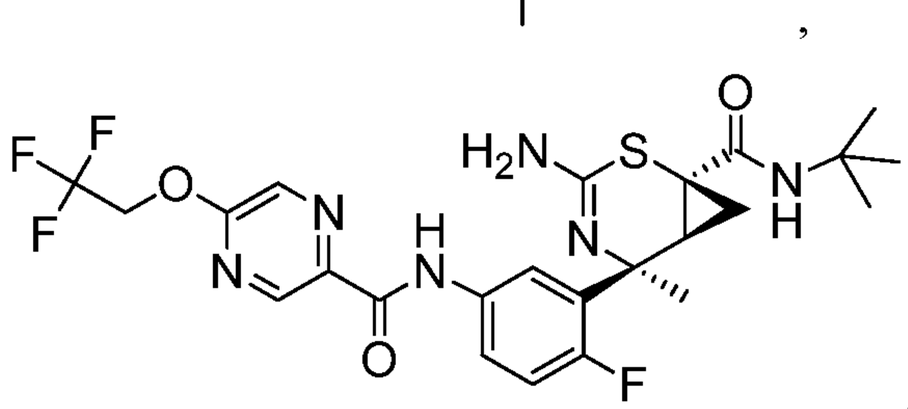

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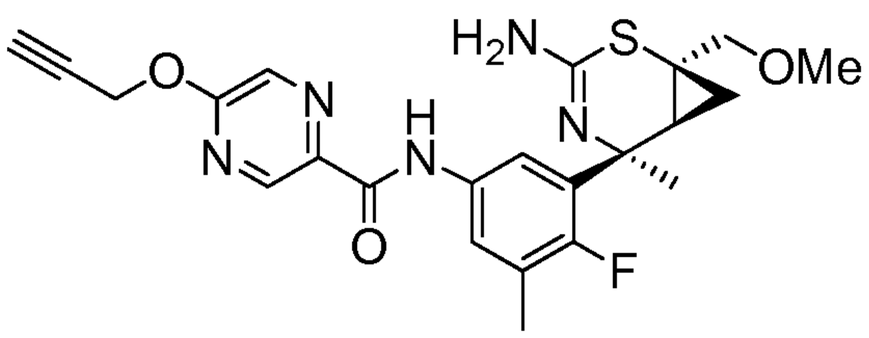

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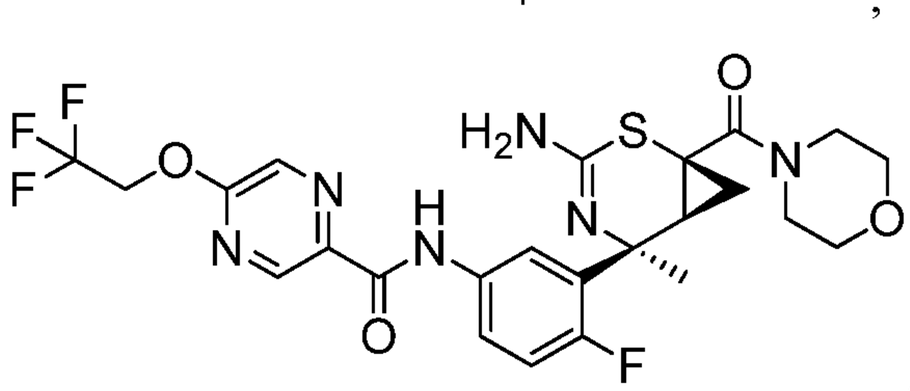

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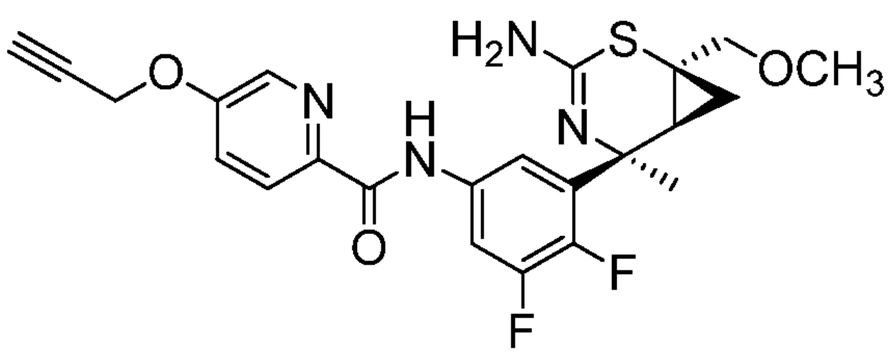

