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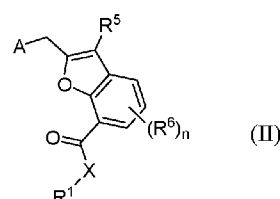
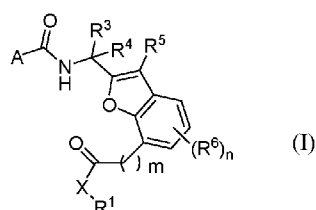
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(54) Title: BENZOFURAN COMPOUNDS AS STING AGONISTS



(57) Abstract: The present invention is directed to compounds of formula (I) and (II), wherein all substituents are defined herein, as well as pharmaceutically acceptable compositions comprising compounds of the invention and methods of using said compositions in the treatment of various disorders.



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BENZOFURAN COMPOUNDS AS STING AGONISTS

CROSS REFERENCE

This application claims the benefit of U.S. Provisional Application Serial No.
5 63/145,541, filed February 4, 2021, which is incorporated herein in its entirety.

FIELD OF THE INVENTION

The invention provides novel compounds, pharmaceutical compositions
comprising the compounds, and methods of using them, for example, for the treatment or
10 prophylaxis of certain cancers and to their use in therapy.

BACKGROUND OF THE INVENTION

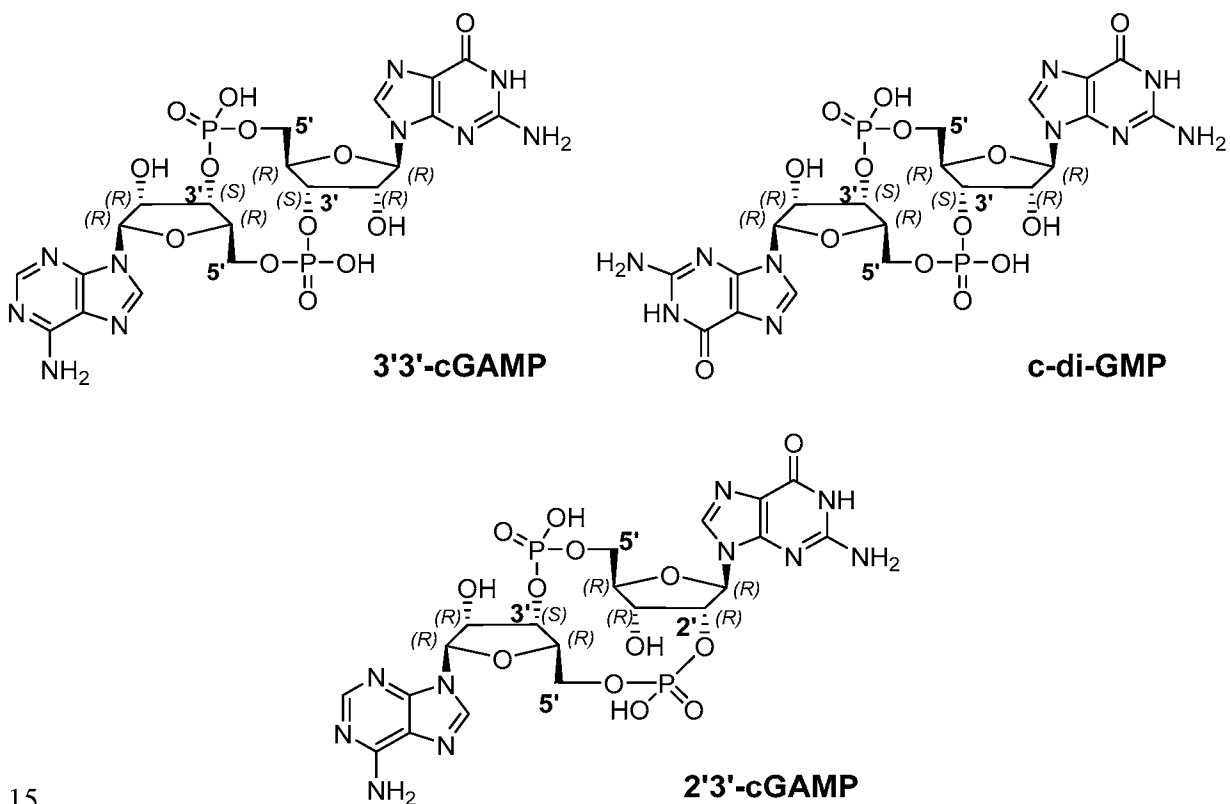
Immunotherapy is a rapidly expanding area of medical treatment in which a
patient's immune system is deliberately activated, suppressed or otherwise modulated for
15 a positive therapeutic effect. Immunotherapy agents include such things as cells,
antigens, antibodies, nucleic acids, proteins, peptides, naturally occurring ligands and
synthetically prepared molecules. Cytokines are small glycoprotein molecules known for
their role in causing immune response through complex signaling networks. Cytokines
have been explored as immunotherapy agents but their direct administration is hampered
20 by many factors including their short half-life in blood which can only be compensated
with frequent and often high doses. One highly promising approach is cytokine induction
in which the patient is treated with an immunomodulatory agent that triggers the
production of one or more therapeutically beneficial cytokines in their body.

One agent in the production of cytokines is the adaptor protein STING
25 (*ST*imulator of *IN*terferon *Genes*; also known as MPYS, TMEM173, MITA and ERIS).
STING is an intracellular receptor situated on the endoplasmic reticulum. The binding to
STING by an agonist activates a signaling pathway culminating in the induction of Type I
IFNs, which are secreted and protect the secreting and nearby cells. STING can be
activated by two different pathways, each involving a different type of cyclic dinucleotide
30 ("CDN") agonist. In the first pathway, the agonist is an exogenous CDN used by bacterial
pathogens as a second messenger (Burdette *et al.* 2013). In the second pathway the
enzyme cyclic GMP-AMP synthase (cGAS) detects cytosolic DNA and, in response,

synthesizes a CDN that functions as an endogenous STING agonist (Ablasser *et al.* 2013; Gao *et al.* 2013; Sun *et al.* 2013).

Activation of STING results in up-regulation of IRF3 and NF- κ B pathways leading to induction of Interferon- β and other cytokines. STING is crucial for responses to cytosolic DNA of pathogen or host origin.

Two exogenous bacterial STING agonist CDNs are 3'3'-cGAMP and c-di-GMP. The endogenous STING agonist CDN made by cGAS is 2'3'-cGAMP. The bacterial CDNs are characterized by two 3'5' phosphodiester bridges, while the cGAS-produced CDN is characterized by one 2'5' and one 3'5' phosphodiester bridge. As a shorthand, the former CDNs are referred to as 3'3' CDNs and the latter as 2'3' CDNs. For historical reasons, 3'3' CDNs also are referred to as the "canonical" form and 2'3' CDNs are referred to as the "non-canonical" form.



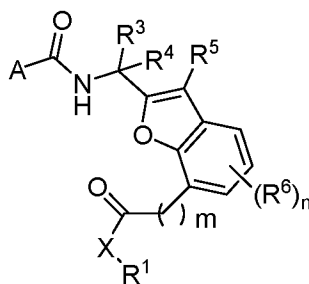
In addition to protecting an organism against pathogen infection, STING activation has also been reported to be beneficial in the treatment of inflammatory diseases and, in an area of particular current interest, cancer. Administration of a synthetic CDN in combination with the cancer vaccine STINGVAX demonstrated enhanced

antitumor efficacy in multiple therapeutic models (Fu *et al.* 2015). Administration of STING agonists alone has been reported to show potent antitumor immune efficacy in a mouse model (Corrales *et al.* 2015a). For reviews on the role of STING in infection, inflammation, and/or cancer, see Ahn *et al.* 2015; Corrales *et al.* 2015b and 2016; and Barber 2015.

The present invention, therefore, provides novel compounds which may be useful for the treatment of cancer.

DESCRIPTION OF THE INVENTION

One aspect of the invention is a compound of formula I



wherein

A is a 5-12 membered heterocyclic group substituted with 0-4 R² groups,
X is O, S or NH,

R¹ is hydrogen, CD₃, CF₃, OH, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, halo C₁₋₃ alkyl, aryl C₁₋₃ alkyl, hydroxy C₁₋₄ alkyl, halo C₁₋₃ alkoxy, NHR', 4-10 membered heterocycle or aryl, all of said alkyl, cycloalkyl, heterocyclyl or aryl groups substituted with 0-4 R^{1a}; with the proviso that R¹ is OH only when X is NH;

R^{1a} is halogen, CN, C₁₋₄ alkyl, halo C₁₋₃ alkyl, 4-10 membered heterocycle or aryl, all of said alkyl, heterocyclyl or aryl groups substituted with 0-2 R^{1b};

R^{1b} is halogen or C₁₋₄ alkyl,

R' is hydrogen, OH, C₁₋₃ alkoxy or C₁₋₃ alkyl;

R² is, independently at each occurrence, hydrogen, halogen, CN, OH, COOH, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, halo C₁₋₃ alkyl, hydroxy C₁₋₄ alkyl, halo C₁₋₃ alkoxy,

NHR', 4-10 membered heterocycle or aryl, all of said alkyl, heterocyclyl or aryl groups substituted with 0-2 R^{2a},

R^{2a} is halogen,

R³ and R⁴ are independently hydrogen or C₁₋₃ alkyl,

5 R⁵ is hydrogen, halogen, CF₃, C₁₋₆ alkyl, C₁₋₆ alkoxy or C₁₋₆ alkenyl,

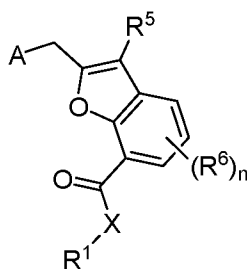
R⁶ is hydrogen, halogen, OH, CF₃, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkenyl, CN or C₃₋₆ cycloalkyl

m is 0 or 1,

n is 0, 1, 2 or 3,

10 or a pharmaceutically acceptable salt thereof.

A second aspect of the invention is a compound of formula II



15

wherein

A is a 5-12 membered heterocyclic group substituted with 0-4 R² groups,

X is O, S or NH,

20 R¹ is hydrogen, CD₃, CF₃, OH, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, halo C₁₋₃ alkyl, aryl C₁₋₃ alkyl, hydroxy C₁₋₄ alkyl, halo C₁₋₃ alkoxy, NHR', 4-10 membered heterocycle or aryl, all of said alkyl, cycloalkyl, heterocyclyl or aryl groups substituted with 0-4 R^{1a}, with the proviso that R¹ is OH only when X is NH;

25 R^{1a} is halogen, CN, C₁₋₄ alkyl, halo C₁₋₃ alkyl, 4-10 membered heterocycle or aryl, all of said alkyl, heterocyclyl or aryl groups substituted with 0-2 R^{1b};

R^{1b} is halogen or C₁₋₄ alkyl,

R' is hydrogen, OH, C₁₋₃ alkoxy or C₁₋₃ alkyl;

R^2 is, independently at each occurrence, hydrogen, halogen, CN, OH, carbonyl, COOH, C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, halo C_{1-3} alkyl, hydroxy C_{1-4} alkyl, halo C_{1-3} alkoxy, NHR^7 , 4-10 membered heterocycle or aryl, all of said alkyl, heterocyclyl or aryl groups substituted with 0-2 R^{2a} ,

5 R^{2a} is halogen,

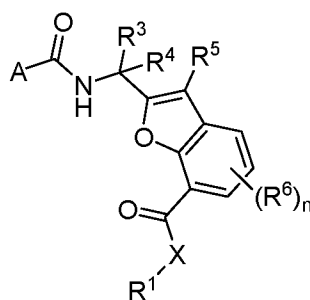
R^5 is hydrogen, halogen, CF_3 , C_{1-6} alkyl, C_{1-6} alkoxy or C_{1-6} alkenyl,

R^6 is hydrogen, halogen, OH, CF_3 , C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkenyl, CN or C_{3-6} cycloalkyl

n is 0, 1, 2 or 3,

10 or a pharmaceutically acceptable salt thereof.

In a third aspect of the invention, within the first aspect is a compound of the formula



15

wherein

A is a 5-12 membered heterocyclic group substituted with 0-4 R^2 groups,

X is O, S or NH,

20 R^1 is hydrogen, CD_3 , CF_3 , OH, C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, halo C_{1-3} alkyl, aryl C_{1-3} alkyl, hydroxy C_{1-4} alkyl, halo C_{1-3} alkoxy, NHR^7 , 4-10 membered heterocycle or aryl, all of said alkyl, cycloalkyl, heterocyclyl or aryl groups substituted with 0-4 R^{1a} , with the proviso that R^1 is OH only when X is NH;

25 R^{1a} is halogen, CN, C_{1-4} alkyl, halo C_{1-3} alkyl, 4-10 membered heterocycle or aryl, all of said alkyl, heterocyclyl or aryl groups substituted with 0-2 R^{1b} ;

R^{1b} is halogen or C_{1-4} alkyl,

R^7 is hydrogen, OH, C_{1-3} alkoxy or C_{1-3} alkyl;

R^2 is, independently at each occurrence, hydrogen, halogen, CN, OH, COOH, C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, halo C_{1-3} alkyl, hydroxy C_{1-4} alkyl, halo C_{1-3} alkoxy, NHR', 4-10 membered heterocycle or aryl, all of said alkyl, heterocyclyl or aryl groups substituted with 0-2 R^{2a} ,

5 R^{2a} is halogen,

R^3 and R^4 are independently hydrogen or C_{1-3} alkyl,

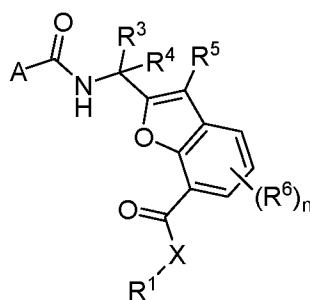
R^5 is hydrogen, halogen, CF_3 , C_{1-6} alkyl, C_{1-6} alkoxy or C_{1-6} alkenyl,

R^6 is hydrogen, halogen, OH, CF_3 , C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkenyl, CN or C_{3-6} cycloalkyl

10 n is 0, 1, 2 or 3,

or a pharmaceutically acceptable salt thereof.

In a 4th aspect of the invention, there is disclosed a compound of the formula



15

wherein

A is a 5-12 membered heterocyclic group substituted with 0-4 R^2 groups,

X is O,

20 R^1 is hydrogen, CD_3 , CF_3 , C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, halo C_{1-3} alkyl, aryl C_{1-3} alkyl, hydroxy C_{1-4} alkyl, halo C_{1-3} alkoxy, NHR', 4-10 membered heterocycle or aryl, all of said alkyl, cycloalkyl, heterocyclyl or aryl groups substituted with 0-4 R^{1a} ;

R^{1a} is halogen, CN, C_{1-4} alkyl, halo C_{1-3} alkyl, 4-10 membered heterocycle or aryl, all of said alkyl, heterocyclyl or aryl groups substituted with 0-2 R^{1b} ;

25 R^{1b} is halogen or C_{1-4} alkyl,

R^2 is hydrogen, OH, C_{1-3} alkoxy or C_{1-3} alkyl;

R^2 is, independently at each occurrence, hydrogen, halogen, CN, OH, COOH, C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, halo C_{1-3} alkyl, hydroxy C_{1-4} alkyl, halo C_{1-3} alkoxy, NHR' , 4-10 membered heterocycle or aryl, all of said alkyl, heterocyclyl or aryl groups substituted with 0-2 R^{2a} ,

5 R^{2a} is halogen,

R^3 and R^4 are independently hydrogen or C_{1-3} alkyl,

R^5 is hydrogen, halogen, CF_3 , C_{1-6} alkyl, C_{1-6} alkoxy or C_{1-6} alkenyl,

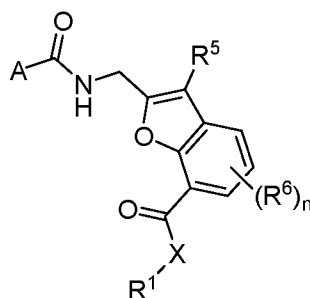
R^6 is hydrogen, halogen, OH, CF_3 , C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkenyl, CN or C_{3-6} cycloalkyl

10 n is 0, 1, 2 or 3,

or a pharmaceutically acceptable salt thereof.

In a 5th aspect of the invention, there is disclosed a compound of the formula

15



wherein

A is a 5-12 membered heterocyclic group substituted with 0-4 R^2 groups,

X is O,

20 R^1 is hydrogen, CD_3 , CF_3 , C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, halo C_{1-3} alkyl, aryl C_{1-3} alkyl, hydroxy C_{1-4} alkyl, halo C_{1-3} alkoxy, NHR' , 4-10 membered heterocycle or aryl, all of said alkyl, cycloalkyl, heterocyclyl or aryl groups substituted with 0-4 R^{1a} ;

R^{1a} is halogen, CN, C_{1-4} alkyl, halo C_{1-3} alkyl, 4-10 membered heterocycle or aryl, all of said alkyl, heterocyclyl or aryl groups substituted with 0-2 R^{1b} ;

25 R^{1b} is halogen or C_{1-4} alkyl,

R' is hydrogen, OH, C_{1-3} alkoxy or C_{1-3} alkyl;

R^2 is, independently at each occurrence, hydrogen, halogen, CN, OH, COOH, C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, halo C_{1-3} alkyl, hydroxy C_{1-4} alkyl, halo C_{1-3} alkoxy, NHR', 4-10 membered heterocycle or aryl, all of said alkyl, heterocyclyl or aryl groups substituted with 0-2 R^{2a} ,

5 R^{2a} is halogen,

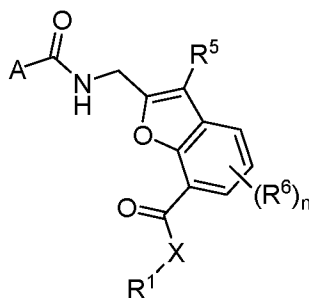
R^5 is hydrogen, halogen, CF_3 , C_{1-6} alkyl, C_{1-6} alkoxy or C_{1-6} alkenyl,

R^6 is hydrogen, halogen, OH, CF_3 , C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkenyl, CN or C_{3-6} cycloalkyl

n is 0, 1, 2 or 3,

10 or a pharmaceutically acceptable salt thereof.

In a 6th aspect of the invention, there is disclosed a compound of the formula



15

wherein

A is a 6-10 membered heterocyclic group substituted with 0-4 R^2 groups,

X is O,

20 R^1 is hydrogen, CD_3 , CF_3 , C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, halo C_{1-3} alkyl, aryl C_{1-3} alkyl, hydroxy C_{1-4} alkyl, halo C_{1-3} alkoxy, NHR', 4-10 membered heterocycle or aryl, all of said alkyl, cycloalkyl, heterocyclyl or aryl groups substituted with 0-4 R^{1a} ;

R^{1a} is halogen, CN, C_{1-4} alkyl, halo C_{1-3} alkyl, 4-10 membered heterocycle or aryl, all of said alkyl, heterocyclyl or aryl groups substituted with 0-2 R^{1b} ;

R^{1b} is halogen or C_{1-4} alkyl,

25 R^3 is hydrogen, OH, C_{1-3} alkoxy or C_{1-3} alkyl;

R^2 is, independently at each occurrence, hydrogen, halogen, CN, OH, COOH, C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, halo C_{1-3} alkyl, hydroxy C_{1-4} alkyl, halo C_{1-3} alkoxy,

NHR', 4-10 membered heterocycle or aryl, all of said alkyl, heterocyclyl or aryl groups substituted with 0-2 R^{2a},

R^{2a} is halogen,

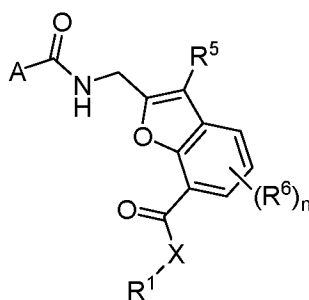
R⁵ is hydrogen, halogen, CF₃, C₁₋₆ alkyl, C₁₋₆ alkoxy or C₁₋₆ alkenyl,

5 R⁶ is hydrogen, halogen, OH, CF₃, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkenyl, CN or C₃₋₆ cycloalkyl

n is 0, 1, 2 or 3,

or a pharmaceutically acceptable salt thereof.

10 In a 7th aspect of the invention, there is disclosed a compound of the formula



wherein

15 A is a pyrazinyl group, a pyrimidinyl group, a pyridinyl group, a pyrazole-pyrimidinyl group, an imidazo-pyridazinyl group, a thiazolo-pyridinyl group, imidazo-pyridinyl group or a naphthyridinyl group, each of said groups substituted with 0-4 R² groups,

X is O,

20 R¹ is hydrogen, CD₃, CF₃, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, halo C₁₋₃ alkyl, aryl C₁₋₃ alkyl, hydroxy C₁₋₄ alkyl, halo C₁₋₃ alkoxy, NHR', 4-10 membered heterocycle or aryl, all of said alkyl, cycloalkyl, heterocyclyl or aryl groups substituted with 0-4 R^{1a};

R^{1a} is halogen, CN, C₁₋₄ alkyl, halo C₁₋₃ alkyl, 4-10 membered heterocycle or aryl, all of said alkyl, heterocyclyl or aryl groups substituted with 0-2 R^{1b};

25 R^{1b} is halogen or C₁₋₄ alkyl,

R' is hydrogen, OH, C₁₋₃ alkoxy or C₁₋₃ alkyl;

R^2 is, independently at each occurrence, hydrogen, halogen, CN, OH, COOH, C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, halo C_{1-3} alkyl, hydroxy C_{1-4} alkyl, halo C_{1-3} alkoxy, NHR', 4-10 membered heterocycle or aryl, all of said alkyl, heterocyclyl or aryl groups substituted with 0-2 R^{2a} ,

5 R^{2a} is halogen,

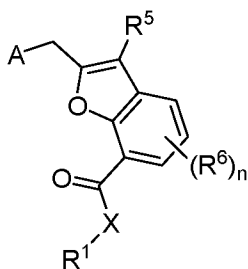
R^5 is hydrogen, halogen, CF_3 , C_{1-6} alkyl, C_{1-6} alkoxy or C_{1-6} alkenyl,

R^6 is hydrogen, halogen, OH, CF_3 , C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkenyl, CN or C_{3-6} cycloalkyl

n is 0, 1, 2 or 3,

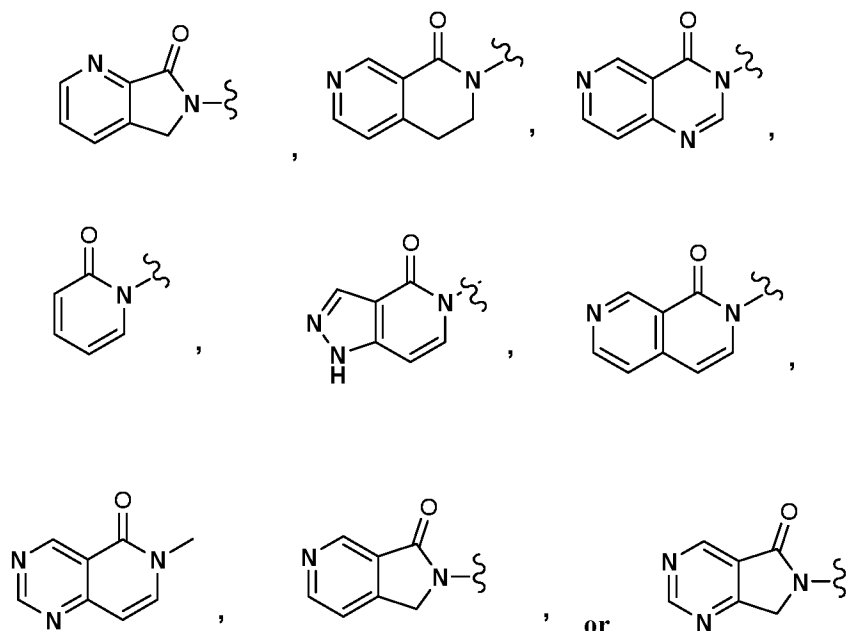
10 or a pharmaceutically acceptable salt thereof.

In another aspect of the invention within the second aspect, there is disclosed a compound of the formula



15

wherein A is



substituted with 0-4 R^2 groups,

X is O, S or NH,

R^1 is hydrogen, CD_3 , CF_3 , OH, C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, halo C_{1-3} alkyl, aryl C_{1-3} alkyl, hydroxy C_{1-4} alkyl, halo C_{1-3} alkoxy, NHR' , 4-10 membered heterocycle or aryl, all of said alkyl, cycloalkyl, heterocyclyl or aryl groups substituted with 0-4 R^{1a} , with the proviso that R^1 is OH only when X is NH;

R^{1a} is halogen, CN, C_{1-4} alkyl, halo C_{1-3} alkyl, 4-10 membered heterocycle or aryl, all of said alkyl, heterocyclyl or aryl groups substituted with 0-2 R^{1b} ;

R^{1b} is halogen or C_{1-4} alkyl,

R' is hydrogen, OH, C_{1-3} alkoxy or C_{1-3} alkyl;

R^2 is, independently at each occurrence, hydrogen, halogen, CN, OH, COOH, C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, halo C_{1-3} alkyl, hydroxy C_{1-4} alkyl, halo C_{1-3} alkoxy, NHR' , 4-10 membered heterocycle or aryl, all of said alkyl, heterocyclyl or aryl groups substituted with 0-2 R^{2a} ,

R^{2a} is halogen,

R^5 is hydrogen, halogen, CF_3 , C_{1-6} alkyl, C_{1-6} alkoxy or C_{1-6} alkenyl,

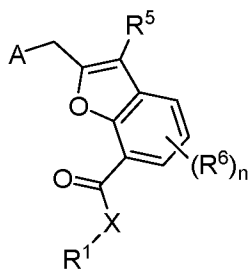
R^6 is hydrogen, halogen, OH, CF_3 , C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkenyl, CN or C_{3-6} cycloalkyl

n is 0, 1, 2 or 3,

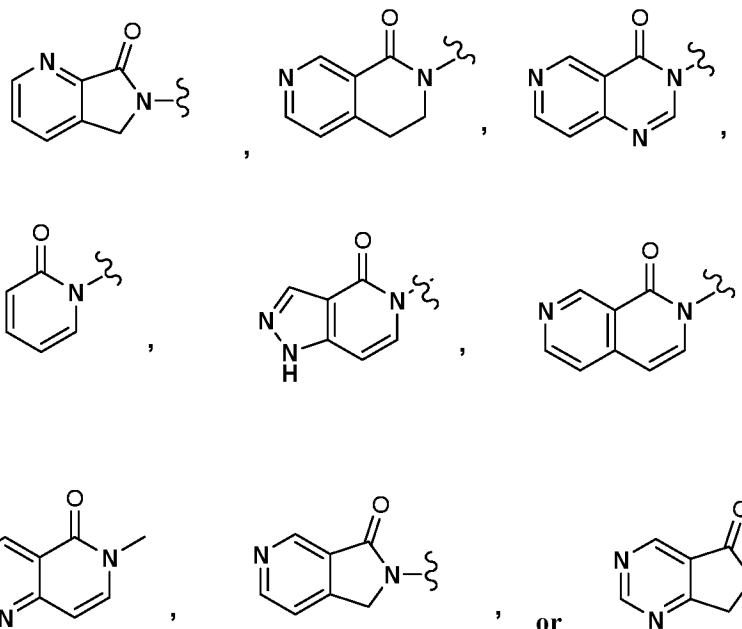
or a pharmaceutically acceptable salt thereof.

In another aspect of the invention within the second aspect, there is disclosed a compound of the formula

5



wherein A is



10

substituted with 0-4 R² groups,

X is O,

R¹ is hydrogen, CD₃, CF₃, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl or halo C₁₋₃ alkyl, all of said alkyl groups substituted with 0-4 R^{1a};

15

R^{1a} is halogen;

R² is, independently at each occurrence, hydrogen, halogen, CN, OH, COOH, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, halo C₁₋₃ alkyl, hydroxy C₁₋₄ alkyl, halo C₁₋₃ alkoxy, NHR', 4-10 membered heterocycle or aryl, all of said alkyl, heterocyclyl or aryl groups substituted with 0-2 R^{2a},

5 R^{2a} is halogen or R^{1a} is halogen,

R⁵ is hydrogen, halogen, CF₃, C₁₋₆ alkyl, C₁₋₆ alkoxy or C₁₋₆ alkenyl,

R⁶ is hydrogen, halogen, OH, CF₃, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkenyl, CN or C₃₋₆ cycloalkyl

n is 0, 1, 2 or 3,

10 or a pharmaceutically acceptable salt thereof.

In another aspect, there is provided a compound selected from the exemplified examples within the scope of the first or second aspects, or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof.

15 In another aspect, there is provided a compound selected from any subset list of compounds within the scope of any of the above aspects.

In another aspect of the invention, there is provided a compound which is

20 *Tert*-butyl 3-((5-chloro-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxyl)oxy)azetidene-1-carboxylate, (247)

Acetoxymethyl 5-chloro-2-((1,3,4-oxadiazole[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate, (259)

((Ethoxycarbonyl)oxy)methyl 5-chloro-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate, (260),

25 1-((Ethoxycarbonyl)oxy)ethyl 5-chloro-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate, (261)

1-Ethoxy-2,2-difluoroethyl 5-fluoro-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate, (323,324)

30 *S*-(2-(Trimethylsilyl)ethyl) 3-chloro-5-fluoro-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carbothioate, (392)

S-(2-(Trimethylsilyl)ethyl) (S)-5-fluoro-2-(1-(pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)ethyl)benzofuran-7-carbothioate (398)

S-(2-(Trimethylsilyl)ethyl) (*S*)-5-chloro-2-(1-(pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)ethyl)benzofuran-7-carbothioate (400)

N-((5-Chloro-7-(1*H*-tetrazol-5-yl)benzofuran-2-yl)methyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (409),

5 *N*-((5-Chloro-7-(1*H*-tetrazol-5-yl)benzofuran-2-yl)methyl)-1,6-naphthyridine-8-carboxamide (410),

N-((5-chloro-7,9-dioxo-8,9-dihydro-7*H*-benzofuro[7,6-*e*][1,3]oxazin-2-yl)methyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide, or

10 1-methyl-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)-1*H*-benzo[*d*]imidazole-4-carboxylic acid, or

a pharmaceutically acceptable salt thereof.

In another aspect of the invention, there is provided a compound which is

N-((5-chloro-7,9-dioxo-8,9-dihydro-7*H*-benzofuro[7,6-*e*][1,3]oxazin-2-yl)methyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide,

15 *N*-((5-Chloro-7-(1*H*-tetrazol-5-yl)benzofuran-2-yl)methyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide,

N-((5-Chloro-7-(1*H*-tetrazol-5-yl)benzofuran-2-yl)methyl)-1,6-naphthyridine-8-carboxamide,

20 1-methyl-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)-1*H*-benzo[*d*]imidazole-4-carboxylic acid,

or a pharmaceutically acceptable salt thereof.

OTHER EMBODIMENTS OF THE INVENTION

25 In another embodiment, the invention provides a pharmaceutical composition, comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of at least one of the compounds of the invention or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof.

In another embodiment, the invention provides a process for making a compound of the invention or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof.

30

In another embodiment, the invention provides a method for the treatment and/or prophylaxis of various types of cancer, comprising administering to a patient in need of such treatment and/or prophylaxis a therapeutically effective amount of one or more compounds of the invention, alone, or, optionally, in combination with another compound of the invention and/or at least one other type of therapeutic agent.

In another embodiment, the invention provides a method for the treatment and/or prophylaxis of various types of cancer, including small cell lung cancer, non-small cell lung cancer, colorectal cancer, melanoma, renal cell carcinoma, head and neck cancer, Hodgkin's lymphoma, bladder cancer, esophageal carcinoma, gastric carcinoma, ovarian carcinoma, cervical carcinoma, pancreatic carcinoma, prostate carcinoma, breast cancers, urinary carcinoma, , brain tumors such as glioblastoma, non-Hodgkin's lymphoma, acute lymphatic leukemia (ALL), chronic lymphatic leukemia (CLL), acute myeloid leukemia (AML), chronic myeloid leukemia (CML), hepatocellular carcinoma, multiple myeloma, gastrointestinal stromal tumors, mesothelioma, and other solid tumors or other hematological cancers

In another embodiment, the invention provides a method for the treatment and/or prophylaxis of various types of cancer, including without limitation, small cell lung cancer, non-small cell lung cancer, colorectal cancer, melanoma, renal cell carcinoma, head and neck cancer, Hodgkin's lymphoma or bladder cancer.

In another embodiment, the invention provides a compound of the present invention for use in therapy.

In another embodiment, the invention provides a combined preparation of a compound of the present invention and additional therapeutic agent(s) for simultaneous, separate or sequential use in therapy.

25

THERAPEUTIC APPLICATIONS

The compounds of the invention induce Type I interferons and/or pro-inflammatory cytokines *in vitro* in human cells, animal cells and human blood. The cytokine-inducing activity of these CDNs requires the presence of STING, as confirmed by *in vitro* experiments in human or animal cells.

30

The CDNs of the invention are agonists of the receptor STING.

The term “agonist” refers to any substance that activates a biologic receptor *in vitro* or *in vivo* to provoke a physiological response.

5 "STING" is an abbreviation of "stimulator of interferon genes", which is also known as "endoplasmic reticulum interferon stimulator (ERIS)", "mediator of IRF3 activation (MITA)", "MPYS" or "transmembrane protein 173 (TM173)". STING is a transmembrane receptor protein that in humans is encoded by the gene TMEM173. Activation of STING by cyclic dinucleotides (CDN) leads to activation of the IRF3 and NF- κ B pathways and consequently, to induction of Type I interferons and of pro-
10 inflammatory cytokines, respectively.

Another object of the present invention is the compounds of Formula (I) or (II), for use in a therapeutic treatment in humans or animals. In particular, the compounds of the present invention may be used for therapeutic or diagnostic applications in human or animal health.

15 The term "therapeutic agent" refers to one or more substances that are administered to a human or animal in order to achieve some kind of therapeutic effect in that human or animal, including to prevent, cure, or mitigate the effects of, infection or disease, and/or to otherwise improve the health of that human or animal.

The term "monotherapy" refers to the use of a single substance and/or strategy to
20 treat a human or animal in any clinical or medical context, as opposed to the use of multiple substances and/or strategies to treat a human or animal in the same clinical or medical context, regardless of whether the multiple substances and/or strategies are used sequentially in any order or concurrently.

The term "chemotherapeutic agent" herein refers to one or more chemical
25 substances that are administered to a human or animal in order to kill tumors, or slow or stop the growth of tumors, and/or slow or stop the division of cancerous cells and/or prevent or slow metastasis. Chemotherapeutic agents are often administered to treat cancer, but are also indicated for other diseases.

The term "chemotherapy" refers to medical treatment of a human or animal with one or more chemotherapeutic agents (see definition above).

The term "chemoimmunotherapy" refers to the combined use, whether sequentially in any order or concurrently, of chemotherapy substances and/or strategies, and immunotherapy substances and/or strategies. Chemoimmunotherapy is often employed to treat cancer, but can also be employed to treat other diseases.

The term "immune system" refers to the ensemble, or to any one or more components, of the molecules, substances (e.g. bodily fluids), anatomic structures (e.g. cells, tissue and organs) and physiologic processes involved in preventing infection in the body, in protecting the body during infection or during disease, and/or in helping the body to recuperate after infection or disease. A complete definition of "immune system" is beyond the scope of this patent; however, this term should be understood by any ordinary practitioner in the field.

The term "immune agent" refers to any endogenous or exogenous substance that can interact with any one or more components of the immune system. The term "immune agent" includes antibodies, antigens, vaccines and their constituent components, nucleic acids, synthetic drugs, natural or synthetic organic compounds, cytokines, natural or modified cells, synthetic analogs thereof, and/or fragments thereof.

The term "antagonist" refers to any substance that inhibits, counteracts, downregulates, and/or desensitizes a biologic receptor *in vitro* or *in vivo* to provoke a physiological response.

The term "immunotherapy" refers to any medical treatment in which one or more components of a human's or animal's immune system is deliberately modulated in order to directly or indirectly achieve some therapeutic benefit, including systemic and/or local effects, and preventative and/or curative effects. Immunotherapy can involve administering one or more immune agents (see definition above), either alone or in any combination, to a human or animal subject by any route (e.g. orally, intravenously, dermally, by injection, by inhalation, etc.), whether systemically, locally or both.

"Immunotherapy" can involve provoking, increasing, decreasing, halting, preventing, blocking or otherwise modulating the production of cytokines, and/or activating or deactivating cytokines or immune cells, and/or modulating the levels of immune cells, and/or delivering one or more therapeutic or diagnostic substances to a particular location in the body or to a particular type of cell or tissue, and/or destroying particular cells or tissue. Immunotherapy can be used to achieve local effects, systemic effects or a combination of both.

The term "immunosuppressed" describes the state of any human or animal subject whose immune system is functionally diminished, deactivated or otherwise compromised, or in whom one or more immune components is functionally diminished, deactivated or otherwise compromised.

"Immunosuppression" can be the cause, consequence or byproduct of disease, infection, exhaustion, malnutrition, medical treatment or some other physiologic or clinical state.

The terms "immunomodulating substance", "immunomodulatory substance", "immunomodulatory agent" and "immunomodulator", used here synonymously, refer to any substance that, upon administration to a human or animal, directly influences the functioning of the immune system of that human or animal. Examples of common immunomodulators include, but are not limited to, antigens, antibodies and small-molecule drugs.

The term "vaccine" refers to a biological preparation administered to a human or animal in order to elicit or enhance a specific immune system response and/or protection against one or more antigens in that human or animal.

The term "vaccination" refers to treatment of a human or animal with a vaccine or to the act of administering a vaccine to a human or animal.

The term "adjuvant" refers to a secondary therapeutic substance that is administered together (either sequentially in any order, or concurrently) with a primary therapeutic substance to achieve some kind of complimentary, synergic or otherwise beneficial effect that could not be achieved through use of the primary therapeutic

substance alone. An adjuvant can be used together with a vaccine, chemotherapy, or some other therapeutic substance. Adjuvants can enhance the efficacy of the primary therapeutic substance, reduce the toxicity or side effects of the primary therapeutic substance, or provide some kind of protection to the subject that receives the primary
5 therapeutic substance, such as, but not limited to, improved functioning of the immune system.

In one embodiment, the compounds of Formulae (I) and (II) can be administered as immunotherapy to a human or an animal to induce *in vivo* production of one or more cytokines that are therapeutically beneficial to that human or animal. This type of
10 immunotherapy could be used alone or in combination with other treatment strategies, whether sequentially in any order, or concurrently. It could be used to prevent, cure, and/or mitigate the effects of infection or disease in that human or animal, and/or to modulate the immune system of that human or animal to achieve some other therapeutic benefit.

15 In one particular embodiment, the compounds of the present invention can be used for cytokine induction immunotherapy of immunosuppressed individuals.

In this example, a compound of Formula (I) or (II) would be administered to an immunosuppressed human or animal subject to induce *in vivo* production of one or more cytokines that directly or indirectly enhance the immune system of that human or animal.
20 Subjects that might benefit from such treatment include those suffering from autoimmune disorders, immune system deficiencies or defects, microbial or viral infections, infectious diseases, or cancer.

The present invention thus discloses a method for inducing cytokine in immunosuppressed individuals, said method comprising administering to a patient in
25 need thereof a compound of Formula (I) or (II) or a pharmaceutically acceptable salt or prodrug thereof.

In another embodiment, the compounds of the present invention can be used for cytokine induction immunotherapy in combination with chemotherapy. In this example, a compound of Formula (I) or (II) would be administered together with one or more

chemotherapeutic agents, sequentially in any order or concomitantly, to a cancer patient to stop the growth of, shrink and/or destroy tumors in that patient. The chemoimmunotherapy resulting from the combination of cytokine induction, provided by the compound(s) of the present invention, and cytotoxicity, provided by the

5 chemotherapeutic agent(s), might be less toxic to the patient, cause fewer side effects in the patient and/or exhibit greater anti-tumor efficacy than would the chemotherapeutic agent(s) when used as monotherapy.

The present invention thus discloses a method for treating cancer, said method comprising administering to a patient in need thereof: a chemotherapeutic agent; and

10 a compound of Formula (I) or (II) or a pharmaceutically acceptable salt or prodrug thereof.

Another object of the present invention is a compound of Formula (I) or (II) for use in the treatment of a bacterial infection, a viral infection or a cancer.

As used herein, "cancer" refers to the physiological condition in subjects that is

15 characterized by unregulated or dysregulated cell growth or death. The term "cancer" includes solid tumors and blood-born tumors, whether malignant or benign.

In a preferred embodiment, the cancer is from the following group: small cell lung cancer, non-small cell lung cancer, colorectal cancer, melanoma, renal cell carcinoma, head and neck cancer, Hodgkin's lymphoma or bladder cancer.

20 The present invention thus discloses a method for treating a bacterial infection, a viral infection or a cancer, said method comprising administering to a patient in need thereof a compound of Formula (I) or (II) or a pharmaceutically acceptable salt or prodrug thereof.

Another object of the present invention is the compound of Formula (I) or (II) for

25 use in the treatment of a pathology that may be alleviated by the induction of an immune response via the STING pathway.

While it is possible that for use in therapy, a compound of formula (I) as well as pharmaceutically acceptable salts thereof may be administered as the compound itself, it is more commonly presented as a pharmaceutical composition.

Pharmaceutical compositions may be presented in unit dose forms containing a predetermined amount of active ingredient per unit dose. Preferred unit dosage compositions are those containing a daily dose or sub-dose, or an appropriate fraction thereof, of an active ingredient. Such unit doses may therefore be administered more than once a day. Preferred unit dosage compositions are those containing a daily dose or sub-dose (for administration more than once a day), as herein above recited, or an appropriate fraction thereof, of an active ingredient.

Types of cancers that may be treated with the compounds of this invention include, but are not limited to, brain cancers, skin cancers, bladder cancers, ovarian cancers, breast cancers, gastric cancers, pancreatic cancers, prostate cancers, colorectal cancers, blood cancers, lung cancers and bone cancers. Examples of such cancer types include neuroblastoma, intestinal carcinoma such as rectal carcinoma, colon carcinomas, familial adenomatous polyposis carcinoma and hereditary non-polyposis colorectal cancer, esophageal carcinoma, labial carcinoma, larynx carcinoma, nasopharyngeal cancers, oral cavity cancers, salivary gland carcinoma, peritoneal cancers, soft tissue sarcoma, urothelial cancers, sweat gland carcinoma, gastric carcinoma, adenocarcinoma, medullary thyroid carcinoma, papillary thyroid carcinoma, renal carcinoma, kidney parenchymal carcinoma, ovarian carcinoma, cervical carcinoma, uterine corpus carcinoma, endometrial carcinoma, pancreatic carcinoma, prostate carcinoma, testis carcinoma, breast cancers including HER2 Negative, urinary carcinoma, melanoma, brain tumors such as glioblastoma, astrocytoma, meningioma, medulloblastoma and peripheral neuroectodermal tumors, Hodgkin's lymphoma, non-Hodgkin's lymphoma, Burkitt lymphoma, acute lymphatic leukemia (ALL), chronic lymphatic leukemia (CLL), acute myeloid leukemia (AML), chronic myeloid leukemia (CML), adult T-cell leukemia lymphoma, diffuse large B-cell lymphoma (DLBCL), hepatocellular carcinoma, multiple myeloma, seminoma, osteosarcoma, chondrosarcoma, anal canal cancers, adrenal cortex carcinoma, chordoma, fallopian tube cancer, gastrointestinal stromal tumors, myeloproliferative diseases, mesothelioma, biliary tract cancers, Ewing sarcoma and other rare tumor types.

Compounds of the invention are useful for the treatment of certain types of cancer by themselves or in combination or co-administration with other therapeutic agents or radiation therapy. Thus, in one embodiment, the compounds of the invention are co-administered with radiation therapy or a second therapeutic agent with cytostatic or antineoplastic activity. Suitable cytostatic chemotherapy compounds include, but are not limited to (i) antimetabolites; (ii) DNA-fragmenting agents, (iii) DNA-crosslinking agents, (iv) intercalating agents (v) protein synthesis inhibitors, (vi) topoisomerase I poisons, such as camptothecin or topotecan; (vii) topoisomerase II poisons, (viii) microtubule-directed agents, (ix) kinase inhibitors (x) miscellaneous investigational agents (xi) hormones and (xii) hormone antagonists. It is contemplated that compounds of the invention may be useful in combination with any known agents falling into the above 12 classes as well as any future agents that are currently in development. In particular, it is contemplated that compounds of the invention may be useful in combination with current Standards of Care as well as any that evolve over the foreseeable future. Specific dosages and dosing regimens would be based on physicians' evolving knowledge and the general skill in the art.

Further provided herein are methods of treatment wherein compounds of the invention are administered with one or more immuno-oncology agents. The immuno-oncology agents used herein, also known as cancer immunotherapies, are effective to enhance, stimulate, and/or up-regulate immune responses in a subject. In one aspect, the administration of a compound of the invention with an immuno-oncology agent has a synergistic effect in inhibiting tumor growth.

In one aspect, the compound(s) of the invention are sequentially administered prior to administration of the immuno-oncology agent. In another aspect, compound(s) of the invention are administered concurrently with the immunology-oncology agent. In yet another aspect, compound(s) of the invention are sequentially administered after administration of the immuno-oncology agent.

In another aspect, compounds of the invention may be co-formulated with an immuno-oncology agent.

Immuno-oncology agents include, for example, a small molecule drug, antibody,

or other biologic molecule. Examples of biologic immuno-oncology agents include, but are not limited to, cancer vaccines, antibodies, and cytokines. In one aspect, the antibody is a monoclonal antibody. In another aspect, the monoclonal antibody is humanized or human.

5 In one aspect, the immuno-oncology agent is (i) an agonist of a stimulatory (including a co-stimulatory) receptor or (ii) an antagonist of an inhibitory (including a co-inhibitory) signal on T cells, both of which result in amplifying antigen-specific T cell responses (often referred to as immune checkpoint regulators).

Certain of the stimulatory and inhibitory molecules are members of the
10 immunoglobulin super family (IgSF). One important family of membrane-bound ligands that bind to co-stimulatory or co-inhibitory receptors is the B7 family, which includes B7-1, B7-2, B7-H1 (PD-L1), B7-DC (PD-L2), B7-H2 (ICOS-L), B7-H3, B7-H4, B7-H5 (VISTA), and B7-H6. Another family of membrane bound ligands that bind to co-stimulatory or co-inhibitory receptors is the TNF family of molecules that bind to cognate
15 TNF receptor family members, which includes CD40 and CD40L, OX-40, OX-40L, CD70, CD27L, CD30, CD30L, 4-1BBL, CD137 (4-1BB), TRAIL/Apo2-L, TRAILR1/DR4, TRAILR2/DR5, TRAILR3, TRAILR4, OPG, RANK, RANKL, TWEAKR/Fn14, TWEAK, BAFFR, EDAR, XEDAR, TACI, APRIL, BCMA, LT β R, LIGHT, DcR3, HVEM, VEGI/TL1A, TRAMP/DR3, EDAR, EDA1, XEDAR, EDA2,
20 TNFR1, Lymphotoxin α /TNF β , TNFR2, TNF α , LT β R, Lymphotoxin α 1 β 2, FAS, FASL, RELT, DR6, TROY, NGFR.

In one aspect, T cell responses can be stimulated by a combination of a compound of the invention and one or more of (i) an antagonist of a protein that inhibits T cell activation (e.g., immune checkpoint inhibitors) such as CTLA-4, PD-1, PD-L1, PD-L2,
25 LAG-3, TIM-3, Galectin 9, CEACAM-1, BTLA, CD69, Galectin-1, TIGIT, CD113, GPR56, VISTA, 2B4, CD48, GARP, PD1H, LAIR1, TIM-1, and TIM-4, and (ii) an agonist of a protein that stimulates T cell activation such as B7-1, B7-2, CD28, 4-1BB (CD137), 4-1BBL, ICOS, ICOS-L, OX40, OX40L, GITR, GITRL, CD70, CD27, CD40, DR3 and CD28H.

30 Other agents that can be combined with compounds of the invention for the treatment of cancer include antagonists of inhibitory receptors on NK cells or agonists of

activating receptors on NK cells. For example, compounds of the invention can be combined with antagonists of KIR, such as lirilumab.

Yet other agents for combination therapies include agents that inhibit or deplete macrophages or monocytes, including but not limited to CSF-1R antagonists such as
5 CSF-1R antagonist antibodies including RG7155 (WO11/70024, WO11/107553, WO11/131407, WO13/87699, WO13/119716, WO13/132044) or FPA-008 (WO11/140249; WO13169264; WO14/036357).

In another aspect, compounds of the invention can be used with one or more of agonistic agents that ligate positive costimulatory receptors, blocking agents that
10 attenuate signaling through inhibitory receptors, antagonists, and one or more agents that increase systemically the frequency of anti-tumor T cells, agents that overcome distinct immune suppressive pathways within the tumor microenvironment (e.g., block inhibitory receptor engagement (e.g., PD-L1/PD-1 interactions), deplete or inhibit Tregs (e.g., using an anti-CD25 monoclonal antibody (e.g., daclizumab) or by ex vivo anti-CD25 bead
15 depletion), inhibit metabolic enzymes such as IDO, or reverse/prevent T cell anergy or exhaustion) and agents that trigger innate immune activation and/or inflammation at tumor sites.

In one aspect, the immuno-oncology agent is a CTLA-4 antagonist, such as an antagonistic CTLA-4 antibody. Suitable CTLA-4 antibodies include, for example,
20 YERVOY (ipilimumab) or tremelimumab.

In another aspect, the immuno-oncology agent is a PD-1 antagonist, such as an antagonistic PD-1 antibody. The PD-1 antibody can be selected from Opdivo (nivolumab), Keytruda (pembrolizumab), PDR001 (Novartis; see WO2015/112900),
25 MEDI-0680 (AMP-514) (AstraZeneca; see WO2012/145493), REGN-2810 (Sanofi/Regeneron; see WO2015/112800), JS001 (Taizhou Junshi), BGB-A317 (Beigene; see WO2015/35606), INCSHR1210 (SHR-1210) (Incyte/Jiangsu Hengrui Medicine; see WO2015/085847), TSR-042 (ANB001) (Tesara/AnaptysBio; see WO2014/179664), GLS-010 (Wuxi/Harbin Gloria Pharmaceuticals), AM-0001 (Armo/Ligand), or STI-1110 (Sorrento; see WO2014/194302). The immuno-oncology agent may also include
30 pidilizumab (CT-011), though its specificity for PD-1 binding has been questioned. Another approach to target the PD-1 receptor is the recombinant protein composed of the extracellular domain of PD-L2 (B7-DC) fused to the Fc portion of IgG1, called AMP-224

In another aspect, the immuno-oncology agent is a PD-L1 antagonist, such as an antagonistic PD-L1 antibody. The PD-L1 antibody can be selected from Tecentriq (atezolizumab), durvalumab, avelumab, STI-1014 (Sorrento; see WO2013/181634), or CX-072 (CytomX; see WO2016/149201)..

5 In another aspect, the immuno-oncology agent is a LAG-3 antagonist, such as an antagonistic LAG-3 antibody. Suitable LAG3 antibodies include, for example, BMS-986016 (WO10/19570, WO14/08218), or IMP-731 or IMP-321 (WO08/132601, WO09/44273).

10 In another aspect, the immuno-oncology agent is a CD137 (4-1BB) agonist, such as an agonistic CD137 antibody. Suitable CD137 antibodies include, for example, urelumab and PF-05082566 (WO12/32433).

In another aspect, the immuno-oncology agent is a GITR agonist, such as an agonistic GITR antibody. Suitable GITR antibodies include, for example, BMS-986153, BMS-986156, TRX-518 (WO06/105021, WO09/009116) and MK-4166 (WO11/028683).

15 In another aspect, the immuno-oncology agent is an IDO antagonist. Suitable IDO antagonists include, for example, INCB-024360 (WO2006/122150, WO07/75598, WO08/36653, WO08/36642), indoximod, or NLG-919 (WO09/73620, WO09/1156652, WO11/56652, WO12/142237).

20 In another aspect, the immuno-oncology agent is an OX40 agonist, such as an agonistic OX40 antibody. Suitable OX40 antibodies include, for example, MEDI-6383 or MEDI-6469.

In another aspect, the immuno-oncology agent is an OX40L antagonist, such as an antagonistic OX40 antibody. Suitable OX40L antagonists include, for example, RG-7888 (WO06/029879).

25 In another aspect, the immuno-oncology agent is a CD40 agonist, such as an agonistic CD40 antibody. In yet another embodiment, the immuno-oncology agent is a CD40 antagonist, such as an antagonistic CD40 antibody. Suitable CD40 antibodies include, for example, lucatumumab or dacetuzumab.

30 In another aspect, the immuno-oncology agent is a CD27 agonist, such as an agonistic CD27 antibody. Suitable CD27 antibodies include, for example, varlilumab.

In another aspect, the immuno-oncology agent is MGA271 (to B7H3) (WO11/109400).

The combination therapy is intended to embrace administration of these therapeutic agents in a sequential manner, that is, wherein each therapeutic agent is administered at a different time, as well as administration of these therapeutic agents, or at least two of the therapeutic agents, in a substantially simultaneous manner.

5 Substantially simultaneous administration can be accomplished, for example, by administering to the subject a single dosage form having a fixed ratio of each therapeutic agent or in multiple, single dosage forms for each of the therapeutic agents. Sequential or substantially simultaneous administration of each therapeutic agent can be effected by any appropriate route including, but not limited to, oral routes, intravenous routes, 10 intratumoral routes, intramuscular routes, and direct absorption through mucous membrane tissues. The therapeutic agents can be administered by the same route or by different routes. For example, a first therapeutic agent of the combination selected may be administered by intravenous injection while the other therapeutic agents of the combination may be administered orally. Alternatively, for example, all therapeutic 15 agents may be administered orally or all therapeutic agents may be administered by intravenous injection. Combination therapy also can embrace the administration of the therapeutic agents as described above in further combination with other biologically active ingredients and non-drug therapies (*e.g.*, surgery or radiation treatment.) Where the combination therapy further comprises a non-drug treatment, the non-drug treatment 20 may be conducted at any suitable time so long as a beneficial effect from the co-action of the combination of the therapeutic agents and non-drug treatment is achieved. For example, in appropriate cases, the beneficial effect is still achieved when the non-drug treatment is temporally removed from the administration of the therapeutic agents, perhaps by days or even weeks.

25 The present invention may be embodied in other specific forms without departing from the spirit or essential attributes thereof. This invention encompasses all combinations of preferred aspects of the invention noted herein. It is understood that any and all embodiments of the present invention may be taken in conjunction with any other embodiment or embodiments to describe additional embodiments. It is also understood 30 that each individual element of the embodiments is its own independent embodiment. Furthermore, any element of an embodiment is meant to be combined with any and all other elements from any embodiment to describe an additional embodiment.

PHARMACEUTICAL COMPOSITIONS AND DOSING

The invention also provides pharmaceutically acceptable compositions which comprise a therapeutically effective amount of one or more of the compounds of Formula I, formulated together with one or more pharmaceutically acceptable carriers (additives) and/or diluents, and optionally, one or more additional therapeutic agents described above. As described in detail below, the pharmaceutical compositions of the present invention may be specially formulated for administration in solid or liquid form, including those adapted for the following: (1) oral administration, for example, drenches (aqueous or non-aqueous solutions or suspensions), tablets, e.g., those targeted for buccal, sublingual, and systemic absorption, boluses, powders, granules, pastes for application to the tongue; (2) parenteral administration, for example, by subcutaneous, intramuscular, intratumoral, intravenous or epidural injection as, for example, a sterile solution or suspension, or sustained release formulation; (3) topical application, for example, as a cream, ointment, or a controlled release patch or spray applied to the skin; or intratumorally.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

The phrase "pharmaceutically acceptable carrier" as used herein means a pharmaceutically acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, manufacturing aid (e.g., lubricant, talc magnesium, calcium or zinc stearate, or steric acid), or solvent encapsulating material, involved in carrying or transporting the subject compound from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient.

Formulations of the present invention include those suitable for oral, intratumoral, nasal, topical (including buccal and sublingual), rectal, vaginal and/or parenteral administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. The amount of active ingredient which can be combined with a carrier material to produce a single

dosage form will vary depending upon the patient being treated and the particular mode of administration. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will generally be that amount of the compound which produces a therapeutic effect. Generally, out of one hundred percent, this amount will range from about 0.1 percent to about ninety-nine percent of active ingredient, preferably from about 5 percent to about 70 percent, most preferably from about 10 percent to about 30 percent.

In certain embodiments, a formulation of the present invention comprises an excipient selected from the group consisting of cyclodextrins, celluloses, liposomes, micelle forming agents, e.g., bile acids, and polymeric carriers, e.g., polyesters and polyanhydrides; and a compound of the present invention. In certain embodiments, an aforementioned formulation renders orally bioavailable a compound of the present invention.

Methods of preparing these formulations or compositions include the step of bringing into association a compound of the present invention with the carrier and, optionally, one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association a compound of the present invention with liquid carriers, or finely divided solid carriers, or both, and then, if necessary, shaping the product.

Formulations of the invention suitable for oral administration may be in the form of capsules, cachets, pills, tablets, lozenges (using a flavored basis, usually sucrose and acacia or tragacanth), powders, granules, or as a solution or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion, or as an elixir or syrup, or as pastilles (using an inert base, such as gelatin and glycerin, or sucrose and acacia) and/or as mouth washes and the like, each containing a predetermined amount of a compound of the present invention as an active ingredient. A compound of the present invention may also be administered as a bolus, electuary or paste.

Pharmaceutical compositions of this invention suitable for parenteral administration comprise one or more compounds of the invention in combination with one or more pharmaceutically acceptable sterile isotonic aqueous or non-aqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be

reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain sugars, alcohols, antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

5 In some cases, in order to prolong the effect of a drug, it is desirable to slow the absorption of the drug from subcutaneous, intratumoral or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material having poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline
10 form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

Injectable depot forms are made by forming microencapsulated matrices of the subject compounds in biodegradable polymers such as polylactide-polyglycolide. Depending on the ratio of drug to polymer, and the nature of the particular polymer
15 employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissue.

When the compounds of the present invention are administered as
20 pharmaceuticals, to humans and animals, they can be given per se or as a pharmaceutical composition containing, for example, 0.1 to 99% (more preferably, 10 to 30%) of active ingredient in combination with a pharmaceutically acceptable carrier.

Regardless of the route of administration selected, the compounds of the present invention, which may be used in a suitable hydrated form, and/or the pharmaceutical
25 compositions of the present invention, are formulated into pharmaceutically acceptable dosage forms by conventional methods known to those of skill in the art.

Actual dosage levels of the active ingredients in the pharmaceutical compositions of this invention may be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition,
30 and mode of administration, without being toxic to the patient.

The selected dosage level will depend upon a variety of factors including the activity of the particular compound of the present invention employed, or the ester, salt or

amide thereof, the route of administration, the time of administration, the rate of excretion or metabolism of the particular compound being employed, the rate and extent of absorption, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compound employed, the age, sex, weight, condition,
5 general health and prior medical history of the patient being treated, and like factors well known in the medical arts.

A physician or veterinarian having ordinary skill in the art can readily determine and prescribe the effective amount of the pharmaceutical composition required. For example, the physician or veterinarian could start doses of the compounds of the
10 invention employed in the pharmaceutical composition at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved.

In general, a suitable daily dose of a compound of the invention will be that amount of the compound which is the lowest dose effective to produce a therapeutic
15 effect. Such an effective dose will generally depend upon the factors described above. Generally, oral, intravenous, intracerebroventricular and subcutaneous doses of the compounds of this invention for a patient will range from about 0.01 to about 50 mg per kilogram of body weight per day.

While it is possible for a compound of the present invention to be administered
20 alone, it is preferable to administer the compound as a pharmaceutical formulation (composition).

DEFINITIONS

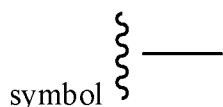
Unless specifically stated otherwise herein, references made in the singular may
25 also include the plural. For example, “a” and “an” may refer to either one, or one or more.

Unless otherwise indicated, any heteroatom with unsatisfied valences is assumed to have hydrogen atoms sufficient to satisfy the valences.

Throughout the specification and the appended claims, a given chemical formula
30 or name shall encompass all stereo and optical isomers and racemates thereof where such isomers exist. Unless otherwise indicated, all chiral (enantiomeric and diastereomeric) and racemic forms are within the scope of the invention. Many geometric isomers of

C=C double bonds, C=N double bonds, ring systems, and the like can also be present in the compounds, and all such stable isomers are contemplated in the present invention. Cis- and trans- (or *E*- and *Z*-) geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms. The present compounds can be isolated in optically active or racemic forms. Optically active forms may be prepared by resolution of racemic forms or by synthesis from optically active starting materials. All processes used to prepare compounds of the present invention and intermediates made therein are considered to be part of the present invention. When enantiomeric or diastereomeric products are prepared, they may be separated by conventional methods, for example, by chromatography or fractional crystallization. Depending on the process conditions the end products of the present invention are obtained either in free (neutral) or salt form. Both the free form and the salts of these end products are within the scope of the invention. If so desired, one form of a compound may be converted into another form. A free base or acid may be converted into a salt; a salt may be converted into the free compound or another salt; a mixture of isomeric compounds of the present invention may be separated into the individual isomers. Compounds of the present invention, free form and salts thereof, may exist in multiple tautomeric forms, in which hydrogen atoms are transposed to other parts of the molecules and the chemical bonds between the atoms of the molecules are consequently rearranged. It should be understood that all tautomeric forms, insofar as they may exist, are included within the invention.

For purposes of clarity and in accordance with standard convention in the art, the



is used in formulas and tables to show the bond that is the point of attachment of the moiety or substituent to the core/nucleus of the structure.

Additionally, for purposes of clarity, where a substituent has a dash (-) that is not between two letters or symbols; this is used to indicate a point of attachment for a substituent. For example, -CONH₂ is attached through the carbon atom.

Additionally, for purposes of clarity, when there is no substituent shown at the end of a solid line, this indicates that there is a methyl (CH₃) group connected to the bond.

The term “alkyl” as used herein, refers to both branched and straight-chain saturated aliphatic hydrocarbon groups containing, for example, from 1 to 12 carbon atoms, from 1 to 6 carbon atoms, and from 1 to 4 carbon atoms. Examples of alkyl groups include, but are not limited to, methyl (Me), ethyl (Et), propyl (*e.g.*, n-propyl and i-propyl), butyl (*e.g.*, n-butyl, i-butyl, sec-butyl, and *t*-butyl), and pentyl (*e.g.*, n-pentyl, isopentyl, neopentyl), n-hexyl, 2-methylpentyl, 2-ethylbutyl, 3-methylpentyl, and 4-methylpentyl. When numbers appear in a subscript after the symbol “C”, the subscript defines with more specificity the number of carbon atoms that a particular group may contain. For example, “C₁₋₄ alkyl” denotes straight and branched chain alkyl groups with one to four carbon atoms.

The term “haloalkyl” which includes the term "fluoroalkyl" as used herein is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups substituted with one or more fluorine atoms. For example, "C₁₋₄ fluoroalkyl" is intended to include C₁, C₂, C₃, and C₄ alkyl groups substituted with one or more fluorine atoms. Representative examples of fluoroalkyl groups include, but are not limited to, -CF₃ and -CH₂CF₃.

The term "hydroxyalkyl" includes both branched and straight-chain saturated alkyl groups substituted with one or more hydroxyl groups. For example, "hydroxyalkyl" includes -CH₂OH, -CH₂CH₂OH, and C₁₋₄ hydroxyalkyl.

The term "alkenyl" refers to a straight or branched chain hydrocarbon radical containing from 2 to 12 carbon atoms and at least one carbon-carbon double bond. Exemplary such groups include ethenyl or allyl. For example, "C₂₋₆ alkenyl" denotes straight and branched chain alkenyl groups with two to six carbon atoms.

The term “cycloalkyl,” as used herein, refers to a group derived from a non-aromatic monocyclic or polycyclic hydrocarbon molecule by removal of one hydrogen atom from a saturated ring carbon atom. Representative examples of cycloalkyl groups include, but are not limited to, cyclopropyl, cyclopentyl, and cyclohexyl. When numbers appear in a subscript after the symbol “C”, the subscript defines with more specificity the

number of carbon atoms that a particular cycloalkyl group may contain. For example, “C₃₋₆ cycloalkyl” denotes cycloalkyl groups with three to six carbon atoms.

The term “alkoxy,” as used herein, refers to an alkyl group attached to the parent molecular moiety through an oxygen atom, for example, methoxy group (-OCH₃). For
5 example, “C₁₋₃ alkoxy” denotes alkoxy groups with one to three carbon atoms.

The terms “fluoroalkoxy” and “-O(fluoroalkyl)” represent a fluoroalkyl group as defined above attached through an oxygen linkage (-O-). For example, “C₁₋₄ fluoroalkoxy” is intended to include C₁, C₂, C₃, and C₄ fluoroalkoxy groups.

The terms “carbocyclo”, “carbocyclic” or “carbocyclyl” may be used
10 interchangeably and refer to cyclic groups having at least one saturated or partially saturated non-aromatic ring wherein all atoms of all rings are carbon. The carbocyclyl ring may be unsubstituted or may contain one or more substituents as valence allows. Thus, the term includes nonaromatic rings such as for example, cycloalkyl, cycloalkenyl, and cycloalkynyl rings. Exemplary bicyclic carbocyclyl groups include, indanyl, indenyl,
15 dihydronaphthalenyl, tetrahydronaphthenyl, hexahydronaphthalenyl, octahydronaphthalenyl, decahydronaphthalenyl, bicycloheptanyl, bicyclooctanyl, and bicyclononanyl.

The term “aryl” as used herein, refers to a group of atoms derived from a molecule containing aromatic ring(s) by removing one hydrogen that is bonded to the aromatic
20 ring(s). Representative examples of aryl groups include, but are not limited to, phenyl and naphthyl. The aryl ring may be unsubstituted or may contain one or more substituents as valence allows.

The term “benzyl,” as used herein, refers to a methyl group in which one of the hydrogen atoms is replaced by a phenyl group. The phenyl ring may be unsubstituted or
25 may contain one or more substituents as valence allows.

The term “heteroatom” refers to oxygen (O), sulfur (S), and nitrogen (N).

The terms “heterocyclo”, “heterocyclic”, or “heterocyclyl” may be used interchangeably and refer to cyclic groups having at least one saturated or partially

saturated non-aromatic ring and wherein one or more of the rings have at least one heteroatom (O, S or N), said heteroatom containing ring preferably having 1 to 3 heteroatoms independently selected from O, S, and/or N. The ring of such a group containing a heteroatom can contain one or two oxygen or sulfur atoms and/or from one to four nitrogen atoms provided that the total number of heteroatoms in each ring is four or less, and further provided that the ring contains at least one carbon atom. The nitrogen and sulfur atoms may optionally be oxidized and the nitrogen atoms may optionally be quaternized. The heterocyclo group may be attached at any available nitrogen or carbon atom. The heterocyclo ring may be unsubstituted or may contain one or more substituents as valence allows.

Exemplary monocyclic heterocyclyl groups include pyrrolidinyl, imidazoliny, oxazolidinyl, isoxazoliny, thiazolidinyl, isothiazolidinyl, tetrahydrofuranyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolodiny, 2-oxoazepiny, azepiny, 4-piperidonyl, tetrahydropyranyl, morpholinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, 1,3-dioxolane, tetrahydro-1,1-dioxothienyl, dihydroisoindolyl, and tetrahydroquinoliny

The term “heteroaryl” refers to substituted and unsubstituted aromatic 5- or 6-membered monocyclic groups and 9- or 10-membered bicyclic groups that have at least one heteroatom (O, S or N) in at least one of the rings, said heteroatom-containing ring preferably having 1, 2, or 3 heteroatoms independently selected from O, S, and/or N. Each ring of the heteroaryl group containing a heteroatom can contain one or two oxygen or sulfur atoms and/or from one to four nitrogen atoms provided that the total number of heteroatoms in each ring is four or less and each ring has at least one carbon atom. The fused rings completing the bicyclic group are aromatic and may contain only carbon atoms. The nitrogen and sulfur atoms may optionally be oxidized and the nitrogen atoms may optionally be quaternized. Bicyclic heteroaryl groups must include only aromatic rings. The heteroaryl group may be attached at any available nitrogen or carbon atom of any ring. The heteroaryl ring system may be unsubstituted or may contain one or more substituents.

Exemplary monocyclic heteroaryl groups include pyrrolyl, pyrazolyl, pyrazolinyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, isothiazolyl, furanyl, thiophenyl, oxadiazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, and triazinyl.

Exemplary bicyclic heteroaryl groups include indolyl, benzothiazolyl,
5 benzodioxolyl, benzoxazolyl, benzothienyl, quinolinyl, tetrahydroisoquinolinyl, isoquinolinyl, benzimidazolyl, benzopyranyl, indolizinyl, benzofuranyl, chromonyl, coumarinyl, benzopyranyl, cinnolinyl, quinoxalinyl, indazolyl, and pyrrolopyridyl.

The term "counter ion" is used to represent a negatively charged species such as chloride, bromide, hydroxide, acetate, and sulfate or a positively charged species such as
10 sodium (Na⁺), potassium (K⁺), ammonium (R_nNH_m⁺ where n=0-4 and m=0-4) and the like.

The term "electron withdrawing group" (EWG) refers to a substituent which polarizes a bond, drawing electron density towards itself and away from other bonded atoms. Examples of EWGs include, but are not limited to, CF₃, CF₂CF₃, CN, halogen,
15 haloalkyl, NO₂, sulfone, sulfoxide, ester, sulfonamide, carboxamide, alkoxy, alkoxyether, alkenyl, alkynyl, OH, C(O)alkyl, CO₂H, phenyl, heteroaryl, -O-phenyl, and -O-heteroaryl. Preferred examples of EWG include, but are not limited to, CF₃, CF₂CF₃, CN, halogen, SO₂(C₁₋₄ alkyl), CONH(C₁₋₄ alkyl), CON(C₁₋₄ alkyl)₂, and heteroaryl. More preferred examples of EWG include, but are not limited to, CF₃ and CN.

20 As used herein, the term "amine protecting group" means any group known in the art of organic synthesis for the protection of amine groups which is stable to an ester reducing agent, a disubstituted hydrazine, R₄-M and R₇-M, a nucleophile, a hydrazine reducing agent, an activator, a strong base, a hindered amine base and a cyclizing agent. Such amine protecting groups fitting these criteria include those listed in Wuts, P. G. M.
25 and Greene, T.W. *Protecting Groups in Organic Synthesis*, 4th Edition, Wiley (2007) and *The Peptides: Analysis, Synthesis, Biology*, Vol. 3, Academic Press, New York (1981), the disclosure of which is hereby incorporated by reference. Examples of amine protecting groups include, but are not limited to, the following: (1) acyl types such as formyl, trifluoroacetyl, phthalyl, and p-toluenesulfonyl; (2) aromatic carbamate types
30 such as benzyloxycarbonyl (Cbz) and substituted benzyloxycarbonyls,

1-(p-biphenyl)-1-methylethoxycarbonyl, and 9-fluorenylmethyloxycarbonyl (Fmoc); (3) aliphatic carbamate types such as *tert*-butyloxycarbonyl (Boc), ethoxycarbonyl, diisopropylmethoxycarbonyl, and allyloxycarbonyl; (4) cyclic alkyl carbamate types such as cyclopentyloxycarbonyl and adamantyloxycarbonyl; (5) alkyl types such as
5 triphenylmethyl and benzyl; (6) trialkylsilane such as trimethylsilane; (7) thiol containing types such as phenylthiocarbonyl and dithiasuccinoyl; and (8) alkyl types such as triphenylmethyl, methyl, and benzyl; and substituted alkyl types such as 2,2,2-trichloroethyl, 2-phenylethyl, and *t*-butyl; and trialkylsilane types such as trimethylsilane.

10 As referred to herein, the term “substituted” means that at least one hydrogen atom is replaced with a non-hydrogen group, provided that normal valencies are maintained and that the substitution results in a stable compound. Ring double bonds, as used herein, are double bonds that are formed between two adjacent ring atoms (*e.g.*, C=C, C=N, or N=N).

15 In cases wherein there are nitrogen atoms (*e.g.*, amines) on compounds of the present invention, these may be converted to N-oxides by treatment with an oxidizing agent (*e.g.*, mCPBA and/or hydrogen peroxides) to afford other compounds of this invention. Thus, shown and claimed nitrogen atoms are considered to cover both the shown nitrogen and its N-oxide (N→O) derivative.

20 When any variable occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-3 R, then said group may optionally be substituted with up to three R groups, and at each occurrence R is selected independently from the definition of R. Also, combinations of substituents
25 and/or variables are permissible only if such combinations result in stable compounds.

When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom on the ring. When a substituent is listed without indicating the atom in which such substituent is bonded to the rest of the compound of a given formula, then such substituent may be bonded via any atom in such
30 substituent. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

The present invention is intended to include all isotopes of atoms occurring in the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include deuterium and tritium. The isotopes of hydrogen can be denoted as ^1H (hydrogen), ^2H (deuterium) and ^3H (tritium). They are also commonly denoted as D for deuterium and T for tritium. In the application, CD_3 denotes a methyl group wherein all of the hydrogen atoms are deuterium. Isotopes of carbon include ^{13}C and ^{14}C .

Isotopically-labeled compounds of the invention can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described herein, using an appropriate isotopically-labeled reagent in place of the non-labeled reagent otherwise employed.

The phrase “pharmaceutically acceptable” is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used herein, “pharmaceutically acceptable salts” refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic groups such as amines; and alkali or organic salts of acidic groups such as carboxylic acids. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, and nitric; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, and isethionic, and the like.

The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound that contains a basic or acidic moiety by conventional

chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington: The Science and Practice of Pharmacy*, 22nd Edition, Allen, L. V. Jr., Ed.; Pharmaceutical Press, London, UK (2012), the disclosure of which is hereby incorporated by reference.

In addition, compounds of formula I may have prodrug forms. Any compound that will be converted *in vivo* to provide the bioactive agent (*i.e.*, a compound of formula I) is a prodrug within the scope and spirit of the invention. Various forms of prodrugs are well known in the art. For examples of such prodrug derivatives, see:

- a) Bundgaard, H., ed., *Design of Prodrugs*, Elsevier (1985), and Widder, K. et al., eds., *Methods in Enzymology*, 112:309-396, Academic Press (1985);
- b) Bundgaard, H., Chapter 5, "Design and Application of Prodrugs," *A Textbook of Drug Design and Development*, pp. 113-191, Krosgaard-Larsen, P. et al., eds., Harwood Academic Publishers (1991);
- c) Bundgaard, H., *Adv. Drug Deliv. Rev.*, 8:1-38 (1992);
- d) Bundgaard, H. et al., *J. Pharm. Sci.*, 77:285 (1988);
- e) Kakeya, N. et al., *Chem. Pharm. Bull.*, 32:692 (1984); and
- f) Rautio, J (Editor). *Prodrugs and Targeted Delivery (Methods and Principles in Medicinal Chemistry)*, Vol 47, Wiley-VCH, 2011.

Compounds containing a carboxy group can form physiologically hydrolyzable esters that serve as prodrugs by being hydrolyzed in the body to yield formula I compounds *per se*. Such prodrugs are preferably administered orally since hydrolysis in many instances occurs principally under the influence of the digestive enzymes. Parenteral administration may be used where the ester *per se* is active, or in those instances where hydrolysis occurs in the blood. Examples of physiologically hydrolyzable esters of compounds of formula I include C₁₋₆alkyl, C₁₋₆alkylbenzyl, 4-methoxybenzyl, indanyl, phthalyl, methoxymethyl, C₁₋₆ alkanoyloxy-C₁₋₆alkyl (*e.g.*, acetoxymethyl, pivaloyloxymethyl or propionyloxymethyl),

C₁₋₆alkoxycarbonyloxy-C₁₋₆alkyl (*e.g.*, methoxycarbonyl-oxymethyl or ethoxycarbonyloxymethyl, glycyloxymethyl, phenylglycyloxymethyl, (5-methyl-2-oxo-1,3-dioxolen-4-yl)-methyl), and other well known physiologically hydrolyzable esters used, for example, in the penicillin and cephalosporin arts. Such esters may be prepared
5 by conventional techniques known in the art.

Preparation of prodrugs is well known in the art and described in, for example, King, F.D., ed., *Medicinal Chemistry: Principles and Practice*, The Royal Society of Chemistry, Cambridge, UK (2nd edition, reproduced, 2006); Testa, B. et al., *Hydrolysis in Drug and Prodrug Metabolism. Chemistry, Biochemistry and Enzymology*, VCHA and
10 Wiley-VCH, Zurich, Switzerland (2003); Wermuth, C.G., ed., *The Practice of Medicinal Chemistry*, 3rd edition, Academic Press, San Diego, CA (2008).

The term "solvate" means a physical association of a compound of this invention with one or more solvent molecules, whether organic or inorganic. This physical association includes hydrogen bonding. In certain instances the solvate will be capable of
15 isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. The solvent molecules in the solvate may be present in a regular arrangement and/or a non-ordered arrangement. The solvate may comprise either a stoichiometric or nonstoichiometric amount of the solvent molecules. "Solvate" encompasses both solution-phase and isolable solvates. Exemplary solvates include, but
20 are not limited to, hydrates, ethanولات, methanولات, and isopropanولات. Methods of solvation are generally known in the art.

As used herein, the term "patient" refers to organisms to be treated by the methods of the present invention. Such organisms preferably include, but are not limited to, mammals (*e.g.*, murines, simians, equines, bovines, porcines, canines, felines, and the
25 like), and most preferably refers to humans.

As used herein, the term "effective amount" means that amount of a drug or pharmaceutical agent, *i.e.*, a compound of the invention, that will elicit the biological or medical response of a tissue, system, animal or human that is being sought, for instance, by a researcher or clinician. Furthermore, the term "therapeutically effective amount"
30 means any amount which, as compared to a corresponding subject who has not received such amount, results in improved treatment, healing, prevention, or amelioration of a

disease, disorder, or side effect, or a decrease in the rate of advancement of a disease or disorder. An effective amount can be administered in one or more administrations, applications or dosages and is not intended to be limited to a particular formulation or administration route. The term also includes within its scope amounts effective to

5 enhance normal physiological function

As used herein, the term “treating” includes any effect, *e.g.*, lessening, reducing, modulating, ameliorating or eliminating, that results in the improvement of the condition, disease, disorder, and the like, or ameliorating a symptom thereof.

As used herein, the term “pharmaceutical composition” refers to the combination
10 of an active agent with a carrier, inert or active, making the composition especially suitable for diagnostic or therapeutic use *in vivo* or *ex vivo*.

Examples of bases include, but are not limited to, alkali metals (*e.g.*, sodium) hydroxides, alkaline earth metals (*e.g.*, magnesium), hydroxides, ammonia, and compounds of formula NW_4^+ , wherein W is C_{1-4} alkyl, and the like.

15 For therapeutic use, salts of the compounds of the present invention are contemplated as being pharmaceutically acceptable. However, salts of acids and bases that are non-pharmaceutically acceptable may also find use, for example, in the preparation or purification of a pharmaceutically acceptable compound.

20

METHODS OF PREPARATION

The compounds of the present invention may be prepared by synthetic routes that include processes analogous to those well-known in the chemical arts, particularly in light of the description provided herein. For illustrative purposes, Schemes 1-23 below show general methods for preparing the compounds of the present invention, as well as key
25 intermediates. For a more detailed description of the individual reaction steps, see the Example section below. Those skilled in the art will appreciate that other synthetic routes may be used to synthesize the inventive compounds. Although specific starting materials and reagents are depicted in the Schemes and discussed below, other starting materials and reagents can easily be substituted to provide a variety of compounds of the present
30 invention. In addition, many of the compounds prepared by the methods below can be further modified in light of this disclosure using conventional chemistry well known to

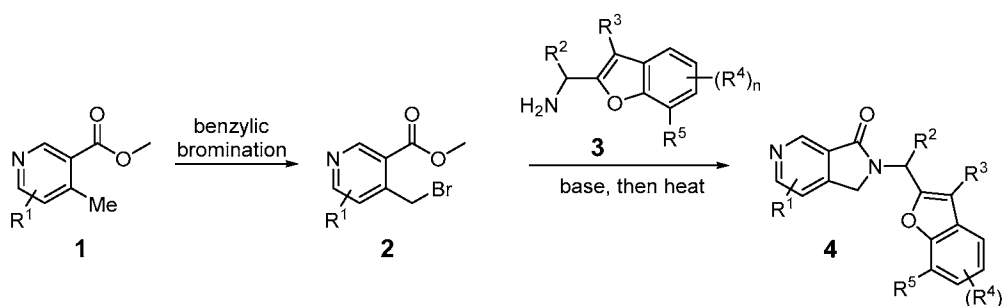
those skilled in the art. The structure numbering and variable numbering shown in the synthetic schemes are distinct from, and should not be confused with, the structure or variable numbering in the claims or the rest of the specification. The variables in the schemes are meant only to illustrate how to make some of the compounds of this

5 invention.

Compound **4** can be prepared from starting material **1** as shown in Scheme 1. First, benzylic bromination of **1** to give bromide intermediate **2** can be performed with a radical brominating reagent such as NBS in the presence of a radical initiator such as AIBN typically using heat or light to initiate the transformation. Benzyl bromide **2** can be
 10 displaced by 2-aminomethyl benzofuran **3** in the presence of a base such as TEA in a variety of solvents including THF. Once displacement has occurred, heating the reaction mixture can lead to intramolecular lactamization yielding lactam **4**. The temperature required to cause lactamization could vary depending on the nature of the ester and substitution pattern of the pyridine ring.

15

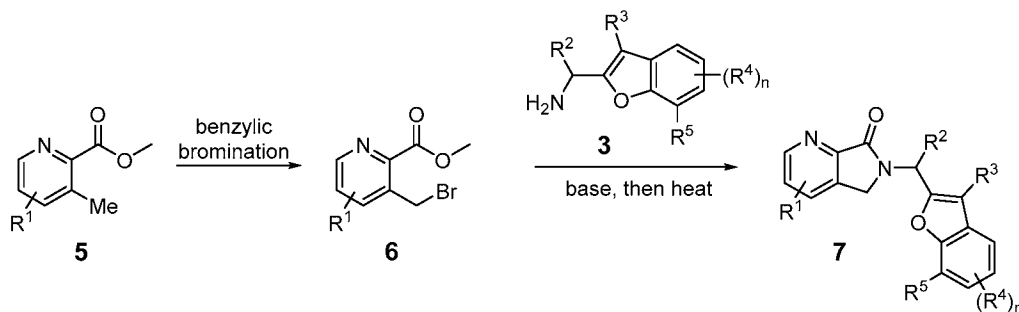
Scheme 1



Lactam **7** can be prepared in an analogous manner as demonstrated in Scheme 2. Picolinic esters **5** are again brominated in the benzylic position and then subsequently treated with 2-aminomethyl benzofuran **3** followed by heat to give the desired compounds

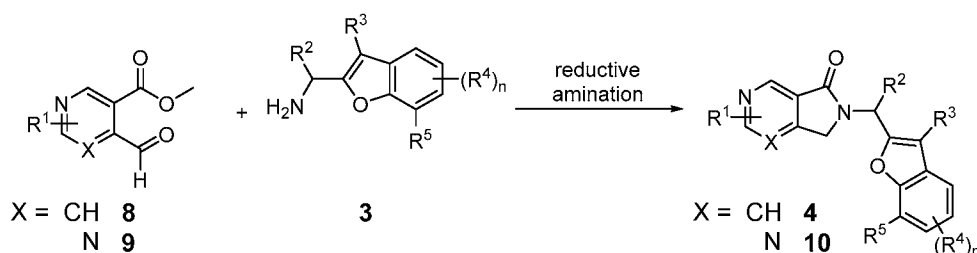
20 7.

Scheme 2



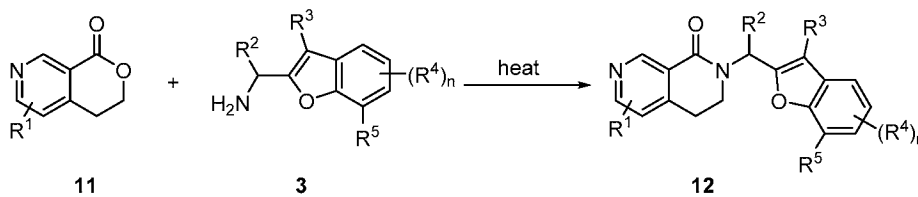
Alternatively, compound **4** can be made from pyridine aldehyde **8** and 2-aminomethyl benzofuran **3** under reductive amination conditions (Scheme 3). In the presence of a reducing agent such as sodium triacetoxyborohydride and often in the presence of an acid such as acetic acid, aldehyde **8** can be coupled to amine **3**. Subsequent, *in situ* intramolecular lactamization can occur to yield **4**. Likewise, pyrimidine aldehyde **9** gives lactam **10** under analogous conditions.

Scheme 3



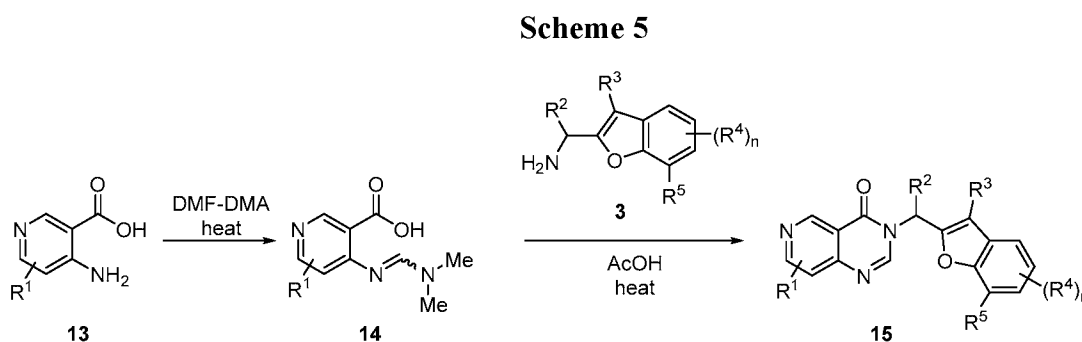
Six-membered ring lactam **12** can be prepared from lactone **11** as shown in Scheme 4. Heating lactone **11** with 2-aminomethyl benzofuran **3** either as a solution or neat, conventionally or in a microwave reactor, with or without a base (such as pyridine), generates lactam **12**.

Scheme 4

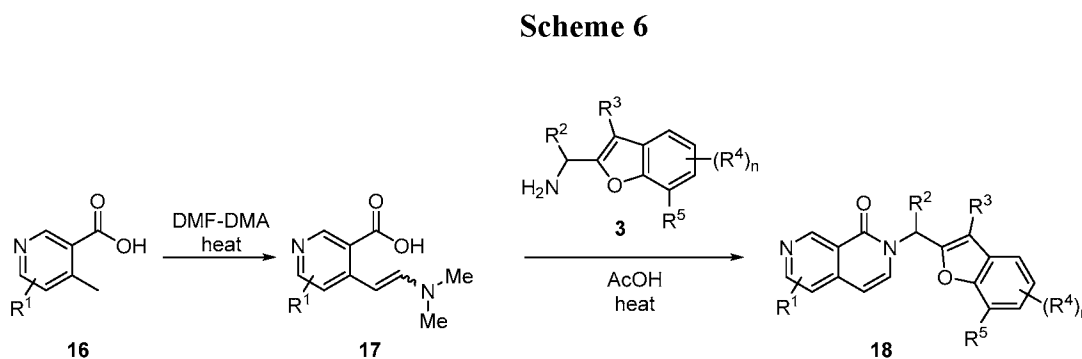


15

Pyridopyrimidinone **15** can be synthesized as outlined in Scheme 5. Nicotinic acid **13** can be heated conventionally or in a microwave reactor in the presence of DMF-DMA to give amidine intermediate **14**. The amidine can then be treated with 2-aminomethylbenzofuran **3** with heating in the presence of an acid, such as acetic acid, to give the desired pyridopyrimidinone **15**.

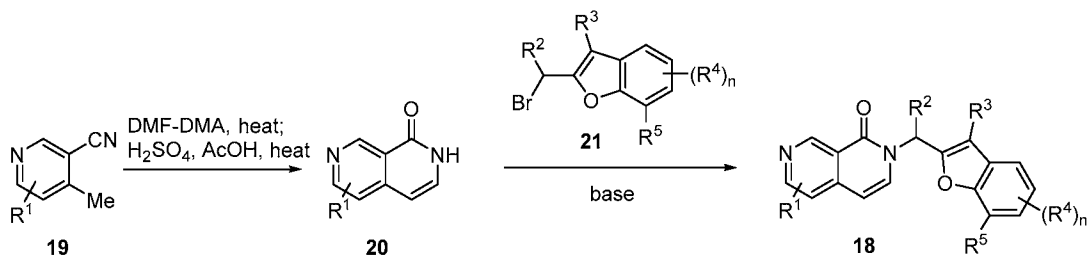


Following a similar protocol, naphthyridinone **18** can be synthesized as shown in Scheme 6. Nicotinic acid **16** can be heated with DMF-DMA to provide enamine **17**. Once again, heating with 2-aminomethyl benzofuran **3** in the presence of an acid such as acetic acid gives naphthyridinone **18**.



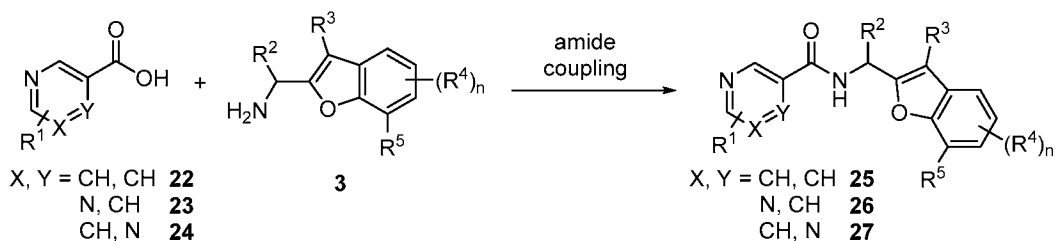
Alternatively, compounds of type **18** can be synthesized from pre-formed naphthyridinones as outlined in Scheme 7. Naphthyridinone **20** can be synthesized from 4-methylnicotinonitrile **19** by heating either conventionally or in a microwave reactor with DMF-DMA, followed by removal of excess DMF-DMA, and further heating in acid (such as acetic acid and/or sulfuric acid). The resulting naphthyridinone **20** can then be alkylated with benzylic bromide **21** in the presence of a base such as sodium hydride in a solvent such as DMF to give **18**.

Scheme 7



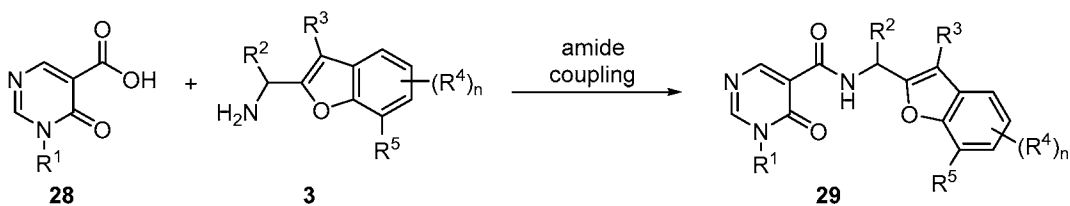
In cases where the amide is not embedded in a ring, as is the case in Scheme 8, standard amide coupling protocols can be employed to join a variety of acids with 2-aminomethyl benzofuran **3**. Indeed, various substituted pyridine-, pyrimidine-, and pyrazine-acids (**22-24**) can be coupled to **3** using a variety of coupling reagents such as BOP or HATU in the presence of a base such as Hunig's base to give the corresponding amides **25-27**. These conditions can also be employed with a variety of other heteroaromatic acids to give, for example, pyrimidinone **29** (Scheme 9), naphthyridine **31** (Scheme 10), imidazopyridine **33** (Scheme 11), pyrazolopyridine **35** (Scheme 12), imidazopyridazine **37** (Scheme 13), and pyrazolopyrimidine **39** (Scheme 14).

Scheme 8

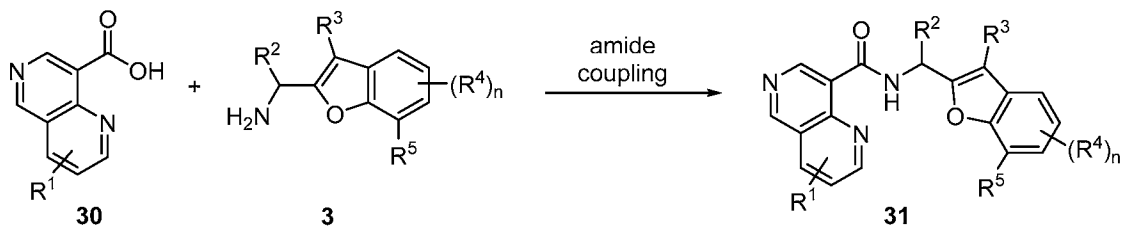


15

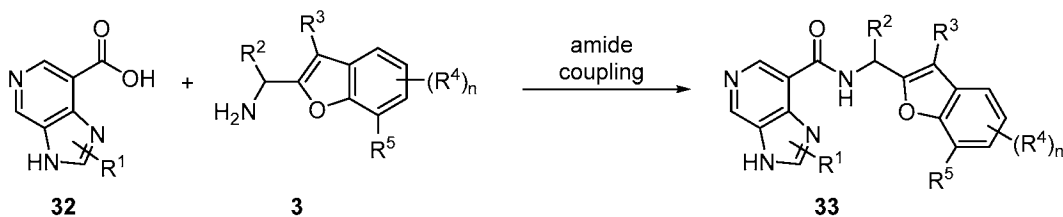
Scheme 9



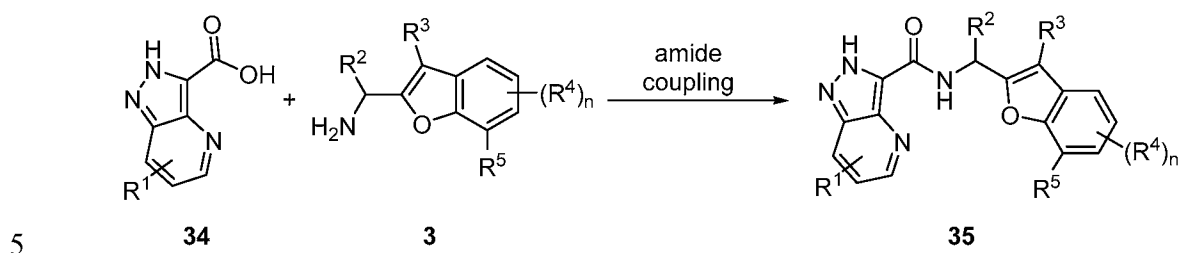
Scheme 10



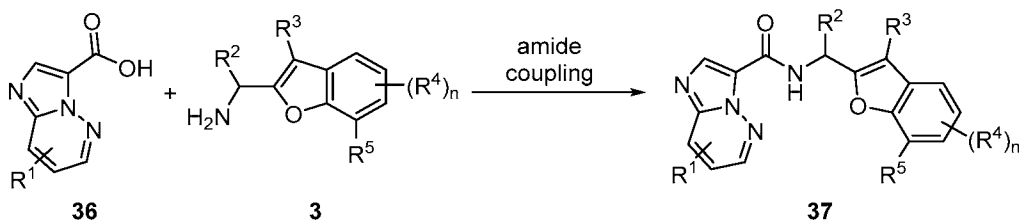
Scheme 11



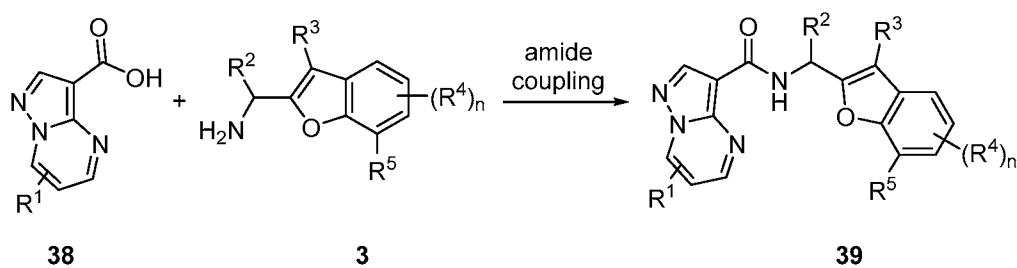
Scheme 12



Scheme 13

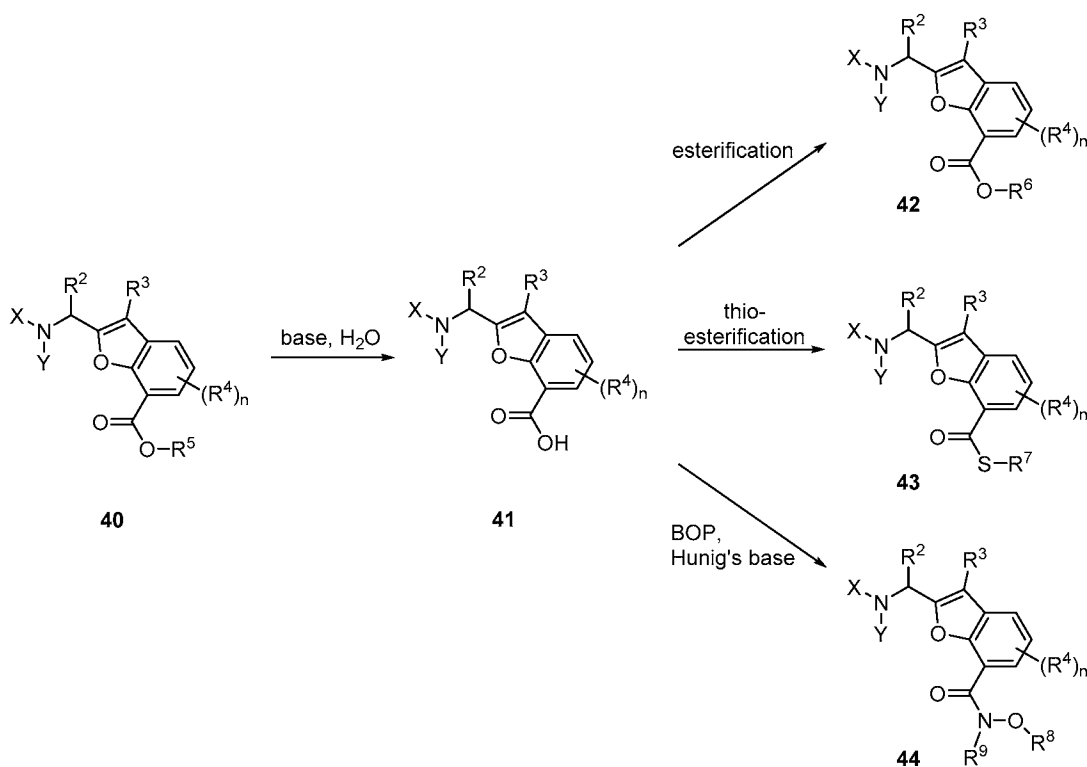


Scheme 14



Benzofuran esters **40** (Scheme 15) can be derivatized by first hydrolyzing them under basic conditions in the presence of water to give acid **41**. The acid can be converted to various alternative esters (**42**) upon activation with a coupling reagent such as BOP or PyBOP, typically in the presence of a base such as Hunig's base, followed by addition of the appropriate alcohol. Thioesterification of acid **41** could be affected by multiple synthetic routes. Conversion of acid **41** to an acid chloride followed by treatment with the sodium salt of the desired thiol gives thioester **43**. Alternatively, acid **41** could be coupled to (trimethylsilyl)ethane-1-thiol in the presence of BOP and Hunig's base. This 2-(trimethylsilyl)ethyl thioester intermediate could be converted to thioester **43** by treating with TBAF in the presence of an alkyl halide. Additionally, hydroxamic acids and esters (**44**) can be synthesized from acid **41** using standard amide coupling conditions such as BOP and Hunig's base.

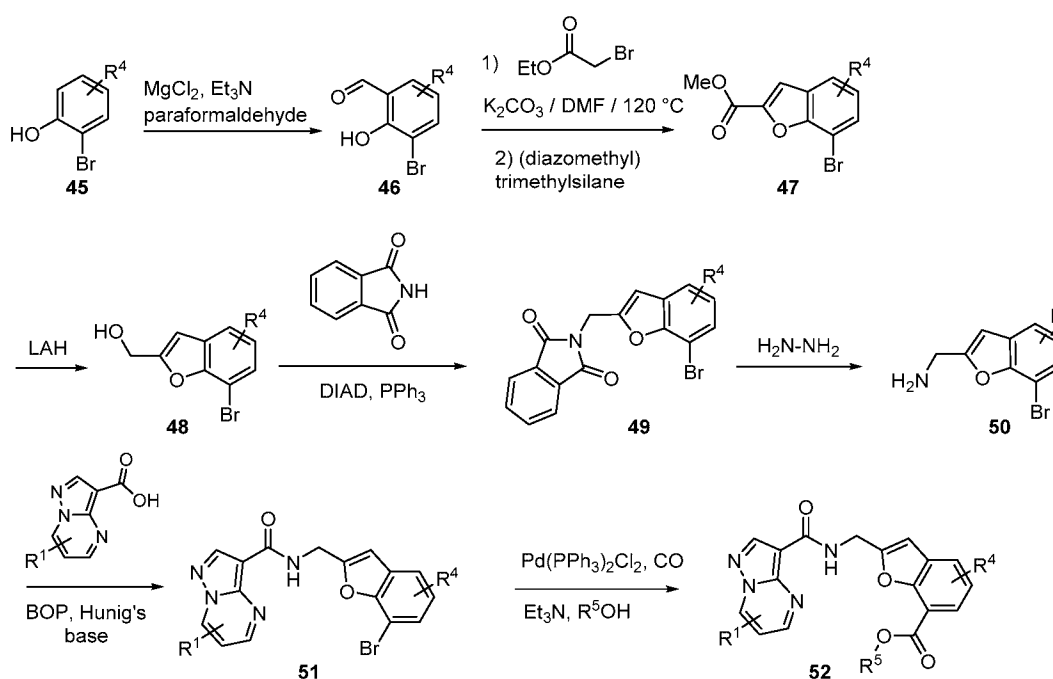
Scheme 15



Benzofuran carboxylic esters **52** can also be prepared as shown in Scheme 16. Substituted 2-bromo phenol **45** can be converted to aldehyde **46** by treating with paraformaldehyde in the presence of magnesium dichloride and triethylamine. Treatment

of **46** with an alpha-halo acetate such as ethyl bromoacetate in the presence of a base such as potassium carbonate at elevated temperatures can lead to benzofuran-2-carboxylic acids that can be readily re-esterified upon treatment with, for example, TMS-diazomethane to give methyl ester **47**. Reduction of the ester using a reducing agent such as LAH in an ethereal solvent like THF or ether gives alcohol **48**. Mitsunobu displacement with phthalimide can give phthalimide protected 2-aminomethyl benzofuran **49**. Deprotection of the phthalimide under basic conditions with a nucleophile such as hydrazine can give primary amine **50**. Amine **50** can then be coupled as described previously to give 7-bromobenzofuran-amide **51**. Finally, the bromide could be converted to **52** by treating with carbon monoxide, a suitable palladium catalyst, and the necessary alcohol.

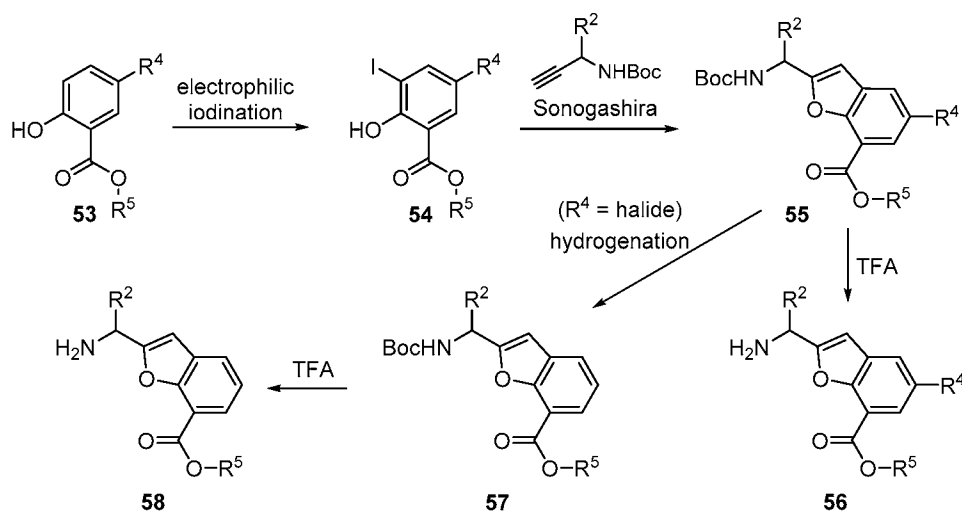
Scheme 16



15 Synthetic strategies to access variously substituted benzofurans **3** are shown in Schemes 17-22. C5-Substituted benzofurans **56** can be prepared starting from phenol **53** (Scheme 17). Electrophilic iodination of phenol **53** using either commercial or *in situ* generated electrophilic iodine sources such as NIS or sodium iodide/chloramine T

respectively gives iodide **54**. Sonogashira coupling of *N*-Boc propargyl amine at elevated temperatures followed by cyclization gives benzofuran **55**. Benzofuran **55** can be deprotected using standard Boc deprotection conditions such as TFA in DCM to provide C5-substituted benzofuran **56**. Alternatively, when R⁴ is an aryl halide, it can be removed *via* hydrogenation with an appropriate palladium catalyst such as palladium on carbon or Pearlman's catalyst in the presence of hydrogen to give Boc-protected amine **57**. The Boc group can be deprotected as described previously with TFA to give **58**.