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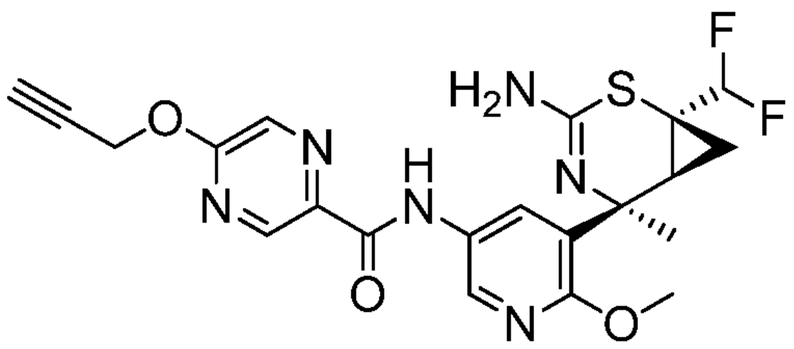

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58. A pharmaceutical composition comprising the compound according to any of Claims 1-57 and a pharmaceutically acceptable excipient.

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59. A pharmaceutical composition comprising the compound according to any of Claims 1-57 or the stereoisomer, or the pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient.

60. Use of a compound according to any one of Claims 1-57 or the pharmaceutical composition according to claim 58 or claim 59 for reducing beta amyloid peptide levels in the cerebral spinal fluid of a subject.

61. Use of a compound according to any one of Claims 1-57 or the pharmaceutical composition according to claim 58 or claim 59 for treating Alzheimer's disease, cognitive impairment or a combination thereof in a subject.

62. Use of a compound according to any one of Claims 1-57 or the pharmaceutical composition according to claim 58 or claim 59 for the treatment of a neurological disorder selected from mild cognitive impairment, Down's syndrome, Hereditary cerebral hemorrhage with dutch-type amyloidosis, cerebral amyloid angiopathy, degenerative dementia, dementia associated with Parkinson's disease, dementia associated with supranuclear palsy, dementia associated with cortical basal degeneration, diffuse lewy body type of Alzheimer's disease or a combination thereof in a subject.

63. Use of a compound according to any one of Claims 1-57 or the pharmaceutical composition according to claim 58 or claim 59 for the reduction of formation of plaque on the brain of a subject.

64. The compound according to any one of Claims 1-57 or the pharmaceutical composition according to claim 58 or claim 59 for reducing beta amyloid peptide levels in the cerebral spinal fluid of a subject.

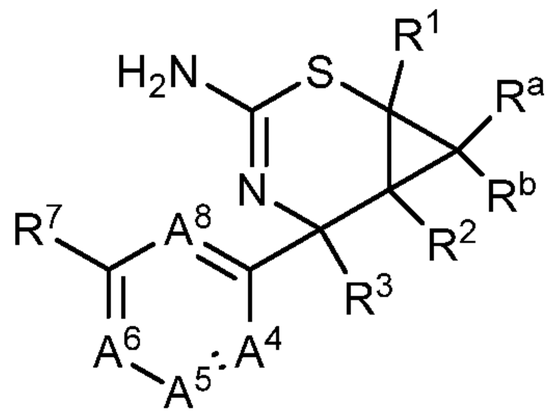
65. The compound according to any one of Claims 1-57 or the pharmaceutical composition according to claim 58 or claim 59 for treating Alzheimer's disease, cognitive impairment or a combination thereof in a subject.

66. The compound according to any one of Claims 1-57 or the pharmaceutical composition according to claim 58 or claim 59 for treating a neurological disorder

selected from mild cognitive impairment, Down's syndrome, Hereditary cerebral hemorrhage with dutch-type amyloidosis, cerebral amyloid angiopathy, degenerative dementia, dementia associated with Parkinson's disease, dementia associated with supranuclear palsy, dementia associated with cortical basal degeneration, diffuse lewy body type of Alzheimer's disease or a combination thereof in a subject.

67. The compound according to any one of Claims 1-57 or the pharmaceutical composition according to claim 58 or claim 59 for use in reducing the formation of plaque on the brain of a subject.