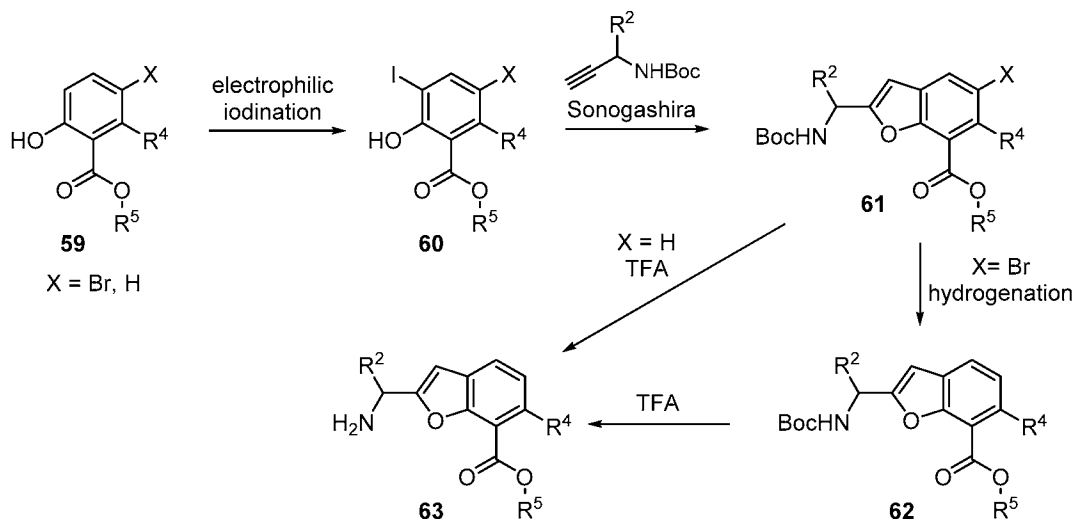
Scheme 17



10

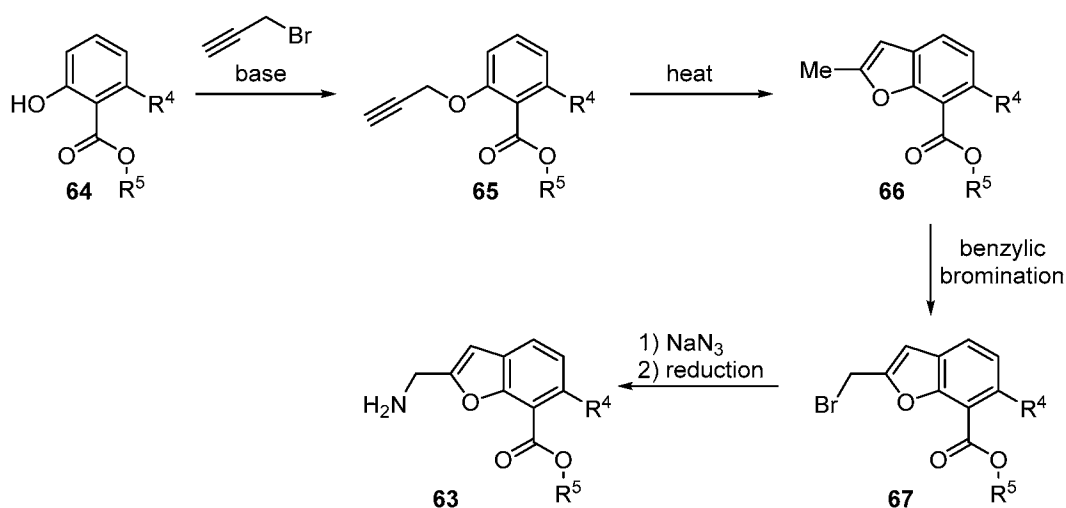
C6-substituted benzofurans **63** can be synthesized as shown in Schemes 18 and 19. Phenol **59** can undergo electrophilic iodination as described previously to give iodide **60**. Sonogashira coupling can furnish the benzofuran **61**. When X is a halide such as bromide, the bromide can be removed by palladium-catalyzed hydrogenation to give Boc-protected amine **62**. The BOC protecting group can be removed under standard conditions, such as treatment with TFA in DCM, to give C6-substituted benzofuran **63**. When X = H, compound **61** can be treated with TFA directly to give C6-substituted benzofuran **63**.

Scheme 18



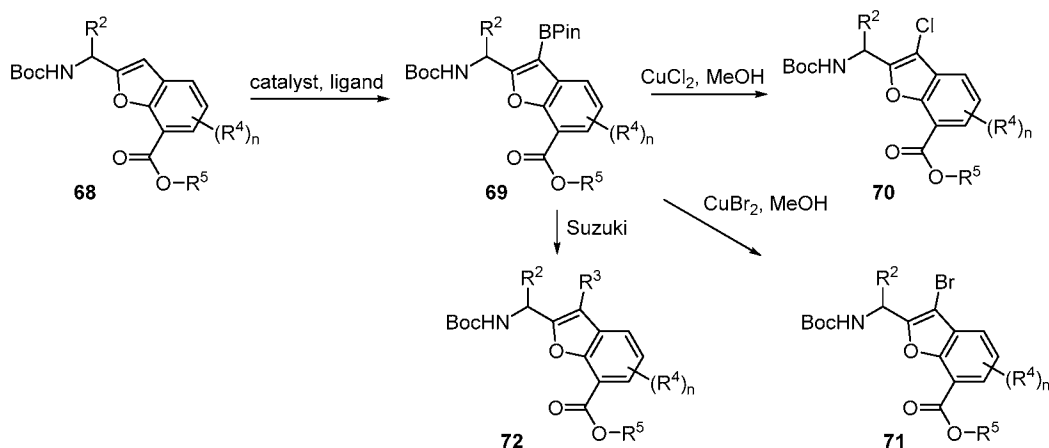
Alternatively, C6-substituted benzofurans can be synthesized as shown in Scheme 19. Phenol **64** can be alkylated with propargyl bromide in the presence of a base such as potassium carbonate to give ether **65**. Heating **65** at elevated temperatures either conventionally or in a microwave provides 2-methyl benzofuran **66**. Benzylic bromination with a radical brominating reagent such as NBS and an initiator like AIBN gives benzyl bromide **67**. Conversion of the bromide to primary amine **63** can be achieved *via* a variety of synthetic sequences including displacement with sodium azide followed by Staudinger reduction. One skilled in the art would be familiar with other routes to achieve this transformation.

Scheme 19



C3-Substituted benzofurans can be synthesized as shown in Scheme 20. Boc-protected benzofuran **68** can undergo iridium catalyzed borylation at C3 in the presence of bis-pinacolatodiboron and an appropriate ligand such as 4,4'-di-*tert*-butyl-2,2'-bipyridine to give **69**. From this intermediate, the boronic ester can be converted to a variety of substituents. Halides **70** and **71** can be prepared upon treatment of the boronic ester **69** with the appropriate cupric halide. A variety of carbon-linked alkyl or aryl groups can be prepared from **69** via transition metal catalyzed cross coupling, for example, Suzuki coupling to give C3-substituted benzofuran **72**. Other groups at R³ could be installed from the boronic ester intermediate **69** by methods familiar to one skilled in the art.

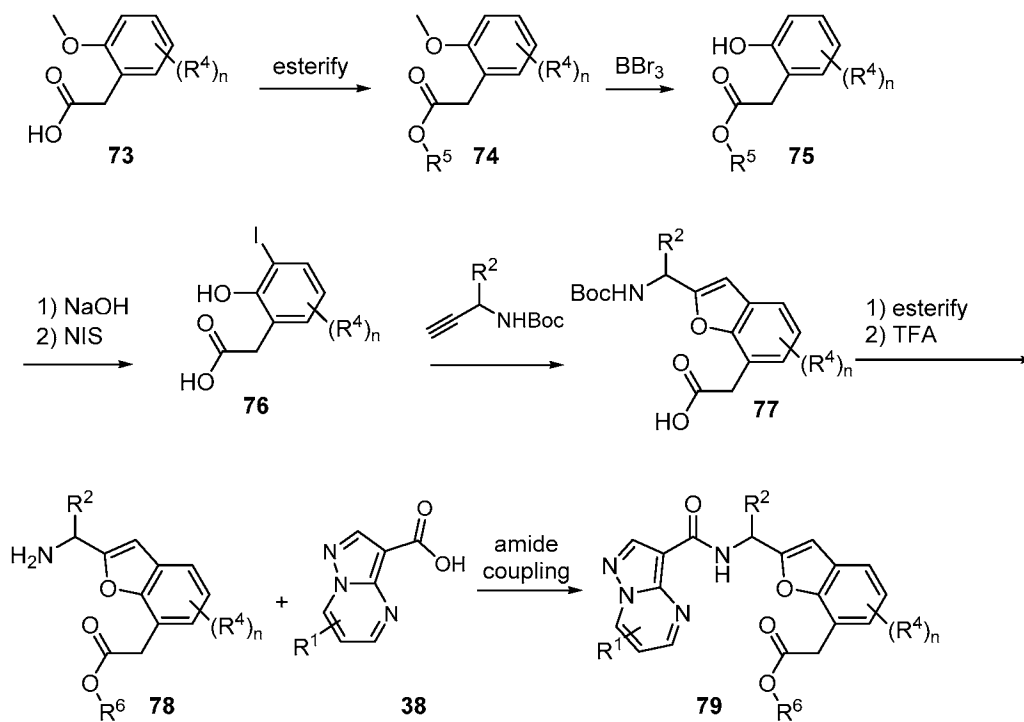
Scheme 20



Benzofuran **79** can be synthesized as outlined in Scheme 21. Phenyl acetic acid **73** can be esterified to give **74** under a variety of conditions including but not limited to trans-esterification with an alcohol in the presence of acid or treatment with TMS-diazomethane. Deprotection of the methoxy group with, for example, BBr₃ gives phenol **75**. Ester hydrolysis and electrophilic iodination (as outlined in the above schemes) provides **76**. Benzofuran formation was again achieved by implementing a Sonogashira coupling with N-Boc progargyl amine to give acid **77**. Esterification with the appropriate alcohol followed by deprotection of the Boc-amine gives 2-aminomethyl benzofuran **78**.

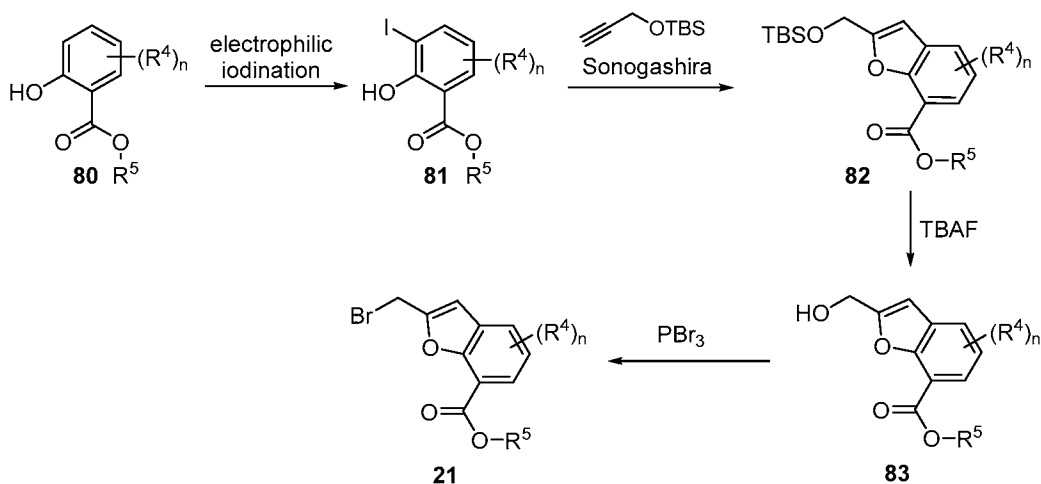
This amine could be coupled to pyrazolopyrimidine acid **38** using standard amide coupling conditions such as BOP and Hunig's base to give benzofuran **79**.

Scheme 21



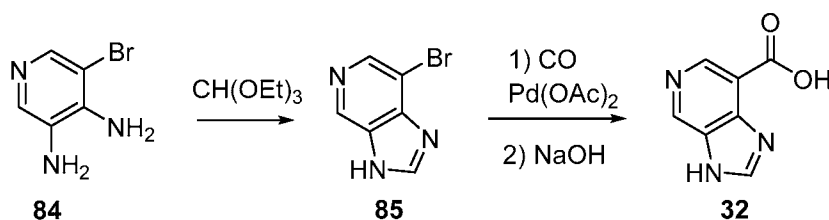
- 5 Bromobenzofuran intermediate **21** can be made *via* the route outlined in Scheme 22. Starting from phenol **80**, iodination can be performed as before to give **81**. Sonogashira coupling with a protected propargyl alcohol such as TBS-protected propargyl alcohol gives benzofuran **82**. Deprotection of the TBS group under a variety of standard conditions such as TBAF gives free alcohol **83**. Conversion of the alcohol to the
- 10 bromide or other suitable halide with, for example, PBr_3 gives bromide **21**.

Scheme 22



Acid **32** can be synthesized from diaminopyridine **84** as shown in Scheme 23. Treatment of the diamine with an orthoformate or orthoformate equivalent with or without the presence of an acid can generate imidazole **85**. Next, palladium catalyzed carbonylation in the presence of an alcohol can first provide an ester. Subsequent hydrolysis under basic conditions gives acid **32**.

Scheme 23



10

EXAMPLES

All reactions were carried out with continuous magnetic stirring under an atmosphere of dry nitrogen or argon. All evaporations and concentrations were carried out on a rotary evaporator under reduced pressure. Commercial reagents were used as received without additional purification. Solvents were commercial anhydrous grades and were used without further drying or purification. Flash chromatography was performed using prepacked RediSep[®] R_f silica gel columns or prepacked RediSep[®] R_f Gold C18 columns on a CombiFlash R_f machine.

Preparative Reverse Phase (RP) HPLC was performed using a Shimadzu HPLC system with linear gradient elution using H₂O/MeCN mixtures buffered with 0.1% trifluoroacetic acid or 10 mM NH₄OAc and detection at 220 nm on one of the following columns:

- 5 **Method A:** XBridge C18 19 x 200 mm (flow rate = 20 mL/min); H₂O/MeCN/TFA
Method B: XBridge C18 19 x 200 mm (flow rate = 20 mL/min); H₂O/MeCN/ NH₄OAc
Method C: C18 Phenomenex Luna S5 ODS 30 x 100 mm (flow rate = 30 mL/min);
H₂O/MeCN/TFA

10 In cases where racemic compounds were initially prepared, enantiomers were separated on a Waters 100 prep HPLC system using the columns and conditions detailed below (detection at 220 nm):

Method D: Column: Chiral AD 30 x 250 mm; Mobile Phase: 85% CO₂/ 15% IPA with 0.1% DEA; Flow Rate: 100 mL/min.

15 **Method E:** Column: Chiral AD 30 x 250 mm; Mobile Phase: 90% CO₂/ 10% 1:1 MeOH-MeCN; Flow Rate: 100 mL/min.

Method F: Column: Chiral AD 25 x 3 cm; Mobile Phase: 80% CO₂/ 20% 1:1 IPA-MeCN with 0.1% DEA; Flow Rate: 100 mL/min.

Method G: Column: Chiral IC 25 x 3 cm; Mobile Phase: 50% CO₂/ 50% MeOH with 0.1% DEA; Flow Rate: 60 - 85 mL/min.

20 **Method H:** Column: Chiral AD 30 x 250 mm; Mobile Phase: 65% CO₂/ 35% MeOH with 0.1% DEA; Flow Rate: 100 mL/min.

Method I: Column: Chiral AD-H 50 x 250 mm; Mobile Phase: 54% CO₂/ 46% MeOH; Flow Rate: 320 mL/min.

25 **Method J:** Column: Chiral AD 25 x 3 cm; Mobile Phase: 80% CO₂/ 20% MeOH with 0.1% DEA; Flow Rate: 100 mL/min.

Method K: Column: Chiral AD, 30 x 250 mm; Mobile Phase: 65% CO₂/ 35% 1:1 IPA-MeCN; Flow Rate: 100 mL/min.

Method L: Column: Chiral AD-H 30 x 250 mm; Mobile Phase: 60% CO₂ / 40% MeOH; Flow Rate: 100 - 200 mL/min.

Method M: Column: Chiral OJ, 30 x 250 mm; Mobile Phase: 70% CO₂ / 30% IPA with 0.1% DEA; Flow Rate: 100 mL/min.

- 5 All final products were characterized by ¹H NMR, RP HPLC and electrospray ionization (ESI) or atmospheric pressure ionization (API) mass spectrometry (MS). ¹H NMR spectra were obtained on a 500 MHz or a 400 MHz Bruker instrument. Field strengths are expressed in units of δ (parts per million, ppm) relative to the solvent peaks, and peak multiplicities are designated as follows: s, singlet; d, doublet; dd, doublet of
10 doublets; t, triplet; q, quartet; sxt, sextet; br, broad; m, multiplet.

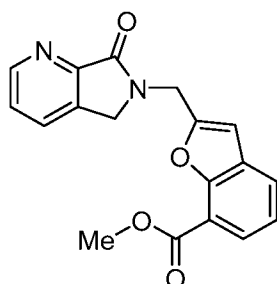
ABBREVIATIONS

Abbreviations used in the synthetic methods, schemes, and examples generally follow conventions used in the art.

Ac	Acetyl
AcOH	Acetic acid
AIBN	Azobisisobutyronitrile
aq	Aqueous
Boc	<i>t</i> -Butoxycarbonyl
Boc ₂ O	Di- <i>t</i> -butyl dicarbonate
BOP	(Benzotriazol-1-yl)oxytris(dimethylamino)phosphonium hexafluorophosphate
Br	Bromide
Conc	Concentrated
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DEA	Diethylamine
DEAD	Diethyl azodicarboxylate

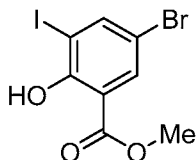
DIAD	Diisopropyl azodicarboxylate
DIPEA	<i>N,N</i> -Diisopropylethylamine
DMAP	4- <i>N,N</i> -dimethylaminopyridine
DME	1,2-Dimethoxyethane
DMF	<i>N,N</i> -Dimethylformamide
DMF-DMA	<i>N,N</i> -Dimethylformamide dimethyl acetate
DMSO	Dimethyl sulfoxide
dppp	1,3-Bis(diphenylphosphanyl)propane
eq	Equivalents
EtOAc	Ethyl acetate
EtOH	Ethanol
Et ₂ O	Diethyl ether
Et ₃ N	Triethylamine
h	Hour(s)
HATU	1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate
HPLC	High performance liquid chromatography
<i>i</i> -PrOH or IPA	Isopropanol
LAH	Lithium aluminum hydride
LiOH	Lithium hydroxide
m or min	Minute(s)
Me	Methyl
MeCN	Acetonitrile
MeOH	Methanol
NaOH	Sodium hydroxide
Na(OAc) ₃ BH	Sodium triacetoxyborohydride
NBS	<i>N</i> -Bromosuccinimide
NH ₄ OAc	Ammonium acetate
NIS	<i>N</i> -Iodosuccinimide

NMP	<i>N</i> -methylpyrrolidinone
NMR	Nuclear magnetic resonance
Pd/C	Palladium on carbon
POCl ₃	Phosphorus(III) oxychloride
PSI	Pounds per square inch
RT or rt	Room temperature
Sat	Saturated
SFC	Supercritical fluid chromatography
<i>t</i> -Bu	Tertiary butyl
<i>t</i> -BuOH	Tertiary butanol
TBAF	Tetra- <i>n</i> -butylammonium fluoride
TEA	Triethylamine
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TMS	Trimethylsilyl

EXAMPLE 1

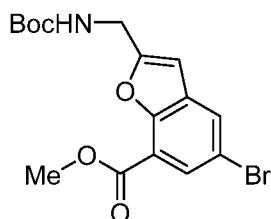
5

Methyl 2-((7-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)methyl)benzofuran-7-carboxylate



A) Methyl 5-bromo-2-hydroxy-3-iodobenzoate

Methyl 5-bromo-2-hydroxybenzoate (10 g, 43.3 mmol) was dissolved in dry DMF (43 ml). Sodium iodide (7.79 g, 51.9 mmol) was added followed by chloramine-T (12.8 g, 51.9 mmol) (reaction immediately turned dark) and the reaction was stirred at room temperature. The reaction was monitored by LCMS. After 6 hours, the reaction was diluted with water and extracted with ether and then EtOAc. Combined organics were dried with magnesium sulfate, filtered, and concentrated *in vacuo*. The resulting pale yellow solid was recrystallized from EtOH (30 mL) to give methyl 5-bromo-2-hydroxy-3-iodobenzoate (9.26 g, 25.9 mmol, 59.9 % yield). ¹H NMR (400 MHz, Chloroform-d) δ 11.57 (s, 1H), 8.05 (d, $J = 2.4$ Hz, 1H), 7.98 (d, $J = 2.4$ Hz, 1H), 3.99 (s, 3H); MS (ESI+) $m/z = 356.9$ (M+H)⁺.

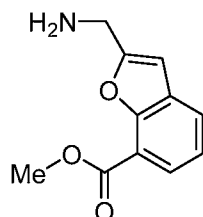


B) Methyl 5-bromo-2-(((tert-butoxycarbonyl)amino)methyl) benzofuran-7-carboxylate

Methyl 5-bromo-2-hydroxy-3-iodobenzoate (9.26 g, 25.9 mmol) was dissolved in triethylamine (130 ml) in a 350 mL sealed tube. *tert*-Butyl prop-2-yn-1-ylcarbamate (3.62 g, 23.4 mmol) was added followed by cuprous iodide (0.247 g, 1.30 mmol) and bis(triphenylphosphine)palladium(II)dichloride (1.82 g, 2.59 mmol). The reaction was degassed with dry nitrogen for 10 minutes before sealing and heating to 85 °C for 2 hours. The reaction was then cooled, filtered, and concentrated *in vacuo*. The resulting crude residue was purified *via* ISCO (120g column, 0-60% EtOAc in hexanes) to give methyl 5-bromo-2-(((tert-butoxycarbonyl)amino)

methyl)benzofuran-7-carboxylate (7.52 g, 19.6 mmol, 75 % yield). ¹H NMR (400 MHz, Chloroform-d) δ 8.02 (d, *J* = 2.0 Hz, 1H), 7.84 (d, *J* = 2.0 Hz, 1H), 6.63 (s, 1H), 5.11 (br s, 1H), 4.51 (br d, *J* = 5.9 Hz, 2H), 4.00 (s, 3H), 1.47 (s, 9H); MS (ESI+) *m/z* = 328.1 (M-*t*Bu+H)⁺.

5

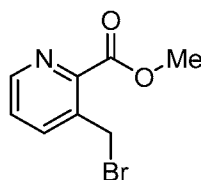


C) Methyl 2-(aminomethyl)benzofuran-7-carboxylate

Methyl 5-bromo-2-(((*tert*-butoxycarbonyl)amino)methyl)benzofuran-7-carboxylate (7.52 g, 19.6 mmol) was taken up in MeOH (78 ml) in a Parr vessel, flushed with nitrogen, and 5% palladium hydroxide on carbon (0.825 g, 0.587 mmol) was added. The reaction was then placed in a Parr apparatus and placed under 45 PSI of hydrogen gas. After 30 minutes, the reaction was filtered over pressed celite and concentrated *in vacuo* to give crude methyl 2-(((*tert*-butoxycarbonyl)amino)methyl) benzofuran-7-carboxylate (4.44 g). (NOTE: partial Boc deprotection occurred in this step)

Crude methyl 2-(((*tert*-butoxycarbonyl)amino)methyl)benzofuran-7-carboxylate (4.44 g, 14.5 mmol) was taken up in DCM (21.8 ml) and cooled to 0 °C over an ice bath. TFA (7.27 ml) was added and the reaction stirred at room temperature. After 3 hours, the reaction was then concentrated *in vacuo* and azeotroped several times with toluene to remove excess TFA. The crude product was taken up in water, basified with saturated aqueous bicarbonate solution, and extracted with EtOAc followed by 30% *i*PrOH in chloroform. The combined organics were dried over sodium sulfate, filtered, and concentrated *in vacuo* to give a solid. This brown solid was found to be methyl 2-(aminomethyl)benzofuran-7-carboxylate (4.16 g, 11.0 mmol, 76 % yield). ¹H NMR (400 MHz, Methanol-d₄) δ 8.00 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.92 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.40 (t, *J* = 7.8 Hz, 1H), 7.08 (s, 1H), 4.41 (s, 2H), 4.00 (s, 3H); MS (ESI+) *m/z* = 411.2

(2M+H)⁺.



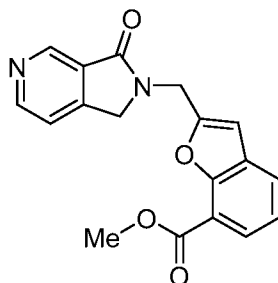
D) Methyl 3-(bromomethyl)picolinate

5 Methyl 3-methylpicolinate (500 mg, 3.31 mmol) was taken up in CCl₄ (13.2 ml). NBS (765 mg, 4.30 mmol) was added followed by AIBN (54.3 mg, 0.331 mmol). The reaction was sealed and heated to 90 °C for 2 hours and then stirred at room temperature overnight. After stirring overnight at room temperature, a precipitate forms, the reaction was filtered, concentrated *in vacuo* and purified directly *via* ISCO (24 g column, 0-50%
10 EtOAc in hexanes) to give methyl 3-(bromomethyl)picolinate (454 mg, 1.97 mmol, 59.7 % yield) as a clear oil that solidifies upon standing. ¹H NMR (400 MHz, Chloroform-d) δ 8.67 (dd, *J* = 4.6, 1.5 Hz, 1H), 7.90 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.48 (dd, *J* = 7.9, 4.6 Hz, 1H), 4.95 (s, 2H), 4.04 (s, 3H); MS (ESI+) *m/z* = 232.0 (M+H)⁺.

15 **E) Methyl 2-((7-oxo-5,7-dihydro-6H-pyrrolo[3,4-*b*]pyridin-6-yl)methyl)benzofuran-7-carboxylate**

Methyl 2-(aminomethyl)benzofuran-7-carboxylate (252 mg, 1.23 mmol) was taken up in ethanol (2.73 mL) and TEA (228 μl, 1.64 mmol) was added followed by dropwise addition of a solution of ethyl 3-(bromomethyl)picolinate (200 mg, 0.819
20 mmol) in 1 mL of ethanol. Once the addition was complete, the reaction was sealed and heated to 100 °C for 1 hour. The reaction was concentrated *in vacuo*. The crude reaction mixture was taken up in DMF, filtered, and purified *via* HPLC (Method B) to give the title compound (23.7 mg, 0.074 mmol, 8.97 % yield). ¹H NMR (500 MHz, DMSO-d₆) δ 8.73 (d, *J* = 4.3 Hz, 1H), 8.08 (d, *J* = 7.6 Hz, 1H), 7.89 (d, *J* = 7.6 Hz, 1H), 7.82 (d, *J* =
25 7.6 Hz, 1H), 7.58 (dd, *J* = 7.8, 4.7 Hz, 1H), 7.35 (t, *J* = 7.6 Hz, 1H), 6.99 (s, 1H), 5.00 (s, 2H), 4.61 (s, 2H), 3.86 (s, 3H); MS (ESI+) *m/z* = 323.3 (M+H)⁺.

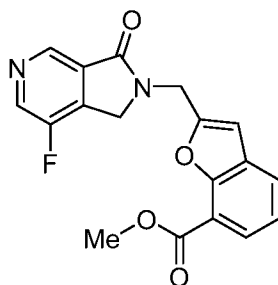
EXAMPLE 2



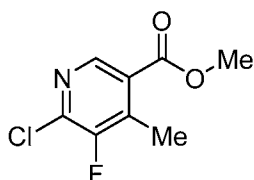
Methyl 2-((3-oxo-1,3-dihydro-2H-pyrrolo[3,4-c]pyridin-2-yl)methyl)benzofuran-7-carboxylate

- 5 Methyl 4-methylnicotinate (500 mg, 3.31 mmol) was taken up in CCl_4 (15.1 ml). NBS (765 mg, 4.30 mmol) was added followed by AIBN (54.3 mg, 0.331 mmol). The reaction was sealed and heated to 90 °C. After 1 hour, the reaction was cooled, filtered, and concentrated *in vacuo* to give crude methyl 4-(bromomethyl)nicotinate. Material was used directly without further purification.
- 10 Methyl 3-(aminomethyl)benzofuran-7-carboxylate (489 mg, 2.38 mmol, Step C of Example 1) was taken up in THF (9.94 mL) and TEA (554 μl , 3.97 mmol) was added. Freshly prepared, crude methyl 4-(bromomethyl)nicotinate was taken up in THF (2 mL) and added dropwise to the benzofuran solution at room temperature and then allowed to stir at room temperature. After 1 hour the reaction was heated to 60 °C for 16 hours.
- 15 After 16 hours, the reaction was filtered, concentrated *in vacuo* and purified *via* ISCO (12 g column, 0-100% EtOAc) to give methyl 2-((3-oxo-1,3-dihydro-2H-pyrrolo[3,4-c]pyridin-2-yl)methyl)benzofuran-7-carboxylate (111 mg, 0.344 mmol, 17.3 % yield). ^1H NMR (500 MHz, DMSO-d_6) δ 8.96 (br s, 1H), 8.77 (br d, $J = 3.7$ Hz, 1H), 7.88 (d, $J = 7.6$ Hz, 1H), 7.83 (d, $J = 7.3$ Hz, 1H), 7.71 (br d, $J = 4.9$ Hz, 1H), 7.36 (t, $J = 7.6$ Hz, 1H),
- 20 6.99 (s, 1H), 4.98 (s, 2H), 4.68 (s, 2H), 3.87 (s, 3H); MS (ESI+) $m/z = 323.2$ (M+H) $^+$.

EXAMPLE 3



Methyl 2-((7-fluoro-3-oxo-1,3-dihydro-2H-pyrrolo[3,4-c]pyridin-2-yl)methyl)benzofuran-7-carboxylate

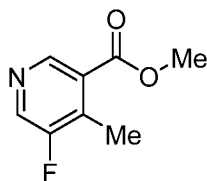


5 **A) Methyl 6-chloro-5-fluoro-4-methylnicotinate**

To a round bottom flask charged with a magnetic stir bar and 2,6-dichloro-5-fluoro-4-methylnicotinic acid (3.66 g, 16.3 mmol) (Reference: *J. Med. Chem.* **1991**, 35, 518-525) was added MeOH (163 ml) and Hunig's Base (5.71 ml, 32.7 mmol). To this solution was carefully added palladium on carbon (0.174 g, 1.63 mmol). The resulting
 10 reaction mixture was purged with nitrogen and placed under an atmosphere of hydrogen (1 atm) using a balloon. The reaction was allowed to stir at ambient temperature for 48 h. The reaction was then filtered through a bed of celite. The filtrate was concentrated *in vacuo* to a volume of ~20 ml and diluted with ether. A precipitate formed which was filtered off using a Buchner funnel. The filtrate was concentrated *in vacuo* to
 15 give a mixture of 6-chloro-5-fluoro-4-methylnicotinic acid and a small amount of 5-fluoro-4-methylnicotinic acid which was used directly without further purification (2.5 g total yield).

Crude 6-chloro-5-fluoro-4-methylnicotinic acid (2.5 g, 13.2 mmol) was taken up in DMF (13.2 ml) and K₂CO₃ (4.56 g, 33.0 mmol) was added. Methyl iodide (1.24 ml,
 20 19.8 mmol) was then added in one portion at room temperature and the reaction was stirred at room temperature overnight. The reaction was diluted with water and then extracted with EtOAc. The combined organic extracts were dried with sodium sulfate, filtered, and concentrated *in vacuo*. The crude residue was purified *via* ISCO (40 g

column, 0-50% EtOAc in hexanes) to give methyl 6-chloro-5-fluoro-4-methylnicotinate (1.33 g, 6.5 mmol). ¹H NMR (400 MHz, Chloroform-d) δ 8.22 (s, 1H), 3.99 (s, 3H), 2.29 (d, *J* = 2.0 Hz, 3H); MS (ESI+) *m/z* = 204.1 (M+H)⁺.



5

B) Methyl 5-fluoro-4-methylnicotinate

To a round bottom flask charged with a magnetic stir bar and methyl 6-chloro-5-fluoro-4-methylnicotinate (1.33g, 6.53 mmol) was added MeOH (65.3 ml) and Hunig's Base (2.28 ml, 13.1 mmol). To this solution was carefully added palladium on carbon
10 (0.070 g, 0.653 mmol). The resulting reaction mixture was purged with nitrogen and placed under an atmosphere of hydrogen gas (1 atm) using a balloon. The reaction was allowed to stir at ambient temperature. After stirring vigorously for 16 hours, the reaction was filtered through a bed of celite and the celite was washed with methanol. The filtrate was concentrated *in vacuo* to a volume of ~25 ml and diluted with EtOAc and extracted
15 with water. The combined organic extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo* to give methyl 5-fluoro-4-methylnicotinate (930 mg, 5.50 mmol, 84 % yield). ¹H NMR (400 MHz, Chloroform-d) δ 8.89 (s, 1H), 8.50 (d, *J* = 0.9 Hz, 1H), 3.95 (s, 3H), 2.56 (d, *J* = 2.0 Hz, 3H); MS (ESI+) *m/z* = 170.1 (M+H)⁺.

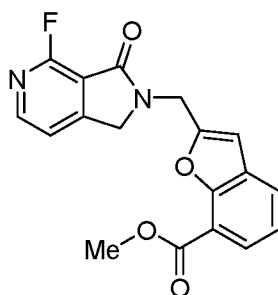
20

C) Methyl 2-((7-fluoro-3-oxo-1,3-dihydro-2H-pyrrolo[3,4-c]pyridin-2-yl)methyl)benzofuran-7-carboxylate

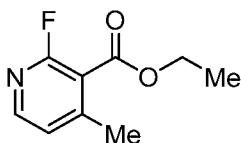
Methyl 5-fluoro-4-methylnicotinate (50 mg, 0.296 mmol) was taken up in CCl₄ (2.96 mL). NBS (63.1 mg, 0.355 mmol) was added followed by AIBN (4.85 mg, 0.030 mmol). The reaction was sealed and heated to 90 °C overnight. After 16 hours, the
25 reaction was cooled, filtered, and concentrated *in vacuo* to give crude methyl 4-(bromomethyl)-5-fluoronicotinate which was used immediately without further purification.

Methyl 3-(aminomethyl)benzofuran-7-carboxylate (60.4 mg, 0.294 mmol, Step C of Example 1) was taken up in THF (2.94 mL) and TEA (123 μ l, 0.883 mmol) was added. The freshly prepared, crude methyl 4-(bromomethyl)-5-fluoronicotinate was taken up in THF (2 mL) and added dropwise to the benzofuran solution at room temperature. The reaction was stirred at room temperature for 30 minutes and then heated to 65 $^{\circ}$ C. After 5 hours, the reaction was concentrated *in vacuo*, taken up in DMF, filtered, and purified *via* HPLC (Method B) to give methyl 2-((7-fluoro-3-oxo-1,3-dihydro-2*H*-pyrrolo[3,4-*c*]pyridin-2-yl)methyl)benzofuran-7-carboxylate (14.6 mg, 0.041 mmol, 14 % yield). 1 H NMR (500 MHz, DMSO- d_6) δ 8.84 (s, 1H), 8.77 (s, 1H), 7.89 (d, J = 7.6 Hz, 1H), 7.83 (d, J = 7.3 Hz, 1H), 7.36 (t, J = 7.6 Hz, 1H), 7.02 (s, 1H), 4.98 (s, 2H), 4.82 (s, 2H), 3.88 (s, 3H); MS (ESI+) m/z = 341.1 (M+H) $^+$.

EXAMPLE 4



Methyl 2-((4-fluoro-3-oxo-1,3-dihydro-2*H*-pyrrolo[3,4-*c*]pyridin-2-yl)methyl)benzofuran-7-carboxylate



A) Ethyl 2-fluoro-4-methylnicotinate

Ethyl 2-fluoro-4-iodonicotinate (1.0 g, 3.39 mmol) (*Org. Lett.* (2005) 7, 1943-1946) was taken up in toluene (7.53 ml), ethanol (0.94 ml), and water (0.941 ml). 2,4,6-Trimethyl-1,3,5,2,4,6-trioxatriborinane (0.57 ml, 4.07 mmol) was added followed by K_2CO_3 (0.70 g, 5.08 mmol). The reaction was bubbled with dry nitrogen gas prior to the

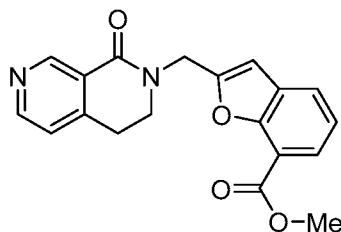
addition of Pd(Ph₃P)₄ (0.98 g, 0.85 mmol) and bubbling continued another 2 minutes before the reaction was sealed and heated to 100 °C overnight. The reaction was concentrated *in vacuo* and purified directly *via* ISCO (24 g column, 0-50% EtOAc) to give ethyl 2-fluoro-4-methylnicotinate (288 mg, 1.57 mmol, 46.4 % yield). ¹H NMR (400 MHz, Chloroform-d) δ 8.13 (d, *J* = 5.1 Hz, 1H), 7.10 - 7.01 (m, 1H), 4.43 (q, *J* = 7.2 Hz, 2H), 2.48 (s, 3H), 1.41 (t, *J* = 7.2 Hz, 3 H); MS (ESI+) *m/z* = 184.1 (M+H)⁺.

B) Methyl 2-((4-fluoro-3-oxo-1,3-dihydro-2*H*-pyrrolo[3,4-*c*]pyridin-2-yl)methyl)benzofuran-7-carboxylate

10 Ethyl 2-fluoro-4-methylnicotinate (50 mg, 0.273 mmol) was taken up in CCl₄ (2.73 mL). NBS (58.3 mg, 0.328 mmol) was added followed by AIBN (4.48 mg, 0.027 mmol). Reaction was sealed and heated to 90 °C overnight. After heating for 16 hours, the reaction was cooled, filtered, and concentrated to give crude methyl 4-(bromomethyl)-2-fluoronicotinate which was used immediately without further purification.

15 Methyl 3-(aminomethyl)benzofuran-7-carboxylate (60.4 mg, 0.294 mmol, Step C of Example 1) was taken up in THF (2.94 mL) and TEA (123 μl, 0.883 mmol) was added. Crude methyl 4-(bromomethyl)-2-fluoronicotinate was taken up in THF (2 mL) and added dropwise to the benzofuran solution at room temperature. The reaction was then allowed to stir at room temperature for 30 minutes and then heated to 65 °C. After stirring for 8
20 hours, the reaction was concentrated *in vacuo*, taken up in DMF, filtered, and purified *via* HPLC (Method B) to give methyl 2-((4-fluoro-3-oxo-1,3-dihydro-2*H*-pyrrolo[3,4-*c*]pyridin-2-yl)methyl)benzofuran-7-carboxylate (15.1 mg, 0.044 mmol, 15.1 % yield). ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.40 (d, *J* = 5.2 Hz, 1H), 7.88 (d, *J* = 7.6 Hz, 1H), 7.83 (d, *J* = 7.0 Hz, 1H), 7.65 (br d, *J* = 2.7 Hz, 1H), 7.36 (t, *J* = 7.6 Hz, 1H), 6.99 (s, 1H), 4.94 (s, 2H), 4.72 (s, 2H), 3.87 (s, 3H); MS (ESI+) *m/z* = 340.9 (M+H)⁺.

EXAMPLE 5

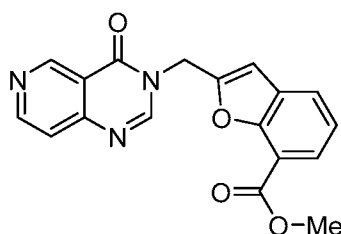


Methyl 2-((1-oxo-3,4-dihydro-2,7-naphthyridin-2(1H)-yl)methyl)benzofuran-7-carboxylate

3,4-Dihydro-1*H*-pyrano[3,4-*c*]pyridin-1-one (30 mg, 0.201 mmol) (WO
 5 2005063768) and methyl 2-(aminomethyl)benzofuran-7-carboxylate (124 mg, 0.603
 mmol, Step C of Example 1) were added to a small pressure relief vial and heated neat at
 100 °C. After 30 minutes, the reaction was heated at 120 °C. After 2 hours, the reaction
 was cooled. The reaction was diluted with 2 mL DMF, filtered, and purified *via* HPLC
 (Method A) to give methyl 2-((1-oxo-3,4-dihydro-2,7-naphthyridin-2(1*H*)-
 10 yl)methyl)benzofuran-7-carboxylate (17.3 mg, 0.051 mmol, 25.3 % yield). ¹H NMR (500
 MHz, DMSO-*d*₆) δ 9.01 (br s, 1H), 8.67 (br d, *J* = 4.9 Hz, 1H), 7.87 (d, *J* = 7.9 Hz, 1H),
 7.82 (d, *J* = 7.3 Hz, 1H), 7.47 (d, *J* = 4.9 Hz, 1H), 7.35 (t, *J* = 7.6 Hz, 1H), 6.98 (s, 1H),
 4.95 (s, 2H), 3.87 (s, 3H), 3.78 (t, *J* = 6.6 Hz, 2H), 3.13 (br t, *J* = 6.6 Hz, 2H); MS (ESI+)
 m/z = 337.0 (M+H)⁺.

15

EXAMPLE 6

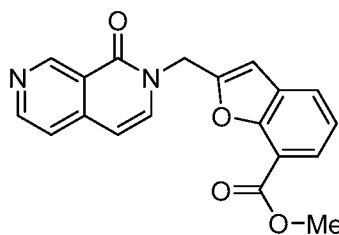


Methyl 2-((4-oxopyrido[4,3-*d*]pyrimidin-3(4*H*)-yl)methyl)benzofuran-7-carboxylate

4-Aminonicotinic acid (25 mg, 0.18 mmol) was taken up in DMF (180 μl) and
 20 1,1-dimethoxy-*N,N*-dimethylmethanamine (54 mg, 0.45 mmol) was added in a 2 mL
 microwave vial. The reaction mixture was heated at 100 °C for 15 minutes in a
 microwave reactor.

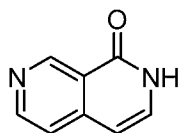
The reaction was then concentrated *in vacuo*, taken up in 0.6 mL of acetic acid and methyl 2-(aminomethyl)benzofuran-7-carboxylate (37 mg, 0.18 mmol, Step C of Example 1) was added. The reaction was once again sealed and heated at 100 °C in a microwave reactor for 15 minutes. The solvent was evaporated and the crude product was taken up in DMF, filtered, and purified *via* HPLC (Method B) to give methyl 2-((4-oxopyrido[4,3-*d*]pyrimidin-3(4*H*)-yl)methyl)benzofuran-7-carboxylate (20.4 mg, 0.061 mmol, 33.6 % yield). ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.33 (s, 1H), 8.87 (d, *J* = 5.6 Hz, 1H), 8.80 (s, 1H), 7.88 (d, *J* = 7.7 Hz, 1H), 7.83 (d, *J* = 7.5 Hz, 1H), 7.65 (d, *J* = 5.6 Hz, 1H), 7.36 (t, *J* = 7.7 Hz, 1H), 7.02 (s, 1H), 5.47 (s, 2H), 3.86 (s, 3H); MS (ESI+) *m/z* = 335.9 (M+H)⁺.

EXAMPLE 7



Methyl 2-((1-oxo-2,7-naphthyridin-2(1*H*)-yl)methyl)benzofuran-7-carboxylate

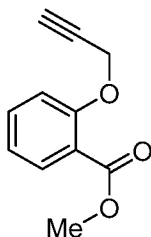
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A) 2,7-Naphthyridin-1(2*H*)-one

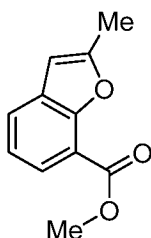
4-Methylnicotinonitrile (250 mg, 2.12 mmol) was taken up DMF (1.4 mL). 1,1-Dimethoxy-*N,N*-dimethylmethanamine (277 mg, 2.33 mmol) was added and the reaction was heated in a microwave reactor at 100 °C for 15 minutes. The reaction was then concentrated *in vacuo*. The residue was taken up in H₂SO₄ (0.7 mL) and acetic acid (0.7 mL) and the reaction was once again heated to 100 °C for 15 minutes in the microwave (conversion was incomplete by LCMS). The reaction was heated again at 100 °C for 15 minutes in the microwave. The reaction was carefully diluted with water and quenched

with ammonium hydroxide. The aqueous mixture was then extracted with chloroform/isopropanol (7:3) three times. The combined organics were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude residue was taken up in DCM / MeOH and purified *via* ISCO (24 g column, 0-15 % MeOH in DCM) to give 2,7-naphthyridin-1(2*H*)-one (28 mg, 0.19 mmol, 9.1 % yield) as a white solid. ¹H NMR (400 MHz, Methanol-d₄) δ 9.40 (s, 1H), 8.66 (d, *J* = 5.6 Hz, 1H), 7.60 (dd, *J* = 5.6, 0.7 Hz, 1H), 7.43 (d, *J* = 7.1 Hz, 1H), 6.65 (d, *J* = 7.2 Hz, 1H); MS (ESI+) *m/z* = 147.0 (M+H)⁺.



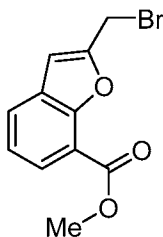
10 **B) Methyl 2-(prop-2-yn-1-yloxy)benzoate**

Methyl 2-hydroxybenzoate (3 g, 19.7 mmol) was taken up in DMF (19.7 ml). Cesium carbonate (7.71 g, 23.7 mmol) was added at room temperature. After 15 minutes, 3-bromoprop-1-yne (3.81 g, 25.6 mmol, 80% solution in xylenes) was added and the reaction was stirred at room temperature for 2.5 hours. The reaction was then diluted with water and extracted with EtOAc. The combined organics were washed with half saturated brine twice, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude residue was purified *via* ISCO (40 g column, 0-50% EtOAc in hexanes) to give methyl 2-(prop-2-yn-1-yloxy)benzoate (3.55 g, 17.7 mmol, 90 % yield). ¹H NMR (400 MHz, Chloroform-d) δ 7.82 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.51 - 7.45 (m, 1H), 7.14 (d, *J* = 8.3 Hz, 1H), 7.05 (td, *J* = 7.5, 0.9 Hz, 1H), 4.80 (d, *J* = 2.3 Hz, 2H), 3.89 (s, 3H), 2.53 (t, *J* = 2.4 Hz, 1H); MS (ESI+) *m/z* = 191.2 (M+H)⁺.



C) Methyl 2-methylbenzofuran-7-carboxylate

Methyl 2-(prop-2-yn-1-yloxy)benzoate (0.5 g, 2.63 mmol) was taken up in *N,N*-diethyl aniline (2.63 ml) in a pressure relief vial and cesium fluoride (0.52 g, 3.42 mmol) was added. The reaction was sealed and heated to 200 °C for 3 hours. The reaction was cooled and the solids were decanted away. The resulting liquid was purified directly *via* silica gel column chromatography (40 g column, 0-20% EtOAc in hexanes) to give methyl 2-methylbenzofuran-7-carboxylate (164 mg, 0.86 mmol, 32.8 % yield). ¹H NMR (400 MHz, Chloroform-d) δ 7.86 (d, *J* = 7.7 Hz, 1H), 7.67 (d, *J* = 7.7 Hz, 1H), 7.24 (t, *J* = 7.7 Hz, 1H), 6.44 (s, 1H), 4.01 (s, 3H), 2.55 (s, 3H); MS (ESI+) *m/z* = 190.8 (M+H)⁺.



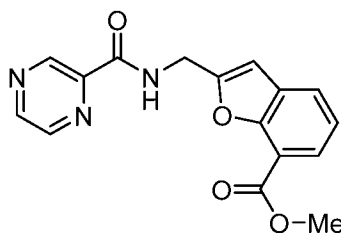
D) Methyl 2-(bromomethyl)benzofuran-7-carboxylate

Methyl 2-methylbenzofuran-7-carboxylate (164 mg, 0.86 mmol) was taken up in CCl₄ (8.6 mL) and NBS (161 mg, 0.91 mmol) and AIBN (35.4 mg, 0.22 mmol) were added. The reaction was sealed in a pressure relief vial and heated to 90 °C for 4 hours. The reaction concentrated *in vacuo* and purified *via* ISCO (12 g column, 0-30% EtOAc in hexanes) to give methyl 2-(bromomethyl)benzofuran-7-carboxylate (185 mg, 0.69 mmol, 80 % yield). ¹H NMR (400 MHz, CHLOROFORM-d) δ 7.99 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.75 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.31 (t, *J* = 7.7 Hz, 1H), 6.83 (s, 1H), 4.66 (s, 2H), 4.03 (s, 3H).

E) Methyl 2-((1-oxo-2,7-naphthyridin-2(1H)-yl)methyl)benzofuran-7-carboxylate

2,7-Naphthyridin-1(2H)-one (15 mg, 0.103 mmol) was taken up in DMF (1.0 mL) and cooled to 0 °C. Sodium hydride (6.2 mg, 0.15 mmol) was added and after 30
5 minutes, methyl 2-(bromomethyl)benzofuran-7-carboxylate (38.7 mg, 0.14 mmol) was added. The reaction was allowed to warm to room temperature. After 30 minutes, the reaction was quenched with a few drops of saturated aqueous ammonium chloride solution, filtered, and purified directly *via* HPLC (Method B) to give methyl 2-((1-oxo-
10 2,7-naphthyridin-2(1H)-yl)methyl)benzofuran-7-carboxylate (24.2 mg, 0.072 mmol, 70.5 % yield). ¹H NMR (500 MHz, DMSO-d₆) δ 9.37 (s, 1H), 8.73 (d, *J* = 5.4 Hz, 1H), 7.94 - 7.78 (m, 3H), 7.60 (d, *J* = 5.4 Hz, 1H), 7.35 (t, *J* = 7.7 Hz, 1H), 6.91 (s, 1H), 6.72 (d, *J* = 7.4 Hz, 1H), 5.44 (s, 2H), 3.88 (s, 3H); MS (ESI+) *m/z* = 335.0 (M+H)⁺.

EXAMPLE 8



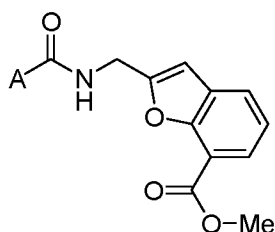
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Methyl 2-((pyrazine-2-carboxamido)methyl)benzofuran-7-carboxylate

Pyrazine-2-carboxylic acid (11 mg, 0.088 mmol) was dissolved in DMF (365 μl) and then DIPEA (51 μl, 0.292 mmol) and methyl 2-(aminomethyl)benzofuran-7-
15 carboxylate (15 mg, 0.073 mmol, Step C of Example 1) were added. BOP (48.5 mg, 0.11 mmol) was added and the reaction was stirred at room temperature for 1 hour. The reaction was diluted with 1.5 mL DMF, filtered, and purified directly *via* HPLC (Method B) to give methyl 2-((pyrazine-2-carboxamido)methyl)benzofuran-7-carboxylate (14.7
20 mg, 0.047 mmol, 64.6 % yield). ¹H NMR (500 MHz, DMSO-d₆) δ 9.53 - 9.36 (m, 1H), 9.22 (s, 1H), 8.88 (d, *J* = 2.3 Hz, 1H), 8.75 (s, 1H), 7.85 (d, *J* = 7.7 Hz, 1H), 7.81 (d, *J* = 7.6 Hz, 1H), 7.33 (t, *J* = 7.7 Hz, 1H), 6.84 (s, 1H), 4.74 (d, *J* = 6.1 Hz, 2H), 3.90 (s, 3H); MS (ESI+) *m/z* = 312.0 (M+H)⁺.

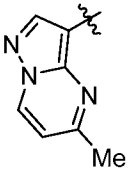
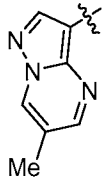
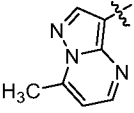
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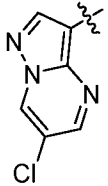
EXAMPLES 9-13



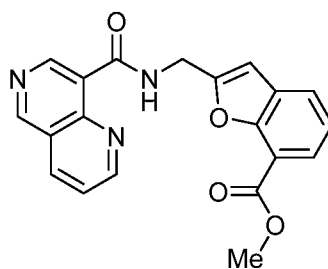
- 5 Example 9 to 13 were prepared according to the procedures described in the synthesis of Example 8 from methyl 2-(aminomethyl)benzofuran-7-carboxylate (Step C of Example 1) and the necessary, commercially available carboxylic acid.

Ex. No.	A	Name	¹ H NMR	LC/MS (M+H) ⁺
9		Methyl 2-((pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.32 (br d, <i>J</i> = 6.7 Hz, 1H), 8.83 (br d, <i>J</i> = 3.1 Hz, 1H), 8.63 (s, 1H), 8.52 (br t, <i>J</i> = 5.6 Hz, 1H), 7.86 (d, <i>J</i> = 7.6 Hz, 1H), 7.81 (d, <i>J</i> = 7.3 Hz, 1H), 7.34 (t, <i>J</i> = 7.6 Hz, 1H), 7.29 (dd, <i>J</i> = 6.9, 4.1 Hz, 1H), 6.86 (s, 1H), 4.81 (br d, <i>J</i> = 5.8 Hz, 2H), 3.89 (s, 3H)	350.9

Ex. No.	A	Name	¹ H NMR	LC/MS (M+H) ⁺
10		Methyl 2-((5-methylpyrazolo[1,5-a]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.07 (br d, <i>J</i> = 7.0 Hz, 1H), 8.57 - 8.49 (m, 2H), 7.88 - 7.79 (m, 2H), 7.34 (t, <i>J</i> = 7.7 Hz, 1H), 7.14 (d, <i>J</i> = 7.2 Hz, 1H), 3.90 (s, 3H), 2.66 (s, 3H)	365.1
11		Methyl 2-((6-methylpyrazolo[1,5-a]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.09 (br s, 1H), 8.72 (s, 1H), 8.53 (s, 1H), 8.44 (br s, 1H), 7.85 (d, <i>J</i> = 7.7 Hz, 1H), 7.81 (d, <i>J</i> = 7.6 Hz, 1H), 7.34 (t, <i>J</i> = 7.7 Hz, 1H), 6.86 (s, 1H), 4.81 (d, <i>J</i> = 5.9 Hz, 2H), 3.90 (s, 3H), 2.40 (s, 3H)	365.1
12		Methyl 2-((7-methylpyrazolo[1,5-a]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO-d ₆) δ 8.70 (br d, <i>J</i> = 4.3 Hz, 1H), 8.63 (s, 1H), 8.57 (br s, 1H), 7.86 (br d, <i>J</i> = 7.7 Hz, 1H), 7.81 (br d, <i>J</i> = 7.7 Hz, 1H), 7.34 (t, <i>J</i> = 7.7 Hz, 1H), 7.21 (br d, <i>J</i> = 3.8 Hz, 1H), 6.86 (s, 1H), 4.82 (br d, <i>J</i> = 5.7 Hz, 2H), 3.93 - 3.88 (s, 3H), 2.81 (s, 3H)	365.2

Ex. No.	A	Name	¹ H NMR	LC/MS (M+H) ⁺
13		Methyl 2-((6-chloropyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.77 - 9.74 (m, 1H), 8.91 - 8.88 (m, 1H), 8.67 (s, 1H), 8.45 (br t, <i>J</i> = 5.8 Hz, 1H), 7.87 (d, <i>J</i> = 7.6 Hz, 1H), 7.82 (d, <i>J</i> = 7.6 Hz, 1H), 7.35 (t, <i>J</i> = 7.6 Hz, 1H), 6.87 (s, 1H), 4.80 (d, <i>J</i> = 5.8 Hz, 2H), 3.90 (s, 3H)	385.1

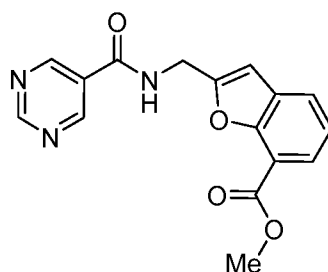
EXAMPLE 14

**Methyl 2-((1,6-naphthyridine-8-carboxamido)methyl)benzofuran-7-carboxylate**

5 A mixture of 1,6-naphthyridine-8-carboxylic acid, HCl (10 mg, 0.047 mmol), methyl 2-(aminomethyl)benzofuran-7-carboxylate, TFA (15.16 mg, 0.047 mmol, Step C of Example 1), HATU (18.05 mg, 0.047 mmol) and Hunig's Base (0.033 mL, 0.190 mmol) in DMF (0.5 mL) was stirred at rt for 3 h. The reaction was quenched with 1:1

10 DMF/AcOH and purified by preparative LC/MS (Method B) to give the title compound (2.3 mg, 5.95 μmol, 12.53 % yield). ¹H NMR (500 MHz, DMSO-*d*₆) δ 10.90 (br s, 1H), 9.63 - 9.59 (m, 1H), 9.39 (s, 1H), 9.30 (br d, *J* = 2.8 Hz, 1H), 8.79 (d, *J* = 6.9 Hz, 1H), 7.91 - 7.85 (m, 2H), 7.83 (d, *J* = 7.7 Hz, 1H), 7.36 (t, *J* = 7.7 Hz, 1H), 6.97 (s, 1H), 4.93 (d, *J* = 5.7 Hz, 2H), 3.19 (br s, 3H); MS (ESI⁺) *m/z* = 362.0 (M+H)⁺.

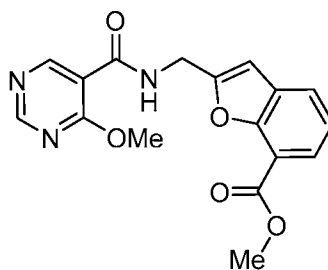
EXAMPLE 15



Methyl 2-((pyrimidine-5-carboxamido)methyl)benzofuran-7-carboxylate

A mixture of methyl 2-(aminomethyl)benzofuran-7-carboxylate, TFA salt (10 mg, 0.031 mmol, Step C of Example 1), pyrimidine-5-carboxylic acid (7.77 mg, 0.063 mmol), HATU (23.82 mg, 0.063 mmol) and Hunig's base (0.022 mL, 0.125 mmol) in DMF (1 mL) was stirred at room temperature for 14 hours. The reaction mixture was quenched with 1:1 DMF/AcOH and purified by preparative HPLC (Method B). The appropriate fractions were combined and dried *via* centrifugal evaporation to afford the title compound (7.2 mg, 73.8 % yield). ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.59 (br t, *J* = 5.3 Hz, 1H), 9.32 (s, 1H), 9.20 (s, 2H), 7.92 - 7.79 (m, 2H), 7.36 (t, *J* = 7.6 Hz, 1H), 6.94 (s, 1H), 4.72 (d, *J* = 5.5 Hz, 2H), 3.65 (br s, 3H); MS (ESI+) *m/z* = 312.0 (M+H)⁺.

EXAMPLE 16



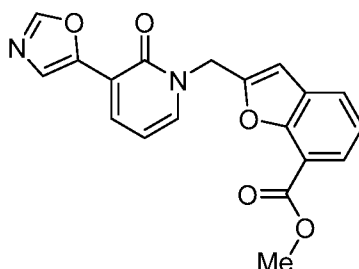
Methyl 2-((4-methoxypyrimidine-5-carboxamido)methyl)benzofuran-7-carboxylate

A mixture of methyl 2-(aminomethyl)benzofuran-7-carboxylate, TFA (10 mg, 0.031 mmol, Step C of Example 1), 4-methoxypyrimidine-5-carboxylic acid (9.7 mg, 0.063 mmol), HATU (23.8 mg, 0.063 mmol) and Hunig's base (0.022 mL, 0.125 mmol) in DMF (1 mL) was stirred at room temperature for 1 hour. The reaction mixture was quenched with 1:1 DMF/AcOH and purified by preparative HPLC (Method B). The

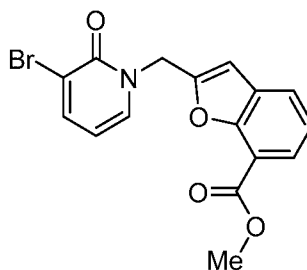
appropriate fractions were combined and dried *via* centrifugal evaporation to afford the title compound (7.8 mg, 71.0 % yield). ¹H NMR (500 MHz, DMSO-d₆) δ 8.99 (br t, *J* = 5.5 Hz, 1H), 8.90 (s, 1H), 8.85 (s, 1H), 7.89 (d, *J* = 7.3 Hz, 1H), 7.83 (d, *J* = 7.6 Hz, 1H), 7.36 (t, *J* = 7.8 Hz, 1H), 6.88 (s, 1H), 4.70 (d, *J* = 5.8 Hz, 2H), 4.06 (s, 3H), 3.91 (s, 3H);

5 MS (ESI+) *m/z* = 341.9 (M+H)⁺.

EXAMPLE 17



10 **Methyl 2-((3-(oxazol-5-yl)-2-oxopyridin-1(2H)-yl)methyl)benzofuran-7-carboxylate**



A) Methyl 2-((3-bromo-2-oxopyridin-1(2H)-yl)methyl)benzofuran-7-carboxylate

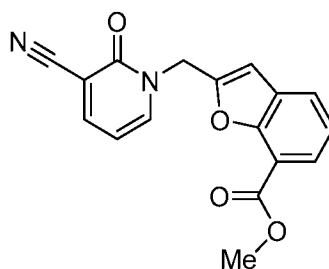
15 A mixture of 3-bromopyridin-2(1H)-one (14 mg, 0.080 mmol), methyl 2-(bromomethyl)benzofuran-7-carboxylate (23.8 mg, 0.089 mmol, Step D of Example 7) and K₂CO₃ (33.4 mg, 0.241 mmol) in DMF (400 μl) was stirred at room temperature for 4 hours. The mixture was loaded on a 24 g silica gel column and eluted with 0-30% EtOAc in hexanes to afford the product. (27.8 mg, 95 % yield). MS (ESI+) *m/z* = 364.0 (M+H)⁺.

20

B. Methyl 2-((3-(oxazol-5-yl)-2-oxopyridin-1(2H)-yl)methyl)benzofuran-7-carboxylate

A mixture of methyl 2-((3-bromo-2-oxopyridin-1(2H)-yl)methyl)benzofuran-7-carboxylate (10 mg, 0.028 mmol), 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oxazole (5.4 mg, 0.028 mmol) and cesium carbonate (18.0 mg, 0.055 mmol) in DMF (270 μ l) and water (5.4 μ l) was degassed. Pd(Ph₃P)₄ (3.2 mg, 2.76 μ mol) was added and the reaction was heated to 100 °C for 2.5 hours. The reaction mixture was quenched with 1:1 DMF/AcOH and purified by preparative HPLC (Method B). The appropriate fractions were combined and dried *via* centrifugal evaporation to afford the title compound (4.4 mg, 45.5 % yield). ¹H NMR (500 MHz, DMSO-d₆) δ 8.45 (s, 1H), 7.97 (br dd, *J* = 14.2, 6.9 Hz, 1H), 7.90 (d, *J* = 7.6 Hz, 1H), 7.85 (d, *J* = 7.6 Hz, 1H), 7.75 (s, 1H), 7.37 (t, *J* = 7.6 Hz, 1H), 6.90 - 6.88 (m, 1H), 6.91 (s, 1H), 6.57 (t, *J* = 6.9 Hz, 1H), 5.50 (s, 2H), 3.90 (s, 3H); MS (ESI+) *m/z* = 351.0 (M+H)⁺.

15

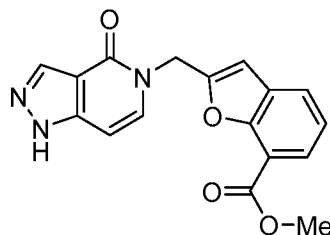
EXAMPLE 18**Methyl 2-((3-cyano-2-oxopyridin-1(2H)-yl)methyl)benzofuran-7-carboxylate**

A mixture of methyl 2-((3-bromo-2-oxopyridin-1(2H)-yl)methyl)benzofuran-7-carboxylate (10 mg, 0.028 mmol, Step A of Example 17) and zinc cyanide (3.9 mg, 0.033 mmol) in DMF (550 μ l) was degassed. Pd(Ph₃P)₄ (3.2 mg, 2.76 μ mol) was added and the reaction was heated to 100 °C for 18 hours. The reaction mixture was quenched with 1:1 DMF/AcOH and purified by preparative HPLC (Method B). The appropriate fractions were combined and dried *via* centrifugal evaporation to afford the title compound (5 mg, 58.7 % yield). ¹H NMR (500 MHz, DMSO-d₆) δ 8.26 - 8.22 (m, 1H), 8.20 (dd, *J* = 7.0, 1.8 Hz, 1H), 7.90 (d, *J* = 7.3 Hz, 1H), 7.85 (d, *J* = 7.6 Hz, 1H), 7.38 (t, *J* = 7.8 Hz, 1H),

25

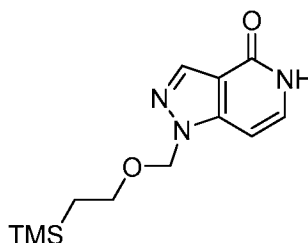
6.95 (s, 1H), 6.53 (t, $J = 7.0$ Hz, 1H), 5.41 (s, 2H), 3.89 (s, 3H); MS (ESI+) $m/z = 309.4$ (M+H)⁺.

EXAMPLE 19



5

Methyl 2-((4-oxo-1H,4H,5H-pyrazolo[4,3-c]pyridin-5-yl)methyl)-1-benzofuran-7-carboxylate



10

A) 1-((2-(Trimethylsilyl)ethoxy)methyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one

To a suspension of 1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one (80 mg, 0.592 mmol) and cesium carbonate (212 mg, 0.651 mmol) in DMF (1.48 mL), was added 2-(trimethylsilyl)ethoxymethyl chloride (1.03 mL, 5.92 mmol) dropwise. The reaction mixture was stirred at room temperature for 3 hours under nitrogen and then poured into water and extracted with a EtOAc three times. The organic phase was washed with saturated aqueous NaCl solution, dried over Na₂SO₄, filtered and concentrated to dryness. The residue was purified by silica gel chromatography (40 g column) eluting with 0-10% MeOH/DCM to give the product (61 mg, 38.8 % yield). MS (ESI+) $m/z = 266.1$ (M+H)⁺.

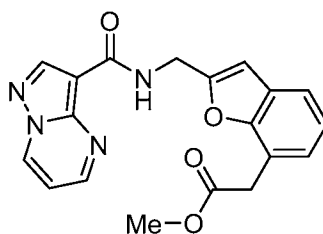
20

B) Methyl 2-((3-(oxazol-5-yl)-2-oxopyridin-1(2H)-yl)methyl)benzofuran-7-carboxylate

A mixture of 1-((2-(trimethylsilyl)ethoxy)methyl)-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridin-4-one (20 mg, 0.075 mmol), methyl 2-(bromomethyl)benzofuran-7-carboxylate (42.6 mg, 0.158 mmol, Step D of Example 7) and K₂CO₃ (31.2 mg, 0.226 mmol) in DMF (377 μl) was stirred at room temperature for 24 hours. The mixture was diluted with water (5 mL) and extracted with EtOAc three times. The organic layer was separated, concentrated and the residue was taken up in DCM (377 μl). 4M HCl in dioxane (94 μl, 0.377 mmol) was added and the reaction was stirred at room temperature for 18 hours.

The solvent was evaporated and the residue was purified by preparative HPLC (Method A). The appropriate fractions were combined and dried *via* centrifugal evaporation to afford the title compound as a TFA salt (7.9 mg, 23.59 % yield). ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.08 (br s, 1H), 8.04 - 8.03 (m, 1H), 7.86 (br d, *J* = 7.7 Hz, 1H), 7.82 (br d, *J* = 7.7 Hz, 1H), 7.60 (br s, 1H), 7.35 (t, *J* = 7.7 Hz, 1H), 6.80 (s, 1H), 6.62 (d, *J* = 7.4 Hz, 1H), 5.38 (br s, 2H), 3.90 (s, 3H); MS (ESI+) *m/z* = 324.2 (M+H)⁺.

EXAMPLE 20



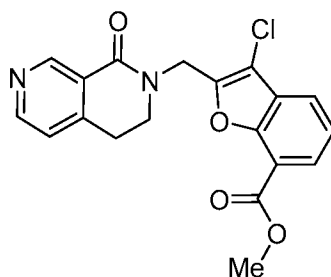
Methyl 2-(2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-yl)acetate

To a solution of methyl 2-(5-bromo-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-yl)acetate (40 mg, 0.090 mmol, Example 80) in DME (1 mL) was added sodium carbonate (0.135 mL, 0.271 mmol), methylboronic acid (16.21 mg, 0.271 mmol), and tetrakis(triphenylphosphine)palladium(0) (10.4 mg, 9.02 μmol).

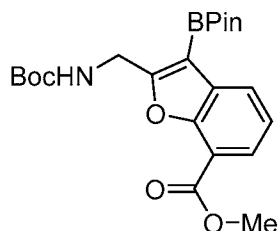
The reaction mixture was degassed by bubbling Ar through it and heated at 80 °C for 18 h. The reaction mixture was concentrated and purified with prep HPLC (Method B) to

give the desired des-bromo byproduct (1.7 mg, 17% yield). ^1H NMR (500 MHz, DMSO- d_6) δ 9.29 (br d, $J = 7.0$ Hz, 1H), 8.82 (br d, $J = 3.1$ Hz, 1H), 8.62 (s, 1H), 8.48 (br t, $J = 5.5$ Hz, 1H), 7.49 (br d, $J = 7.0$ Hz, 1H), 7.28 (dd, $J = 6.9, 4.1$ Hz, 1H), 7.21 - 7.11 (m, 2H), 6.77 (s, 1H), 4.75 (br d, $J = 5.8$ Hz, 2H), 3.92 (s, 2H), 3.58 (s, 3H); MS (ESI+) $m/z =$
 5 365.2 (M+H) $^+$.

EXAMPLE 21



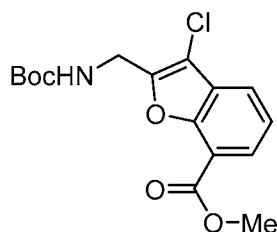
**Methyl 3-chloro-2-((1-oxo-3,4-dihydro-2,7-naphthyridin-2(1H)-
 10 yl)methyl)benzofuran-7-carboxylate**



**A) Methyl-2-(aminomethyl)-5-methyl-3-(4,4,5,5-tetramethyl-1,3,2-
 15 dioxaborolan-2-yl)benzofuran-7-carboxylate**

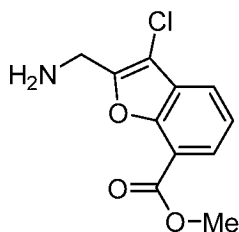
A vial was charged with methyl 2-(((*tert*-butoxycarbonyl)amino)methyl) benzofuran-7-carboxylate (0.5 g, 1.638 mmol, Step B of Example 1), 4,4'-di-*tert*-butyl-2,2'-bipyridine (0.044 g, 0.164 mmol), bis(pinacolato)diboron (0.474 g, 1.876 mmol) and (1,5-cyclooctadiene)(methoxy)iridium (I) dimer (0.065 g, 0.098 mmol) in hexane (15 ml). The reaction mixture was purged with nitrogen and heated to 80°C for 16 hours. The
 20 reaction mixture was filtered and concentrated *in vacuo*. The crude product mixture was purified by a silica gel ISCO 40 g column eluting with 0-20% ethyl acetate in hexanes

over a 15 minute gradient. The appropriate fractions were isolated and concentrated *in vacuo* to afford the product (0.373 g, 53 % yield) as a solid. ¹H NMR (400 MHz, Chloroform-d) δ 8.09 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.97 - 7.85 (m, 1H), 7.34 - 7.25 (m, 1H), 4.73 (br d, *J* = 4.6 Hz, 2H), 4.02 - 3.95 (m, 3H), 1.47 (s, 9H), 1.41 - 1.35 (m, 12H); MS (ESI+) *m/z* = 376.1 (M-55+H)⁺.



B) Methyl 2-(((tert-butoxycarbonyl)amino)methyl)-3-chlorobenzofuran-7-carboxylate

10 A vial was charged with a mixture of methyl 2-(((tert-butoxycarbonyl) amino)methyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-7-carboxylate (113 mg, 0.262 mmol), copper(II) chloride (70.5 mg, 0.524 mmol) and MeOH (3 mL). The reaction mixture was heated to 50 °C for 16 hours. The solution was filtered through celite and concentrated *in vacuo*. The crude product mixture was purified by a silica gel
15 ISCO 12 g column eluting with 0-100% ethyl acetate in hexanes over a 15 minute gradient. The appropriate fractions were isolated and concentrated *in vacuo* to afford the product (0.040 g, 45 % yield) as a solid. ¹H NMR (400 MHz, Chloroform-d) δ 7.99 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.74 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.36 (t, *J* = 7.7 Hz, 1H), 4.67 - 4.50 (m, 2H), 4.06 - 3.96 (m, 3H), 1.48 (s, 9H); MS (ESI+) *m/z* = 376.1 (M-55+H)⁺.



20

C) Methyl 2-(aminomethyl)-3-chlorobenzofuran-7-carboxylate, TFA

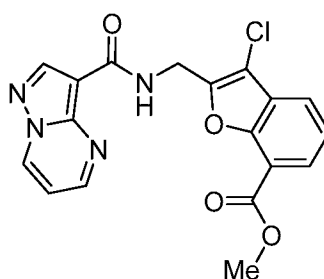
To a solution of the above intermediate (0.04 g, 0.118 mmol) in CH₂Cl₂ (2 mL)

was added TFA (0.5 mL). The reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated *in vacuo* to afford the product methyl 2-(aminomethyl)-3-chlorobenzofuran-7-carboxylate as a TFA salt (41 mg, 89 % yield). ¹H NMR (400 MHz, CHLOROFORM-*d*) δ 8.11 - 7.97 (m, 1H), 7.86 (br d, *J* = 7.8 Hz, 1H), 7.55 - 7.40 (m, 1H), 4.44 (s, 2H), 4.04 - 3.91 (m, 3H); MS (ESI+) *m/z* = 223.0 (M-16)⁺.

D) Methyl 3-chloro-2-((1-oxo-3,4-dihydro-2,7-naphthyridin-2(1H)-yl)methyl)benzofuran-7-carboxylate

A mixture of 3,4-dihydro-1*H*-pyrano[3,4-*c*]pyridin-1-one, HCl (20 mg, 0.108 mmol) (WO 2005063768), methyl 2-(aminomethyl)-3-chlorobenzofuran-7-carboxylate, TFA salt (38.1 mg, 0.108 mmol) and pyridine (216 μl) was heated at 110° C for 2 hours. The reaction was diluted with MeOH. The crude material was purified *via* preparative HPLC (Method C) to yield the title compound (5.78 mg, 14 % yield). ¹H NMR (400 MHz, Methanol-*d*₄) δ 9.05 (s, 1H), 8.59 (d, *J* = 5.1 Hz, 1H), 8.00 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.86 - 7.79 (m, 1H), 7.49 - 7.42 (m, 1H), 7.42 - 7.37 (m, 1H), 5.09 (s, 2H), 3.98 - 3.91 (m, 3H), 3.90 - 3.84 (m, 2H), 3.23 - 3.12 (m, 2H); MS (ESI+) *m/z* = 371.1 (M+H)⁺.

EXAMPLE 22

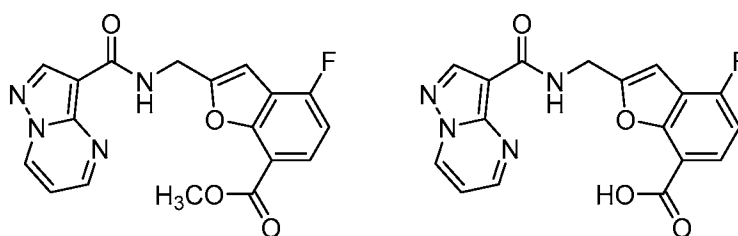


20 Methyl 3-chloro-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate

To a suspension of pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (15 mg, 0.092 mmol) and BOP (48.8 mg, 0.110 mmol) in DMF (2 mL) was added methyl 2-(aminomethyl)-3-chlorobenzofuran-7-carboxylate, TFA salt (32.5 mg, 0.092 mmol, Step 25 C of Example 21) and DIPEA (0.064 mL, 0.368 mmol). The reaction was stirred at room

temperature for 2 hours. The reaction was quenched with water, and a precipitate resulted. The precipitate was collected *via* filtration, and then dissolved in 2 mL of DMF for purification. The crude material was purified *via* preparative HPLC (Method B) to afford the product (19.6 mg, 54.6 % yield). ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.30 - 9.27 (m, 1H), 8.84 (d, *J* = 2.7 Hz, 1H), 8.61 (s, 1H), 8.54 (br t, *J* = 5.6 Hz, 1H), 7.93 (d, *J* = 7.3 Hz, 1H), 7.85 (d, *J* = 7.6 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 1H), 7.28 (dd, *J* = 6.7, 4.3 Hz, 1H), 4.87 (d, *J* = 5.8 Hz, 2H), 3.86 (s, 3H); MS (ESI+) *m/z* = 385.3 (M+H)⁺.

EXAMPLE 23 and EXAMPLE 24



10

Methyl 4-fluoro-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)-benzofuran-7-carboxylate

and

4-Fluoro-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylic acid

15

To a solution of 2,2,2-trifluoroethyl 4-fluoro-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate (137 mg, 0.314 mmol, Example 222) in THF (4 mL) and MeOH (4 mL) was added a 3M aqueous sodium hydroxide solution (0.314 mL, 0.942 mmol). The reaction mixture was stirred at rt for 1h and then neutralized with 4 N HCl in 1,4-dioxane to pH ~2. The mixture was concentrated *in vacuo*. The residue was dissolved in MeOH and purified by prep HPLC (Method B) to give methyl 4-fluoro-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)-benzofuran-7-carboxylate, Example 23 (47 mg, 40 % yield) and 4-fluoro-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylic acid, Example 24 (40 mg, 41% yield).

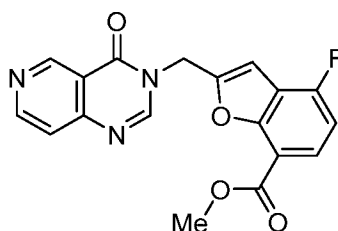
25

Example 23: ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.28 (br d, *J* = 6.9 Hz, 1H), 8.84 (br d, *J* =

3.4 Hz, 1H), 8.62 (s, 1H), 8.50 (br s, 1H), 7.89 (dd, $J = 8.3, 5.5$ Hz, 1H), 7.28 (dd, $J = 6.8, 4.3$ Hz, 1H), 7.20 (t, $J = 8.9$ Hz, 1H), 6.95 (s, 1H), 4.84 (br d, $J = 5.8$ Hz, 2H), 3.90 (s, 3H); MS (ESI+) $m/z = 369.0$ (M+H)⁺.

Example 24: ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.23 (br d, $J = 6.5$ Hz, 1H), 8.81 (br d, $J = 2.9$ Hz, 1H), 8.60 (s, 1H), 8.54 - 8.47 (m, 1H), 7.85 (br dd, $J = 8.1, 5.8$ Hz, 1H), 7.26 (br s, 1H), 7.15 (br t, $J = 8.8$ Hz, 1H), 6.92 (s, 1H), 4.81 (br d, $J = 5.7$ Hz, 2H); MS (ESI+) $m/z = 355.0$ (M+H)⁺.

EXAMPLE 25



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Methyl 4-fluoro-2-((4-oxo-3,4-dihydropyrido[4,3-*d*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate

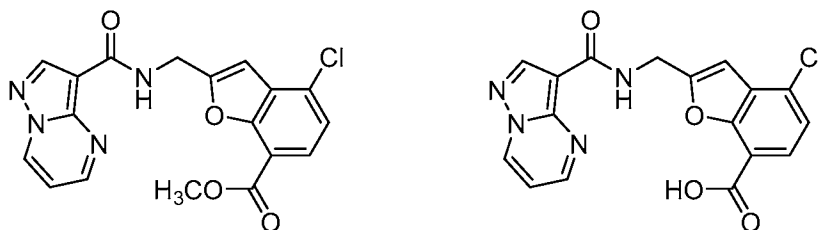
To a solution of 2,2,2-trifluoroethyl 4-fluoro-2-((4-oxopyrido[4,3-*d*]pyrimidin-3(4*H*)-yl)methyl)benzofuran-7-carboxylate (20 mg, 0.047 mmol, Example 226) in MeOH (1 mL) and THF (1 mL) was added 3 M aqueous sodium hydroxide solution (0.047 mL, 0.142 mmol). The reaction mixture was stirred at room temperature for 2 hours, and acidified to pH 2-3 with 1 N aqueous HCl solution. The reaction mixture was concentrated *in vacuo* and purified by prep HPLC (Method C) to give the desired acid (10 mg). MS (ESI+) $m/z = 340.0$ (M+H)⁺.

To a solution of the above benzofuran-7-carboxylic acid (10 mg, 0.029 mmol) in DCM (1 mL) and MeOH (0.2 mL) at room temperature was added (diazomethyl)trimethylsilane, 2 M in diethyl ether (0.029 mL, 0.059 mmol) dropwise. The reaction mixture was stirred for 1 h, and concentrated *in vacuo*. The residue was purified with prep HPLC, Method B, to give the desired product (2.8 mg, 27%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.33 (s, 1H), 8.87 (d, $J = 5.5$ Hz, 1H), 8.77 (s, 1H), 7.90 (dd, $J = 8.5, 5.2$ Hz, 1H), 7.65 (d, $J = 5.8$ Hz, 1H), 7.22 (t, $J = 8.9$ Hz, 1H), 7.17 (s, 1H), 5.48 (s,

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2H), 3.85 (s, 3H); MS (ESI+) $m/z = 354.0$ (M+H)⁺.

EXAMPLE 26 and EXAMPLE 27



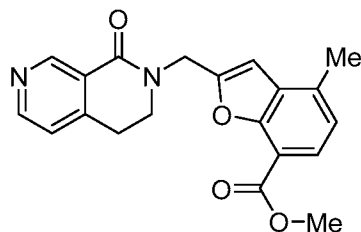
5 Methyl 4-chloro-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate

To the solution of *N*-((7-bromo-4-chlorobenzofuran-2-yl)methyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (21 mg, 0.052 mmol, Step F of Example 227) in DMSO (4 mL) was added methanol (33.2 mg, 1.035 mmol), palladium(II) acetate (1.2 mg, 5.18 μmol), 1,3-bis(diphenylphosphanyl)propane, dppp (2.1 mg, 5.18 μmol), and triethylamine (0.072 mL, 0.518 mmol). The reaction mixture was degassed by bubbling Ar through and heated at 80 °C under a CO atmosphere for 4 hours. The reaction mixture was concentrated *in vacuo*. The residue was purified by prep HPLC (Method A) to give both Example 26 (7.9 mg, 39 % yield) and Example 27 (3.1 mg, 16% yield).

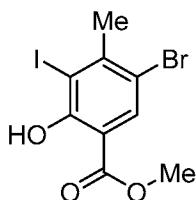
15 Example 26: ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.30 (br d, *J* = 7.0 Hz, 1H), 8.84 (br d, *J* = 2.7 Hz, 1H), 8.64 (s, 1H), 8.59 (s, 1H), 7.84 (d, *J* = 8.2 Hz, 1H), 7.46 (d, *J* = 8.2 Hz, 1H), 7.29 (dd, *J* = 7.0, 4.3 Hz, 1H), 6.89 (s, 1H), 4.83 (br d, *J* = 5.8 Hz, 2H), 3.90 (s, 3H); MS (ESI+) $m/z = 385.0$ (M+H)⁺.

20 Example 27: ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.25 (br s, 1H), 8.82 (br s, 1H), 8.61 (s, 1H), 8.52 (br s, 1H), 7.77 (br d, *J* = 8.2 Hz, 1H), 7.39 (br d, *J* = 8.2 Hz, 1H), 7.30 - 7.23 (m, 1H), 6.85 (s, 1H), 4.82 (br d, *J* = 5.6 Hz, 2H); MS (ESI+) $m/z = 371.0$ (M+H)⁺.

Example 28



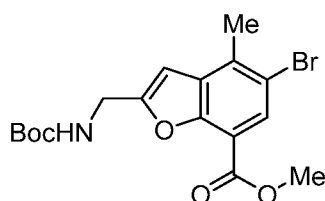
Methyl 4-methyl-2-((1-oxo-3,4-dihydro-2,7-naphthyridin-2(1H)-yl)methyl)benzofuran-7-carboxylate



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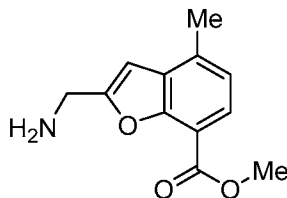
A) Methyl 5-bromo-2-hydroxy-3-iodo-4-methylbenzoate

To a solution of methyl 5-bromo-2-hydroxy-4-methylbenzoate (1.2 g, 4.90 mmol) in *N,N*-dimethylformamide (10 mL) was added sodium iodide (0.88 g, 5.88 mmol), followed by slow addition of chloramine T trihydrate (1.52 g, 5.39 mmol). The resulting mixture was stirred at room temperature for 2 hours. The reaction mixture was diluted with ethyl acetate and 1 N aqueous HCl solution. The organic layer was separated and then washed with brine and Na₂S₂O₃ solution. The combined organics were dried over MgSO₄ and filtered. The filtrate was concentrated *in vacuo* to give a light yellow solid. The solid was mixed with MeOH and the resulting white solid was filtered to give crude methyl 5-bromo-2-hydroxy-3-iodo-4-methylbenzoate (1.4 g, 77 % yield). ¹H NMR (499 MHz, Chloroform-*d*) δ 11.67 (s, 1H), 8.05 (s, 1H), 3.99 (s, 3H), 2.75 (s, 3H); MS (ESI+) *m/z* = 370.8 (M+H)⁺.



B) Methyl 5-bromo-2-(((tert-butoxycarbonyl)amino)methyl)-4-methylbenzofuran-7-carboxylate

The reaction mixture of methyl 5-bromo-2-hydroxy-3-iodo-4-methylbenzoate (1.6 g, 4.31 mmol), *tert*-butyl prop-2-yn-1-ylcarbamate (0.77 g, 4.96 mmol), TEA (12.0 mL, 86 mmol), copper(I) iodide (0.082 g, 0.43 mmol) in DMF (10 mL) was purged with nitrogen stream for 5 mins, then bis(triphenylphosphine)palladium(II) chloride (0.30 g, 0.43 mmol) was added. The resulting mixture was heated at 80 °C for 3 hours. The reaction mixture was diluted with ethyl acetate and saturated aqueous NaHCO₃ solution. The organic layer was separated, washed with brine, dried over MgSO₄, filtered, and concentrated *in vacuo*. The crude product was dissolved in DCM and then purified by silica gel column chromatography (80 gram column, eluted with 0 - 30% EtOAc in hexanes) to give methyl 5-bromo-2-(((tert-butoxycarbonyl)amino)methyl)-4-methylbenzofuran-7-carboxylate (0.55 g, 32%). ¹H NMR (400 MHz, Chloroform-d) δ 8.08 (s, 1H), 6.68 (s, 1H), 4.51 (d, *J* = 6.1 Hz, 2H), 3.99 (s, 3H), 2.57 (s, 3H), 1.48 (s, 9H); MS (ESI+) *m/z* = 344.0 (M-54)⁺.



C) Methyl 2-(aminomethyl)-4-methylbenzofuran-7-carboxylate

The reaction mixture of methyl 5-bromo-2-(((tert-butoxycarbonyl)amino)methyl)-4-methylbenzofuran-7-carboxylate (0.55 g, 1.38 mmol) and palladium hydroxide on carbon (0.14 g, 0.21 mmol) in MeOH (15 mL) was evacuated and filled with hydrogen (balloon). The reaction was stirred under hydrogen atmosphere at room temperature overnight. The reaction mixture was filtered and concentrated *in vacuo*. To the residue was added DCM (6 mL) and TFA (1.5 mL, 19.5 mmol). The reaction mixture was stirred at room temperature for 3 hours. The reaction mixture was concentrated *in vacuo* and the residue was mixed with saturated aqueous NaHCO₃ solution and ethyl acetate. The organic layer was separated, washed with brine, dried over MgSO₄, filtered,

and concentrated *in vacuo* to give methyl 2-(aminomethyl)-4-methylbenzofuran-7-carboxylate (0.21 g, 69 % yield). $^1\text{H NMR}$ (400 MHz, Chloroform- d) δ 7.81 (d, $J = 7.8$ Hz, 1H), 7.06 (dd, $J = 7.8, 0.7$ Hz, 1H), 6.61 (s, 1H), 4.07 (d, $J = 0.8$ Hz, 2H), 3.99 (s, 3H), 2.53 (s, 3H); MS (ESI+) $m/z = 439.2$ (M+H) $^+$.

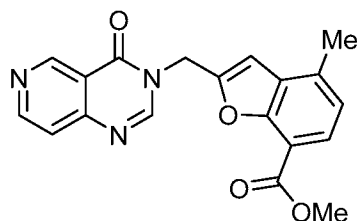
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D) Methyl 4-methyl-2-((1-oxo-3,4-dihydro-2,7-naphthyridin-2(1H)-yl)methyl)benzofuran-7-carboxylate

3,4-Dihydro-1H-pyrano[3,4-*c*]pyridin-1-one (25 mg, 0.17 mmol) (WO 2005063768) and methyl 2-(aminomethyl)-4-methylbenzofuran-7-carboxylate (73.5 mg, 0.33 mmol) were added to a pressure relief vial and heated neat at 120 °C. After heating for 4 hours, the reaction was cooled, taken up in 2 mL DMF, filtered and purified *via* HPLC (Method B) to give methyl 4-methyl-2-((1-oxo-3,4-dihydro-2,7-naphthyridin-2(1H)-yl)methyl)benzofuran-7-carboxylate (17.2 mg, 0.049 mmol, 29.3 % yield). $^1\text{H NMR}$ (500 MHz, DMSO- d_6) δ 8.99 (s, 1H), 8.64 (br d, $J = 4.6$ Hz, 1H), 7.75 (d, $J = 7.6$ Hz, 1H), 7.40 (d, $J = 4.6$ Hz, 1H), 7.17 (d, $J = 7.9$ Hz, 1H), 7.04 (s, 1H), 4.95 (s, 2H), 3.87 (s, 3H), 3.78 (t, $J = 6.4$ Hz, 2H), 3.12 (br t, $J = 6.4$ Hz, 2H), 2.53 (s, 3H); MS (ESI+) $m/z = 351.1$ (M+H) $^+$.

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EXAMPLE 29



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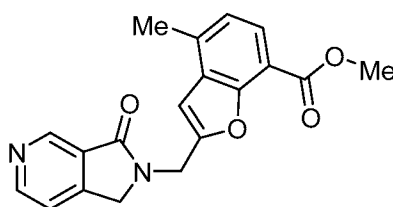
Methyl 4-methyl-2-((4-oxopyrido[4,3-*d*]pyrimidin-3(4H)-yl)methyl)benzofuran-7-carboxylate

4-Aminonicotinic acid (28.4 mg, 0.205 mmol) and *N,N*-dimethylformamide dimethyl acetal (0.092 mL, 0.684 mmol) were taken up in DMF (0.3 mL) in a 0.2-0.5 mL of microwave vial. The vial was sealed and heated to 100 °C for 15 min in a microwave reactor. After, 15 minutes, the reaction was removed from the reactor, cooled, and

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concentrated *in vacuo*. To the residue was added 1 mL of acetic acid and methyl 2-(aminomethyl)-4-methylbenzofuran-7-carboxylate (30 mg, 0.137 mmol, Step C in Example 28). The vial was re-sealed and heated at 120 °C in a microwave for another 15 minutes. The reaction mixture was cooled and concentrated *in vacuo*. The residue was diluted with water and extracted with EtOAc. The organics were separated, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was dissolved in MeOH, filtered, and purified *via* HPLC (method B) to give the title compound (3 mg, 6.0% yield). ¹H NMR (500 MHz, DMSO-d₆) δ 9.35 (s, 1H), 8.89 (d, *J* = 5.5 Hz, 1H), 8.80 (s, 1H), 7.76 (d, *J* = 7.9 Hz, 1H), 7.67 (d, *J* = 5.8 Hz, 1H), 7.18 (d, *J* = 7.9 Hz, 1H), 7.09 (s, 1H), 5.48 (s, 2H), 3.86 (s, 3H), 2.50 (s, 3H); MS (ESI+) *m/z* = 350.2 (M+H)⁺.

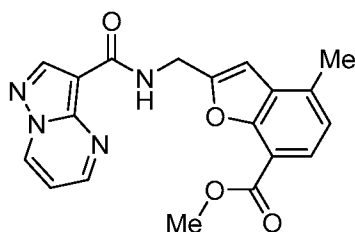
EXAMPLE 30



Methyl 4-methyl-2-((3-oxo-1,3-dihydro-2H-pyrrolo[3,4-c]pyridin-2-yl)methyl)benzofuran-7-carboxylate

To a solution of methyl 2-(aminomethyl)-4-methylbenzofuran-7-carboxylate (51.5 mg, 0.235 mmol, Step C of Example 28) in THF (1 mL) was added TEA (0.182 mL, 1.304 mmol). Subsequently, a solution of crude methyl 2-(bromomethyl)nicotinate (150 mg, 0.130 mmol, prepared as in Example 2) in THF (1 mL) was added. The reaction mixture was stirred at room temperature for 0.6 hours, then heated at 70 °C for 2 hours. After 2 hours, the reaction was cooled and concentrated *in vacuo*. The residue was taken up in DMSO, filtered, and purified *via* HPLC (method B) to give the title compound (2.6 mg, 4.4%). ¹H NMR (500 MHz, DMSO-d₆) δ 9.00 (s, 1H), 8.80 (d, *J* = 4.9 Hz, 1H), 7.82 - 7.71 (m, 2H), 7.30 - 7.00 (m, 2H), 4.99 (s, 2H), 4.73 (s, 2H), 3.86 (s, 3H), 2.56 (s, 3H); MS (ESI+) *m/z* = 337.1 (M+H)⁺.

EXAMPLE 31

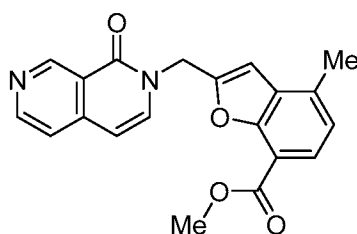


Methyl 4-methyl-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate

- 5 To a solution of 4-methyl-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylic acid (25 mg, 0.071 mmol, Example 127) in DCM (1 mL) and MeOH (0.2 mL) at room temperature was added (diazomethyl)trimethylsilane, 2 M in diethyl ether (0.071 mL, 0.143 mmol) dropwise. The reaction mixture was stirred for 4 hours. The reaction mixture was concentrated and
- 10 the residue was purified with prep HPLC, Method B, to give the desired product (4.6 mg, 18% yield). ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.27 (br d, *J* = 7.0 Hz, 1H), 8.85 (br d, *J* = 3.1 Hz, 1H), 8.65 (s, 1H), 8.60 (br t, *J* = 5.5 Hz, 1H), 7.75 (d, *J* = 7.9 Hz, 1H), 7.30 (dd, *J* = 6.9, 4.1 Hz, 1H), 7.18 (br d, *J* = 7.6 Hz, 1H), 6.92 (s, 1H), 4.82 (br d, *J* = 5.8 Hz, 2H), 3.88 (s, 3H), 2.51 (s, 3H); MS (ESI+) *m/z* = 365.0 (M+H)⁺.

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EXAMPLE 32

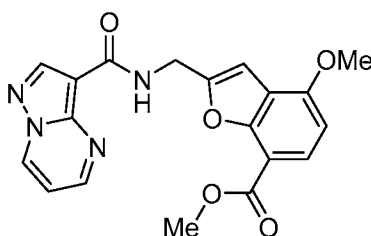


Methyl 4-methyl-2-((1-oxo-1,2-dihydro-2,7-naphthyridine-2-carboxamido)methyl)benzofuran-7-carboxylate

- 20 To a solution of 4-methyl-2-((1-oxo-2,7-naphthyridin-2(1H)-yl)methyl)benzofuran-7-carboxylic acid (30 mg, 0.090 mmol, Step B of Example 232) in DCM (1 mL) and MeOH (0.2 mL) at room temperature was added

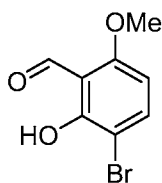
(diazomethyl)trimethylsilane, 2 M in diethyl ether (0.090 mL, 0.179 mmol) dropwise. The reaction mixture was stirred for 2 h. The reaction mixture was purified with prep HPLC (Method A) to afford the product (5.4 mg, 17% yield). ¹H NMR (500 MHz, DMSO-d₆) δ 7.88 (d, *J* = 7.3 Hz, 1H), 7.75 (d, *J* = 7.9 Hz, 1H), 7.65 (br s, 1H), 7.27 (br s, 1H), 7.17 (br d, *J* = 7.6 Hz, 1H), 7.07 (br s, 1H), 6.98 (s, 1H), 6.76 (d, *J* = 7.3 Hz, 1H), 5.44 (s, 2H), 3.86 (s, 3H), 2.50 (s, 3H); MS (ESI+) *m/z* = 349.0 (M+H)⁺.

EXAMPLE 33



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Methyl 4-methoxy-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate

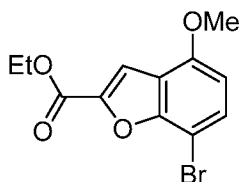


A) 3-Bromo-2-hydroxy-6-methoxybenzaldehyde

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A mixture of paraformaldehyde (3.64 g, 121 mmol), magnesium chloride (7.69 g, 81 mmol) and triethylamine (11.3 mL, 81 mmol) was stirred at rt for 10 minutes. Then, 2-bromo-5-methoxyphenol (8.2 g, 40.4 mmol) was added. The reaction mixture was stirred at 85 °C for 4 hours and then concentrated *in vacuo*. The residue was dissolved in hydrochloric acid (10% aqueous solution, 50 mL) and stirred at room temperature for 20 30 minutes. Ethyl acetate (200 mL) was added and the layers were separated. The organic layer was dried over sodium sulfate and concentrated *in vacuo*. The residue was purified through ISCO, 330 column, eluting with 0-20% EtOAc in hexane to give the desired product as a light yellow solid (4.34 g, 47%). ¹H NMR (400 MHz, Methanol-d₄) δ

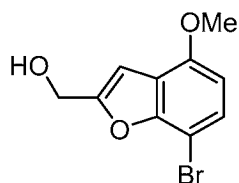
9.81 (br s, 1H), 7.62 - 7.49 (m, 2H), 3.81 (s, 3H); MS (ESI+) $m/z = 230.8 (M+H)^+$.



B) Ethyl 7-bromo-4-methoxybenzofuran-2-carboxylate

5 To a solution of 3-bromo-2-hydroxy-6-methoxybenzaldehyde (1.0 g, 4.33 mmol) in DMF (5 mL) was added ethyl 2-bromoacetate (2.17 g, 13.0 mmol) and cesium carbonate (4.9 g, 15.1 mmol). The reaction mixture was stirred at 120 °C for 8 h. After cooling to rt, the reaction was acidified with 1 N aqueous HCl solution to pH 2-3 and then extracted with EtOAc, three times. The combined organic extracts were dried over
 10 sodium sulfate, filtered, concentrated, and purified with ISCO, 120 g column, eluting with 0-30% EtOAc in hexanes to give the product as a light yellow solid. (0.52 g, 40%). ¹H NMR (400 MHz, Chloroform-d) δ 7.68 (s, 1H), 7.52 (d, $J = 8.5$ Hz, 1H), 6.62 (d, $J = 8.6$ Hz, 1H), 4.46 (q, $J = 7.1$ Hz, 2H), 3.96 (s, 3H), 1.45 (t, $J = 7.1$ Hz, 3H); MS (ESI+) $m/z = 298.9 (M+H)^+$.

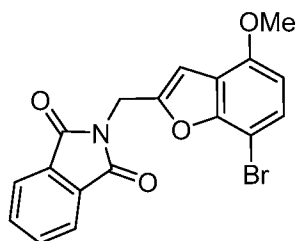
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C) (7-Bromo-4-methoxybenzofuran-2-yl)methanol

To a stirred solution of ethyl 7-bromo-4-methoxybenzofuran-2-carboxylate (520 mg, 1.74 mmol) in THF (20 mL) at -30 °C under N₂ was added lithium aluminum
 20 hydride (1.74 mL, 1.74 mmol) dropwise *via* syringe over 5 min. The reaction mixture was stirred at this temperature for 2 hours. The reaction was quenched with Fieser Method (at -30 °C add 0.5 ml of water, add 0.5 ml of 15% NaOH, add 0.5 ml of water, and stirred at room temperature for 30 min). Some anhydrous magnesium sulfate was added and the mixture was stirred for 15 min and then filtered over celite. The filtrate was concentrated

to give the desired product as a white solid (440 mg, 98%). ¹H NMR (400 MHz, CHLOROFORM-d) δ 7.35 (d, *J* = 8.5 Hz, 1H), 6.83 (s, 1H), 6.58 (d, *J* = 8.5 Hz, 1H), 4.80 (s, 2H), 3.93 (s, 3H), 2.23 (br s, 1H).

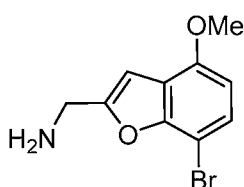


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D) 2-((7-Bromo-4-methoxybenzofuran-2-yl)methyl)isoindoline-1,3-dione

To a stirred solution of (7-bromo-4-methoxybenzofuran-2-yl)methanol (0.5 g, 1.95 mmol) and phthalimide (0.286 g, 1.95 mmol) in THF (20 mL) under N₂ was added triphenylphosphine (0.612 g, 2.33 mmol) and DIAD (0.454 mL, 2.33 mmol). After stirring at rt for 18 h, the reaction was concentrated *in vacuo*. The residue was purified by flash chromatography, with a 80 g ISCO column, eluting with 0-30% EtOAc in hexanes to give the desired product as a white solid (0.54 g, 72%). ¹H NMR (400 MHz, CHLOROFORM-d) δ 7.92 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.77 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.32 (d, *J* = 8.6 Hz, 1H), 6.84 (s, 1H), 6.55 (d, *J* = 8.5 Hz, 1H), 5.06 (d, *J* = 0.9 Hz, 2H), 3.90 (s, 3H).

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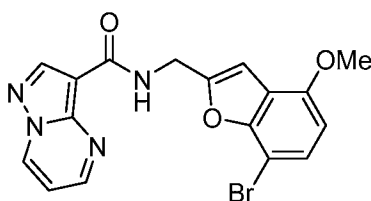


E) 2-((7-Bromo-4-methoxybenzofuran-2-yl)methyl)isoindoline-1,3-dione

To a stirred suspension of 2-((7-bromo-4-methoxybenzofuran-2-yl)methyl)isoindoline-1,3-dione (0.47 g, 1.22 mmol) in ethanol (20 mL) was added hydrazine (0.873 mL, 9.74 mmol). The reaction was heated at 50 °C with stirring. After 15 min the reaction mixture reached a homogeneous solution. After 10 more min, a white solid formed gradually. After stirring at 50 °C for 45 min, the reaction mixture was

20

cooled to rt. Et₂O (50 mL) was added and the mixture was stirred for 10 min. The solid was removed by filtration and washed with Et₂O. The filtrate was concentrated to give an oil. To the oil was added 50 ml of ether. Some more solid formed. The solid was removed by filtration and washed with ether. The filtrate was concentrated to give the
 5 desired product as an oil (0.30 g, 96%). ¹H NMR (400 MHz, Chloroform-d) δ 7.29 (d, *J* = 8.5 Hz, 1H), 6.67 (s, 1H), 6.54 (d, *J* = 8.5 Hz, 1H), 3.98 (d, *J* = 0.7 Hz, 2H), 3.90 (s, 3H), 1.74 (br s, 2H); MS (ESI+) *m/z* = 238.9 (M-NH₂)⁺.