68. A process for preparing a compound of Formula I



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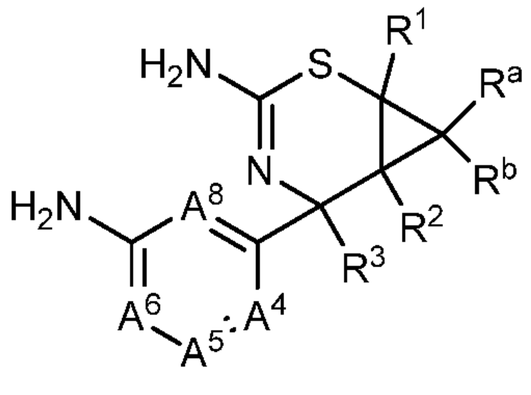
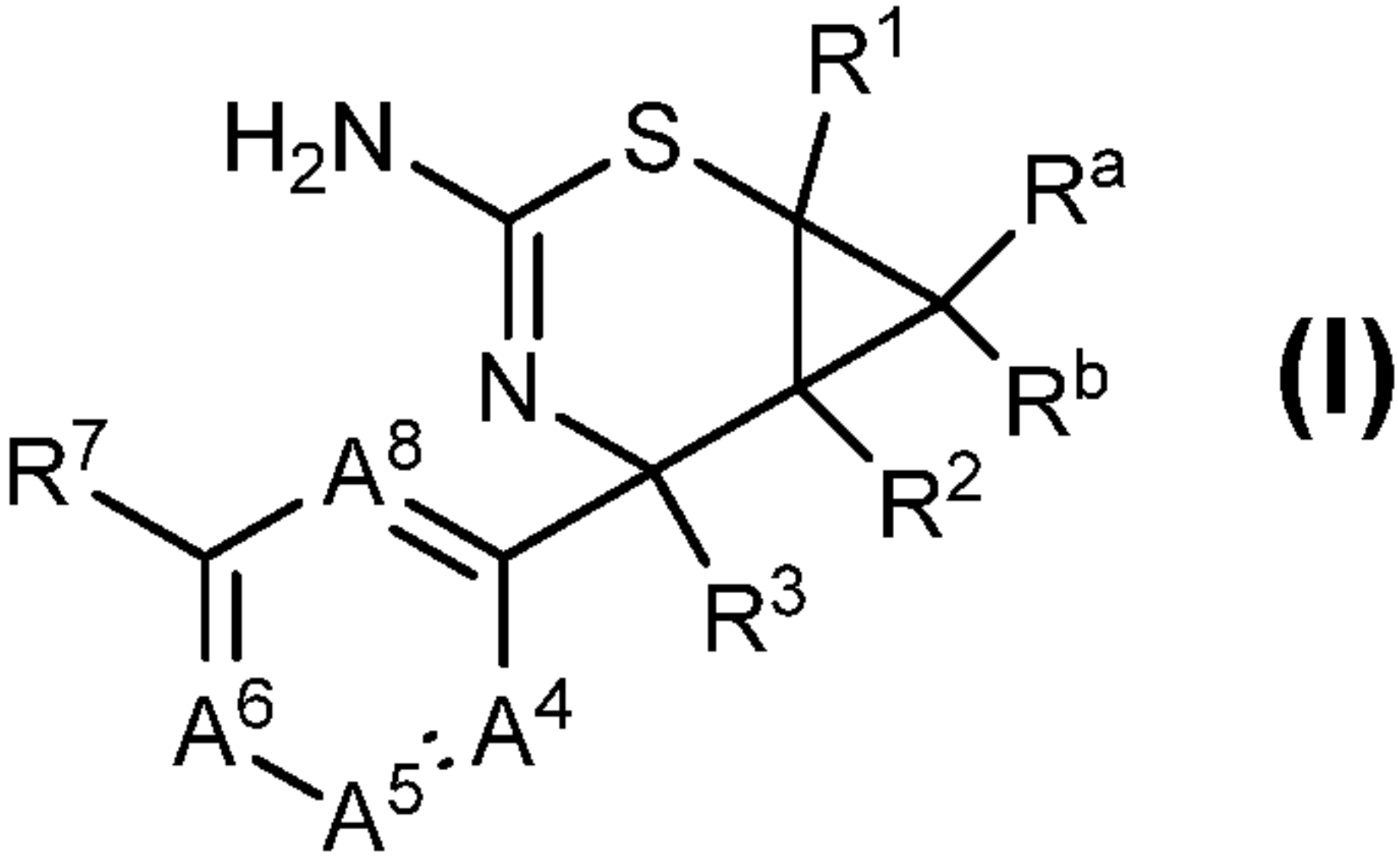
according to Claim 4, the process comprising the step of reacting a protected compound 20



20

wherein each of R^a, R^b, R^1, R^2 and R^3 and A^4, A^5, A^6 and A^8 of compound 20 are as defined in claim 4, with a compound having the structure R^9-C(=O)OH in the presence of an anhydride or an acid activating agent, or a structure R^9-Cl in the presence of an acid, wherein R^9 is as defined in claim 4 to prepare the compound according to claim 4.



(I)