10 **F) N-((7-Bromo-4-methoxybenzofuran-2-yl)methyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide**

To a solution of (7-bromo-4-methoxybenzofuran-2-yl)methanamine (120 mg, 0.469 mmol) in DMF (2 mL) was added pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (76 mg, 0.469 mmol), ((1H-benzo[*d*][1,2,3]triazol-1-yl)oxy)tris(dimethylamino)
 15)phosphonium hexafluorophosphate(V) (311 mg, 0.703 mmol), and DIPEA (182 mg, 1.41 mmol). The reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was diluted with water and the solid formed was collected by filtration, washed with water and ether, and dried under vacuum to provide the product (152 mg, 81%). MS (ESI+) *m/z* = 401.1 (M+H)⁺.

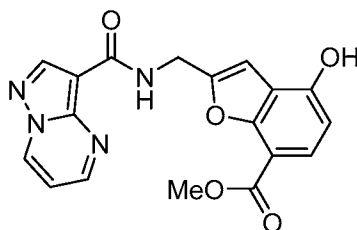
20

G) Methyl 4-methoxy-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate

To a suspension of *N*-((7-bromo-4-methoxybenzofuran-2-yl)methyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (152 mg, 0.379 mmol) in DMF (1.5 mL) and MeOH (0.5
 25 mL) was added triethylamine (383 mg, 3.79 mmol), diacetoxypalladium (8.5 mg, 0.038 mmol), and 1,3-bis(diphenylphosphanyl)propane (15.6 mg, 0.038 mmol). The reaction mixture was degassed by bubbling argon through and heated under CO at 100 °C for 20

h. The reaction mixture was concentrated *in vacuo*. The residue was washed with MeOH. The solid formed was collected by filtration as the desired product (130 mg, 90% yield). ¹H NMR (500 MHz, DMSO-d₆) δ 9.19 (br d, *J* = 7.0 Hz, 1H), 8.80 (br d, *J* = 4.1 Hz, 1H), 8.60 (s, 1H), 8.50 (br s, 1H), 7.83 (d, *J* = 8.2 Hz, 1H), 7.25 (dd, *J* = 6.2, 4.8 Hz, 1H), 6.90 (d, *J* = 8.4 Hz, 1H), 6.79 (s, 1H), 4.77 (d, *J* = 5.8 Hz, 2H), 3.94 (s, 3H), 3.84 (s, 3H); MS (ESI+) *m/z* = 381.1 (M+H)⁺.

EXAMPLE 34



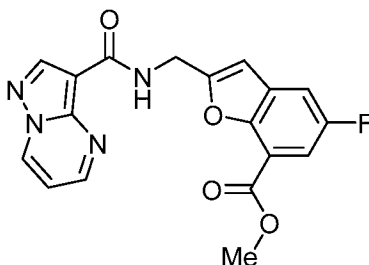
10

Methyl 4-hydroxy-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate

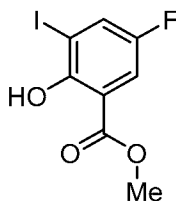
To a solution of methyl 4-methoxy-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate (40 mg, 0.105 mmol, Example 33) in DCM (2 mL) at 0 °C was added tribromoborane (0.020 mL, 0.210 mmol). The reaction mixture was stirred at 0 °C for 4 h and then diluted with DCM. The organic layer was washed with sat. NaCl, dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by prep HPLC (Method B) to give the product as a white solid (4.6 mg, 12% yield). ¹H NMR (500 MHz, DMSO-d₆) δ 9.32 - 9.25 (m, 1H), 8.83 (dd, *J* = 4.0, 1.4 Hz, 1H), 8.62 (s, 1H), 8.43 (br t, *J* = 5.7 Hz, 1H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.27 (dd, *J* = 7.0, 4.2 Hz, 1H), 6.85 (s, 1H), 6.66 (d, *J* = 8.5 Hz, 1H), 4.77 (d, *J* = 5.8 Hz, 2H), 3.83 (s, 3H); MS (ESI+) *m/z* = 367.1 (M+H)⁺.

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EXAMPLE 35



Methyl 5-fluoro-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate

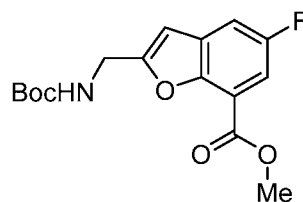


5

A) Methyl 5-fluoro-2-hydroxy-3-iodobenzoate

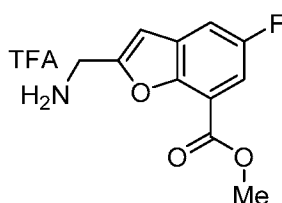
To a solution of methyl 5-fluoro-2-hydroxybenzoate (2.0 g, 11.8 mmol) in *N,N*-dimethylformamide (20 mL) was added sodium iodide (2.11 g, 14.1 mmol), followed by addition of chloramine T trihydrate (3.64 g, 12.9 mmol) slowly. The resulting mixture was stirred at room temperature for 20 hours. The reaction mixture was diluted with ethyl acetate and 1 N aqueous HCl solution. The organic layer was separated and washed with brine, Na₂S₂O₃ solution and dried over MgSO₄. The filtrate was concentrated *in vacuo* to give a light yellow oil. To the residue was added MeOH. This slurry was allowed to stand at room temperature for 30 minutes before being sonicated. A white solid precipitated out and the solid was filtered to give the desired product. The filtrate also contained the product. The filtrate was concentrated *in vacuo*, dissolved in DCM, and then purified by flash chromatography (ISCO 80g column, 0 - 15% ethyl acetate in hexanes) to give the title compound. Both isolates were combined to give methyl 5-fluoro-2-hydroxy-3-iodobenzoate (2.5 g, 72% yield) as a white solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 11.40 (s, 1H), 7.73 (dd, *J* = 7.3, 3.1 Hz, 1H), 7.59 (dd, *J* = 8.4, 3.1 Hz, 1H), 4.01 (s, 3H); MS (ESI⁺) *m/z* = 297 (M+H)⁺.

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B) Methyl 2-(((*tert*-butoxycarbonyl)amino)methyl)-5-fluorobenzofuran-7-carboxylate

A mixture of methyl 5-fluoro-2-hydroxy-3-iodobenzoate (2.5 g, 8.44 mmol, Step
 5 A of Example 64), *tert*-butyl prop-2-yn-1-ylcarbamate (1.51 g, 9.71 mmol), TEA (14.1 mL, 101 mmol), and copper(I) iodide (0.161 g, 0.844 mmol) in DMF (10 mL) was purged with a stream of nitrogen for 5 min, then bis(triphenylphosphine)
 palladium(II) chloride (0.296 g, 0.422 mmol) was added. The resulting mixture was heated at 80 °C for 2 hours. The reaction mixture was cooled to rt and diluted with ethyl
 10 acetate and saturated aqueous NaHCO₃ solution. The organic layer was separated, washed with brine, and dried over MgSO₄. The filtrate was concentrated *in vacuo*. The residue was dissolved in DCM and purified by flash chromatography (ISCO 80g column, 0 - 30% ethyl acetate in hexanes) to give the title compound (2.5 g, 92% yield) as a light brown oily solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.64 (dd, *J* = 9.5, 2.7 Hz, 1H), 7.41 (dd,
 15 *J* = 7.8, 2.6 Hz, 1H), 6.67 (s, 1H), 5.10 (br s, 1H), 4.52 (br d, *J* = 5.9 Hz, 2H), 4.02 (s, 3H), 1.49 (s, 9H); MS (ESI+) *m/z* = 268.1 [M+H-55]⁺.



C) Methyl 2-(aminomethyl)-5-fluorobenzofuran-7-carboxylate TFA salt

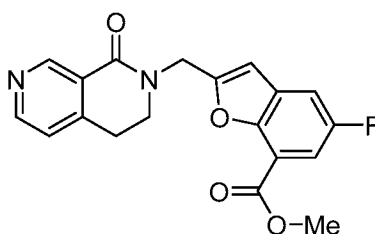
20 To a solution of methyl 2-(((*tert*-butoxycarbonyl)amino)methyl)-5-fluorobenzofuran-7-carboxylate (0.5 g, 1.55 mmol) in CH₂Cl₂ (8 mL) was added TFA (0.95 mL, 12.4 mmol). The reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was concentrated *in vacuo* to give the title compound (0.45 g, 86% yield) as a light brown oily solid. ¹H NMR (499 MHz, Methanol-*d*₄) δ 7.74 (dd,

$J = 9.5, 2.7$ Hz, 1H), 7.68 (dd, $J = 7.9, 2.7$ Hz, 1H), 7.10 (s, 1H), 4.42 (s, 2H), 4.03 (s, 3H); MS (ESI+): $m/z = 207.2$ [M-16+H]⁺.

5 **D) Methyl 5-fluoro-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate**

To a suspension of pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (12.6 mg, 0.077 mmol) and BOP (26 mg, 0.059 mmol) in DMF (2 mL) was added methyl 2-(aminomethyl)-5-fluorobenzofuran-7-carboxylate, TFA salt (20 mg, 0.059 mmol) and DIPEA (0.041 mL, 0.24 mmol). The reaction mixture turned into a clear solution and was stirred at room temperature for 1 h. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in DMF, filtered and purified by preparative HPLC (Method B). Fractions containing the desired product were combined and dried *via* centrifugal evaporation to give the title compound (20 mg, 87% yield). ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.31 (br d, $J = 7.0$ Hz, 1H), 8.84 (br d, $J = 2.7$ Hz, 1H), 8.63 (s, 1H), 8.55 (br t, $J = 5.8$ Hz, 1H), 7.73 (dd, $J = 8.2, 2.4$ Hz, 1H), 7.56 (dd, $J = 9.8, 2.4$ Hz, 1H), 7.29 (dd, $J = 7.0, 4.3$ Hz, 1H), 6.87 (s, 1H), 4.81 (br d, $J = 5.8$ Hz, 2H), 3.91 (s, 3H); MS (ESI+) $m/z = 369.09$ (M+H)⁺.

EXAMPLE 36



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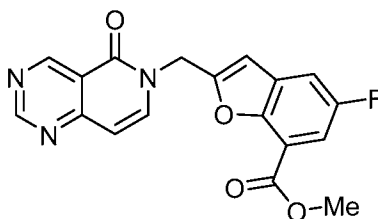
Methyl 5-fluoro-2-((1-oxo-3,4-dihydro-2,7-naphthyridin-2(1H)-yl)methyl)benzofuran-7-carboxylate

3,4-Dihydro-1*H*-pyrano[3,4-*c*]pyridin-1-one (20 mg, 0.134 mmol) (WO 2005063768) and methyl 2-(aminomethyl)-5-fluorobenzofuran-7-carboxylate (44.9 mg, 0.201 mmol, Step C of Example 35) were added to a pressure relief vial and heated neat at 100 °C. After 30 minutes, the reaction was heated to 120 °C. After 4 hours, the reaction

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was cooled, taken up in DMF, filtered, and purified *via* HPLC (Method B) to give methyl 5-fluoro-2-((1-*oxo*-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)methyl)benzofuran-7-carboxylate (16.3 mg, 0.045 mmol, 33.6 % yield). ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.96 (s, 1H), 8.63 (d, *J* = 5.0 Hz, 1H), 7.74 (dd, *J* = 8.2, 2.6 Hz, 1H), 7.57 (dd, *J* = 9.6, 2.6 Hz, 1H), 7.38 (d, *J* = 5.0 Hz, 1H), 6.98 (s, 1H), 4.93 (s, 2H), 3.88 (s, 3H), 3.75 (t, *J* = 6.6 Hz, 2H), 3.09 (t, *J* = 6.5 Hz, 2H); MS (ESI+) *m/z* = 355.0 (M+H)⁺.

EXAMPLE 37

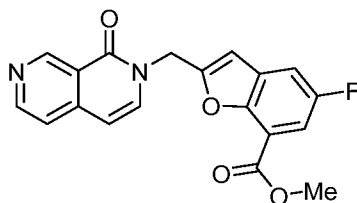


10 Methyl 5-fluoro-2-((5-oxopyrido[4,3-d]pyrimidin-6(5*H*)-yl)methyl)benzofuran-7-carboxylate

A mixture of ethyl 4-methylpyrimidine-5-carboxylate (37.5 mg, 0.225 mmol), and 1,1-dimethoxy-*N,N*-dimethylmethanamine (0.12 mL, 0.91 mmol) in DMF (0.5 mL) in a microwave tube was heated in a microwave reactor at 160 °C for 40 min. The reaction mixture was concentrated *in vacuo*. To the residue was added 1 mL of acetic acid and methyl 2-(aminomethyl)-5-fluorobenzofuran-7-carboxylate TFA salt (38 mg, 0.113 mmol, Step C of Example 35) and the mixture was again heated in a microwave at 110 °C for 25 min. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in DMF, filtered and purified by preparative HPLC (Method B). Fractions containing the desired product were combined and dried *via* centrifugal evaporation to give the title compound (37 mg, 67%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.50 (s, 1H), 9.37 (s, 1H), 8.16 (d, *J* = 7.6 Hz, 1H), 7.73 (dd, *J* = 8.2, 2.4 Hz, 1H), 7.58 (dd, *J* = 9.6, 2.3 Hz, 1H), 6.96 (s, 1H), 6.78 (d, *J* = 7.6 Hz, 1H), 5.48 (s, 2H), 3.90 (s, 3H); MS (ESI+) *m/z* = 353.1 (M+H)⁺.

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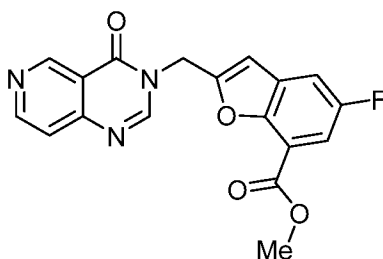
EXAMPLE 38



Methyl 5-fluoro-2-((1-oxo-2,7-naphthyridin-2(1H)-yl)methyl)benzofuran-7-carboxylate

Methyl 4-methylnicotinate (35.9 mg, 0.237 mmol) and *N,N*-dimethylformamide dimethyl acetal (0.127 mL, 0.949 mmol) were taken up in DMF (0.5 mL) in a 0.5-2 mL
 5 microwave vial. The vial was sealed and heated 160 °C for 40 minutes in a microwave reactor. After 40 minutes, the reaction mixture was cooled and concentrated *in vacuo*. The resulting residue was dissolved in DCM and concentrated again *in vacuo*. To this residue was added Acetic Acid (0.5 mL) and methyl 2-(aminomethyl)-5-
 10 fluorobenzofuran-7-carboxylate, TFA (40 mg, 0.119 mmol, Step C of Example 35). The vial was then sealed and heated at 110 °C for 25 minutes in a microwave reactor. After 25 minutes, the reaction was again cooled and concentrated *in vacuo*. The residue was taken up in DMF and MeOH, filtered, and purified *via* HPLC (method B) to give the title compound (21 mg, 50% yield). ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.36 (br s, 1H), 8.73 (br s, 1H), 7.85 (d, *J* = 7.3 Hz, 1H), 7.73 (dd, *J* = 8.1, 2.3 Hz, 1H), 7.63 (br d, *J* = 4.3 Hz, 1H), 7.57 (dd, *J* = 9.5, 2.4 Hz, 1H), 6.92 (s, 1H), 6.75 (d, *J* = 7.3 Hz, 1H), 5.42 (s, 2H), 3.86 (s, 3H); MS (ESI+) *m/z* = 352.9 (M+H)⁺.

EXAMPLE 39

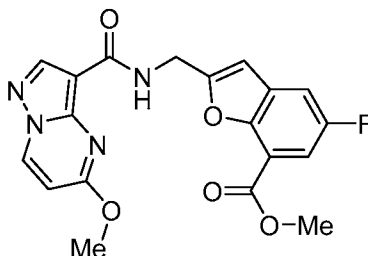


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Methyl 5-fluoro-2-((4-oxopyrido[4,3-*d*]pyrimidin-3(4H)-yl)methyl)benzofuran-7-carboxylate

4-Aminonicotinic acid (40 mg, 0.290 mmol) and *N,N*-dimethylformamide dimethyl acetal (0.116 mL, 0.869 mmol) were taken up in DMF (0.5 mL) in a 0.2- 5 mL of microwave vial. The vial was sealed and heated to 100 °C for 15 minutes in a microwave reactor. After 15 minutes, the reaction mixture was cooled and concentrated *in vacuo*. To this residue was added 1 mL of acetic acid and methyl 2-(aminomethyl)-5-fluorobenzofuran-7-carboxylate (64.6 mg, 0.290 mmol, Step C of Example 35). The vial was then sealed and heated to 120 °C for an additional 15 min in a microwave reactor. The reaction was again cooled and concentrated *in vacuo*. The residue was diluted with ethyl acetate and saturated NaHCO₃ solution. The organic layer was separated and concentrated *in vacuo*. The residue was taken up in DMF, filtered, and purified *via* HPLC (method B) to give the title compound (11.8 mg, 11% yield). ¹H NMR (500 MHz, DMSO-d₆) δ 9.34 (s, 1H), 8.88 (d, *J* = 5.6 Hz, 1H), 8.76 (s, 1H), 7.73 (dd, *J* = 8.2, 2.6 Hz, 1H), 7.64 (d, *J* = 5.6 Hz, 1H), 7.57 (dd, *J* = 9.6, 2.6 Hz, 1H), 7.03 (s, 1H), 5.48 (s, 2H), 3.88 (s, 3H); MS (ESI+) *m/z* = 354.0 (M+H)⁺.

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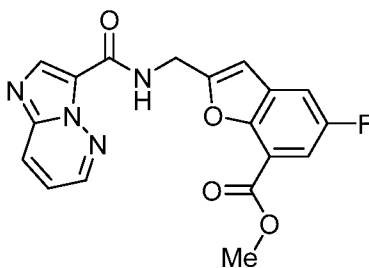
EXAMPLE 40**Methyl 5-fluoro-2-((5-methoxypyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate**

5-Methoxypyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (25 mg, 0.129 mmol) (WO 2016/177658 A1) was dissolved in DMF (260 μl). DIPEA (90 μl, 0.518 mmol) and methyl 2-(aminomethyl)-5-fluorobenzofuran-7-carboxylate, TFA salt (49.9 mg, 0.155 mmol, Step C of Example 35) were added. BOP (86 mg, 0.194 mmol) was added and the reaction was stirred at room temperature. After 3 hours, a solid formed and the reaction was diluted with 1.5 mL DMSO and precipitate went back into solution. The reaction was stirred an additional 3 hours before it was filtered and purified directly *via*

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preparative HPLC (Method B) to give methyl 5-fluoro-2-((5-methoxypyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate (9.6 mg, 0.024 mmol, 18.51 % yield). ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.01 (d, *J* = 7.6 Hz, 1H), 8.40 (s, 1H), 8.23 (br t, *J* = 5.6 Hz, 1H), 7.73 (dd, *J* = 8.2, 2.4 Hz, 1H), 7.55 (dd, *J* = 9.6, 2.6 Hz, 1H), 6.89 (s, 1H), 6.73 (d, *J* = 7.3 Hz, 1H), 4.79 (br d, *J* = 5.8 Hz, 2H), 4.03 (s, 3H), 3.90 (s, 3H); MS (ESI+) *m/z* = 399.2 (M+H)⁺.

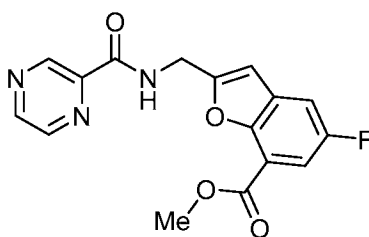
EXAMPLE 41



10 Methyl 5-fluoro-2-((imidazo[1,2-*b*]pyridazine-3-carboxamido)methyl)benzofuran-7-carboxylate

A suspension of imidazo[1,2-*b*]pyridazine-3-carboxylic acid (94 mg, 0.58 mmol) and BOP (275 mg, 0.62 mmol) in DMF (3 mL) was stirred at room temperature for 10 min. A solution of methyl 2-(aminomethyl)-5-fluorobenzofuran-7-carboxylate, TFA salt (150 mg, 0.445 mmol, Step C of Example 35) in THF (2 mL) and DIPEA (0.31 mL, 1.78 mmol) was added. The reaction mixture became clear and was stirred at room temperature for 1 hour. The reaction was diluted with ethyl acetate and saturated aqueous NaHCO₃ solution. The organic layer was separated, washed with brine, and dried over MgSO₄. The filtrate was concentrated *in vacuo*. A portion (1/10) of the residue was dissolved in DMF, filtered and purified by preparative HPLC (Method A). Fractions containing the desired product were combined and dried *via* centrifugal evaporation to give the title compound as a TFA salt (9.7 mg, 4.5% yield). ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.24 (br t, *J* = 5.6 Hz, 1H), 8.79 (d, *J* = 3.4 Hz, 1H), 8.46 - 8.24 (m, 2H), 7.72 (dd, *J* = 8.2, 2.4 Hz, 1H), 7.56 (dd, *J* = 9.6, 2.6 Hz, 1H), 7.49 (dd, *J* = 9.2, 4.6 Hz, 1H), 6.91 (s, 1H), 4.84 (d, *J* = 5.8 Hz, 2H), 3.90 (s, 3H); MS (ESI+) *m/z* = 369.1 (M+H)⁺.

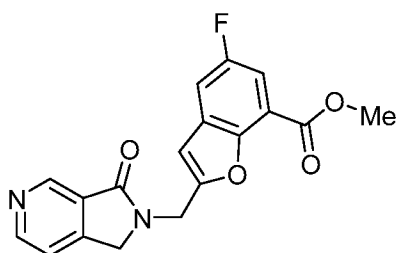
EXAMPLE 42



Methyl 5-fluoro-2-((pyrazine-2-carboxamido)methyl)benzofuran-7-carboxylate

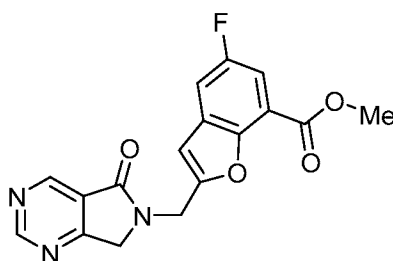
To a solution of pyrazine-2-carboxylic acid (8.8 mg, 0.071 mmol) in DMF (1 mL) were added BOP (34.1 mg, 0.077 mmol), methyl 2-(aminomethyl)-5-fluorobenzofuran-7-carboxylate TFA salt (20 mg, 0.059 mmol) (step C of Example 35) and DIPEA (0.03 mL, 0.178 mmol). The reaction mixture was stirred at rt for 1 h. LC-MS showed new peak at $t_r = 0.78$ min, $[M+H]^+ = 330.2$ as the desired product peak. The reaction mixture was diluted with ethyl acetate and saturated aqueous NaHCO_3 solution. The organic layer was separated, dried over MgSO_4 , and filtered. The filtrate was concentrated *in vacuo* and the residue was dissolved in DMF, filtered and purified by preparative HPLC (Method B). Fractions containing the desired product were combined and dried *via* centrifugal evaporation to give the title compound (7.9 mg, 40%). $^1\text{H NMR}$ (500 MHz, DMSO-d_6) δ 9.45 (br s, 1H), 9.23 (s, 1H), 8.89 (s, 1H), 8.76 (s, 1H), 7.78 - 7.66 (m, 1H), 7.55 (dd, $J = 9.6, 2.1$ Hz, 1H), 6.86 (s, 1H), 4.74 (br d, $J = 6.0$ Hz, 2H), 3.92 (s, 3H); MS (ESI+) $m/z = 330.2$ (M+H) $^+$.

EXAMPLE 43



Methyl 5-fluoro-2-((3-oxo-1,3-dihydro-2H-pyrrolo[3,4-c]pyridin-2-yl)methyl)benzofuran-7-carboxylate

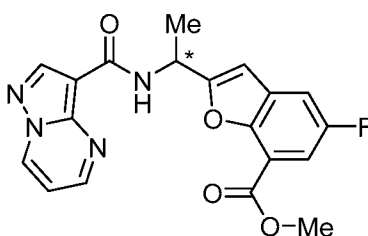
To a mixture of methyl 4-methylnicotinate (0.15 g, 0.99 mmol) and NBS (0.20 g, 1.14 mmol) in carbon tetrachloride (10 mL) was added AIBN (0.021 g, 0.13 mmol). The vial was purged with nitrogen and sealed. The resulting mixture was heated at 90 °C for 1.5 hours. The reaction was cooled (brown solid forms during reaction and cooling) and the liquid was decanted off. The decanted liquid was concentrated *in vacuo* to give the crude benzyl bromide intermediate which used immediately. To methyl 2-(aminomethyl)-5-fluorobenzofuran-7-carboxylate (43.7 mg, 0.196 mmol, Step C of Example 35) in THF (1 mL) was added TEA (0.136 mL, 0.978 mmol) followed by a solution of crude methyl 4-(bromomethyl)nicotinate (150 mg, 0.098 mmol) in THF (1 mL). The reaction mixture was stirred at room temperature for 1 hour and then heated at 70 °C for 2 hours. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in MeOH, filtered, and purified by preparative HPLC (Method A). Fractions containing the desired product were combined and dried *via* centrifugal evaporation to give the title compound as a TFA salt (5.1 mg, 11%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.97 (s, 1H), 8.78 (br d, *J* = 4.9 Hz, 1H), 7.77 (dd, *J* = 8.2, 2.4 Hz, 1H), 7.72 (br s, 1H), 7.59 (dd, *J* = 9.6, 2.3 Hz, 1H), 7.02 (br d, *J* = 13.4 Hz, 1H), 4.99 (s, 2H), 4.69 (s, 2H), 3.88 (s, 3H); MS (ESI+) *m/z* = 341.0 (M+H)⁺.

EXAMPLE 44**Methyl 5-fluoro-2-((5-oxo-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidin-6-yl)methyl)benzofuran-7-carboxylate**

Ethyl 4-formylpyrimidine-5-carboxylate (28 mg, 0.155 mmol) in THF (0.8 mL) and methyl 2-(aminomethyl)-5-fluorobenzofuran-7-carboxylate (34.7 mg, 0.155 mmol, Step C of Example 35) in THF (1 mL) was stirred at room temperature for 40 minutes. After 40 minutes, acetic acid (0.1 mL, 1.747 mmol) and sodium triacetoxyborohydride

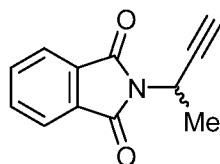
(49.4 mg, 0.233 mmol) were added. The resulting mixture was stirred at room temperature for 20 hours. After 20 hours, saturated NaHCO₃ solution was added and the mixture was stirred at room temperature for 5 min. The mixture was diluted with water and extracted with ethyl acetate. The organic layer was separated, washed with brine, dried over sodium sulfate, and filtered. The filtrate was concentrated *in vacuo*. The residue was taken up in DMF, filtered, and purified *via* HPLC (method B) to give the title compound (3.1 mg, 6%). ¹H NMR (500 MHz, DMSO-d₆) δ 9.40 (s, 1H), 9.20 (s, 1H), 7.87 - 7.72 (m, 1H), 7.59 (dd, *J* = 9.6, 2.4 Hz, 1H), 7.05 (s, 1H), 5.02 (s, 2H), 4.76 (s, 2H), 3.90 (s, 3H); MS (ESI+) *m/z* = 342.1 (M+H)⁺.

10

EXAMPLE 45

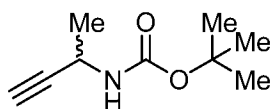
Methyl 5-fluoro-2-(1-(pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)ethyl)benzofuran-7-carboxylate

15

**A) 2-(But-3-yn-2-yl)isoindoline-1,3-dione**

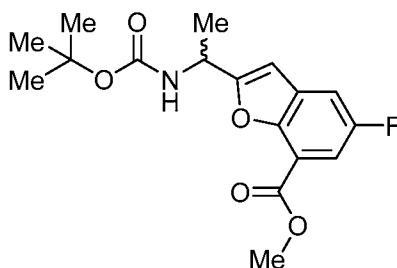
To a solution of 1-pentyn-3-ol (2.1 mL, 22.2 mmol) in THF (35 mL) was added isoindoline-1,3-dione (3.92 g, 26.7 mmol) and triphenylphosphine (6.70 g, 25.6 mmol). The reaction mixture was cooled with an ice bath and then DEAD (4.22 mL, 26.7 mmol) was added dropwise. The resulting mixture was then warmed up to room temperature and stirred overnight. The reaction mixture was diluted with ethyl acetate and saturated aqueous NaHCO₃ solution. The organic layer was separated and washed with brine and 1 N aqueous HCl solution successively. The organic layer was separated, dried over

MgSO₄, and filtered. The filtrate was concentrated *in vacuo*. The residue was dissolved in DCM and purified by flash chromatography (ISCO column 80 g, 0 - 30% ethyl acetate in hexanes) to give the title compound (1.5 g, 70%) as a white solid. ¹H NMR (500 MHz, CHLOROFORM-d) δ 7.89 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.80 - 7.67 (m, 2H), 5.24 (dd, *J* = 7.2, 2.5 Hz, 1H), 2.37 (d, *J* = 2.5 Hz, 1H), 1.74 (d, *J* = 7.1 Hz, 3H).



B) *tert*-Butyl but-3-yn-2-ylcarbamate

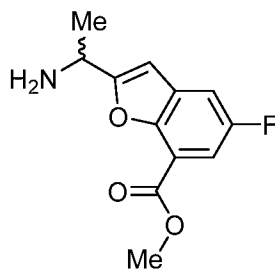
To a suspension of 2-(but-3-yn-2-yl)isoindoline-1,3-dione (3.0 g, 15.06 mmol) in ethanol (50 mL) and H₂O (2 mL) was added hydrazine (0.52 mL, 16.6 mmol). The reaction mixture was heated at 76 °C for 60 min. The reaction mixture turned into clear solution in the beginning and after 30 min, a solid crashed out. The reaction mixture was filtered. To the filtrate was added Boc₂O (4.55 mL, 19.6 mmol) and DIPEA (5.26 mL, 30.1 mmol). The reaction mixture was stirred at rt for 2 h. The reaction mixture was diluted with ethyl acetate and saturated aqueous NaHCO₃ solution. The organic layer was separated, washed with brine, dried over MgSO₄, and filtered. The filtrate was concentrated *in vacuo*. The residue was dissolved in DCM and purified by flash chromatography (ISCO column 40 g, 0 - 30% ethyl acetate in hexanes) to give the title compound (2.0 g, 78%) as a white solid. ¹H NMR (400 MHz, CHLOROFORM-d) δ 4.88 - 4.63 (m, 1H), 4.57 - 4.35 (m, 1H), 2.27 (d, *J* = 2.2 Hz, 1H), 1.47 (s, 9H), 1.42 (d, *J* = 6.9 Hz, 3H).



C) Methyl 2-(1-((*tert*-butoxycarbonyl)amino)ethyl)-5-fluorobenzofuran-7-carboxylate

25

A mixture of methyl 5-fluoro-2-hydroxy-3-iodobenzoate (1.0 g, 3.38 mmol, Step A of Example 35), *tert*-butyl but-3-yn-2-ylcarbamate (0.66 g, 3.88 mmol), TEA (7.06 mL, 50.7 mmol), and copper(I) iodide (0.064 g, 0.338 mmol) in DMF (8 mL) was purged with a nitrogen stream for 5 mins. Bis(triphenylphosphine)palladium(II) chloride (0.119 g, 0.169 mmol) was then added. The resulting mixture was heated at 80 °C for 2 hours. The reaction mixture was cooled down. The reaction mixture was diluted with ethyl acetate and saturated aqueous NaHCO₃ solution. The organic layer was separated, washed with brine, dried over MgSO₄, and filtered. The filtrate was concentrated *in vacuo*. The residue was dissolved in DCM and purified by flash chromatography (ISCO column 40 g, 0 - 20% ethyl acetate in hexanes) to give the title compound (1.0 g, 88 %) as a light brown solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.63 (dd, *J* = 9.6, 2.6 Hz, 1H), 7.40 (dd, *J* = 7.9, 2.7 Hz, 1H), 6.61 (s, 1H), 5.20 - 4.86 (m, 1H), 3.99 (s, 3H), 1.60 - 1.58 (m, 3H), 1.48 (s, 9H); MS (ESI+) *m/z* = 282.2 (M-55+H)⁺.



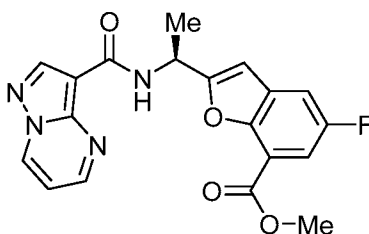
D) Methyl 2-(1-aminoethyl)-5-fluorobenzofuran-7-carboxylate

To a solution of methyl 2-(1-((*tert*-butoxycarbonyl)amino)ethyl)-5-fluorobenzofuran-7-carboxylate (1.1 g, 2.61 mmol) in DCE (10 mL) was added TFA (2.01 mL, 26.1 mmol). The reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated *in vacuo* to give the crude title compound (TFA salt) as light brown solid (1.1 g, 96%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.90 (dd, *J* = 8.2, 2.7 Hz, 1H), 7.67 (dd, *J* = 9.6, 2.7 Hz, 1H), 7.13 (s, 1H), 4.96 - 4.69 (m, 1H), 4.02 (s, 3H), 1.63 (d, *J* = 6.8 Hz, 3H); MS (ESI+) *m/z* = 221.3 (M-16+H)⁺.

E) Methyl (*S*)-5-fluoro-2-(1-(pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)ethyl)benzofuran-7-carboxylate

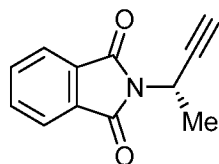
A mixture of pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (178 mg, 1.09 mmol) and BOP (524 mg, 1.18 mmol) in DMF (10 mL) was stirred at rt for 10 min. A solution of methyl 2-(1-aminoethyl)-5-fluorobenzofuran-7-carboxylate, TFA salt (400 mg, 0.911 mmol) in THF (2 mL) and DIPEA (0.95 mL, 5.47 mmol) were added. The reaction mixture was stirred at rt for 2 h. The reaction mixture was diluted with ethyl acetate and saturated aqueous NaHCO₃ solution. The organic layer was separated, washed with brine, dried over MgSO₄, and filtered. The filtrate was concentrated *in vacuo*. Roughly 1/3 of the crude product was dissolved in DMF, filtered and purified by preparative HPLC (Method B). Fractions containing the desired product were combined and dried *via* centrifugal evaporation to give the racemic product (21.4 mg, 36% yield). A portion of the material (20 mg) was further purified using SFC-chiral chromatography (Method H) to give two isomers. The first isomer as the titled compound (8.1 mg, 13%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.45 - 9.21 (m, 1H), 8.84 (d, *J* = 2.7 Hz, 1H), 8.64 (s, 1H), 8.38 (br d, *J* = 8.2 Hz, 1H), 7.74 (dd, *J* = 8.2, 2.4 Hz, 1H), 7.57 (dd, *J* = 9.6, 2.6 Hz, 1H), 7.29 (dd, *J* = 6.7, 4.3 Hz, 1H), 6.93 (s, 1H), 5.50 (br t, *J* = 7.3 Hz, 1H), 3.89 (s, 3H), 3.18 (d, *J* = 5.2 Hz, 1H), 1.66 (d, *J* = 7.0 Hz, 3H); MS (ESI+) *m/z* = 383.0 (M+H)⁺.

EXAMPLE 46



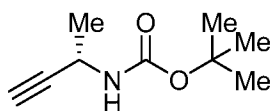
20

Methyl (*S*)-5-fluoro-2-(1-(pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)ethyl)benzofuran-7-carboxylate



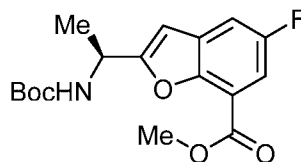
A) (*S*)-2-(but-3-yn-2-yl)isoindoline-1,3-dione

To a solution of 1-pentyn-3-ol (2.1 mL, 22.2 mmol) in THF (35 mL) was added isoindoline-1,3-dione (3.92 g, 26.7 mmol) and triphenylphosphine (6.70 g, 25.6 mmol). The reaction mixture was cooled with an ice bath and then DEAD (4.22 mL, 26.7 mmol) was added dropwise. The resulting mixture was then warmed up to room temperature and stirred overnight. The reaction mixture was diluted with ethyl acetate and saturated aqueous NaHCO₃ solution. The organic layer was separated and washed with brine and 1 N aqueous HCl solution successively. The organic layer was separated, dried over MgSO₄, and filtered. The filtrate was concentrated *in vacuo*. The residue was dissolved in DCM and purified by flash chromatography (ISCO column 80 g, 0 - 30% ethyl acetate in hexanes) to give the title compound (1.5 g, 70%) as a white solid. ¹H NMR (500 MHz, Chloroform-d) δ 7.89 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.80 - 7.67 (m, 2H), 5.24 (dd, *J* = 7.2, 2.5 Hz, 1H), 2.37 (d, *J* = 2.5 Hz, 1H), 1.74 (d, *J* = 7.1 Hz, 3H).



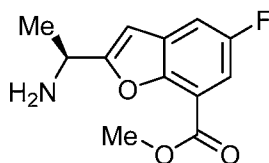
15 **B) *tert*-butyl (*S*)-but-3-yn-2-ylcarbamate**

To a suspension of (*S*)-2-(but-3-yn-2-yl)isoindoline-1,3-dione (1.5 g, 7.53 mmol) in Ethanol (30 mL) and H₂O (1 mL) was added hydrazine (0.260 mL, 8.28 mmol). The reaction mixture was heated at 76 °C for 60 min. The reaction mixture turned into clear solution in the beginning and after 30 min, solid crashed out. The reaction mixture was cooled down and filtered. To the filtrate was added Boc₂O (2.273 mL, 9.79 mmol) and DIPEA (2.63 mL, 15.06 mmol). The reaction mixture was stirred at rt for 16 h. The reaction mixture was diluted with ethyl acetate and saturated aqueous NaHCO₃ solution. The organic layer was separated, washed with brine, dried over MgSO₄, and filtered. The filtrate was concentrated *in vacuo*. The residue was dissolved in DCM and purified by flash chromatography (ISCO column 40 g, 0 - 30% ethyl acetate in hexanes) to give the title compound (0.8 g, 63%) as a white solid. ¹H NMR (400 MHz, Chloroform-d) δ 4.84 - 4.59 (m, 1H), 4.56 - 4.35 (m, 1H), 2.28 (d, *J*=2.2 Hz, 1H), 1.52 - 1.46 (s, 9H), 1.43 (d, *J*=6.8 Hz, 3H).



C) Methyl (S)-2-(1-((tert-butoxycarbonyl)amino)ethyl)-5-fluorobenzofuran-7-carboxylate

The reaction mixture of methyl 5-fluoro-2-hydroxy-3-iodobenzoate (1.539 g, 5.20 mmol), tert-butyl (S)-but-3-yn-2-ylcarbamate (0.8 g, 4.73 mmol), TEA (9.88 mL, 70.9 mmol), copper(I) iodide (0.090 g, 0.473 mmol) in DMF (8 mL) was purged with nitrogen stream for 5 mins, then bis(triphenylphosphine)palladium(II) chloride (0.166 g, 0.236 mmol) was added. The resulting mixture was heated at 80 °C for 4 h. The reaction mixture was cooled down and diluted with ethyl acetate and saturated aqueous NaHCO₃ solution. The organic layer was separated, washed with brine, dried over MgSO₄, and filtered. The filtrate was concentrated *in vacuo*. The residue was dissolved in DCM and purified by flash chromatography (ISCO column 40 g, 0 - 20% ethyl acetate in hexanes) to give the title compound (1.25g g, 78%) as light yellow oil. ¹H NMR (400 MHz, Chloroform-d) δ 7.63 (dd, J=9.6, 2.7 Hz, 2H), 7.40 (dd, J=7.9, 2.7 Hz, 1H), 6.61 (s, 1H), 5.17 - 4.89 (m, 2H), 4.02 - 3.98 (m, 3H), 1.61 (br d, J=6.9 Hz, 3H), 1.48 (s, 9H); MS (ESI⁺) m/z = 282.0 (M-55+H)⁺.



D) Methyl (S)-2-(1-aminoethyl)-5-fluorobenzofuran-7-carboxylate

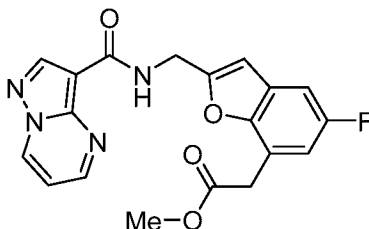
To a solution of methyl (S)-2-(1-((tert-butoxycarbonyl)amino)ethyl)-5-fluorobenzofuran-7-carboxylate (1.2 g, 3.56 mmol) in DCM (10 mL) was added TFA (2.192 mL, 28.5 mmol). The reaction mixture was stirred at rt for 3 h. The reaction mixture was concentrated *in vacuo* and dried on high vacuum over night to give the title compound TFA salt (1.2 g, 96%) as brown oil. MS (ESI⁺) m/z = 221.1 (M-17+H)⁺.

25

E) Methyl (S)-5-fluoro-2-(1-(pyrazolo[1,5-a]pyrimidine-3-carboxamido)ethyl)benzofuran-7-carboxylate

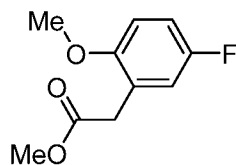
The reaction mixture of methyl 5-fluoro-2-hydroxy-3-iodobenzoate (1.539 g, 5.20 mmol), tert-butyl (S)-but-3-yn-2-ylcarbamate (0.8 g, 4.73 mmol), TEA (9.88 mL, 70.9 mmol), copper(I) iodide (0.090 g, 0.473 mmol) in DMF (8 mL) was purged with nitrogen stream for 5 mins, then bis(triphenylphosphine)palladium(II) chloride (0.166 g, 0.236 mmol) was added. The resulting mixture was heated at 80 °C for 4 h. The reaction mixture was cooled down and diluted with ethyl acetate and saturated aqueous NaHCO₃ solution. The organic layer was separated, washed with brine, dried over MgSO₄, and filtered. The filtrate was concentrated *in vacuo*. The residue was dissolved in DCM and purified by flash chromatography (ISCO column 40 g, 0 - 20% ethyl acetate in hexanes) to give the title compound (1.25g g, 78%) as light yellow oil. ¹H NMR (400 MHz, Chloroform-d) δ 7.63 (dd, J=9.6, 2.7 Hz, 2H), 7.40 (dd, J=7.9, 2.7 Hz, 1H), 6.61 (s, 1H), 5.17 - 4.89 (m, 2H), 4.02 - 3.98 (m, 3H), 1.61 (br d, J=6.9 Hz, 3H), 1.48 (s, 9H); MS (ESI+) m/z = 282.0 (M-55+H)+.

EXAMPLE 47



Methyl 2-(5-fluoro-2-((pyrazolo[1,5-a]pyrimidine-3-carboxamido)methyl)benzofuran-7-yl)acetate

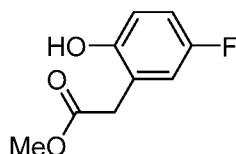
20



A) Methyl 2-(5-fluoro-2-methoxyphenyl)acetate

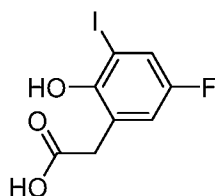
To a solution of 2-(5-fluoro-2-methoxyphenyl)acetic acid (3 g, 16.3 mmol) in

DCM (40 mL) and MeOH (8 mL) at 0 °C was added (diazomethyl)trimethylsilane, 2 M in diethyl ether (9.8 mL, 19.6 mmol). The reaction mixture was stirred at 0 °C for 30 minutes and room temperature for 1 hour. The reaction mixture was concentrated and purified by ISCO, 120 g column, eluting with 0-20% EtOAc in hexanes to give the
5 desired product (3.11 g, 96% yield). ¹H NMR (400 MHz, Chloroform-d) δ 7.00 - 6.92 (m, 2H), 6.85 - 6.78 (m, 1H), 3.82 (s, 3H), 3.72 (s, 3H), 3.64 (s, 2H); MS (ESI+) m/z = 199.2 (M+H)⁺.



10 **B) Methyl 2-(5-fluoro-2-hydroxyphenyl)acetate**

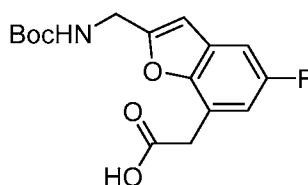
To a solution of methyl 2-(5-fluoro-2-methoxyphenyl)acetate (3.11 g, 15.7 mmol) in DCM (50 mL) at 0 °C was added tribromoborane (2.27 mL, 23.5 mmol). The reaction mixture was stirred at 0 °C for 1 h and room temperature for 1 h. The reaction mixture was concentrated and purified by ISCO, 120 g column, eluting with 0-40% EtOAc in
15 hexanes to give the desired product as a white solid (2.61 g, 90%). ¹H NMR (400 MHz, Chloroform-d) δ 7.16 (s, 1H), 6.95 - 6.89 (m, 1H), 6.85 (dd, *J* = 8.2, 1.5 Hz, 1H), 3.79 (s, 3H), 3.67 (s, 2H); MS (ESI+) m/z = 185.1 (M+H)⁺.



20 **C) 2-(5-Fluoro-2-hydroxy-3-iodophenyl)acetic acid**

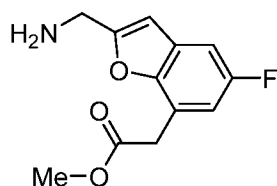
To a solution of methyl 2-(5-fluoro-2-hydroxyphenyl)acetate (0.2 g, 1.09 mmol) in THF (5 mL) and MeOH (5 mL) at room temperature was added 3 M aqueous sodium hydroxide solution (1.09 mL, 3.26 mmol). The reaction mixture was stirred at room temperature for 18 hours, acidified to pH 2-3 with 1 N aqueous HCl solution and
25 extracted with DCM. The organic layer was dried over sodium sulfate, filtered, and

concentrated to give the hydrolyzed product. To a solution of the above acid (0.1 g, 0.588 mmol) in CH₃CN (2 mL) at room temperature was added NIS (0.132 g, 0.588 mmol). The reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was concentrated and purified by ISCO, 24 g column, eluting with 0-5% MeOH in DCM to give the desired product (100 mg, 58% yield). ¹H NMR (400 MHz, Chloroform-d) δ 7.30 (dd, *J* = 7.7, 3.0 Hz, 1H), 6.81 (dd, *J* = 8.7, 3.0 Hz, 1H), 3.57 (s, 2H); MS (ESI+) *m/z* = 296.8 (M+H)⁺.



10 **D) 2-(2-(((*tert*-Butoxycarbonyl)amino)methyl)-5-fluorobenzofuran-7-yl)acetic acid**

To a solution of 2-(5-fluoro-2-hydroxy-3-iodophenyl)acetic acid (100 mg, 0.338 mmol) in DMF (0.5 mL) and TEA (0.5 mL) was added copper(I) iodide (6.4 mg, 0.034 mmol), *tert*-butyl prop-2-yn-1-ylcarbamate (79 mg, 0.507 mmol) and
 15 bis(triphenylphosphine)palladium(II) chloride (23.7 mg, 0.034 mmol). The reaction mixture was degassed by bubbling Ar through and stirred at 80 °C for 3 hours. The reaction mixture was concentrated and the residue was dissolved in MeOH and purified by prep HPLC, Method C, to give the desired product as a brown semi-solid (35 mg, 32%
 20 yield). ¹H NMR (400 MHz, Chloroform-d) δ 7.12 (dd, *J* = 8.3, 2.5 Hz, 1H), 6.96 (dd, *J* = 9.7, 2.4 Hz, 1H), 6.59 (br s, 1H), 5.04 (br s, 1H), 4.44 (br s, 2H), 3.93 (s, 2H), 1.48 (s, 9H); MS (ESI+) *m/z* = 322.1 (M-H)⁺.



25 **E) Methyl 2-(2-(aminomethyl)-5-fluorobenzofuran-7-yl)acetate**

To a solution of 2-(2-(((*tert*-butoxycarbonyl)amino)methyl)-5-fluorobenzofuran-

7-yl)acetic acid (35 mg, 0.108 mmol) in DCM (2 mL) and MeOH (0.4 mL) at 0 °C was added (diazomethyl)trimethylsilane, 2 M in diethyl ether (0.081 mL, 0.162 mmol). The reaction mixture was stirred at 0 °C for 30 min and then room temperature for 18 hours. The reaction mixture was concentrated and purified by ISCO, 12 g column, eluting with
5 0-30% EtOAc in hexanes to give the desired product.

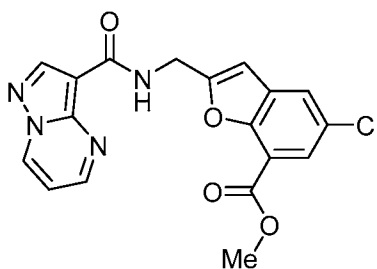
To a solution of the above product (30 mg, 0.089 mmol) in DCM (1.5 mL) was added TFA (0.5 mL). The reaction mixture was stirred at room temperature for 1 hour and concentrated *in vacuo* to give the desired product (21 mg, 100% yield). ¹H NMR (400 MHz, Chloroform-d) δ 7.11 (dd, *J* = 8.3, 2.5 Hz, 1H), 6.95 (dd, *J* = 9.8, 2.5 Hz, 1H), 6.59
10 (s, 1H), 4.45 (br d, *J* = 5.7 Hz, 2H), 3.90 (s, 2H), 3.75 (s, 3H); MS (ESI+) *m/z* = 221.0 (M+H)⁺.

F) Methyl 2-(5-fluoro-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-yl)acetate

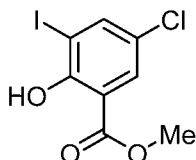
To a solution of methyl 2-(2-(aminomethyl)-5-fluorobenzofuran-7-yl)acetate (21 mg, 0.089 mmol) in DMF (1 mL) was added pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (14.4 mg, 0.089 mmol), BOP (58.7 mg, 0.133 mmol) and DIPEA (0.046 mL, 0.266 mmol). The reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated *in vacuo* and purified by preparative HPLC, Method B, to give
20 the desired product (18.8 mg, 54% yield). ¹H NMR (500 MHz, DMSO-d₆) δ 9.29 (br d, *J* = 7.0 Hz, 1H), 8.82 (br d, *J* = 3.4 Hz, 1H), 8.62 (s, 1H), 8.50 (br t, *J* = 5.6 Hz, 1H), 7.37 - 7.21 (m, 2H), 7.05 (dd, *J* = 9.9, 2.0 Hz, 1H), 6.78 (s, 1H), 4.74 (br d, *J* = 5.8 Hz, 2H), 3.93 (s, 2H), 3.63 (s, 3H); MS (ESI+) *m/z* = 383.1 (M+H)⁺.

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EXAMPLE 48

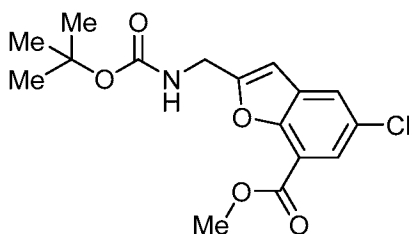


Methyl 5-chloro-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate



5 **A) Methyl 5-chloro-2-hydroxy-3-iodobenzoate**

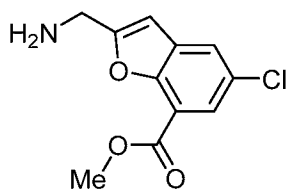
To a solution of methyl 5-chloro-2-hydroxybenzoate (5.0 g, 26.8 mmol) in *N,N*-dimethylformamide (50 mL) was added sodium iodide (4.82 g, 32.2 mmol), followed by chloramine T trihydrate (8.68 g, 30.8 mmol) in several batches. The resulting mixture turned into a brown solution and was stirred at room temperature for 18 hours. The reaction mixture was diluted with ethyl acetate and saturated aqueous NaHCO₃ solution. The organic layer was separated, washed with brine followed by Na₂S₂O₃ solution, dried over MgSO₄, and filtered. The filtrate was concentrated *in vacuo* to give a light yellow solid. The crude solid was mixed with MeOH and filtered to give the title compound (4.6 g, 69%) as a white solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 11.56 (s, 1H), 7.93 (d, *J* = 2.5 Hz, 1H), 7.86 (d, *J* = 2.5 Hz, 1H), 4.01 (s, 3H); MS (ESI+) *m/z* = 313 (M+H)⁺.



20 **B) Methyl 2-(((*tert*-butoxycarbonyl)amino)methyl)-5-chlorobenzofuran-7-carboxylate**

A mixture of methyl 5-chloro-2-hydroxy-3-iodobenzoate (1.5 g, 4.8 mmol), *tert*-butyl prop-2-yn-1-ylcarbamate (0.86 g, 5.5 mmol), TEA (11.4 mL, 82 mmol), and copper(I) iodide (0.091 g, 0.48 mmol) in DMF (10 mL) was purged with a stream of nitrogen for 5 mins. Bis(triphenylphosphine)palladium(II) chloride (0.17 g, 0.24 mmol) was then added. The resulting mixture was heated at 80 °C for 2 hours. The reaction was

diluted with ethyl acetate and saturated aqueous NaHCO₃ solution. The organic layer was separated, washed with brine, dried over MgSO₄, and filtered. The filtrate was concentrated *in vacuo* and the residue was dissolved in DCM and then purified by flash chromatography (ISCO 80g column, 0 - 20% ethyl acetate in hexanes) to give the title compound (0.86 g, 72%) as a light brown oily solid. ¹H NMR (400 MHz, Chloroform-d) δ 7.88 - 7.81 (m, 1H), 7.67 - 7.62 (m, 1H), 6.61 (br s, 1H), 5.26 - 5.11 (m, 1H), 4.50 (br d, *J* = 5.7 Hz, 2H), 3.99 (d, *J* = 1.0 Hz, 3H), 1.47 (s, 9H); MS (ESI+) *m/z* = 284.1 (M-55+H)⁺.



10

C) Methyl 2-(aminomethyl)-5-chlorobenzofuran-7-carboxylate

To a solution of methyl 2-(((*tert*-butoxycarbonyl)amino)methyl)-5-chlorobenzofuran-7-carboxylate (0.6 g, 1.77 mmol) in DCM (8 mL) was added TFA (1.91 mL, 24.7 mmol). The reaction was stirred at room temperature for 1 hour. The reaction mixture was concentrated *in vacuo* to give the title compound (TFA salt) as a brown solid (0.6 g, 96%). ¹H NMR (400 MHz, Chloroform-d) δ 7.92 (d, *J* = 2.2 Hz, 1H), 7.76 (d, *J* = 2.2 Hz, 1H), 6.88 (s, 1H), 4.44 (s, 2H), 3.97 (s, 3H); MS (ESI+) *m/z* = 240.1 (M+H)⁺.

15

20

D) Methyl 5-chloro-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate

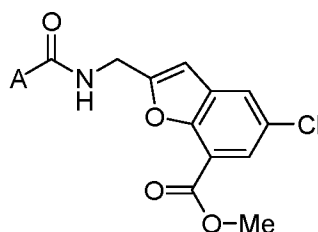
To a suspension of pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (12 mg, 0.074 mmol) and BOP (25 mg, 0.057 mmol) in DMF (2 mL) was added methyl 2-(aminomethyl)-5-chlorobenzofuran-7-carboxylate, TFA (20 mg, 0.057 mmol) and DIPEA (0.040 mL, 0.226 mmol). The reaction was stirred at room temperature for 2 hours. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in DMF, filtered and purified by preparative HPLC (Method B). Fractions containing the desired product were combined and dried *via* centrifugal evaporation to give the title

25

compound (8.5 mg, 36% yield). $^1\text{H NMR}$ (500 MHz, DMSO- d_6) δ 9.28 (br d, $J = 6.9$ Hz, 1H), 8.83 (br d, $J = 2.7$ Hz, 1H), 8.62 (s, 1H), 8.55 - 8.46 (m, 1H), 7.94 (s, 1H), 7.74 (s, 1H), 7.31 - 7.13 (m, 1H), 6.87 (s, 1H), 4.82 (br d, $J = 5.9$ Hz, 2H), 3.92 (s, 3H); MS (ESI+) $m/z = 385.1$ (M+H) $^+$.

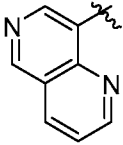
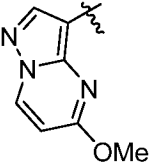
5

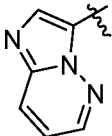
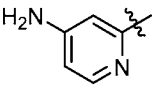
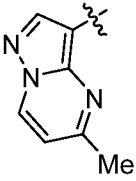
EXAMPLES 49-62

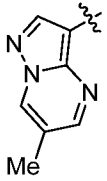
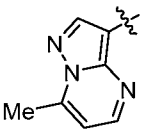
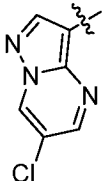


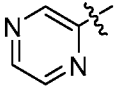
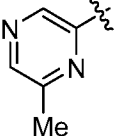
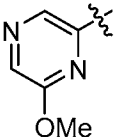
10 Examples 49 to 62 were prepared according to the procedures described in the synthesis of Example 48 from the required 5-Cl benzofuran amine (Step C in Example 48) and a carboxylic acid.

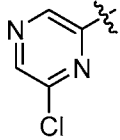
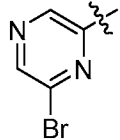
Ex. No.	A	Name	$^1\text{H NMR}$	LC/MS (M+H) $^+$
49		Methyl 2-((2 <i>H</i> -pyrazolo[4,3- <i>b</i>]pyridine-3-carboxamido) methyl)-5-chloro benzofuran-7-carboxylate	$^1\text{H NMR}$ (500 MHz, DMSO- d_6) δ 9.27 (br s, 1H), 8.70 (br d, $J = 4.0$ Hz, 1H), 8.19 (br d, $J = 8.2$ Hz, 1H), 7.97 (d, $J = 1.8$ Hz, 1H), 7.74 (d, $J = 1.8$ Hz, 1H), 7.52 (dd, $J = 8.5, 4.3$ Hz, 1H), 6.89 (s, 1H), 4.87 (br d, $J = 6.1$ Hz, 2H), 3.90 (s, 3H)	385.1

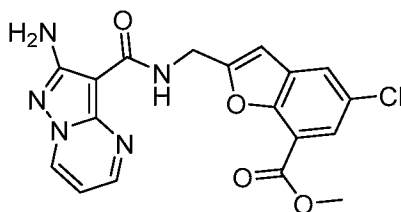
Ex. No.	A	Name	¹ H NMR	LC/MS (M+H) ⁺
50		Methyl 2-((1,6-naphthyridine-8-carboxamido)methyl)-5-chlorobenzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO-d ₆) δ 10.96 (br t, <i>J</i> = 5.3 Hz, 1H), 9.60 (s, 1H), 9.34 (s, 1H), 9.29 (br d, <i>J</i> = 2.4 Hz, 1H), 8.79 (br d, <i>J</i> = 8.2 Hz, 1H), 7.97 (d, <i>J</i> = 2.1 Hz, 1H), 7.87 (dd, <i>J</i> = 8.2, 4.3 Hz, 1H), 7.74 (d, <i>J</i> = 1.8 Hz, 1H), 6.96 (s, 1H), 4.91 (br d, <i>J</i> = 5.5 Hz, 2H), 3.90 (s, 3H)	396.2
51		Methyl 5-chloro-2-((5-methoxypyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO-d ₆) δ 8.98 (d, <i>J</i> = 7.5 Hz, 1H), 8.39 (s, 1H), 8.19 (br t, <i>J</i> = 5.4 Hz, 1H), 7.94 (d, <i>J</i> = 1.9 Hz, 1H), 7.74 (d, <i>J</i> = 1.9 Hz, 1H), 6.88 (s, 1H), 6.71 (d, <i>J</i> = 7.5 Hz, 1H), 4.80 (d, <i>J</i> = 5.8 Hz, 2H), 4.04 (s, 3H), 3.91 (s, 3H)	415.2

Ex. No.	A	Name	¹ H NMR	LC/MS (M+H) ⁺
52		Methyl 5-chloro-2-((imidazo[1,2- <i>b</i>]pyridazine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.40 - 9.14 (m, 1H), 8.80 (br d, <i>J</i> = 4.3 Hz, 1H), 8.49 - 8.22 (m, 2H), 7.97 (d, <i>J</i> = 1.8 Hz, 1H), 7.76 (d, <i>J</i> = 1.8 Hz, 1H), 7.50 (dd, <i>J</i> = 9.3, 4.4 Hz, 1H), 6.91 (s, 1H), 4.85 (br d, <i>J</i> = 5.8 Hz, 2H), 4.01 - 3.82 (m, 3H)	385.0
53		Methyl 2-((4-aminopyridin-2-yl)methyl)-5-chlorobenzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.68 (br s, 1H), 8.09 (br d, <i>J</i> = 6.4 Hz, 1H), 7.97 (s, 1H), 7.77 (d, <i>J</i> = 1.2 Hz, 1H), 7.33 (s, 1H), 6.91 (s, 1H), 6.84 (br d, <i>J</i> = 5.6 Hz, 1H), 4.73 (br d, <i>J</i> = 5.5 Hz, 2H), 3.93 (s, 3H)	360.2
54		Methyl 5-chloro-2-((5-methylpyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (400 MHz, CHLOROFORM- <i>d</i>) δ 8.67 - 8.62 (m, 2H), 8.52 (br t, <i>J</i> = 5.8 Hz, 1H), 7.91 - 7.86 (m, 1H), 7.70 - 7.66 (m, 1H), 6.87 (d, <i>J</i> = 7.2 Hz, 1H), 6.74 (s, 1H), 4.97 - 4.92 (m, 2H), 4.02 (s, 3H), 2.75 - 2.65 (m, 3H)	399.0

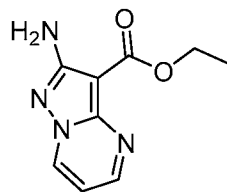
Ex. No.	A	Name	¹ H NMR	LC/MS (M+H) ⁺
55		Methyl 5-chloro-2-((6-methyl pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (400 MHz, CHLOROFORM- <i>d</i>) δ 8.66 - 8.64 (m, 1H), 8.62 - 8.59 (m, 1H), 8.55 (d, <i>J</i> =2.0 Hz, 1H), 8.42 (br t, <i>J</i> =5.5 Hz, 1H), 7.88 (d, <i>J</i> =2.2 Hz, 1H), 7.68 (d, <i>J</i> =2.1 Hz, 1H), 6.74 (s, 1H), 4.93 (d, <i>J</i> =6.0 Hz, 2H), 4.02 (s, 3H), 2.48 (d, <i>J</i> =0.9 Hz, 3H)	399.0
56		Methyl 5-chloro-2-((7-methyl pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.76 - 8.69 (m, 1H), 8.68 - 8.59 (m, 2H), 8.01 - 7.92 (m, 1H), 7.78 - 7.71 (m, 1H), 7.29 - 7.20 (m, 1H), 6.89 - 6.83 (m, 1H), 4.88 - 4.76 (m, 2H), 3.96 - 3.84 (m, 3H), 2.87 - 2.76 (m, 3H)	398.9
57		Methyl 5-chloro-2-((6-chloropyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.68 (s, 1H), 8.87 (s, 1H), 8.64 (s, 1H), 8.52 (br s, 1H), 7.95 (s, 1H), 7.74 (s, 1H), 6.86 (s, 1H), 4.78 (br d, <i>J</i> =5.8 Hz, 2H), 3.90 (s, 3H)	419.3

Ex. No.	A	Name	¹ H NMR	LC/MS (M+H) ⁺
58		Methyl 5-chloro-2- ((pyrazine-2- carboxamido)methyl) benzofuran-7- carboxylate	¹ H NMR (400 MHz, DMSO-d ₆) δ 9.61 (t, <i>J</i> = 6.1 Hz, 1H), 9.23 (d, <i>J</i> = 1.5 Hz, 1H), 8.91 (d, <i>J</i> = 2.5 Hz, 1H), 8.78 (dd, <i>J</i> = 2.5, 1.5 Hz, 1H), 7.96 (d, <i>J</i> = 2.2 Hz, 1H), 7.75 (d, <i>J</i> = 2.2 Hz, 1H), 6.84 (s, 1H), 4.72 (d, <i>J</i> = 5.4 Hz, 2H), 3.91 (s, 3H)	346.1
59		Methyl 5-chloro-2-((6- methylpyrazine-2- carboxamido)methyl) benzofuran-7- carboxylate	¹ H NMR (400 MHz, DMSO-d ₆) δ 9.47 (t, <i>J</i> = 6.0 Hz, 1H), 9.02 (s, 1H), 8.80 (s, 1H), 7.97 (d, <i>J</i> = 2.2 Hz, 1H), 7.75 (d, <i>J</i> = 2.2 Hz, 1H), 6.84 (s, 1H), 4.72 (d, <i>J</i> = 5.8 Hz, 2H), 3.91 (s, 3H), 2.62 (s, 3H)	360.1
60		Methyl 5-chloro-2-((6- methoxypyrazine-2- carboxamido)methyl)be nzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.31 (br t, <i>J</i> = 5.7 Hz, 1H), 8.74 (s, 1H), 8.48 (d, <i>J</i> = 1.9 Hz, 1H), 7.93 (d, <i>J</i> = 2.1 Hz, 1H), 7.73 (s, 1H), 6.85 (s, 1H), 4.73 (d, <i>J</i> = 6.1 Hz, 2H), 4.05 (s, 3H), 3.90 (s, 3H)	376.1

Ex. No.	A	Name	¹ H NMR	LC/MS (M+H) ⁺
61		Methyl 5-chloro-2-((6-chloropyrazine-2-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (400 MHz, DMSO-d ₆) δ 9.60 (t, <i>J</i> = 6.0 Hz, 1H), 9.17 (s, 1H), 9.05 (s, 1H), 7.96 (d, <i>J</i> = 2.2 Hz, 1H), 7.74 (d, <i>J</i> = 2.2 Hz, 1H), 6.86 (s, 1H), 4.70 (d, <i>J</i> = 6.0 Hz, 2H), 3.91 (s, 3H)	380.2
62		Methyl 2-((6-bromopyrazine-2-carboxamido)methyl)-5-chlorobenzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.56 (br t, <i>J</i> = 5.6 Hz, 1H), 9.17 (s, 1H), 9.08 (s, 1H), 7.95 (s, 1H), 7.74 (s, 1H), 6.87 (s, 1H), 4.70 (br d, <i>J</i> = 5.8 Hz, 2H), 3.90 (s, 3H)	423.9

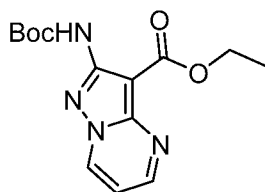
EXAMPLE 63

5 **Methyl 2-((2-aminopyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)-5-chlorobenzofuran-7-carboxylate**



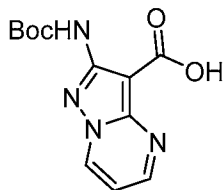
A) Ethyl 2-(amino)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate

To a solution of ethyl 3,5-diamino-1H-pyrazole-4-carboxylate (15.11 g, 89 mmol, Example 1 in WO 2015/073267) in HCl (60.5 ml, 121 mmol) was added 1,1,3,3-tetramethoxypropane (13.29 ml, 81 mmol). The reaction was heated at 55 °C for 24 hours. The reaction was quenched with 2N NaOH to pH 9, then extracted with 10 % MeOH/DCM (2x). The combined organic extracts were dried with anhydrous sodium sulfate and concentrated *in vacuo* to give the crude product mixture. The crude product mixture was purified by a silica gel ISCO 80 g column eluting with 0-5 % methanol / DCM over a 15 minute gradient. The appropriate fractions were isolated and concentrated *in vacuo* to afford the title compound (9.2 g, 55.3 % yield) as a solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.59 (dd, *J* = 4.3, 1.8 Hz, 1H), 8.45 (dd, *J* = 6.7, 1.8 Hz, 1H), 6.85 (dd, *J* = 6.8, 4.4 Hz, 1H), 4.50 (q, *J* = 7.1 Hz, 2H), 1.47 (t, *J* = 7.1 Hz, 3H); MS (ESI+) *m/z* = 207.1 (M+H)⁺.

**B) Ethyl 2-((tert-butoxycarbonyl)amino)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate**

In a vial was added ethyl 2-aminopyrazolo[1,5-*a*]pyrimidine-3-carboxylate (500 mg, 2.425 mmol), BOC-anhydride (1.126 mL, 4.85 mmol), TEA (1.014 mL, 7.27 mmol), catalytic DMAP in DCM (5 mL). The solution was stirred at room temperature for 24 hours. The solution was quenched with water, washed with saturated sodium bicarbonate, water, saturated sodium chloride solution, dried with anhydrous sodium sulfate, and concentrated *in vacuo*. The crude product mixture was purified by a silica gel ISCO 12 g column eluting with 0-40 % EA / DCM over a 15 minute gradient. The appropriate fractions were isolated and concentrated *in vacuo* to afford the title compound (640 mg, 86 % yield). ¹H NMR (400 MHz, Chloroform-*d*) δ 8.87 - 8.77 (m, 1H), 8.75 -

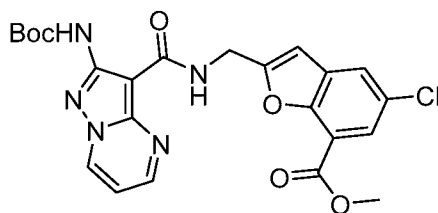
8.64 (m, 1H), 7.14 - 6.99 (m, 1H), 4.49 - 4.33 (m, 2H), 1.52 - 1.43 (m, 9H), 1.41 (t, $J=7.1$ Hz, 3H); MS (ESI+) $m/z = 307.1$ (M+H)⁺.



5 **C) 2-((Tert-butoxycarbonyl)amino)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid**

The reaction mixture of methyl 5-fluoro-2-hydroxy-3-iodobenzoate (1.539 g, 5.20 mmol), tert-butyl (S)-but-3-yn-2-ylcarbamate (0.8 g, 4.73 mmol), TEA (9.88 mL, 70.9 mmol), copper(I) iodide (0.090 g, 0.473 mmol) in DMF (8 mL) was purged with nitrogen stream for 5 mins, then bis(triphenylphosphine)palladium(II) chloride (0.166 g, 0.236 mmol) was added. The resulting mixture was heated at 80 °C for 4 h. The reaction mixture was cooled down and diluted with ethyl acetate and saturated aqueous NaHCO₃ solution. The organic layer was separated, washed with brine, dried over MgSO₄, and filtered. The filtrate was concentrated *in vacuo*. The residue was dissolved in DCM and purified by flash chromatography (ISCO column 40 g, 0 - 20% ethyl acetate in hexanes) to give the title compound (1.25 g, 78%) as light yellow oil. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.63 (dd, $J=9.6, 2.7$ Hz, 2H), 7.40 (dd, $J=7.9, 2.7$ Hz, 1H), 6.61 (s, 1H), 5.17 - 4.89 (m, 2H), 4.02 - 3.98 (m, 3H), 1.61 (br d, $J=6.9$ Hz, 3H), 1.48 (s, 9H); MS (ESI+) $m/z = 282.0$ (M-55+H)⁺.

20



D) Methyl 2-((2-((tert-butoxycarbonyl)amino)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)-5-chlorobenzofuran-7-carboxylate

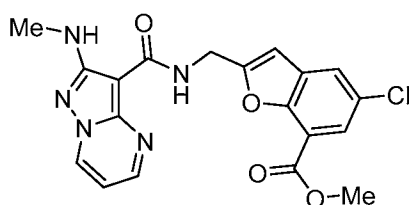
The reaction mixture of methyl 5-fluoro-2-hydroxy-3-iodobenzoate (1.539 g, 5.20 mmol), tert-butyl (S)-but-3-yn-2-ylcarbamate (0.8 g, 4.73 mmol), TEA (9.88 mL, 70.9 mmol), copper(I) iodide (0.090 g, 0.473 mmol) in DMF (8 mL) was purged with nitrogen stream for 5 mins, then bis(triphenylphosphine)palladium(II) chloride (0.166 g, 0.236 mmol) was added. The resulting mixture was heated at 80 °C for 4 h. The reaction mixture was cooled down and diluted with ethyl acetate and saturated aqueous NaHCO₃ solution. The organic layer was separated, washed with brine, dried over MgSO₄, and filtered. The filtrate was concentrated *in vacuo*. The residue was dissolved in DCM and purified by flash chromatography (ISCO column 40 g, 0 - 20% ethyl acetate in hexanes) to give the title compound (1.25g g, 78%) as light yellow oil. ¹H NMR (400 MHz, Chloroform-d) δ 7.63 (dd, J=9.6, 2.7 Hz, 2H), 7.40 (dd, J=7.9, 2.7 Hz, 1H), 6.61 (s, 1H), 5.17 - 4.89 (m, 2H), 4.02 - 3.98 (m, 3H), 1.61 (br d, J=6.9 Hz, 3H), 1.48 (s, 9H); MS (ESI+) m/z = 282.0 (M-55+H)+.

15 **E) Methyl 2-((2-aminopyrazolo[1,5-a]pyrimidine-3-carboxamido)methyl)-5-chlorobenzofuran-7-carboxylate**

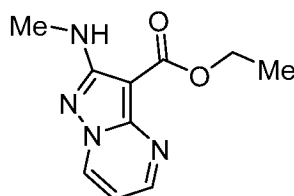
The reaction mixture of methyl 5-fluoro-2-hydroxy-3-iodobenzoate (1.539 g, 5.20 mmol), tert-butyl (S)-but-3-yn-2-ylcarbamate (0.8 g, 4.73 mmol), TEA (9.88 mL, 70.9 mmol), copper(I) iodide (0.090 g, 0.473 mmol) in DMF (8 mL) was purged with nitrogen stream for 5 mins, then bis(triphenylphosphine)palladium(II) chloride (0.166 g, 0.236 mmol) was added. The resulting mixture was heated at 80 °C for 4 h. The reaction mixture was cooled down and diluted with ethyl acetate and saturated aqueous NaHCO₃ solution. The organic layer was separated, washed with brine, dried over MgSO₄, and filtered. The filtrate was concentrated *in vacuo*. The residue was dissolved in DCM and purified by flash chromatography (ISCO column 40 g, 0 - 20% ethyl acetate in hexanes) to give the title compound (1.25g g, 78%) as light yellow oil. ¹H NMR (400 MHz, Chloroform-d) δ 7.63 (dd, J=9.6, 2.7 Hz, 2H), 7.40 (dd, J=7.9, 2.7 Hz, 1H), 6.61 (s, 1H), 5.17 - 4.89 (m, 2H), 4.02 - 3.98 (m, 3H), 1.61 (br d, J=6.9 Hz, 3H), 1.48 (s, 9H); MS (ESI+) m/z = 282.0 (M-55+H)+.

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EXAMPLE 64



Methyl 5-chloro-2-((2-(methylamino)pyrazolo[1,5-a]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate



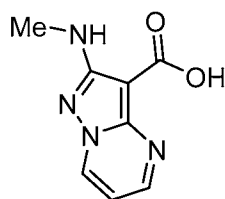
5

A) Ethyl 2-(methylamino)pyrazolo[1,5-a]pyrimidine-3-carboxylate

In a vial was added ethyl 2-aminopyrazolo[1,5-a]pyrimidine-3-carboxylate (520 mg, 2.52 mmol, Step A of Example 63), potassium carbonate (349 mg, 2.52 mmol), methyl iodide (0.158 mL, 2.52 mmol) in DMF (4 mL). The solution was stirred at 140 °C for 16 hours. The solution was quenched with DCM and water. The separated organics were washed with saturated sodium bicarbonate, water, and saturated sodium chloride. The washed organics were then dried with anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product mixture was purified by a silica gel ISCO 12 g column eluting with 0-5 % Methanol / DCM over a 15 minute gradient. The appropriate fractions were isolated and concentrated *in vacuo* to afford the title compound (160 mg, 28.8 % yield). ¹H NMR (400 MHz, Methanol-d₄) δ 8.75 (dd, J = 6.7, 1.7 Hz, 1H), 8.51 (dd, J = 4.4, 1.6 Hz, 1H), 7.00 (dd, J = 6.7, 4.6 Hz, 1H), 4.41 (q, J = 7.1 Hz, 2H), 3.04 (s, 3H), 1.40 (t, J = 7.1 Hz, 3H); MS (ESI⁺) m/z = 221.0 (M+H)⁺.

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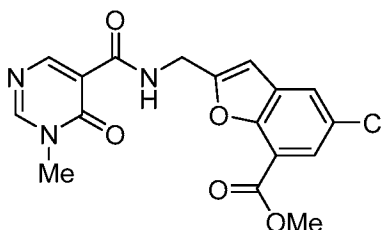
B) 2-(Methylamino)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid

A vial was charged with ethyl 2-(methylamino)pyrazolo[1,5-a]pyrimidine-3-carboxylate (75 mg, 0.341 mmol), methanol (4 mL) and tetrahydrofuran (2 mL). To the solution was added lithium hydroxide (0.341 mL, 0.681 mmol, 2M) and the reaction stirred at 80 °C for 16 hours. The reaction was concentrated in vacuo, acidified with 1N HCl and extracted with DCM, the organic layer was dried with anhydrous sodium sulfate and concentrated in vacuo to give the title compound (45 mg, 68.8 % yield), used as is in the next reaction. ¹H NMR (400 MHz, Methanol-d₄) δ 8.78 - 8.67 (m, 1H), 8.52 - 8.45 (m, 1H), 7.07 - 6.91 (m, 1H), 3.03 (s, 3H); MS (ESI+) m/z = 192.9 (M-55)+.

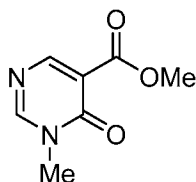
10 **C) Methyl 2-((2-aminopyrazolo[1,5-a]pyrimidine-3-carboxamido)methyl)-5-chlorobenzofuran-7-carboxylate**

To a solution of 2-(methylamino)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (45 mg, 0.234 mmol) and methyl 2-(aminomethyl)-5-chlorobenzofuran-7-carboxylate, TFA (83 mg, 0.234 mmol, Step C of Example 48) in DMF (5 mL) were added BOP (155 mg, 0.351 mmol) and DIPEA (0.123 mL, 0.702 mmol). The reaction mixture was stirred at room temperature for 16 hours. The sample was quenched with water, the resulting product precipitate was filtered. The crude product was purified via preparative HPLC (Method C) to yield the title compound (5 mg, 4.85 % yield). ¹H NMR (400 MHz, Methanol-d₄) δ 8.99 - 8.91 (m, 1H), 8.85 - 8.76 (m, 1H), 8.23 - 8.15 (m, 1H), 8.09 - 8.02 (m, 1H), 7.91 - 7.84 (m, 2H), 7.31 - 7.20 (m, 1H), 7.13 - 7.07 (m, 1H), 5.20 (s, 2H), 4.49 - 4.25 (m, 3H), 3.48 - 3.21 (m, 3H); MS (ESI+) m/z = 414.0 (M+H)+.

EXAMPLE 65



25 **Methyl 5-chloro-2-((1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamido)methyl)benzofuran-7-carboxylate**



A) Methyl 1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxylate

To a solution of methyl 4-hydroxypyrimidine-5-carboxylate (100 mg, 0.649 mmol) in NMP (3.2 mL) under N₂ was added NaH (31.1 mg, 0.779 mmol). The reaction mixture was stirred for 15 min, iodomethane (138 mg, 0.973 mmol) was added, and the reaction mixture was stirred for 14 hours. The reaction mixture was quenched with a saturated aqueous solution of NH₄Cl and extracted with a 3:1 (v/v) solution of CHCl₃:iPrOH. The organic layers were combined, washed with a 10% aqueous solution of LiCl, washed with brine, dried over MgSO₄, filtered, and concentrated *in vacuo*. The residue was dissolved in DCM and purified by flash chromatography (ISCO 40 g column, 0 - 10% MeOH in DCM) to give the title compound (30.2 mg, 27%). ¹H NMR (500 MHz, Chloroform-d) δ 8.65 (s, 1H), 8.31 (s, 1H), 3.92 (s, 3H), 3.59 (s, 3H); MS (ESI+) m/z = 169.1 (M+H)⁺.

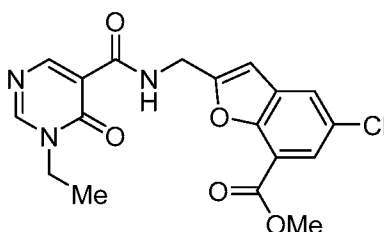
B) Methyl 5-chloro-2-((1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamido)methyl)benzofuran-7-carboxylate

To a solution of methyl 1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxylate (30.2 mg, 0.180 mmol) in THF (72 μL), water (72 μL), and MeOH (36 μL) was added lithium hydroxide monohydrate (7.54 mg, 0.180 mmol). The reaction mixture was stirred at room temperature for 16 hours. An additional portion of lithium hydroxide monohydrate (7.54 mg, 0.180 mmol) was added and the reaction mixture was stirred for 6 hours at room temperature. The reaction mixture was concentrated *in vacuo* to obtain a residue that was used without further purification.

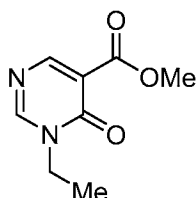
To the obtained residue was added methyl 2-(aminomethyl)-5-chlorobenzofuran-7-carboxylate, TFA (57.9 mg, 0.164 mmol, Step C of Example 48) and ((1H-benzo[d][1,2,3]triazol-1-yl)oxy)tris(dimethylamino)phosphonium hexafluorophosphate(V) (80 mg, 0.180 mmol). DMF (818 μL) and DIPEA (57.0 μL,

0.327 mmol) were added and the reaction mixture was stirred at room temperature for 15 h. The reaction mixture was diluted with water and extracted with EtOAc. The organic layers were combined, washed with brine, dried over MgSO₄, filtered, and concentrated *in vacuo*. A sixth of the obtained residue was dissolved in 2 mL DMSO, filtered through a syringe filter, and purified by preparative LC/MS (Method B). Fractions containing the desired product were combined and dried *via* centrifugal evaporation to give the title compound (1.2 mg, 2%). The remaining obtained residue contained additional semipure title compound (45.7 mg) that was used without further purification. ¹H NMR (500 MHz, DMSO-d₆) δ 9.64 (br s, 1H), 8.74 (s, 1H), 8.69 (s, 1H), 7.98 (d, *J*=2.1 Hz, 1H), 7.75 (d, *J*=1.8 Hz, 1H), 6.84 (s, 1H), 4.76 (br d, *J*=5.8 Hz, 2H), 3.92 (s, 3H), 3.40 (br s, 3H); MS (ESI+) *m/z* = 376.0 (M+H)⁺.

EXAMPLE 66



15 **Methyl 5-chloro-2-((1-ethyl-6-oxo-1,6-dihydropyrimidine-5-carboxamido)methyl)benzofuran-7-carboxylate**



A) Methyl 1-ethyl-6-oxo-1,6-dihydropyrimidine-5-carboxylate

To a solution of methyl 4-hydroxypyrimidine-5-carboxylate (100 mg, 0.649 mmol) in NMP (3.2 mL) under N₂ was added NaH (31.1 mg, 0.779 mmol). The reaction mixture was stirred for 30 min, iodoethane (78 μL, 0.973 mmol) was added, and the reaction mixture was stirred for 15 h. The reaction mixture was quenched with MeOH and then concentrated *in vacuo*. The residue was dissolved in DCM and purified by flash

chromatography (ISCO 12 g column, 0 - 100% EtOAc in hexanes, followed by 0 - 10% MeOH in DCM) to give the title compound (73.4 mg, 62%). ¹H NMR (500 MHz, Chloroform-d) δ 8.64 - 8.59 (m, 1H), 8.28 (s, 1H), 4.07 - 4.00 (m, 2H), 3.92 - 3.88 (m, 3H), 1.44 - 1.38 (m, 3H); MS (ESI+) m/z = 183.1 (M+H)⁺.

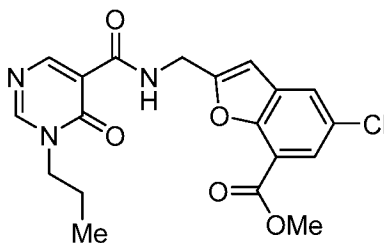
5

B) Methyl 5-chloro-2-((1-ethyl-6-oxo-1,6-dihydropyrimidine-5-carboxamido)methyl)benzofuran-7-carboxylate

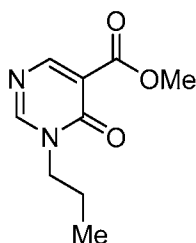
To a solution of methyl 1-ethyl-6-oxo-1,6-dihydropyrimidine-5-carboxylate (73.4 mg, 0.403 mmol) in THF (1.6 mL), water (1.6 mL), and MeOH (0.81 mL) was added
10 lithium hydroxide monohydrate (33.8 mg, 0.806 mmol). The reaction mixture was stirred at room temperature for 3 h. The reaction mixture was filtered through a fritted funnel and concentrated *in vacuo* to obtain a residue that was used without further purification.

To half of the obtained residue (41.7 mg) was added methyl 2-(aminomethyl)-5-chlorobenzofuran-7-carboxylate, TFA (64.3 mg, 0.182 mmol, Step C of Example 48) and
15 ((1H-benzo[d][1,2,3]triazol-1-yl)oxy)tris(dimethylamino)phosphonium hexafluorophosphate(V) (88 mg, 0.200 mmol). DMF (909 μL) and DIPEA (95 μL, 0.545 mmol) were added and the reaction mixture was stirred at room temperature for 4 h. The reaction mixture was diluted with water and extracted with EtOAc. The organic layers were combined, washed with brine, dried over MgSO₄, filtered, and concentrated *in*
20 *vacuo*. A third of the obtained residue was dissolved in 2 mL DMSO, filtered through a syringe filter, and purified by preparative LC/MS (Method B). Fractions containing the desired product were combined and dried *via* centrifugal evaporation to give the title compound (5.9 mg, 8%). The remaining obtained residue contained additional semipure title compound (43.3 mg) that was used without further purification. ¹H NMR (500 MHz,
25 DMSO-d₆) δ 9.59 (br s, 1H), 8.75 (s, 1H), 8.70 (s, 1H), 7.95 (s, 1H), 7.75 (s, 1H), 6.86 (s, 1H), 4.76 (br d, *J*=5.7 Hz, 2H), 4.06 (q, *J*=7.1 Hz, 2H), 3.93 (s, 3H), 1.32 (t, *J*=7.1 Hz, 3H); MS (ESI+) m/z = 389.8 (M+H)⁺.

EXAMPLE 67



Methyl 5-chloro-2-((1-propyl-6-oxo-1,6-dihydropyrimidine-5-carboxamido)methyl)benzofuran-7-carboxylate



5

A) Methyl 1-propyl-6-oxo-1,6-dihydropyrimidine-5-carboxylate

To a solution of methyl 4-hydroxypyrimidine-5-carboxylate (100 mg, 0.649 mmol) in NMP (3.2 mL) under N₂ was added NaH (31.1 mg, 0.779 mmol). The reaction mixture was stirred for 40 min, 1-iodopropane (95 μL, 0.973 mmol) was added, and the reaction mixture was stirred for 15 h. The reaction mixture was quenched with MeOH and then concentrated *in vacuo*. The residue was dissolved in DCM and purified by flash chromatography (ISCO 12 g column, 0 - 100% EtOAc in hexanes) to give the title compound (57.4 mg, 45%). ¹H NMR (500 MHz, Chloroform-d) δ 8.63 (s, 1H), 8.24 (s, 1H), 3.94 (t, *J*=7.3 Hz, 2H), 3.91 (s, 3H), 1.83 (sxt, *J*=7.4 Hz, 2H), 0.98 (t, *J*=7.4 Hz, 3H); MS (ESI+) *m/z* = 197.0 (M+H)⁺.

15

B) Methyl 5-chloro-2-((1-propyl-6-oxo-1,6-dihydropyrimidine-5-carboxamido)methyl)benzofuran-7-carboxylate

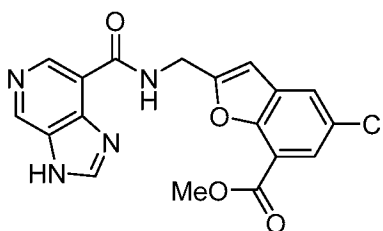
To a solution of methyl 1-propyl-6-oxo-1,6-dihydropyrimidine-5-carboxylate (57.4 mg, 0.293 mmol) in THF (1.2 mL), water (1.2 mL), and MeOH (0.59 mL) was added lithium hydroxide monohydrate (24.6 mg, 0.585 mmol). The reaction mixture was stirred at room temperature for 22 h. The reaction mixture was filtered through a fritted

20

funnel and concentrated *in vacuo* to obtain a residue that was used without further purification.

To half of the obtained residue (37.1 mg) was added methyl 2-(aminomethyl)-5-chlorobenzofuran-7-carboxylate, TFA (76 mg, 0.215 mmol, Step C of Example 48) and ((1H-benzo[*d*][1,2,3]triazol-1-yl)oxy)tris(dimethylamino)phosphonium hexafluorophosphate(V) (105 mg, 0.237 mmol). DMF (1.1 mL) and DIPEA (112 μ L, 0.645 mmol) were added and the reaction mixture was stirred at room temperature for 3.5 h. The reaction mixture was diluted with water and extracted with EtOAc. The organic layers were combined, washed with brine, dried over MgSO₄, filtered, and concentrated *in vacuo*. A third of the obtained residue was dissolved in 2 mL DMSO, filtered through a syringe filter, and purified by preparative LC/MS (Method B). Fractions containing the desired product were combined and dried *via* centrifugal evaporation to give the title compound (7.1 mg, 8%). The remaining obtained residue contained additional semipure title compound (58.8 mg) that was used without further purification. ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.67 - 9.59 (m, 1H), 8.74 (s, 1H), 8.69 (s, 1H), 7.96 (s, 1H), 7.74 (d, *J*=1.5 Hz, 1H), 6.85 (s, 1H), 4.74 (br d, *J*=5.8 Hz, 2H), 3.96 (br t, *J*=7.2 Hz, 2H), 3.91 (s, 3H), 1.76 - 1.64 (m, 2H), 0.87 (t, *J*=7.3 Hz, 3H); MS (ESI+) *m/z* = 404.1 (M+H)⁺.

EXAMPLE 68



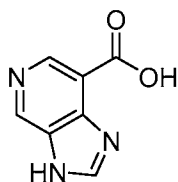
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Methyl 2-((3H-imidazo[4,5-c]pyridine-7-carboxamido)methyl)-5-chlorobenzofuran-7-carboxylate



A) 7-Bromo-3H-imidazo[4,5-c]pyridine

To the suspension of 5-bromopyridine-3,4-diamine (0.2 g, 1.064 mmol) in triethoxymethane (1.77 ml, 10.6 mmol) was added (1*R*)-(-)-camphor-10-sulfonic acid (0.012 g, 0.053 mmol). The reaction mixture was stirred at 150 °C for 2 hours and cooled to room temperature. The solid formed was collected by filtration and washed with DCM to give the desired product as a brown solid (0.19 g, 90% yield). ¹H NMR (400 MHz, Methanol-*d*₄) δ 8.89 (s, 1H), 8.49 (s, 1H), 8.47 (s, 1H); MS (ESI+) *m/z* = 199.8 (M+H)⁺.



B) 3H-Imidazo[4,5-c]pyridine-7-carboxylic acid

To a solution of 7-bromo-3H-imidazo[4,5-c]pyridine (190 mg, 0.959 mmol) in DMF (1 mL) and MeOH (0.5 mL) was added triethylamine (485 mg, 4.80 mmol), diacetoxypalladium (21.5 mg, 0.096 mmol), and 1,3-bis(diphenylphosphanyl)propane (39.6 mg, 0.096 mmol). The reaction mixture was degassed by bubbling argon through and heated under CO at 100 °C for 16 hours. The reaction mixture was concentrated. The residue was washed with MeOH. The solid which is insoluble in MeOH was collected by filtration to give the methyl ester product as a brown solid.

To the solution of the above solid (70 mg, 0.395 mmol) in THF (1 mL) and MeOH (1 mL) was added 3 M aqueous sodium hydroxide solution (0.66 mL, 1.98 mmol). The reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was acidified with 2 M aqueous HCl solution to pH ~2, and concentrated. The residue was dissolved in MeOH and purified with prep HPLC, Method C, to give the desired product as a light yellow TFA salt (81 mg, 74% yield). ¹H NMR (400 MHz, Deuterium

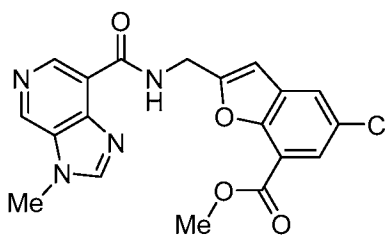
Oxide) δ 9.16 (s, 1H), 8.75 (s, 1H), 8.64 (s, 1H); MS (ESI+) m/z = 164.0 (M+H)⁺.

C) Methyl 2-((3*H*-imidazo[4,5-*c*]pyridine-7-carboxamido)methyl)-5-chlorobenzofuran-7-carboxylate

5 To a solution of 3*H*-imidazo[4,5-*c*]pyridine-7-carboxylic acid, TFA salt (25 mg, 0.090 mmol) in DMF (1 mL) was added methyl 2-(aminomethyl)-5-chlorobenzofuran-7-carboxylate (21.6 mg, 0.090 mmol, Step C in Example 48), BOP (59.8 mg, 0.135 mmol) and DIPEA (0.095 mL, 0.541 mmol). The reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated and purified with prep
10 HPLC (Method A) to give the desired product (13.2 mg, 37% yield). ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.78 (br s, 1H), 9.09 (s, 1H), 8.90 (s, 1H), 8.55 (br s, 1H), 7.96 (d, *J* = 1.8 Hz, 1H), 7.74 (d, *J* = 1.8 Hz, 1H), 6.92 (s, 1H), 4.85 (br d, *J* = 4.9 Hz, 2H), 3.89 (s, 3H); MS (ESI+) m/z = 384.8 (M+H)⁺.

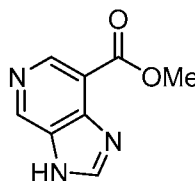
15

EXAMPLE 69



Methyl 5-chloro-2-((3-methyl-3*H*-imidazo[4,5-*c*]pyridine-7-carboxamido)methyl)benzofuran-7-carboxylate

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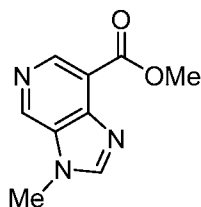


A) Methyl 3*H*-imidazo[4,5-*c*]pyridine-7-carboxylate

To a solution of 7-bromo-3*H*-imidazo[4,5-*c*]pyridine (420 mg, 2.121 mmol) in

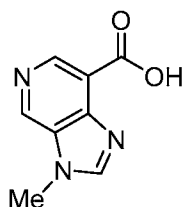
DMF (3 mL) and MeOH (1 mL) were added triethylamine (1073 mg, 10.60 mmol), diacetoxypalladium (47.6 mg, 0.212 mmol), and 1,3-bis(diphenylphosphanyl)propane (87 mg, 0.212 mmol). The reaction mixture was degassed by bubbling Ar through and heated under CO (20 psi) at 100 °C for 16 h. The reaction mixture was concentrated *in vacuo*.

- 5 The residue was washed with MeOH. The solid was collected by filtration to give the desired product (270 mg, 72%). ¹H NMR (400 MHz, Methanol-d₄) δ 9.42 (s, 1H), 9.09 (s, 1H), 8.79 (s, 1H), 4.13 (s, 3H); MS (ESI+) *m/z* = 178.0 (M+H)⁺.



10 **B) Methyl 3-methyl-3H-imidazo[4,5-c]pyridine-7-carboxylate**

- To a solution of methyl 3H-imidazo[4,5-c]pyridine-7-carboxylate (100 mg, 0.564 mmol) in DMF (1 mL) were added cesium carbonate (368 mg, 1.129 mmol) and iodomethane (0.071 mL, 1.129 mmol). The reaction mixture was stirred at rt for 2 h. The reaction mixture was concentrated. MeOH was added to the residue and filtered to
- 15 remove the solid. The filtrate was purified by prep HPLC (Method C) to give the desired product (12 mg, 11%) as the TFA salt. ¹H NMR (400 MHz, Methanol-d₄) δ 9.40 (s, 1H), 9.03 (s, 1H), 8.70 (s, 1H), 4.26 (s, 3H), 4.10 (s, 3H); MS (ESI+) *m/z* = 191.9 (M+H)⁺.



20 **C) 3-Methyl-3H-imidazo[4,5-c]pyridine-7-carboxylic acid**

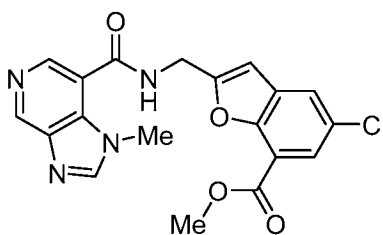
To the solution of methyl 3-methyl-3H-imidazo[4,5-c]pyridine-7-carboxylate (50 mg, 0.262 mmol) in MeOH (1 mL) and THF (1 mL) was added 3 M sodium hydroxide (0.262 mL, 0.785 mmol). The reaction mixture was stirred at rt for 4 h. The reaction

mixture was neutralized with 2 N HCl and concentrated *in vacuo*, and used for next reaction without purification. MS (ESI+) $m/z = 177.9 (M+H)^+$.

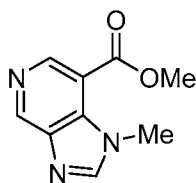
5 **D) Methyl 5-chloro-2-((3-methyl-3*H*-imidazo[4,5-*c*]pyridine-7-carboxamido)methyl)benzofuran-7-carboxylate**

To a solution of methyl 2-(aminomethyl)-5-chlorobenzofuran-7-carboxylate, TFA (19.96 mg, 0.056 mmol, Step A of Example 48) in DMF (1 mL) were added 3-methyl-3*H*-imidazo[4,5-*c*]pyridine-7-carboxylic acid (10 mg, 0.056 mmol), BOP (37.4 mg, 0.085 mmol) and DIPEA (36.5 mg, 0.282 mmol). The reaction mixture was stirred at rt for 18 h.
10 The reaction mixture was concentrated *in vacuo*. The residue was dissolved with MeOH and purified by prep HPLC (Method C) (3.5 mg, 11%) as the TFA salt. ¹H NMR (400 MHz, Methanol-*d*₄) δ 9.38 (s, 1H), 9.07 (s, 1H), 8.80 (s, 1H), 7.94 - 7.79 (m, 2H), 6.90 (s, 1H), 5.05 - 4.94 (m, 2H), 4.16 (s, 3H), 3.92 (s, 3H); MS (ESI+) $m/z = 399.1 (M+H)^+$.

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EXAMPLE 70

Methyl 5-chloro-2-((1-methyl-1*H*-imidazo[4,5-*c*]pyridine-7-carboxamido)methyl)benzofuran-7-carboxylate

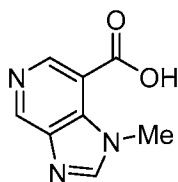


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A) Methyl 3-methyl-3*H*-imidazo[4,5-*c*]pyridine-7-carboxylate

To a solution of methyl 3*H*-imidazo[4,5-*c*]pyridine-7-carboxylate (100 mg, 0.564 mmol, Step A of Example 69) in DMF (1 mL) were added cesium carbonate (368 mg,

1.129 mmol), and iodomethane (0.071 mL, 1.129 mmol). The reaction mixture was stirred at rt for 2 h. The reaction mixture was concentrated. MeOH was added to the residue and filtered to remove the solid. The filtrate was purified by prep HPLC (Method C) to give the desired product (31 mg, 29%) as the TFA salt. ¹H NMR (400 MHz, Methanol-d₄) 9.42 (s, 1H), 9.09 (s, 1H), 8.96 (s, 1H), 4.18 (s, 3H), 4.08 (s, 3H); MS (ESI+) m/z = 191.9 (M+H)⁺.



B) 1-Methyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid

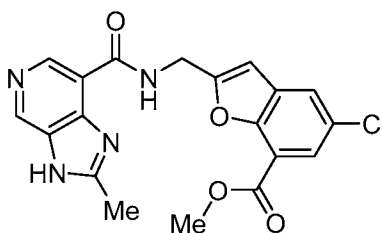
10 To the solution of methyl 3-methyl-3H-imidazo[4,5-c]pyridine-7-carboxylate (50 mg, 0.262 mmol) in MeOH (1 mL) and THF (1 mL) was added 3 M sodium hydroxide (0.262 mL, 0.785 mmol). The reaction mixture was stirred at rt for 4 h. The reaction mixture was neutralized with 2 N HCl, concentrated *in vacuo*, and used for next reaction without purification. MS (ESI+) m/z = 177.9 (M+H)⁺.

15

C) Methyl 5-chloro-2-((1-methyl-1H-imidazo[4,5-c]pyridine-7-carboxamido)methyl)benzofuran-7-carboxylate

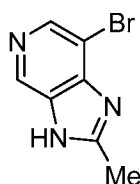
To a solution of methyl 2-(aminomethyl)-5-chlorobenzofuran-7-carboxylate, TFA (19.96 mg, 0.056 mmol, Step A of Example 48) in DMF (1 mL) were added 1-methyl-
20 1H-imidazo[4,5-c]pyridine-7-carboxylic acid (10 mg, 0.056 mmol), BOP (37.4 mg, 0.085 mmol) and DIPEA (36.5 mg, 0.282 mmol). The reaction mixture was stirred at rt for 18 h. The reaction mixture was concentrated *in vacuo*. The residue was dissolved with MeOH and purified by prep HPLC (Method C) (4.6 mg, 15%) as the TFA salt. ¹H NMR (400 MHz, Methanol-d₄) δ 9.33 (s, 1H), 8.76 (s, 1H), 8.65 (s, 1H), 7.89 (s, 2H), 6.97 (s, 1H),
25 4.91 (s, 2H), 4.05 (s, 3H), 4.00 (s, 3H); MS (ESI+) m/z = 399.0 (M+H)⁺.

EXAMPLE 71



Methyl 5-chloro-2-((2-methyl-3H-imidazo[4,5-c]pyridine-7-carboxamido)methyl)benzofuran-7-carboxylate

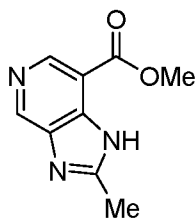
5



A) 7-Bromo-2-methyl-3H-imidazo[4,5-c]pyridine

To a suspension of 5-bromopyridine-3,4-diamine (0.2 g, 1.064 mmol) in 1,1,1-triethoxyethane (1.035 g, 6.38 mmol) was added acetic acid (0.365 mL, 6.38 mmol). The reaction mixture was stirred at 120 °C for 2 h, and concentrated *in vacuo*. The residue was washed with DCM. The solid was collected by filtration, and washed with DCM to give the desired product as an off-white solid (125 mg, 43% yield). ¹H NMR (400 MHz, Chloroform-d) δ 8.71 (s, 1H), 8.38 (s, 1H), 2.66 (s, 3H); MS (ESI+) m/z = 211.8 (M+H)⁺.

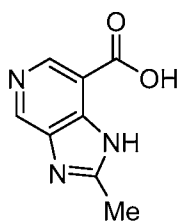
15



B) Methyl 2-methyl-1H-imidazo[4,5-c]pyridine-7-carboxylate

To a solution of 7-bromo-2-methyl-3H-imidazo[4,5-c]pyridine (770 mg, 2.83 mmol) in DMF (10 mL) and MeOH (2 mL) were added triethylamine (859 mg, 8.49

mmol), diacetoxypalladium (63.5 mg, 0.283 mmol), and 1,3-bis(diphenylphosphanyl)propane (117 mg, 0.283 mmol). The reaction mixture was degassed with argon and heated at 100 °C under CO (30 psi) for 16 h. The reaction mixture was concentrated *in vacuo* and the residue was purified by a flash chromatography (ISCO 120 g column, eluting with 0-10% MeOH in DCM over a 25 minute gradient) to give the desired product as an off white solid (460 mg, 85% yield). ¹H NMR (400 MHz, Chloroform-d) δ 9.13 (s, 1H), 8.98 (s, 1H), 4.06 (s, 3H), 2.74 (s, 3H); MS (ESI+) m/z = 191.9 (M+H)⁺.



10

C) 2-Methyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid

To the solution of methyl 2-methyl-3H-imidazo[4,5-c]pyridine-7-carboxylate (175 mg, 0.915 mmol) in MeOH (1 mL) and THF (1 mL) was added sodium hydroxide, 3 M in water (0.915 mL, 2.75 mmol). The reaction mixture was stirred at rt for 18 h, and neutralized to pH ~ 7 with 1 N HCl. The mixture was extracted with 20% MeOH in DCM. The combined organic extracts were dried and concentrated *in vacuo* to give the desired product as a white solid (177 mg, 100% yield). MS (ESI+) m/z = 177.9 (M+H)⁺.

15

D) Methyl 5-chloro-2-((2-methyl-3H-imidazo[4,5-c]pyridine-7-carboxamido)methyl)benzofuran-7-carboxylate

20

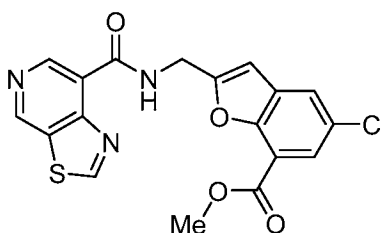
To a solution of methyl 2-(aminomethyl)-5-chlorobenzofuran-7-carboxylate, TFA (19.96 mg, 0.056 mmol, Step C in Example 48) in DMF (1 mL) were added 2-methyl-3H-imidazo[4,5-c]pyridine-7-carboxylic acid (10 mg, 0.056 mmol), BOP (37.4 mg, 0.085 mmol) and DIPEA (36.5 mg, 0.282 mmol). The reaction mixture was stirred at rt for 18 h. The reaction mixture was concentrated *in vacuo*. The residue was purified by prep HPLC (Method B) to give the product (4.4 mg, 20% yield). ¹H NMR (500 MHz, DMSO-d₆) δ

25

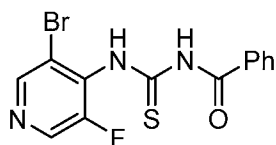
8.91 (s, 1H), 8.84 (s, 1H), 7.96 (d, $J = 2.0$ Hz, 1H), 7.75 (d, $J = 2.0$ Hz, 1H), 6.91 (s, 1H), 4.86 (br d, $J = 5.2$ Hz, 2H), 3.92 (s, 3H), 2.63 (s, 3H); MS (ESI+) $m/z = 399.1$ (M+H)⁺.

EXAMPLE 72

5



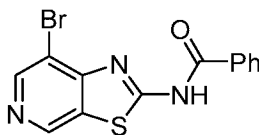
Methyl 5-chloro-2-((thiazolo[5,4-c]pyridine-7-carboxamido)methyl)benzofuran-7-carboxylate



10

A) N-((3-Bromo-5-fluoropyridin-4-yl)carbamothioyl)benzamide

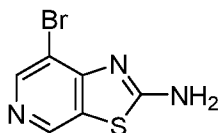
To a solution of 3-bromo-5-fluoropyridin-4-amine (900 mg, 4.71 mmol) in acetone (15 mL) was added benzoyl isothiocyanate (1153 mg, 7.07 mmol). The reaction mixture was stirred at 60 °C for 24 h. The reaction mixture was concentrated *in vacuo* and purified by flash chromatography (120g ISCO column, 0 - 30% ethyl acetate in DCM) to give the title compound (1.08 g, 65% yield) as a yellow solid. ¹HNMR (400 MHz, Methanol-d₄) δ 8.70 (s, 1H), 8.56 (d, $J = 1.2$ Hz, 1H), 8.02 (dd, $J = 8.4, 1.2$ Hz, 2H), 7.73 - 7.67 (m, 1H), 7.62 - 7.54 (m, 2H); MS (ESI+) $m/z = 355.9$ (M+H)⁺.



B) N-(7-Bromothiazolo[5,4-c]pyridin-2-yl)benzamide

To a solution of *N*-((3-bromo-5-fluoropyridin-4-yl)carbamothioyl)benzamide (1080 mg, 3.05 mmol) in DMF (10 mL) was added cesium carbonate (1987 mg, 6.10 mmol). The reaction mixture was heated at 85 °C for 2 h. The reaction mixture was diluted with cold water. The solid formed was collected by filtration and dried under vacuum to give the product (750 mg, 74% yield). ¹H NMR (400 MHz, Methanol-d₄) δ 8.72 (s, 1H), 8.43 (s, 1H), 8.25 - 8.16 (m, 2H), 7.52 - 7.40 (m, 3H); MS (ESI+) *m/z* = 335.9 (M+H)⁺.

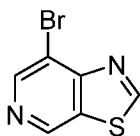
10



C) 7-Bromothiazolo[5,4-c]pyridin-2-amine

A suspension of *N*-(7-bromothiazolo[5,4-c]pyridin-2-yl)benzamide (750 mg, 2.244 mmol) in hydrochloric acid, 37% (10 mL) was heated at 90 °C for 8 h. The reaction mixture was concentrated *in vacuo*. To the residue was washed with DCM. The solid was collected by filtration and dried under vacuum to give the desired product as a tan solid (340 mg, 66% yield). ¹H NMR (400 MHz, Chloroform-d) δ 8.84 (s, 1H), 8.57 (s, 1H); MS (ESI+) *m/z* = 229.8 (M+H)⁺.

20

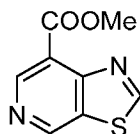


D) 7-Bromothiazolo[5,4-c]pyridine

To a suspension of 7-bromothiazolo[5,4-c]pyridin-2-amine (200 mg, 0.869 mmol) in THF (10 mL) was added isopentyl nitrite (509 mg, 4.35 mmol). The reaction mixture

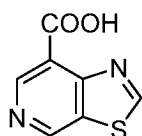
was heated at 85 °C for 4 h. The reaction mixture was concentrated *in vacuo* and purified by flash chromatography (40g ISCO column, 0 - 10% MeOH in DCM) to give the title compound as a light yellow solid (151 mg, 81%). ¹H NMR (400 MHz, Chloroform-d) δ 9.33 (s, 1H), 9.22 (s, 1H), 8.83 (s, 1H); MS (ESI+) m/z = 229.8 (M+H)⁺.

5



E) Methyl thiazolo[5,4-c]pyridine-7-carboxylate

To a solution of 7-bromothiazolo[5,4-c]pyridine (100 mg, 0.465 mmol) in DMF (2 mL) and MeOH (0.5 mL) were added triethylamine (235 mg, 2.325 mmol),
10 diacetoxypalladium (10.44 mg, 0.046 mmol), and 1,3-bis(diphenylphosphanyl)propane (19.18 mg, 0.046 mmol). The reaction mixture was degassed by bubbling Ar through and heated under 30 psi CO at 100 °C for 16 h. The reaction mixture was filtered and concentrated *in vacuo*. The residue was purified with prep HPLC (Method C) to give the desired product (51 mg, 57%) as the TFA salt. ¹H NMR (400 MHz, Methanol-d₄)
15 Shift 9.71 (s, 1H), 9.55 (s, 1H), 9.22 (s, 1H), 3.99 (s, 3H); MS (ESI+) m/z = 194.9 (M+H)⁺.



F) Thiazolo[5,4-c]pyridine-7-carboxylic acid

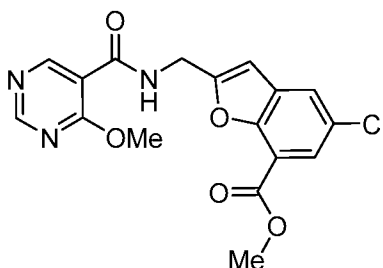
20 To the solution of methyl thiazolo[5,4-c]pyridine-7-carboxylate (51 mg, 0.263 mmol) in THF (1 mL) and MeOH (1 mL) was added sodium hydroxide, 3 M in water (0.438 mL, 1.313 mmol). The reaction mixture was stirred at rt for 2 h and neutralized to pH ~ 7 with 1 N HCl. The mixture was extracted with 20% MeOH in DCM. The combined organic extracts were dried over sodium sulfate, filtered, and concentrated *in*

vacuo to give the desired product (34 mg, 71% yield). MS (ESI+) $m/z = 180.9 (M+H)^+$.

G) Methyl 5-chloro-2-((thiazolo[5,4-*c*]pyridine-carboxamido)methyl)benzofuran-7-carboxylate

5 To a solution of methyl 2-(aminomethyl)-5-chlorobenzofuran-7-carboxylate, TFA (20 mg, 0.057 mmol, Step C of Example 48) in DMF (1 mL) were added thiazolo[5,4-*c*]pyridine-7-carboxylic acid (10.19 mg, 0.057 mmol), BOP (37.5 mg, 0.085 mmol) and DIPEA (36.5 mg, 0.283 mmol). The reaction mixture was stirred at rt for 18 h. The reaction mixture was filtered and concentrated *in vacuo*. The residue was purified by
10 prep HPLC (Method B) to give the desired product (4.7 mg, 19%). $^1\text{H NMR}$ (500 MHz, DMSO- d_6) δ 9.92 (s, 2H), 9.65 (s, 1H), 9.15 (s, 1H), 7.97 (s, 1H), 7.74 (s, 1H), 6.94 (s, 1H), 4.90 (br d, $J = 5.8$ Hz, 2H), 3.90 (s, 3H); MS (ESI+) $m/z = 402.0 (M+H)^+$.

EXAMPLE 73

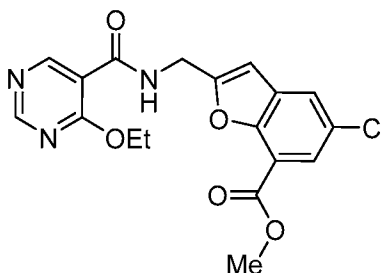


15

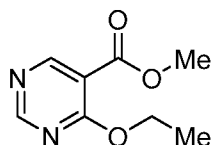
Methyl 5-chloro-2-((4-methoxypyrimidine-5-carboxamido)methyl)benzofuran-7-carboxylate

A mixture of methyl 2-(aminomethyl)-5-chlorobenzofuran-7-carboxylate, TFA (50.5 mg, 0.143 mmol, Step C in Example 48), 4-methoxypyrimidine-5-carboxylic acid
20 (20 mg, 0.130 mmol), HATU (54.3 mg, 0.143 mmol) and Hunig's base (0.091 mL, 0.519 mmol) in DMF (1 mL) was stirred at room temperature for 1 hour. The reaction mixture was quenched with 1:1 DMF/AcOH and purified by preparative HPLC (Method B). The appropriate fractions were combined and dried *via* centrifugal evaporation to afford the title compound (6.4 mg, 13.13 % yield). $^1\text{H NMR}$ (500 MHz, DMSO- d_6) δ 9.01 (br t, $J = 5.5$ Hz, 1H), 8.91 (s, 1H), 8.85 (s, 1H), 7.98 (d, $J = 1.8$ Hz, 1H), 7.75 (d, $J = 1.8$ Hz, 1H),
25

6.87 (s, 1H), 4.70 (br d, $J = 5.8$ Hz, 2H), 4.06 (s, 3H), 3.92 (s, 3H); MS (ESI+) $m/z = 376.1$ (M+H)⁺.

EXAMPLE 74

5

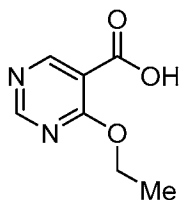
Methyl 5-chloro-2-((4-ethoxypyrimidine-5-carboxamido)methyl)benzofuran-7-carboxylate

10

A) Methyl 4-ethoxypyrimidine-5-carboxylate

A mixture of methyl 4-hydroxypyrimidine-5-carboxylate (200 mg, 1.3 mmol), Hunig's base (240 μ l, 1.43 mmol) and POCl₃ (133 μ l, 1.43 mmol) was heated to 80 °C for 2 h. The reaction was transferred to a flask containing EtOH (20 mL). The solvent was evaporated and the residue was suspended in ice cold saturated sodium bicarbonate solution. The aqueous layer was extracted with EtOAc (3x). The organic layer was separated, dried over sodium sulfate, filtered, and concentrated. The residue was purified by silica gel chromatography eluting with 0-40% EtOAc in hexanes. The appropriate fractions were combined and concentrated *in vacuo* to afford the product (103 mg, 43.6 % yield). MS (ESI+) $m/z = 183.0$ (M+H)⁺.

20



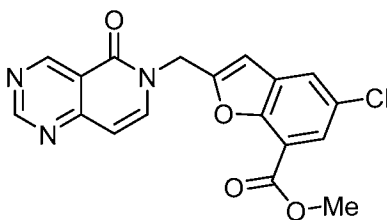
B) 4-Ethoxypyrimidine-5-carboxylic acid

A mixture of methyl 4-ethoxypyrimidine-5-carboxylate (100 mg, 0.549 mmol) and lithium hydroxide monohydrate (46.1 mg, 1.098 mmol) in THF (2.2 mL) and water (0.55 mL) was stirred at room temperature for 1.5 hours. The reaction mixture was quenched with 1N aqueous HCl solution (1.1 mL, 1.1 mmol). The mixture was concentrated and dried on high vacuum to afford the product as an HCl salt (111 mg, 99 % yield). MS (ESI+) $m/z = 169.0$ (M+H)⁺.

C) Methyl 5-chloro-2-((4-ethoxypyrimidine-5-carboxamido)methyl)benzofuran-7-carboxylate

A mixture of methyl 2-(aminomethyl)-5-chlorobenzofuran-7-carboxylate, TFA (41.6 mg, 0.118 mmol, Step C in Example 48), 4-ethoxypyrimidine-5-carboxylic acid (18 mg, 0.107 mmol), HATU (44.8 mg, 0.118 mmol) and Hunig's base (0.075 mL, 0.428 mmol) in DMF (1 mL) was stirred at room temperature for 1 hour. The reaction mixture was quenched with 1:1 DMF/AcOH and purified by preparative HPLC (Method B). The appropriate fractions were combined and dried *via* centrifugal evaporation to afford the title compound (4.8 mg, 11.50 % yield). ¹H NMR (500 MHz, DMSO-d₆) δ 8.83 (br d, $J = 11.0$ Hz, 2H), 8.79 (br d, $J = 5.8$ Hz, 1H), 7.94 (s, 1H), 7.74 (s, 1H), 6.87 (s, 1H), 4.71 (d, $J = 5.8$ Hz, 2H), 4.54 (q, $J = 7.1$ Hz, 2H), 3.91 (s, 3H), 1.36 (td, $J = 7.0, 1.6$ Hz, 3H); MS (ESI+) $m/z = 390.2$ (M+H)⁺.

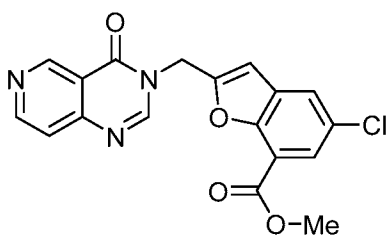
EXAMPLE 75



Methyl 5-chloro-2-((5-oxopyrido[4,3-d]pyrimidin-6(5H)-yl)methyl)benzofuran-7-carboxylate

A mixture of ethyl 4-methylpyrimidine-5-carboxylate (35.7 mg, 0.215 mmol), and
 5 1,1-dimethoxy-*N,N*-dimethylmethanamine (0.12 mL, 0.91 mmol) in DMF (0.5 mL) in a
 microwave tube was heated in a microwave reactor at 160 °C for 40 min. The reaction
 mixture was concentrated *in vacuo*. To the residue was added 1 mL of acetic acid and
 methyl 2-(aminomethyl)-5-chlorobenzofuran-7-carboxylate TFA salt (38 mg, 0.107
 mmol, Step C in Example 48) and the mixture was again heated in a microwave at 110 °C
 10 for 25 min. The reaction mixture was concentrated *in vacuo*. The residue was dissolved
 in DMF, filtered and purified by preparative HPLC (Method B). Fractions containing the
 desired product were combined and dried *via* centrifugal evaporation to give the title
 compound (28 mg, 67%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.49 (s, 1H), 9.36 (s, 1H),
 8.14 (d, *J* = 7.7 Hz, 1H), 7.96 (s, 1H), 7.76 (s, 1H), 6.95 (s, 1H), 6.77 (d, *J* = 7.6 Hz, 1H),
 15 5.47 (s, 2H), 3.90 (s, 3H); MS (ESI+) *m/z* = 370.1 (M+H)⁺.

EXAMPLE 76



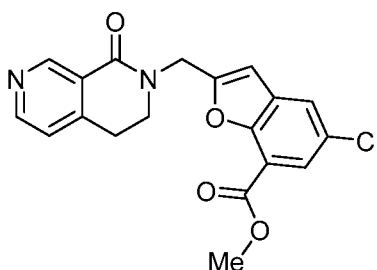
Methyl 5-chloro-2-((4-oxopyrido[4,3-d]pyrimidin-3(4H)-yl)methyl)benzofuran-7-carboxylate

20

4-Aminonicotinic acid (19.92 mg, 0.144 mmol) and *N,N*- dimethylformamide
 dimethyl acetal (0.114 mL, 0.848 mmol) were taken up in DMF (4 mL) in a microwave
 vial. The vial was sealed and heated to 110 °C for 40 minutes in a microwave reactor.

The reaction mixture was cooled and concentrated *in vacuo*. To the residue was added 1 mL of acetic acid and methyl 2-(aminomethyl)-5-chlorobenzofuran-7-carboxylate, TFA (30 mg, 0.085 mmol, Step C in Example 48). The reaction was sealed and again heated in a microwave reactor to 110 °C for 35 minutes. The reaction mixture was cooled and concentrated *in vacuo*. The residue was dissolved in MeOH and 0.1 mL of DMF, filtered, and purified *via* HPLC (method B) to give the title compound (7.6 mg, 24% yield). ¹H NMR (500 MHz, DMSO-d₆) δ 9.33 (s, 1H), 8.88 (d, *J* = 5.5 Hz, 1H), 8.78 (s, 1H), 7.98 (d, *J* = 2.1 Hz, 1H), 7.76 (d, *J* = 1.8 Hz, 1H), 7.65 (d, *J* = 5.8 Hz, 1H), 7.02 (s, 1H), 5.48 (s, 2H), 3.87 (s, 3H); MS (ESI+) *m/z* = 370.3 (M+H)⁺.

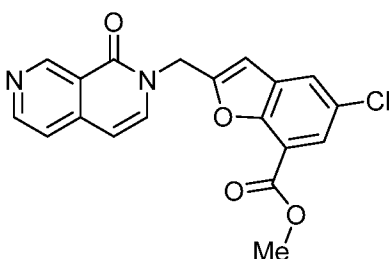
10

EXAMPLE 77**Methyl 5-chloro-2-((1-oxo-3,4-dihydro-2,7-naphthyridin-2(1H)-yl)methyl)benzofuran-7-carboxylate**

15 A mixture of 3,4-dihydro-1*H*-pyrano[3,4-*c*]pyridin-1-one, HCl (87 mg, 0.47 mmol) (WO 2005063768) and methyl 2-(aminomethyl)-5-chlorobenzofuran-7-carboxylate TFA salt (150 mg, 0.424 mmol, Step C of Example 48) in pyridine (2 mL) was heated at 128 °C for 5 hours in a vial with pressure relief septum. The reaction was concentrated *in vacuo*. A portion of the sample was taken up in DMF, filtered, and purified by preparative HPLC (Method B). Fractions containing the desired product were combined and dried *via* centrifugal evaporation to give the title compound (7.4 mg, 18%). ¹H NMR (500 MHz, DMSO-d₆) δ 8.94 (s, 1H), 8.58 (br d, *J* = 4.6 Hz, 1H), 7.92 (s, 1H), 7.73 (s, 1H), 7.36 (br d, *J* = 4.9 Hz, 1H), 6.93 (s, 1H), 4.91 (s, 2H), 3.86 (s, 3H), 3.61 - 3.47 (m, 2H), 3.08 - 3.00 (m, 2H); MS (ESI+) *m/z* = 371.0 (M+H)⁺.

25

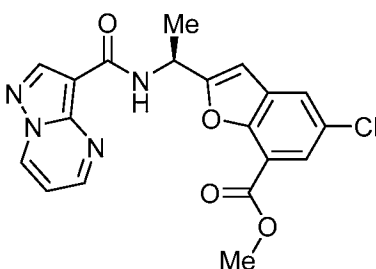
EXAMPLE 78



Methyl 5-chloro-2-((1-oxo-2,7-naphthyridin-2(1H)-yl)methyl)benzofuran-7-carboxylate

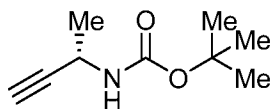
- 5 Methyl 4-methylnicotinate (34.2 mg, 0.226 mmol) and *N,N*-dimethylformamide dimethylacetal (0.121 mL, 0.905 mmol) were taken up in DMF in a microwave vial. The vial was sealed and heated to 160 °C for 40 minutes in a microwave reactor. The reaction mixture was cooled and concentrated *in vacuo*. The residue was dissolved in DCM and concentrated *in vacuo* once again. To the resulting residue was added acetic acid (0.5
- 10 mL) and methyl 2-(aminomethyl)-5-chlorobenzofuran-7-carboxylate, TFA (40 mg, 0.113 mmol, Step C in Example 48). The vial was then sealed and heated to 110 °C for 25 minutes in a microwave reactor. The reaction was again cooled and concentrated *in vacuo*. The residue was dissolved in DMF and MeOH, filtered, and purified *via* HPLC (method B) to give the title compound (29 mg, 69% yield). ¹H NMR (500 MHz, DMSO-
- 15 d₆) δ 9.35 (s, 1H), 8.73 (d, *J* = 5.2 Hz, 1H), 7.96 (d, *J* = 2.1 Hz, 1H), 7.86 (d, *J* = 7.3 Hz, 1H), 7.75 (d, *J* = 1.8 Hz, 1H), 7.63 (d, *J* = 5.5 Hz, 1H), 6.91 (s, 1H), 6.75 (d, *J* = 7.3 Hz, 1H), 5.43 (s, 2H), 3.87 (s, 3H); MS (ESI+) *m/z* = 368.9 (M+H)⁺.

EXAMPLE 79



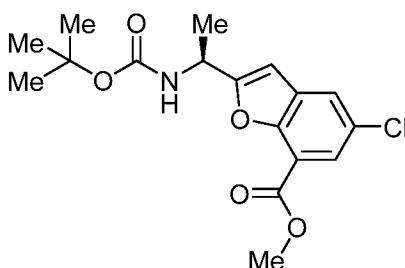
20

Methyl (*S*)-5-chloro-2-(1-(pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)ethyl)benzofuran-7-carboxylate



5 **A) *tert*-Butyl (*S*)-but-3-yn-2-ylcarbamate**

To a suspension of (*S*)-2-(but-3-yn-2-yl)isoindoline-1,3-dione (1.6 g, 8.03 mmol) in ethanol (30 mL) and H₂O (1 mL) was added hydrazine (0.30 mL, 9.64 mmol). The reaction mixture was heated at 76 °C for 60 min. The reaction mixture turned into clear solution and after 30 min, a solid crashed out. The reaction mixture was cooled down and
 10 filtered. To the filtrate was added Boc₂O (2.42 mL, 10.44 mmol) and DIPEA (2.81 mL, 16.06 mmol). The reaction mixture was stirred at room temperature for 16 hours. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in DCM and purified by flash chromatography (ISCO column 40 g, 0 - 20% ethyl acetate in hexanes) to give the title compound (1.2 g, 88 %) as a white solid. ¹H NMR (499 MHz,
 15 CHLOROFORM-*d*) δ 4.87 - 4.59 (m, 1H), 4.58 - 4.33 (m, 1H), 2.28 (d, *J* = 2.2 Hz, 1H), 1.47 (s, 9H), 1.42 (d, *J* = 6.9 Hz, 3H).

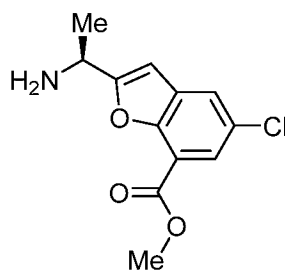


20 **B) Methyl (*S*)-2-(1-((*tert*-butoxycarbonyl)amino)ethyl)-5-chlorobenzofuran-7-carboxylate**

A mixture of methyl 5-chloro-2-hydroxy-3-iodobenzoate (1.95 g, 6.24 mmol, Step A of Example 94), *tert*-butyl (*S*)-but-3-yn-2-ylcarbamate (1.21 g, 7.18 mmol), TEA (14.8 mL, 106 mmol), and copper(I) iodide (0.12 g, 0.62 mmol) in DMF (15 mL) was purged with a nitrogen stream for 5 mins. Bis(triphenylphosphine)-palladium(II) chloride (0.219

g, 0.312 mmol) was then added. The resulting mixture was heated at 80 °C for 2 hours. The reaction mixture was cooled down and diluted with ethyl acetate and saturated aqueous NaHCO₃ solution. The organic layer was separated, washed with brine, dried over MgSO₄, and filtered. The filtrate was concentrated *in vacuo*. The residue was dissolved in DCM and purified by flash chromatography (ISCO column 80 g, 0 - 20% ethyl acetate in hexanes) to give the title compound (2.0 g, 91%) as a light brown solid. ¹H NMR (400 MHz, Chloroform-d) δ 7.89 (d, *J* = 2.1 Hz, 1H), 7.68 (d, *J* = 2.2 Hz, 1H), 6.58 (s, 1H), 5.18 - 4.89 (m, 2H), 4.02 (s, 3H), 1.65 - 1.59 (m, 3H), 1.48 (s, 9H); MS (ESI+) *m/z* = 298.2 (M-55+H)⁺.

10



C) Methyl (*S*)-2-(1-aminoethyl)-5-chlorobenzofuran-7-carboxylate

To a solution of methyl (*S*)-2-(1-((*tert*-butoxycarbonyl)amino)ethyl)-5-chlorobenzofuran-7-carboxylate (0.26 g, 0.735 mmol) in DCM (3 mL) was added TFA (0.57 mL, 7.35 mmol). The reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated *in vacuo* to give the title compound (TFA salt) as a brown solid (250 mg, 93%). MS (ESI+) *m/z* = 237.1 (M-16+H)⁺.

15

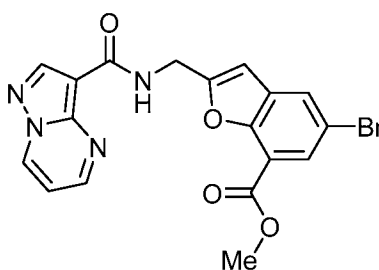
D) Methyl (*S*)-5-chloro-2-(1-(pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)ethyl)benzofuran-7-carboxylate

20

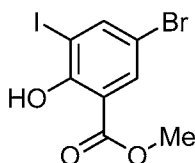
A mixture of pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (144 mg, 0.884 mmol) and BOP (421 mg, 0.952 mmol) in DMF (4 mL) was stirred at rt for 15 min. A solution of methyl (*S*)-2-(1-aminoethyl)-5-chlorobenzofuran-7-carboxylate, TFA salt (250 mg, 0.680 mmol) in THF (2 mL) and DIPEA (0.71 mL, 4.08 mmol) were added. The reaction mixture turned into clear solution after addition of the amine and was stirred at rt for 3 h.

The reaction mixture was diluted with ethyl acetate and saturated aqueous NaHCO₃ solution. The organic layer was separated, washed with brine, dried over MgSO₄, and filtered. The filtrate was concentrated *in vacuo* to give the title compound as a white solid (220 mg, 81%). A portion of the sample was dissolved in DMF and purified by
5 preparative HPLC (Method B). Fractions containing the desired product were combined and dried *via* centrifugal evaporation to give the title compound. ¹H NMR (500 MHz, DMSO-d₆) δ 9.31 - 9.18 (m, 1H), 8.82 (br d, *J* = 4.1 Hz, 1H), 8.61 (s, 1H), 8.36 (br d, *J* = 8.1 Hz, 1H), 7.95 (s, 1H), 7.74 (d, *J* = 1.1 Hz, 1H), 7.27 (dd, *J* = 6.6, 4.5 Hz, 1H), 6.91 (s, 1H), 5.50 (br t, *J* = 7.3 Hz, 1H), 3.89 (s, 3H), 1.67 (d, *J* = 6.9 Hz, 3H); MS (ESI+) *m/z* =
10 399.1 (M+H)⁺.

EXAMPLE 80



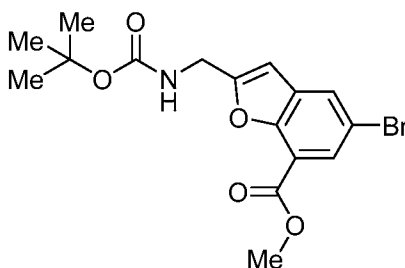
Methyl 5-bromo-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate
15



A) Methyl 5-bromo-2-hydroxy-3-iodobenzoate

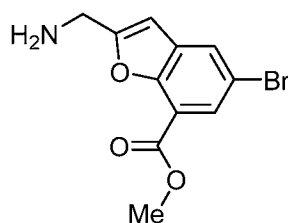
To a solution of methyl 5-bromo-2-hydroxybenzoate (4.0 g, 17.3 mmol) in *N,N*-
20 dimethylformamide (50 mL) was added sodium iodide (3.11 g, 20.8 mmol), followed by chloramine T trihydrate (5.36 g, 19.0 mmol) slowly. The resulting mixture was stirred at room temperature for 20 hours. The reaction mixture was diluted with ethyl acetate and 1 N aqueous HCl solution. The organic layer was separated, washed with brine followed by

Na₂S₂O₃ solution, dried over MgSO₄, and filtered. The filtrate was concentrated *in vacuo* to give a light yellow oil. To the residue was added MeOH and the resulting precipitate was filtered to give the title compound as a white solid (5.1 g, 83%). ¹H NMR (400 MHz, CHLOROFORM-d) δ 11.59 (s, 1H), 8.06 (d, *J* = 2.3 Hz, 1H), 7.99 (d, *J* = 2.3 Hz, 1H), 4.01 (s, 3H).



B) Methyl 5-bromo-2-(((tert-butoxycarbonyl)amino)methyl) benzofuran-7-carboxylate

10 A mixture of methyl 5-bromo-2-hydroxy-3-iodobenzoate (5.1 g, 14.3 mmol), *tert*-butyl prop-2-yn-1-ylcarbamate (2.55 g, 16.4 mmol), TEA (23.9 mL, 171 mmol), and copper(I) iodide (0.272 g, 1.43 mmol) in DMF (20 mL) was purged with a nitrogen stream for 5 mins, then bis(triphenylphosphine)palladium(II) chloride (0.85 g, 1.21 mmol) was added. The resulting mixture was heated at 80 °C for 2 hours. The reaction
 15 was cooled down and diluted with ethyl acetate and saturated aqueous NaHCO₃ solution. The organic layer was separated, washed with brine, dried over MgSO₄, and filtered. The filtrate was concentrated *in vacuo*. The residue was dissolved in DCM and purified by flash chromatography (ISCO 80g column, 0-25% ethyl acetate in hexanes) to give the title compound (4.2 g, 77% yield) as a light brown solid. ¹H NMR (400 MHz,
 20 Chloroform-d) δ 8.01 (d, *J* = 2.0 Hz, 1H), 7.83 (d, *J* = 2.0 Hz, 1H), 6.63 (s, 1H), 5.20 - 5.03 (m, 1H), 4.52 (br d, *J* = 5.9 Hz, 2H), 4.01 (s, 3H), 1.48 (s, 9H); MS (ESI+) *m/z* = 330 (M-54+H)⁺.



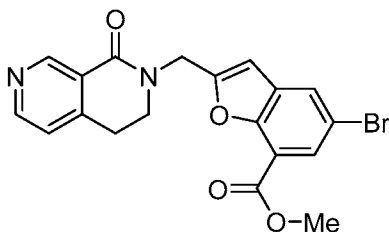
C) Methyl 2-(aminomethyl)-5-bromobenzofuran-7-carboxylate

To a solution of methyl 5-bromo-2-(((*tert*-butoxycarbonyl)amino)methyl) benzofuran-7-carboxylate (260 mg, 0.677 mmol) in DCE (3 mL) was added TFA (1.04 mL, 13.5 mmol). The reaction mixture was stirred at room temperature for 3 hours. The reaction mixture was concentrated *in vacuo* to give the crude title compound (TFA salt) as a brown solid (260 mg, 87%). MS (ESI+) $m/z = 269.1$ (M-17+H)⁺.

D) Methyl 5-bromo-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl) benzofuran-7-carboxylate

To a suspension of pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (12.3 mg, 0.075 mmol) and BOP (33.3 mg, 0.075 mmol) in DMF (1 mL) was added methyl 2-(aminomethyl)-5-bromobenzofuran-7-carboxylate, TFA (25 mg, 0.063 mmol) and DIPEA (0.04 mL, 0.25 mmol). The reaction mixture turned into a clear solution and was stirred at room temperature for 3 hours. Solid formed in the reaction mixture. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in DMF, filtered and purified by preparative HPLC (Method B). Fractions containing the desired product were combined and dried via centrifugal evaporation to give the title compound (5.6 mg, 16.3%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.35 (br s, 1H), 9.01 - 8.76 (m, 1H), 8.65 (s, 2H), 8.10 (d, $J = 1.5$ Hz, 1H), 7.86 (d, $J = 1.5$ Hz, 1H), 7.46 - 7.22 (m, 1H), 6.86 (s, 1H), 4.82 (br d, $J = 5.2$ Hz, 2H), 3.92 (s, 3H); MS (ESI+) $m/z = 429.1$ (M+H)⁺.

Example 81

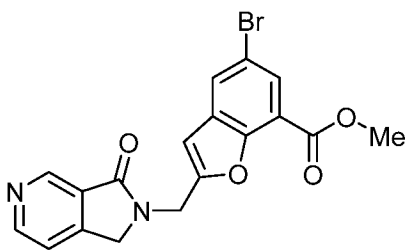


Methyl 5-bromo-2-((1-oxo-3,4-dihydro-2,7-naphthyridin-2(1H)-yl)methyl)benzofuran-7-carboxylate

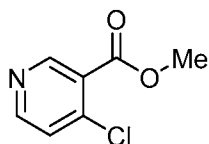
3,4-Dihydro-1*H*-pyrano[3,4-*c*]pyridin-1-one (20 mg, 0.134 mmol) (WO
 5 2005063768) and methyl 2-(aminomethyl)-5-bromobenzofuran-7-carboxylate (76 mg,
 0.27 mmol, Step C in Example 80) were added to a pressure relief vial and heated neat at
 120 °C. After 4 hours, the reaction was cooled, taken up in 2 mL DMF, filtered, and
 purified *via* HPLC (Method B) to give methyl 5-bromo-2-((1-oxo-3,4-dihydro-2,7-
 naphthyridin-2(1*H*)-yl)methyl)benzofuran-7-carboxylate (9.5 mg, 0.022 mmol, 16.2 %
 10 yield). ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.96 (s, 1H), 8.62 (d, *J* = 4.9 Hz, 1H), 8.09 (d, *J*
 = 1.8 Hz, 1H), 7.86 (d, *J* = 1.8 Hz, 1H), 7.38 (d, *J* = 5.2 Hz, 1H), 6.96 (s, 1H), 4.94 (s,
 2H), 3.88 (s, 3H), 3.75 (t, *J* = 6.6 Hz, 2H), 3.09 (t, *J* = 6.4 Hz, 2H); MS (ESI+) *m/z* 415.0
 (M+H)⁺.

15

EXAMPLE 82



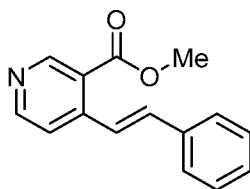
Methyl 5-bromo-2-((3-oxo-1,3-dihydro-2*H*-pyrrolo[3,4-*c*]pyridin-2-yl)methyl)benzofuran-7-carboxylate



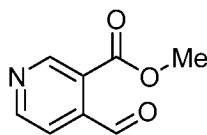
20

A) Methyl 4-chloronicotinate

To a suspension of 4-chloronicotinic acid (4.0 g, 25.4 mmol) in DMF (35 mL) were added K₂CO₃ (5.26 g, 38.1 mmol) and iodomethane (1.75 mL, 27.9 mmol). The reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate and water. The organic layer was separated, washed with brine, dried over MgSO₄, and filtered. The filtrate was concentrated *in vacuo*. The residue was dissolved in DCM and purified by flash chromatography (ISCO column 80 g, 0 - 25% ethyl acetate in DCM) to give the title compound (3.1 g, 71%) as a colorless oil. ¹H NMR (400 MHz, Chloroform-d) δ 9.06 (s, 1H), 8.61 (d, *J* = 5.3 Hz, 1H), 7.44 (d, *J* = 5.3 Hz, 1H), 4.00 (s, 3H); MS (ESI+) *m/z* = 172.1 (M+H)⁺.

**B) Methyl (*E*)-4-styrylnicotinate**

A mixture of (*E*)-4,4,5,5-tetramethyl-2-styryl-1,3,2-dioxaborolane (8.37 g, 36.4 mmol), methyl 4-chloronicotinate (5.2 g, 30.3 mmol) in 1,4-dioxane (35 mL) and water (8 mL) was purged with a nitrogen stream for 5 min. PdCl₂(dppf) (1.33 g, 1.82 mmol) was then added. The reaction mixture was heated at 95 °C under nitrogen atmosphere for 5 hours. The reaction mixture was cooled down and diluted with ethyl acetate and saturated aqueous NaHCO₃ solution. The organic layer was separated, washed with brine, dried over MgSO₄, and filtered. The filtrate was concentrated *in vacuo*. The residue was dissolved in DCM and purified by flash chromatography (ISCO column 120 g, 0 - 35% ethyl acetate in hexanes) to give the title compound (5.2 g, 72%) as a brown oil. ¹H NMR (499 MHz, Chloroform-d) δ 9.15 (d, *J* = 0.6 Hz, 1H), 8.69 (d, *J* = 5.3 Hz, 1H), 8.05 (d, *J* = 16.3 Hz, 1H), 7.71 - 7.57 (m, 3H), 7.47 - 7.39 (m, 2H), 7.38 - 7.33 (m, 1H), 7.26 (d, *J* = 16.3 Hz, 1H), 4.00 (s, 3H); MS (ESI+) *m/z* = 240.2 (M+H)⁺.



C) Methyl 4-formylnicotinate

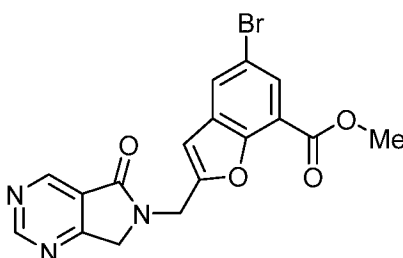
The reaction mixture of methyl (*E*)-4-styrylnicotinate (1.0 g, 4.18 mmol) and pyridine (1.0 mL, 12.5 mmol) in DCM (15 mL) was cooled to $-78\text{ }^{\circ}\text{C}$. A stream of O_3/O_2 was bubbled through the reaction solution for 10 minutes. The brown reaction mixture changed from yellow to colorless and purple. The O_3 generator was turned off and O_2 was bubbled for a few minutes until the purple color dissipated and the solution returned to light yellow in color. The reaction mixture was purged with nitrogen for 3 min and stirred at $-78\text{ }^{\circ}\text{C}$ for 20 minutes. The reaction was diluted with DCM and saturated aqueous NaHCO_3 solution. The organic layer was separated, washed with brine, dried over MgSO_4 , and filtered. The filtrate was concentrated *in vacuo*. The residue was dissolved in DCM and purified by flash chromatography (ISCO column 40 g, 0 - 50% ethyl acetate in hexanes) to give the title compound (0.34 g, 49%) as a white solid. ^1H NMR (500 MHz, CDCl_3) δ 10.74 (d, $J = 0.6$ Hz, 1H), 9.30 (s, 1H), 8.97 (d, $J = 4.9$ Hz, 1H), 7.72 (dd, $J = 4.9, 0.7$ Hz, 1H), 4.04 (s, 3H); MS (ESI+) $m/z = 166.1$ ($\text{M}+\text{H}$) $^+$.

D) Methyl 5-bromo-2-((3-oxo-1,3-dihydro-2*H*-pyrrolo[3,4-*c*]pyridin-2-yl)methyl)benzofuran-7-carboxylate

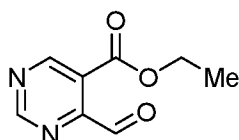
A mixture of methyl 4-formylnicotinate (20 mg, 0.112 mmol) in THF (0.8 mL) was charged with a solution of methyl 2-(aminomethyl)-5-bromobenzofuran-7-carboxylate (33.3 mg, 0.117 mmol, Step C in Example 80) in THF (2 mL). After stirring at room temperature for 40 min, acetic acid (0.1 mL, 1.75 mmol) and sodium triacetoxyborohydride (35.5 mg, 0.167 mmol) were added. The resulting mixture was stirred at room temperature for 20 hours. After 20 hours, more ethyl 4-formylnicotinate (15 mg) in THF (1 mL) was added. The reaction mixture was stirred at room temperature for an additional hour, and then sodium triacetoxyborohydride (35.5 mg, 0.167 mmol) was added. The reaction mixture was stirred at room temperature for another 4 hours before being diluted with saturated aqueous NaHCO_3 solution. After stirring the

quenched reaction for 5 minutes, the resulting mixture was extracted with ethyl acetate. The organic layer was separated and concentrated *in vacuo*. The residue was dissolved in DMF and purified by preparative HPLC (Method B). Fractions containing the desired product were combined and dried *via* centrifugal evaporation to give the title compound (7.5 mg, 12%). ¹H NMR (500 MHz, DMSO-d₆) δ 8.97 (s, 1H), 8.78 (d, *J* = 5.0 Hz, 1H), 8.13 (d, *J* = 1.9 Hz, 1H), 7.88 (d, *J* = 2.0 Hz, 1H), 7.73 (br d, *J* = 4.8 Hz, 1H), 7.00 (s, 1H), 5.00 (s, 2H), 4.69 (s, 2H), 3.91 (s, 3H); MS (ESI+) *m/z* = 400.9 (M+H)⁺.

EXAMPLE 83



Methyl 5-bromo-2-((5-oxo-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidin-6-yl)methyl)benzofuran-7-carboxylate



A) Ethyl 4-formylpyrimidine-5-carboxylate

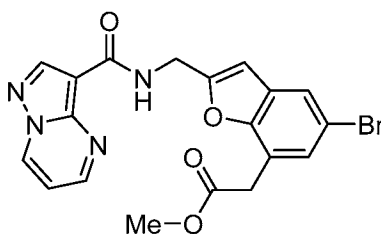
A mixture of ethyl 4-methylpyrimidine-5-carboxylate (1.0 g, 6.02 mmol) and selenium dioxide (0.708 g, 6.38 mmol) in 1,4-dioxane (10 mL) in a sealed tube was heated at 95 °C overnight. The reaction mixture was diluted with ethyl acetate and saturated aqueous NaHCO₃ solution. The organic layer was separated, washed with brine, dried over MgSO₄, and filtered. The filtrate was concentrated *in vacuo*. The residue was dissolved in DCM and purified by flash chromatography (ISCO column 40 g, 0 - 50% ethyl acetate in hexanes) to give the title compound (0.21 g, 19 %) as a brown oil. ¹H

NMR (500 MHz, Chloroform-*d*) δ 10.38 (s, 1H), 9.49 (s, 1H), 9.27 (s, 1H), 4.47 (q, J = 7.2 Hz, 2H), 1.42 (t, J = 7.2 Hz, 3H); MS (ESI+) m/z = 181.1 (M+H)⁺.

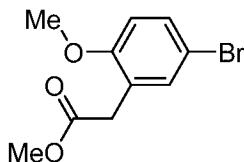
5 **B) Methyl 5-bromo-2-((5-oxo-5,7-dihydro-6H-pyrrolo[3,4-*d*]pyrimidin-6-yl)methyl)benzofuran-7-carboxylate**

A mixture of of ethyl 4-formylpyrimidine-5-carboxylate (20 mg, 0.111 mmol) and methyl 2-(aminomethyl)-5-bromobenzofuran-7-carboxylate (37.8 mg, 0.133 mmol, Step C of Example 80) in THF (2 mL) was stirred at room temperature for 40 min. Acetic acid (0.1 mL, 1.75 mmol) and sodium triacetoxyborohydride (35 mg, 0.167 mmol) were
10 added. The resulting mixture was stirred at room temperature for 7 hours. To the reaction mixture was added saturated aqueous NaHCO₃ solution and the mixture was stirred for 5 min. The mixture was then extracted with ethyl acetate. The organic layer was separated, washed with brine, dried over MgSO₄, and filtered. The filtrate was concentrated *in vacuo*. The residue was dissolved in DMF and purified by preparative HPLC (Method
15 B). Fractions containing the desired product were combined and dried *via* centrifugal evaporation to give the title compound (4.1 mg, 9%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.40 (s, 1H), 9.20 (s, 1H), 8.13 (d, J = 1.8 Hz, 1H), 7.89 (d, J = 1.8 Hz, 1H), 7.04 (s, 1H), 5.03 (s, 2H), 4.76 (s, 2H), 3.91 (s, 3H); MS (ESI+) m/z = 403.9 (M+H)⁺.

20

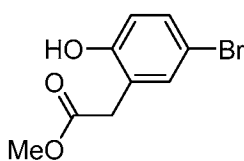
EXAMPLE 84

Methyl 2-(5-bromo-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-yl)acetate



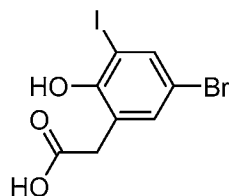
A) Methyl 2-(5-bromo-2-methoxyphenyl)acetate

To a solution of 2-(5-bromo-2-methoxyphenyl)acetic acid (1.5 g, 6.12 mmol) in DCM (20 mL) and MeOH (4 mL) at 0 °C was added (diazomethyl)trimethylsilane, 2 M in diethyl ether (3.67 mL, 7.34 mmol). The reaction mixture was stirred at 0 °C for 30 min and room temperature for 1 hour. The reaction mixture was concentrated and purified by ISCO, 80 g column, eluting with 0-20% EtOAc in hexanes to give the desired product as a colorless oil (1.41 g, 89% yield). ¹H NMR (400 MHz, CHLOROFORM-d) δ 7.37 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.32 (d, *J* = 2.5 Hz, 1H), 6.77 (d, *J* = 8.7 Hz, 1H), 3.82 (s, 3H), 3.72 (s, 3H), 3.61 (s, 2H).



B) Methyl 2-(5-bromo-2-hydroxyphenyl)acetate

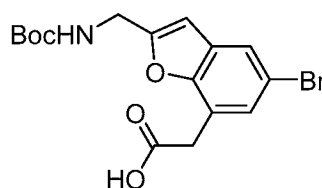
To a solution of methyl 2-(5-bromo-2-methoxyphenyl)acetate (1.41 g, 5.44 mmol) in DCM (30 mL) at 0 °C was added tribromoborane (0.787 mL, 8.16 mmol). The reaction mixture was stirred at 0 °C for 1 hour and then at room temperature for 1 hour. The reaction mixture was concentrated *in vacuo* and purified by ISCO, 80 g column, eluting with 0-40% EtOAc in hexanes to give the desired product as a white solid (1.30 g, 97% yield). ¹H NMR (400 MHz, Chloroform-d) δ 7.32 - 7.21 (m, 2H), 6.79 (d, *J* = 8.4 Hz, 1H), 3.77 (s, 3H), 3.65 (s, 2H); MS (ESI+) *m/z* = 245.0 (M+H)⁺.



C) 2-(5-Bromo-2-hydroxy-3-iodophenyl)acetic acid

To a solution of methyl 2-(5-bromo-2-hydroxyphenyl)acetate (1.3 g, 5.30 mmol) in THF (10 mL) and MeOH (10 mL) at room temperature was added 3 N aqueous sodium hydroxide solution (5.30 mL, 15.9 mmol). The reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was acidified with 3 N aqueous HCl solution to pH 2-3 and extracted with EtOAc. The organic layer was dried over sodium sulfate, filtered, and concentrated to give the desired acid.

To a solution of the above acid (1.22 g, 5.28 mmol) in CH₃CN (2 mL) at room temperature was added NIS (1.19 g, 5.28 mmol). The reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was concentrated and purified by ISCO, 24 g column, eluting with 0-5% MeOH in DCM to give the desired product (1.18 g, 63% yield). ¹H NMR (400 MHz, Chloroform-d) δ 7.76 (d, *J* = 2.2 Hz, 1H), 7.31 (d, *J* = 2.2 Hz, 1H), 3.73 (s, 2H); MS (ESI+) *m/z* = 356.8 (M-H)⁺.



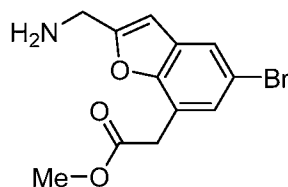
15

D) 2-(5-Bromo-2-(((tert-butoxycarbonyl)amino)methyl)benzofuran-7-yl)acetic acid

To a solution of 2-(5-bromo-2-hydroxy-3-iodophenyl)acetic acid (1.18 g, 3.31 mmol) in DMF (5 mL) and TEA (5 mL) was added copper(I) iodide (63.0 mg, 0.331 mmol), *tert*-butyl prop-2-yn-1-ylcarbamate (770 mg, 4.96 mmol) and bis(triphenylphosphine)palladium(II) chloride (232 mg, 0.331 mmol). The reaction mixture was degassed by bubbling Ar through and stirred at 80 °C for 2 h. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in EtOAc and washed with 10% aqueous citric acid solution. The organic layer was dried over sodium sulfate, filtered, concentrated *in vacuo*, and purified by ISCO, 80 g column, eluting with 0-50% EtOAc in DCM to give the desired product as a brown semi-solid (805 mg, 63% yield). ¹H NMR (400 MHz, Chloroform-d) δ 7.58 (d, *J* = 1.9 Hz, 1H), 7.31 (d, *J* = 1.8 Hz, 1H),

25

6.56 (br s, 1H), 5.04 (br s, 1H), 4.45 (br d, $J = 4.4$ Hz, 2H), 3.90 (s, 2H), 1.48 (s, 9H); MS (ESI+) $m/z = 327.9$ (M-55+H)⁺.



5 **E) Methyl 2-(2-(aminomethyl)-5-bromobenzofuran-7-yl)acetate**

To a solution of 2-(5-bromo-2-(((*tert*-butoxycarbonyl)amino)methyl) benzofuran-7-yl)acetic acid (800 mg, 2.08 mmol) in DCM (20 mL) and MeOH (4 mL) at 0 °C was added (diazomethyl)trimethylsilane, 2 M in diethyl ether (1.25 mL, 2.5 mmol). The reaction mixture was stirred at rt for 1 h. The reaction mixture was concentrated and
10 purified by ISCO, 80 g column, eluting with 0-30% EtOAc in hexanes to give the desired product (740 mg, 89%).

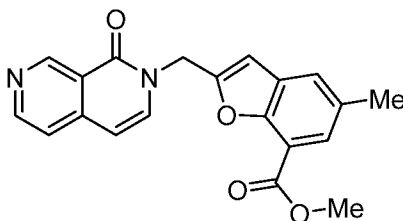
To a solution of the above compound (740 mg, 1.86 mmol) in DCM (1.5 mL) was added TFA (0.5 mL). The reaction mixture was stirred at room temperature for 1 hour and concentrated to give the desired product (765 mg, 100% yield). ¹H NMR (400 MHz,
15 Chloroform-*d*) δ 7.58 (d, $J = 1.9$ Hz, 1H), 7.31 (d, $J = 1.9$ Hz, 1H), 6.56 (s, 1H), 4.45 (br d, $J = 5.6$ Hz, 2H), 3.88 (s, 2H), 3.74 (s, 3H); MS (ESI+) $m/z = 297.9$ (M+H)⁺.

F) Methyl 2-(5-bromo-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-yl)acetate

20 To a solution of methyl 2-(2-(aminomethyl)-5-bromobenzofuran-7-yl)acetate, TFA (400 mg, 0.970 mmol) in DMF (1 mL) was added pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (158 mg, 0.970 mmol), BOP (644 mg, 1.456 mmol) and DIPEA (0.509 mL, 2.91 mmol). The reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated and purified with ISCO, 40 g column, eluting with 50-
25 100% EtOAc in DCM to give the desired product as a white solid (310 mg, 72% yield). ¹H NMR (400 MHz, Chloroform-*d*) δ 8.81 (dd, $J = 7.0, 1.8$ Hz, 1H), 8.73 (s, 1H), 8.67 (dd, $J = 4.2, 1.8$ Hz, 1H), 8.37 (br t, $J = 5.4$ Hz, 1H), 7.57 (d, $J = 1.9$ Hz, 1H), 7.31 (d, $J =$

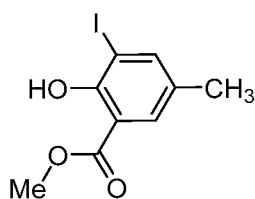
2.0 Hz, 1H), 7.03 (dd, $J = 7.0, 4.1$ Hz, 1H), 6.66 (s, 1H), 4.87 (dd, $J = 5.8, 0.7$ Hz, 2H), 3.91 (s, 2H), 3.72 (s, 3H); MS (ESI+) $m/z = 444.8$ (M+H)⁺.

EXAMPLE 85



5

Methyl 5-methyl-2-((1-oxo-2,7-naphthyridin-2(1H)-yl)methyl)benzofuran-7-carboxylate

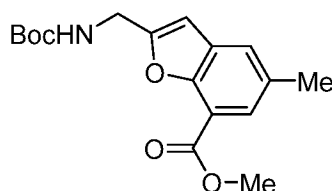


10

A) Methyl-2-hydroxy-3-iodo-5-methylbenzoate

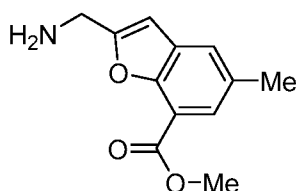
To a solution of methyl 5-methylsalicylate (5 g, 30.1 mmol) in *N,N*-dimethylformamide (40 mL) was added sodium iodide (5.41 g, 36.1 mmol) followed by chloramine T trihydrate (10.17 g, 36.1 mmol) slowly in portions. The reaction was stirred at room temperature for 3 hours. The reaction mixture was quenched with ethyl acetate and 1N aqueous HCl solution. The organic layer was separated, washed with saturated aqueous sodium chloride solution followed by 10% aqueous Na₂S₂O₃ solution, and dried with anhydrous sodium sulfate. The dried organic extracts were filtered and concentrated *in vacuo*. The crude product mixture was purified by a silica gel ISCO 120 g column eluting with 0 - 20% ethyl acetate / hexane over a 15 minute gradient. The appropriate fractions were isolated and concentrated *in vacuo* to afford the product (8.2 g, 93% yield) as a solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 11.52 - 11.27 (m, 1H), 7.86 - 7.72 (m, 1H), 7.72 - 7.52 (m, 1H), 4.09 - 3.89 (m, 3H), 2.39 - 2.08 (m, 3H); MS (ESI+) $m/z = 293.1$ (M+H)⁺.

20



B) Methyl 2-(((*tert*-butoxycarbonyl)amino)methyl)-5-methylbenzofuran-7-carboxylate

5 A 100 ml flask was charged with methyl 2-hydroxy-3-iodo-5-methylbenzoate (8.2 g, 28.1 mmol), *tert*-butyl prop-2-yn-1-ylcarbamate (5.01 g, 32.3 mmol), and copper(I) iodide (0.428 g, 2.25 mmol) in DMF (20 mL) and TEA (30 mL). The reaction was purged with nitrogen, then bis(triphenylphosphine)palladium(II) chloride (0.985 g, 1.404 mmol) was added. The resulting mixture was heated at 80 °C for 4 hours. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate, washed with saturated aqueous sodium bicarbonate solution followed by saturated aqueous sodium chloride solution, dried with anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude product mixture was purified by a silica gel ISCO 80 g column eluting with 0-35 % ethyl acetate / hexane over a 15 minute gradient. The appropriate fractions were isolated and concentrated *in vacuo* to afford the title compound (6 g, 67 % yield) as a light brown solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.86 - 7.66 (m, 1H), 7.63 - 7.38 (m, 1H), 6.75 - 6.43 (m, 1H), 4.62 - 4.43 (m, 2H), 4.20 - 3.75 (m, 3H), 2.70 - 2.16 (m, 3H), 1.55 - 1.28 (m, 9H) ; MS (ESI+) *m/z* = 264.1 (M-55+H)⁺.



20

C) Methyl 2-(aminomethyl)-5-methylbenzofuran-7-carboxylate, TFA salt

To a solution of methyl 2-(((*tert*-butoxycarbonyl)amino)methyl)-5-methylbenzofuran-7-carboxylate (0.5 g, 1.57 mmol, Step B of Example 230) in CH₂Cl₂ (8 mL) was added TFA (1.21 mL, 15.7 mmol). The reaction mixture was stirred at room

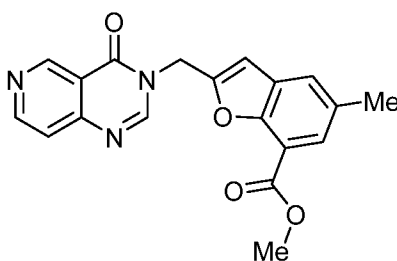
temperature for 2 hours. The reaction mixture was concentrated *in vacuo* to afford the product methyl 2-(aminomethyl)-5-methylbenzofuran-7-carboxylate as a TFA salt (250 mg, 47.9 % yield). ¹H NMR (400 MHz, Methanol-d₄) δ 7.94 - 7.75 (m, 1H), 7.77 - 7.65 (m, 1H), 7.10 - 6.87 (m, 1H), 4.49 - 4.26 (m, 2H), 4.10 - 3.78 (m, 3H), 2.61 - 2.30 (m, 3H); MS (ESI+) m/z = 203.1 (M-16)⁺.

D) Methyl 5-methyl-2-((1-oxo-2,7-naphthyridin-2(1H)-yl)methyl)benzofuran-7-carboxylate

The reaction mixture of methyl 4-methylnicotinate (68.0 mg, 0.450 mmol), *N,N*-dimethylformamide dimethyl acetal (0.321 mL, 2.401 mmol) in DMF (0.5 mL) was heated in the microwave at 150 °C for 60 minutes. The reaction solution was concentrated *in vacuo*. The residue was mixed with acetic acid (0.5 mL) and methyl 2-(aminomethyl)-5-methylbenzofuran-7-carboxylate, TFA salt (50 mg, 0.150 mmol) and heated at 120 °C in the microwave for 30 minutes. The reaction mixture was concentrated *in vacuo*. The crude material was purified *via* preparative HPLC (Method C), to afford the product (25 mg, 45% yield) as a solid. ¹H NMR (400 MHz, Chloroform-d) δ 9.64 (s, 1H), 8.74 (d, *J* = 5.4 Hz, 1H), 7.77 (s, 1H), 7.60 (d, *J* = 7.3 Hz, 1H), 7.56 - 7.51 (m, 1H), 7.41 - 7.30 (m, 1H), 6.79 (s, 1H), 6.52 (d, *J* = 7.5 Hz, 1H), 5.39 (s, 2H), 3.99 (s, 3H), 2.46 (s, 3H); MS (ESI+) m/z = 349.0 (M+H)⁺.

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EXAMPLE 86

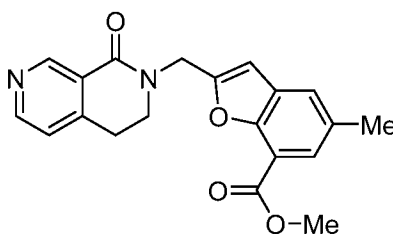


Methyl 5-methyl-2-((4-oxopyrido[4,3-*d*]pyrimidin-3(4H)-yl)methyl)benzofuran-7-carboxylate

4-Aminonicotinic acid (40 mg, 0.290 mmol) and *N,N*-dimethylformamide dimethyl acetal (0.116 mL, 0.869 mmol) were taken up in DMF (1 mL) in a 0.5-2 mL

microwave vial. The vial was sealed and heated to 100 °C for 15 minutes in a microwave reactor. After 15 minutes, the reaction mixture was cooled and concentrated *in vacuo*. To this residue was added 1 mL of acetic acid and methyl 2-(aminomethyl)-5-methylbenzofuran-7-carboxylate (63.5 mg, 0.290 mmol, Step C in Example 85). The vial was sealed and heated to 120 °C for 15 min in a microwave reactor. The reaction mixture was again cooled and concentrated *in vacuo*. The residue was diluted with water and extracted with EtOAc. The combined organic extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was taken up in DMF and MeOH, filtered, and purified *via* HPLC (method B) to give the title compound (18 mg, 18% yield). ¹H NMR (500 MHz, DMSO-d₆) δ 9.35 (s, 1H), 8.89 (d, *J* = 5.8 Hz, 1H), 8.81 (s, 1H), 7.81 - 7.50 (m, 3H), 6.95 (s, 1H), 5.47 (s, 2H), 3.87 (s, 3H), 2.42 (s, 3H); MS (ESI+) *m/z* = 350.0 (M+H)⁺.

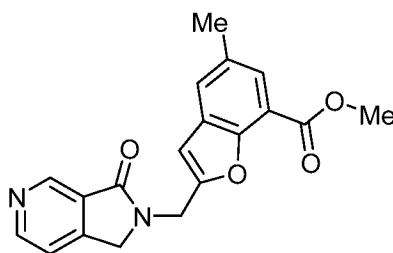
EXAMPLE 87



Methyl 5-methyl-2-((1-oxo-3,4-dihydro-2,7-naphthyridin-2(1H)-yl)methyl)benzofuran-7-carboxylate

3,4-Dihydro-1*H*-pyrano[3,4-*c*]pyridin-1-one (15 mg, 0.101 mmol) (WO 2005063768) and methyl 2-(aminomethyl)-5-methylbenzofuran-7-carboxylate (26.5 mg, 0.121 mmol, Step C of Example 85) were added to a pressure relief vial and heated neat at 120 °C. After 4 hours, the reaction was cooled, diluted with 2 mL DMF, filtered, and purified *via* HPLC (Method B) to give methyl 5-methyl-2-((1-oxo-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)methyl)benzofuran-7-carboxylate (9.0 mg, 0.025 mmol, 25.0 % yield). ¹H NMR (500 MHz, DMSO-d₆) δ 8.96 (s, 1H), 8.62 (d, *J* = 4.9 Hz, 1H), 7.65 (s, 1H), 7.63 (s, 1H), 7.37 (d, *J* = 4.9 Hz, 1H), 6.88 (s, 1H), 4.91 (s, 2H), 3.86 (s, 3H), 3.74 (t, *J* = 6.6 Hz, 2H), 3.08 (br t, *J* = 6.4 Hz, 2H), 2.41 (s, 3H); MS (ESI+) *m/z* 351.1 (M+H)⁺.

EXAMPLE 88



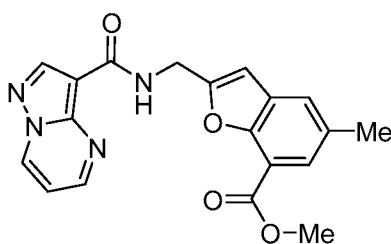
Methyl 5-methyl-2-((3-oxo-1,3-dihydro-2H-pyrrolo[3,4-c]pyridin-2-yl)methyl)benzofuran-7-carboxylate

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Methyl 2-(aminomethyl)-5-methylbenzofuran-7-carboxylate (34.3 mg, 0.156 mmol, Step C in Example 85) was taken up in THF (1 mL). TEA (0.109 mL, 0.782 mmol) was added followed by the addition of a solution of crude methyl 4-(bromomethyl)nicotinate (120 mg, 0.078 mmol, as prepared in Example 2) in THF (1 mL). The reaction mixture was stirred at room temperature for 1 hour, then heated at 70 °C for 16 hours. The reaction mixture was then concentrated *in vacuo*. The crude residue was dissolved in MeOH, filtered, and purified *via* HPLC (method B) to give the title compound (3.5 mg, 13% yield). ¹H NMR (500 MHz, DMSO-d₆) δ 9.30 - 8.74 (m, 2H), 7.80 - 7.72 (m, 1H), 7.69 (s, 1H), 7.67 - 7.64 (m, 1H), 6.92 (s, 1H), 4.97 (s, 2H), 4.68 (s, 2H), 3.89 - 3.85 (m, 3H), 2.43 (s, 3H); MS (ESI⁺) m/z 337.1 (M+H)⁺.

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EXAMPLE 89



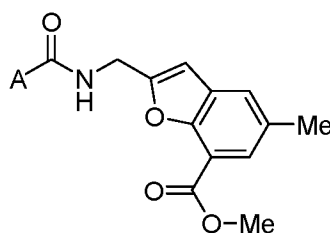
Methyl 5-methyl-2-((pyrazolo[1,5-a]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate

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To a suspension of pyrazole[1,5-a]pyrimidine-3-carboxylic acid (20 mg, 0.123

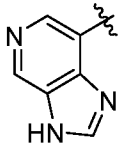
mmol) and BOP (41.7 mg, 0.094 mmol) in DMF (2 mL) was added methyl 2-(aminomethyl)-5-methylbenzofuran-7-carboxylate, TFA salt (31.4 mg, 0.094 mmol, Step C of Example 85) and DIPEA (0.066 mL, 0.377 mmol). The reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was quenched with water, extracted with DCM, dried with anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified *via* preparative HPLC (Method C) to give the title compound as a solid (21 mg, 58 % yield). ¹H NMR (400 MHz, Methanol-d₄) δ 9.09 (dd, *J* = 7.0, 1.7 Hz, 1H), 8.80 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.62 (s, 1H), 7.71 (d, *J* = 1.2 Hz, 1H), 7.65 - 7.56 (m, 1H), 7.22 (dd, *J* = 7.0, 4.2 Hz, 1H), 6.75 (s, 1H), 4.87 (br m, 2H), 3.97 (s, 3H), 2.45 (s, 3H); MS (ESI+) *m/z* = 365 (M+H)⁺.

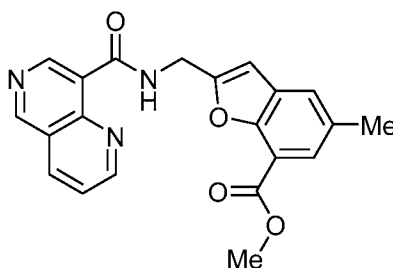
EXAMPLE 90-91



Example 90-91 were prepared according to the procedure described for the synthesis of Example 89 from the benzofuran intermediate synthesized in Step C in Example 85 and a carboxylic acid.

Ex. No.	A	Name	¹ H NMR	LC/MS [M+H] ⁺
90		Methyl 5-methyl-2-((6-methyl pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.10 (s, 1H), 8.72 (s, 1H), 8.53 (s, 1H), 8.41 (br t, <i>J</i> = 5.6 Hz, 2H), 7.63 (br d, <i>J</i> = 9.3 Hz, 2H), 6.77 (s, 1H), 4.78 (br d, <i>J</i> = 5.8 Hz, 2H), 3.92 - 3.87 (m, 3H), 2.41 (s, 3H), 2.39 (m, 3H)	379.2

Ex. No.	A	Name	¹ H NMR	LC/MS [M+H] ⁺
91		Methyl 2-((3 <i>H</i> -imidazo[4,5- <i>c</i>]pyridine-7-carboxamido)methyl)-5-methylbenzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.74 (br s, 1H), 9.09 (s, 1H), 8.91 (s, 1H), 8.56 (br s, 1H), 7.67 (s, 1H), 7.64 (s, 1H), 6.84 (s, 1H), 4.83 (br d, <i>J</i> = 4.3 Hz, 2H), 3.88 (s, 3H), 2.42 (s, 3H)	364.9

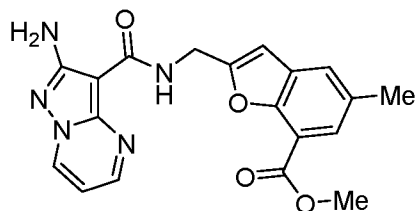
EXAMPLE 92

methyl 2-((1,6-naphthyridine-8-carboxamido)methyl)-5-methylbenzofuran-7-carboxylate

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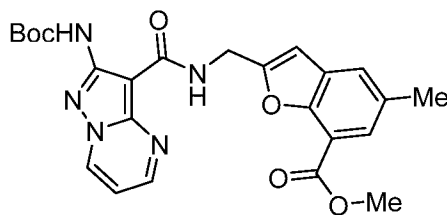
A mixture of 1,6-naphthyridine-8-carboxylic acid, HCl (10 mg, 0.047 mmol), methyl 2-(aminomethyl)-5-methylbenzofuran-7-carboxylate, TFA (15.82 mg, 0.047 mmol, Step C of Example 85), HATU (18.05 mg, 0.047 mmol) and Hunig's Base (0.033 mL, 0.190 mmol) in DMF (0.5 mL) was stirred at rt for 48 h. The reaction was quenched with 1:1 DMF/AcOH and purified by preparative LC/MS (Method B) to give the title compound (2.5 mg, 6.66 μmol, 14.03 % yield). ¹H NMR (500 MHz, DMSO-*d*₆) δ 10.95 (br s, 1H), 9.59 (s, 1H), 9.36 (s, 1H), 9.29 (br s, 1H), 8.78 (br d, *J*=7.9 Hz, 1H), 7.86 (br dd, *J*=8.1, 4.4 Hz, 1H), 7.66 (s, 1H), 7.64 - 7.60 (m, 1H), 6.87 (s, 1H), 4.88 (br d, *J*=5.5 Hz, 2H), 3.88 (s, 3H), 2.41 (s, 3H); MS (ESI⁺) *m/z* = 376.0 (M+H)⁺.

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EXAMPLE 93

166

Methyl 2-((2-aminopyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)-5-methylbenzofuran-7-carboxylate



5 **A) Methyl 2-((2-((*tert*-butoxycarbonyl)amino)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)-5-methylbenzofuran-7-carboxylate**

To a solution of 2-((*tert*-butoxycarbonyl)amino)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (75 mg, 0.270 mmol, Step C of Example 63) and methyl 2-(aminomethyl)-5-methylbenzofuran-7-carboxylate, TFA (90 mg, 0.270 mmol, Step A of Example 85) in DMF (5 mL) were added BOP (179 mg, 0.404 mmol) and DIPEA (0.141 mL, 0.809 mmol). The reaction mixture was stirred at RT for 16 hours. The sample was quenched with water, the resulting product precipitate was filtered. The crude product was purified via preparative HPLC (Method C) to yield methyl 2-((2-((*tert*-butoxycarbonyl)amino)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)-5-methylbenzofuran-7-carboxylate (55 mg, 42.4 % yield). ¹H NMR (400 MHz, Chloroform-*d*) δ 9.84 - 9.70 (m, 1H), 8.87 - 8.80 (m, 1H), 8.61 - 8.57 (m, 1H), 8.48 - 8.40 (m, 1H), 7.75 (d, *J* = 1.3 Hz, 1H), 7.57 - 7.48 (m, 1H), 6.98 - 6.88 (m, 1H), 6.72 - 6.67 (m, 1H), 4.93 - 4.80 (m, 2H), 4.05 - 3.96 (m, 3H), 2.45 (s, 3H), 1.63 - 1.53 (m, 9H); MS (ESI+) *m/z* = 480 (M+H)⁺.

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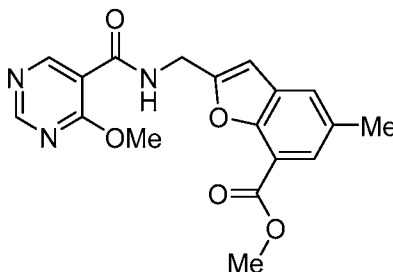
B) Methyl 2-((2-aminopyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)-5-methylbenzofuran-7-carboxylate

In a vial was added methyl 2-((2-((*tert*-butoxycarbonyl)amino)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)-5-methylbenzofuran-7-carboxylate (10 mg, 0.208 mmol) DCM (5 mL) and TFA (0.5 mL). The reaction solution was stirred at room temperature for 2 hours. The solution was concentrated in vacuo and purified via

25

preparative HPLC (Method C) to yield the title compound (6 mg, 75 % yield). ¹H NMR (400 MHz, Chloroform-d) δ 8.50 - 8.44 (m, 1H), 8.44 - 8.37 (m, 1H), 8.32 - 8.22 (m, 1H), 7.77 - 7.72 (m, 1H), 7.53 - 7.48 (m, 1H), 6.84 - 6.76 (m, 1H), 6.71 - 6.65 (m, 1H), 5.78 - 5.65 (m, 2H), 4.95 - 4.86 (m, 2H), 4.04 - 3.97 (m, 3H), 2.46 (s, 3H); MS (ESI+) m/z = 380 (M+H)⁺.

EXAMPLE 94



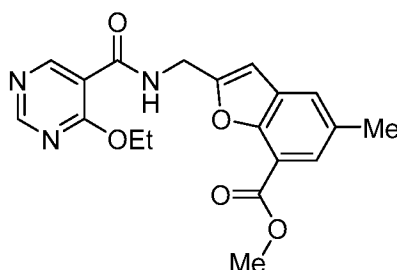
Methyl 2-((4-methoxypyrimidine-5-carboxamido)methyl)-5-methylbenzofuran-7-carboxylate

10

A mixture of methyl 2-(aminomethyl)-5-methylbenzofuran-7-carboxylate, TFA (47.6 mg, 0.143 mmol, Step C of Example 85), 4-methoxypyrimidine-5-carboxylic acid (20 mg, 0.130 mmol), HATU (54.3 mg, 0.143 mmol) and Hunig's base (0.091 mL, 0.519 mmol) in DMF (1 mL) was stirred at room temperature for 1 hour. The reaction mixture was quenched with 1:1 DMF/AcOH and purified by preparative HPLC (Method B). The appropriate fractions were combined and dried *via* centrifugal evaporation to afford the title compound (5.1 mg, 10.93 % yield). ¹H NMR (500 MHz, DMSO-d₆) δ 8.86 (br d, *J* = 16.3 Hz, 3H), 7.64 (d, *J* = 16.2 Hz, 2H), 6.77 (s, 1H), 4.68 (d, *J* = 5.7 Hz, 2H), 4.07 (s, 3H), 3.90 (s, 3H), 2.41 (s, 3H); MS (ESI+) m/z = 356.1 (M+H)⁺.

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EXAMPLE 95



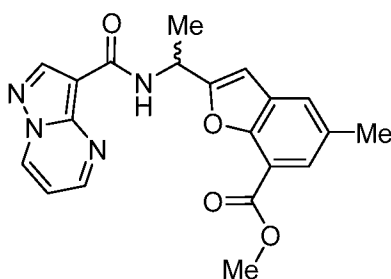
5 **Methyl 2-((4-ethoxypyrimidine-5-carboxamido)methyl)-5-methylbenzofuran-7-carboxylate**

A mixture of methyl 2-(aminomethyl)-5-methylbenzofuran-7-carboxylate, TFA (21.80 mg, 0.065 mmol, Step C of Example 85), 4-ethoxypyrimidine-5-carboxylic acid (10 mg, 0.059 mmol), HATU (24.9 mg, 0.065 mmol) and Hunig's base (0.042 mL, 0.238 mmol) in DMF (1 mL) was stirred at room temperature for 1 hour. The reaction mixture was quenched with 1:1 DMF/AcOH and purified by preparative HPLC (Method B). The appropriate fractions were combined and dried *via* centrifugal evaporation to afford the title compound (0.7 mg, 3.06 % yield). ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.85 (d, *J* = 14.8 Hz, 3H), 7.65 (br d, *J* = 12.5 Hz, 2H), 6.81 (s, 1H), 4.70 (d, *J* = 5.7 Hz, 2H), 4.55 (q, *J* = 7.0 Hz, 2H), 3.91 (s, 3H), 1.72 (br s, 3H), 1.38 (t, *J* = 7.0 Hz, 3H); MS (ESI+) *m/z* = 370.2 (M+H)⁺.

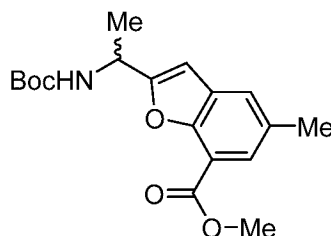
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EXAMPLE 96

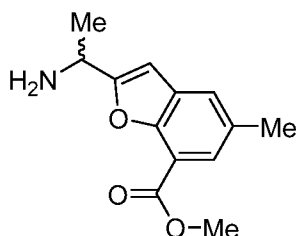


20 **Methyl 5-methyl-2-(1-(pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)ethyl)benzofuran-7-carboxylate (racemic)**



A) Methyl 2-(1-((*tert*-butoxycarbonyl)amino)ethyl)-5-methylbenzofuran-7-carboxylate

The reaction mixture of methyl 2-hydroxy-3-iodo-5-methylbenzoate (1.0 g, 3.42 mmol, Step A in Example 85), *tert*-butyl but-3-yn-2-ylcarbamate (0.66 g, 3.94 mmol, Step B in Example 45), TEA (7.16 mL, 51.4 mmol), and copper(I) iodide (0.065 g, 0.342 mmol) in DMF (8 mL) was purged with a nitrogen stream for 5 mins, then bis(triphenylphosphine)palladium(II) chloride (0.120 g, 0.171 mmol) was added. The resulting mixture was heated at 80 °C for 2 hours. After cooling to RT, the reaction mixture was diluted with ethyl acetate, washed with saturated aqueous sodium bicarbonate solution followed by saturated aqueous sodium chloride solution, dried with anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude product mixture was purified by a silica gel ISCO column eluting with 0-25% ethyl acetate in hexanes over a 15 minute gradient. The appropriate fractions were isolated and concentrated *in vacuo* to afford the product (0.804 g, 70 % yield) as a solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.78 - 7.67 (m, 1H), 7.56 - 7.47 (m, 1H), 6.66 - 6.37 (m, 1H), 5.16 - 4.98 (m, 1H), 4.07 - 3.87 (m, 3H), 2.55 - 2.36 (m, 3H), 1.66 - 1.54 (m, 3H), 1.54 - 1.40 (m, 9H); MS (ESI+) *m/z* = 278.1 (M-55+H)⁺.



B) Methyl 2-(1-aminoethyl)-5-methylbenzofuran-7-carboxylate

A vial was charged methyl 2-(((*tert*-butoxycarbonyl)amino)methyl)-3-chlorobenzofuran-7-carboxylate (0.4 g, 1.2 mmol), DCM (20 mL) and TFA (2 mL). The reaction solution was stirred at room temperature for 2 hours. The reaction mixture was

concentrated *in vacuo* to afford methyl 2-(1-aminoethyl)-5-methylbenzofuran-7-carboxylate as a TFA salt (0.4 g, 96% yield) as a solid. ¹H NMR (400 MHz, Chloroform-d) δ 7.86 - 7.61 (m, 1H), 7.54 (d, *J* = 0.8 Hz, 1H), 6.75 (s, 1H), 4.84 - 4.67 (m, 1H), 3.90 (s, 3H), 2.52 - 2.41 (m, 3H), 1.84 - 1.73 (m, 3H); MS (ESI+) *m/z* = 217.1 (M-16)⁺.

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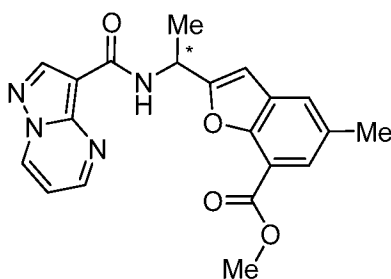
C) Methyl 5-methyl-2-(1-(pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)ethyl)benzofuran-7-carboxylate

To a solution of pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (188 mg, 1.152 mmol) and BOP (764 mg, 1.728 mmol) in DMF (10 mL), was added methyl 2-(1-aminoethyl)-5-methylbenzofuran-7-carboxylate TFA salt (0.4 g, 1.15 mmol) and DIPEA (0.805 mL, 4.61 mmol) The reaction mixture was stirred at room temperature for 16 hours. The solution was diluted with ethyl acetate, and washed with saturated sodium bicarbonate, water and saturated sodium chloride. The organic layer was dried with anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product mixture was purified by a silica gel ISCO 24 g column eluting with 0-10% methanol in DCM over a 15 minute gradient. The appropriate fractions were isolated and concentrated *in vacuo* to afford the product (450 mg, 103% yield, 90% pure). A portion of the product mixture (70 mg) was purified *via* preparative HPLC (Method A) to afford the racemate product as a TFA salt (25 mg, 67 % yield). ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.27 (br d, *J* = 6.6 Hz, 1H), 8.82 (br d, *J* = 3.3 Hz, 1H), 8.61 (s, 1H), 8.33 (br d, *J* = 8.2 Hz, 1H), 7.66 (s, 1H), 7.63 (s, 1H), 7.27 (dd, *J* = 6.6, 4.3 Hz, 1H), 6.83 (s, 1H), 5.53 - 5.45 (m, 1H), 3.87 (s, 3H), 2.42 (s, 3H), 1.66 (d, *J* = 6.9 Hz, 3H); MS (ESI+) *m/z* = 379.0 (M+H)⁺.

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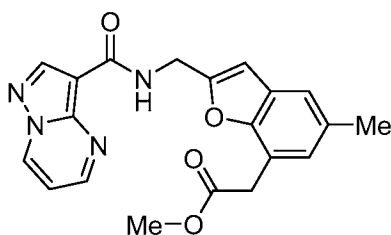
EXAMPLE 97



Methyl-5-methyl-2-(1-(pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)ethyl)benzofuran-7-carboxylate

The racemic mixture of methyl 5-methyl-2-(1-(pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)ethyl)benzofuran-7-carboxylate (25 mg, 0.066 mmol, Example 96) was separated into the two enantiomers using chiral SFC (Method K) to give the first eluting enantiomer as the title compound (9.8 mg, 39 %) (white solid). ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.29 (br d, *J* = 6.7 Hz, 1H), 8.85 - 8.80 (m, 1H), 8.63 (s, 1H), 8.37 (br d, *J* = 8.2 Hz, 1H), 7.68 - 7.65 (m, 1H), 7.63 (s, 1H), 7.30 - 7.25 (m, 1H), 6.84 (s, 1H), 5.52 - 5.43 (m, 1H), 3.86 (s, 3H), 2.41 (s, 3H), 1.65 (br d, *J* = 6.7 Hz, 3H); MS (ESI+) *m/z* = 379.2 (M+H)⁺; Chiral purity > 95% ee.

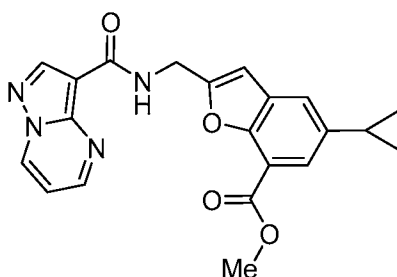
EXAMPLE 98



Methyl 2-(5-methyl-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-yl)acetate

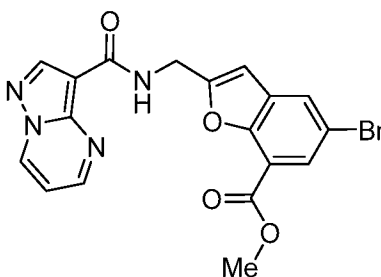
To a solution of methyl 2-(5-bromo-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-yl)acetate (20 mg, 0.045 mmol, Example 84) in dioxane (4 mL) and water (0.4 mL) was added methylboronic acid (5.4 mg, 0.09 mmol), K₂CO₃ (18.7 mg, 0.135 mmol) and PdCl₂(dppf)-CH₂Cl₂ (3.7 mg, 4.51 μmol). The reaction mixture was degassed by bubbling argon through it and heated at 80 °C for 6 hours. The reaction mixture was concentrated. The residue was purified with prep HPLC, Method B, to give the desired product (2.6 mg, 15% yield). ¹H NMR (400 MHz, Chloroform-*d*) δ 8.84 - 8.75 (m, 1H), 8.66 - 8.57 (m, 2H), 8.42 (br s, 1H), 7.15 (s, 1H), 7.06 - 6.97 (m, 1H), 6.90 (s, 1H), 6.56 (s, 1H), 4.76 (br d, *J* = 5.6 Hz, 2H), 3.82 (s, 2H), 3.62 (s, 3H), 2.33 (s, 3H); MS (ESI+) *m/z* = 379.2 (M+H)⁺.

EXAMPLE 99



Methyl 5-cyclopropyl-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate

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A) Methyl 5-bromo-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate

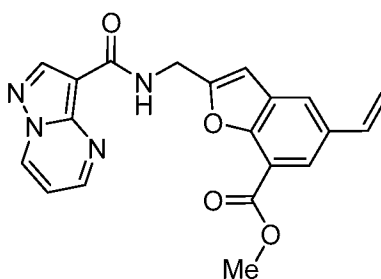
To a solution of methyl 2-(aminomethyl)-5-bromobenzofuran-7-carboxylate,
 10 TFA (1.3 g, 2.29 mmol, Step C of Example 80) and pyrazolo[1,5-*a*]pyrimidine-3-
 carboxylic acid (0.373 g, 2.29 mmol) in DMF (2 mL) was added BOP (1.52 g, 3.43
 mmol) and DIPEA (1.6 mL, 9.14 mmol). The reaction mixture was stirred at room
 temperature for 16 hours. The solution was diluted with ethyl acetate and washed with
 saturated sodium bicarbonate, water, and saturated sodium chloride, dried with anhydrous
 15 sodium sulfate and concentrated *in vacuo*. The crude product mixture was purified by a
 silica gel ISCO 80 g column eluting with 0-10% methanol in DCM over a 15 minute
 gradient. The appropriate fractions were isolated and concentrated *in vacuo* to afford the
 product as a solid (0.38 g, 38.7 % yield). ¹H NMR (400 MHz, Chloroform-*d*) δ 8.85 -
 8.80 (m, 1H), 8.73 (s, 1H), 8.70 - 8.66 (m, 1H), 8.54 - 8.45 (m, 1H), 8.05 - 7.99 (m, 1H),
 20 7.86 - 7.81 (m, 1H), 7.05 (dd, *J* = 7.0, 4.2 Hz, 1H), 6.76 - 6.70 (m, 1H), 4.94 (dd, *J* = 6.0,

0.7 Hz, 2H), 4.02 (s, 3H); MS (ESI+) $m/z = 431.1$ (M+H)⁺.

B) Methyl 5-cyclopropyl-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate

5 A vial was charged with methyl 5-bromo-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate (45 mg, 0.105 mmol), 2-cyclopropyl-6-methyl-1,2,6,2-dioxazaborocane-4,8-dione (41.3 mg, 0.210 mmol), potassium phosphate tribasic (0.140 mL, 0.419 mmol, 3M aqueous solution), and 1,1'-bis(diphenylphosphino)ferrocene-palladium (II) dichloride dichloromethane (17.12 mg, 10 0.021 mmol) in toluene (2 mL). The solution was degassed and heated to 90°C for 16 hours. The solution was diluted with ethyl acetate and washed with saturated sodium bicarbonate, water, and saturated sodium chloride, dried with anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude material was purified via preparative HPLC (Method A) to afford the product as a TFA salt (1.5 mg, 3% yield). 1H NMR (500 15 MHz, DMSO-*d*₆) δ 9.16 - 9.10 (m, 1H), 8.81 - 8.76 (m, 1H), 8.64 (br t, *J* = 5.8 Hz, 1H), 8.58 (s, 1H), 7.52 (s, 1H), 7.51 - 7.46 (m, 1H), 7.24 (dd, *J* = 6.9, 4.4 Hz, 1H), 6.77 (s, 1H), 4.74 (br d, *J* = 5.8 Hz, 2H), 3.84 (s, 3H), 2.14 - 1.90 (m, 1H), 1.06 - 0.86 (m, 2H), 0.70 - 0.53 (m, 2H); MS (ESI+) $m/z = 391.3$ (M+H)⁺.

EXAMPLE 100

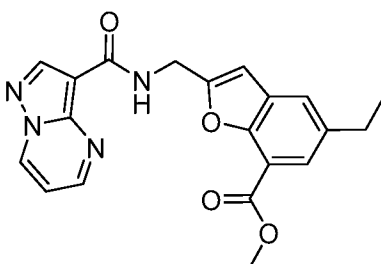


Methyl 2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)-5-vinylbenzofuran-7-carboxylate

The reaction mixture of methyl 5-fluoro-2-hydroxy-3-iodobenzoate (1.539 g, 5.20 mmol), tert-butyl (S)-but-3-yn-2-ylcarbamate (0.8 g, 4.73 mmol), TEA (9.88 mL, 70.9 25 mmol), copper(I) iodide (0.090 g, 0.473 mmol) in DMF (8 mL) was purged with nitrogen

stream for 5 mins, then bis(triphenylphosphine)palladium(II) chloride (0.166 g, 0.236 mmol) was added. The resulting mixture was heated at 80 °C for 4 h. The reaction mixture was cooled down and diluted with ethyl acetate and saturated aqueous NaHCO₃ solution. The organic layer was separated, washed with brine, dried over MgSO₄, and filtered. The filtrate was concentrated *in vacuo*. The residue was dissolved in DCM and purified by flash chromatography (ISCO column 40 g, 0 - 20% ethyl acetate in hexanes) to give the title compound (1.25g g, 78%) as light yellow oil. ¹H NMR (400 MHz, Chloroform-d) δ 7.63 (dd, J=9.6, 2.7 Hz, 2H), 7.40 (dd, J=7.9, 2.7 Hz, 1H), 6.61 (s, 1H), 5.17 - 4.89 (m, 2H), 4.02 - 3.98 (m, 3H), 1.61 (br d, J=6.9 Hz, 3H), 1.48 (s, 9H); MS (ESI+) m/z = 282.0 (M-55+H)+.

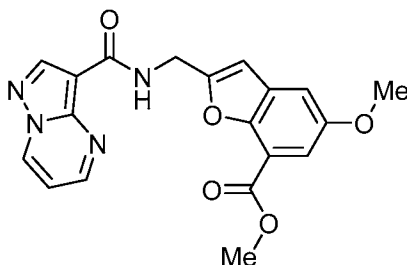
EXAMPLE 101



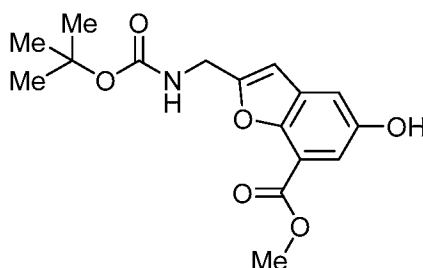
Methyl 5-ethyl-2-((pyrazolo[1,5-a]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate

A flask was charged with methyl 2-((pyrazolo[1,5-a]pyrimidine-3-carboxamido)methyl)-5-vinylbenzofuran-7-carboxylate (50 mg, 0.133 mmol, Example 100), ethyl acetate (5 mL), Pd/C (2.83 mg, 0.027 mmol). The reaction was purged with nitrogen, and then charged with hydrogen (balloon) for 3 hours. The solution was flushed with nitrogen, filtered through celite and concentrated *in vacuo*. The crude material was purified via preparative HPLC (Method B) to yield the title compound (4.2 mg, 8.4 % yield). ¹H NMR (500 MHz, DMSO-d₆) δ 9.28 (br d, J = 6.7 Hz, 1H), 8.82 (br d, J = 3.4 Hz, 1H), 8.62 (s, 1H), 8.52 (br t, J = 5.6 Hz, 1H), 7.68 (s, 1H), 7.66 - 7.62 (m, 1H), 7.27 (dd, J = 6.7, 4.3 Hz, 1H), 6.80 (s, 1H), 4.78 (br d, J = 5.8 Hz, 2H), 3.88 (s, 2H), 2.71 (q, J = 7.3 Hz, 2H), 1.20 (t, J = 7.5 Hz, 3H); MS (ESI+) m/z = 379.2 (M+H)+.

EXAMPLE 102



Methyl 5-methoxy-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate



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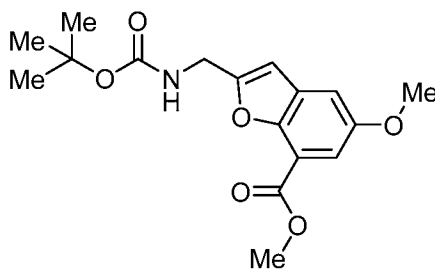
A) Methyl 2-(((*tert*-butoxycarbonyl)amino)methyl)-5-hydroxybenzofuran-7-carboxylate

A mixture of methyl 5-bromo-2-(((*tert*-butoxycarbonyl)amino)methyl)benzofuran-7-carboxylate (1.05 g, 2.73 mmol, Step B of Example 80), potassium acetate (0.54 g, 5.47 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (2.08 g, 8.20 mmol) in 1,4-dioxane (25 mL) was purged with nitrogen for 5 min. X-PHOS (0.13 g, 0.27 mmol) and Pd₂(dba)₃ (0.125 g, 0.137 mmol) were then added. The reaction mixture was heated at 90 °C for 20 hours. The reaction mixture was cooled down and diluted with ethyl acetate and saturated aqueous NaHCO₃ solution. The organic layer was separated, washed with brine, dried over MgSO₄, and filtered. The filtrate was concentrated *in vacuo*. To the residue was added THF (20 mL), water (8 mL), and sodium perborate tetrahydrate (1.26 g, 8.20 mmol). The resulting mixture was stirred at room temperature overnight. To the reaction mixture was added water and 1 N aqueous HCl solution and ethyl acetate. The organic layer was separated, washed with brine, dried over MgSO₄, and filtered. The filtrate was concentrated *in vacuo*. The residue was dissolved in DCM and purified by flash chromatography (ISCO 80g column, 0 - 40% ethyl acetate in hexanes) to give the title compound (0.88 g, 99% yield) as a viscous solid. ¹H NMR (400

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MHz, Chloroform-d) δ 7.43 (d, $J = 2.6$ Hz, 1H), 7.17 (d, $J = 2.6$ Hz, 1H), 6.57 (s, 1H), 5.28 - 5.06 (m, 1H), 4.50 (br d, $J = 5.9$ Hz, 2H), 4.01 (s, 3H), 1.49 (s, 9H); MS (ESI+) $m/z = 266.1$ (M-55+H)⁺.

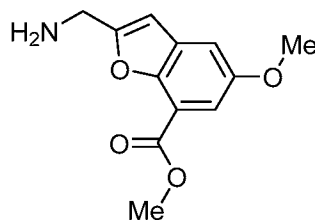


5

B) Methyl 2-(((tert-butoxycarbonyl)amino)methyl)-5-methoxybenzofuran-7-carboxylate

To a solution of methyl 2-(((tert-butoxycarbonyl)amino)methyl)-5-hydroxybenzofuran-7-carboxylate (0.4 g, 1.25 mmol) in DMF (8 mL) was added K₂CO₃ (0.43 g, 3.11 mmol) and methyl iodide (0.09 mL, 1.49 mmol). The reaction mixture was stirred at room temperature for 4 hours. The reaction mixture was diluted with ethyl acetate and saturated aqueous NaHCO₃ solution. The organic layer was separated, washed with brine, dried over MgSO₄, and filtered. The filtrate was concentrated *in vacuo* to give the crude title compound (0.41 g, 98%) as a white solid. ¹H NMR (400 MHz, Chloroform-d) δ 7.51 (d, $J = 2.7$ Hz, 1H), 7.23 (d, $J = 2.7$ Hz, 1H), 6.61 (s, 1H), 5.10 (br s, 1H), 4.50 (br d, $J = 5.9$ Hz, 2H), 4.01 (s, 3H), 3.89 (s, 3H), 1.49 (s, 9H); MS (ESI+) $m/z = 280.2$ (M-55+H)⁺.

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C) Methyl 2-(aminomethyl)-5-methoxybenzofuran-7-carboxylate

To a solution of methyl 2-(((tert-butoxycarbonyl)amino)methyl)-5-methoxybenzofuran-7-carboxylate (0.41 g, 1.223 mmol) in DCM (8 mL) was added TFA (0.94 mL, 12.23 mmol). The reaction mixture was stirred at room temperature for 2 hours.

The reaction mixture was concentrated *in vacuo* to give the title compound (0.42 g, 93%, TFA salt) as a light brown solid. $^1\text{H NMR}$ (400 MHz, Methanol- d_4) δ 7.56 (d, $J = 2.6$ Hz, 1H), 7.46 (d, $J = 2.6$ Hz, 1H), 7.02 (s, 1H), 4.39 (s, 2H), 4.01 (s, 3H), 3.89 (s, 3H); MS (ESI+) $m/z = 219.1$ (M-16+H) $^+$.

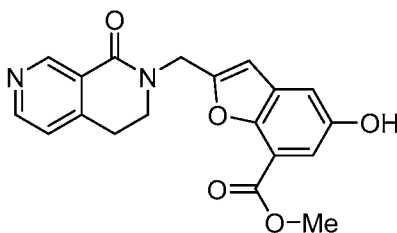
5

D) Methyl 5-methoxy-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate

To a suspension of pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (15.2 mg, 0.093 mmol) and BOP (31.7 mg, 0.072 mmol) in DMF (2 mL) was added methyl 2-(aminomethyl)-5-methoxybenzofuran-7-carboxylate, TFA (25 mg, 0.072 mmol) and DIPEA (0.05 mL, 0.29 mmol). The reaction mixture turned into a clear solution and was stirred at room temperature for 1 hour. The reaction mixture was diluted with ethyl acetate and saturated aqueous NaHCO_3 solution. The organic layer was separated, washed with brine, dried over MgSO_4 , and filtered. The filtrate was concentrated *in vacuo*. The residue was dissolved in DMF, filtered and purified by preparative HPLC (Method B). Fractions containing the desired product were combined and dried *via* centrifugal evaporation to give the title compound (17.6 mg, 65%). $^1\text{H NMR}$ (500 MHz, DMSO- d_6) δ 9.31 (br d, $J = 6.1$ Hz, 1H), 8.84 (br d, $J = 2.7$ Hz, 1H), 8.64 (s, 1H), 8.53 (br t, $J = 5.8$ Hz, 1H), 7.43 (d, $J = 2.4$ Hz, 1H), 7.33 (d, $J = 2.4$ Hz, 1H), 7.29 (dd, $J = 6.9, 4.1$ Hz, 1H), 6.80 (s, 1H), 4.78 (br d, $J = 5.8$ Hz, 2H), 3.90 (s, 3H), 3.81 (s, 3H); MS (ESI+) $m/z = 381.1$ (M+H) $^+$.

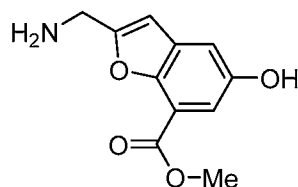
20

EXAMPLE 103



25

Methyl 5-hydroxy-2-((1-oxo-3,4-dihydro-2,7-naphthyridin-2(1H)-yl)methyl)benzofuran-7-carboxylate



A) Methyl 2-(aminomethyl)-5-hydroxybenzofuran-7-carboxylate

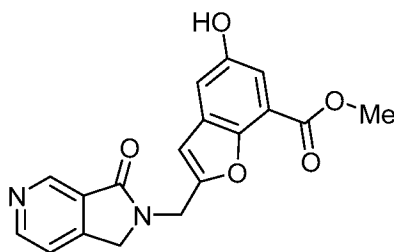
To a solution of methyl 2-(((*tert*-butoxycarbonyl)amino)methyl)-5-hydroxybenzofuran-7-carboxylate (0.5 g, 1.556 mmol, Step A of Example 102) in DCM (8 mL) was added TFA (3 mL, 39 mmol). The reaction mixture was stirred at room temperature for 3 hours. The reaction mixture was then concentrated *in vacuo*. The residue was mixed with ethyl acetate and extracted with saturated aqueous NaHCO₃ solution. The organic layer was separated, washed with brine, dried over MgSO₄, and filtered. The filtrate was concentrated *in vacuo* to give methyl 2-(aminomethyl)-5-hydroxybenzofuran-7-carboxylate (0.20 g, 58% yield) as a light yellow solid. ¹H NMR (400 MHz, Methanol-d₄) δ 7.33 (d, *J* = 2.4 Hz, 1H), 7.16 (d, *J* = 2.6 Hz, 1H), 6.64 (s, 1H), 3.98 (s, 2H), 3.96 (s, 3H); MS (ESI+) *m/z* = 443.1 (2M+H)⁺.

B) Methyl 5-hydroxy-2-((1-oxo-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)methyl)benzofuran-7-carboxylate

3,4-Dihydro-1*H*-pyrano[3,4-*c*]pyridin-1-one (15 mg, 0.101 mmol) (WO 2005063768) and methyl 2-(aminomethyl)-5-hydroxybenzofuran-7-carboxylate (27 mg, 0.12 mmol) were added to a pressure relief vial and heated neat at 120 °C. After heating for 4 hours, the reaction was cooled, then diluted with 2 mL DMF, filtered and purified *via* HPLC (Method B) to give methyl 5-hydroxy-2-((1-oxo-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)methyl)benzofuran-7-carboxylate (10 mg, 0.028 mmol, 27.9 % yield). ¹H NMR (500 MHz, DMSO-d₆) δ 8.96 (s, 1H), 8.62 (br d, *J* = 4.9 Hz, 1H), 7.37 (d, *J* = 4.9 Hz, 1H), 7.24 (d, *J* = 2.4 Hz, 1H), 7.18 (d, *J* = 2.4 Hz, 1H), 6.80 (s, 1H), 4.87 (s, 2H), 3.84 (s, 3H), 3.73 (t, *J* = 6.6 Hz, 2H), 3.08 (br t, *J* = 6.6 Hz, 2H); MS (ESI+) *m/z* = 353.0 (M+H)⁺.

25

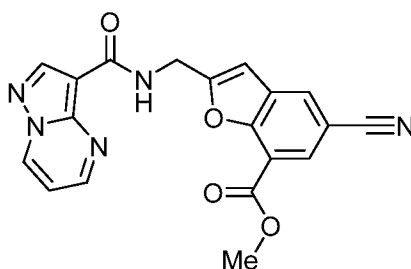
EXAMPLE 104



Methyl 5-hydroxy-2-((3-oxo-1,3-dihydro-2H-pyrrolo[3,4-c]pyridin-2-yl)methyl)benzofuran-7-carboxylate

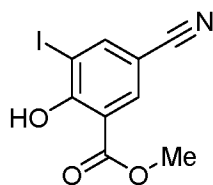
Ethyl 4-formylnicotinate (80 mg, 0.446 mmol) and methyl 2-(aminomethyl)-5-hydroxybenzofuran-7-carboxylate (104 mg, 0.469 mmol, Step A in Example 103) were taken up in THF (3 mL) was stirred at rt for 40 min. After 40 minutes, acetic acid (0.1 mL, 1.747 mmol) and sodium triacetoxyborohydride (142 mg, 0.670 mmol) were added. The resulting mixture was stirred at room temperature for 4 hours. After 4 hours, the reaction mixture was diluted with saturated NaHCO₃ solution and the mixture was stirred at rt for 5 min. The mixture was further diluted with water and extracted with ethyl acetate. The organics were separated and combined. The combined organics were washed with brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified *via* ISCO (12 g column, eluting with 0-10% MeOH in DCM) to give the title compound (46 mg, 30%). ¹H NMR (499 MHz, DMSO-d₆) δ 9.52 (s, 1H), 8.96 (d, *J* = 1.1 Hz, 1H), 8.78 (d, *J* = 5.0 Hz, 1H), 7.71 (dd, *J* = 5.1, 0.8 Hz, 1H), 7.27 (d, *J* = 2.6 Hz, 1H), 7.19 (d, *J* = 2.4 Hz, 1H), 6.83 (s, 1H), 4.93 (s, 2H), 4.67 (s, 2H), 3.86 (s, 3H); MS (ESI+) *m/z* = 339.1 (M+H)⁺.

EXAMPLE 105



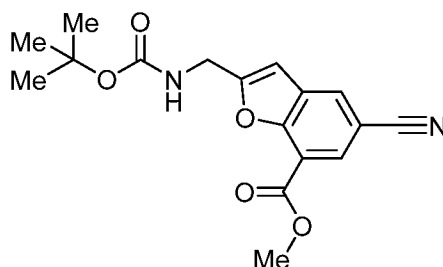
20

Methyl 5-cyano-2-((pyrazolo[1,5-a]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate



A) Methyl 5-cyano-2-hydroxy-3-iodobenzoate

To a solution of methyl 5-cyano-2-hydroxybenzoate (3.0 g, 16.9 mmol) in *N,N*-
 5 dimethylformamide (30 mL) was added sodium iodide (3.05 g, 20.3 mmol), followed by
 chloramine T trihydrate (5.25 g, 18.6 mmol) slowly. The resulting mixture was stirred at
 room temperature for 2 hours, then heated at 95 °C overnight. The reaction mixture was
 diluted with ethyl acetate and 1 N aqueous HCl solution. The organic layer was separated,
 washed with brine followed by Na₂S₂O₃ solution, dried over MgSO₄, and filtered. The
 10 filtrate was concentrated *in vacuo* to give a light yellow oil. To the residue was added
 MeOH and the solid was filtered to give the title compound as a white solid (2.1 g, 41%).
¹H NMR (400 MHz, CHLOROFORM-*d*) δ 12.19 (s, 1H), 8.22 - 8.14 (m, 2H), 4.05 (s,
 3H).

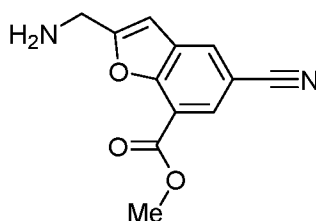


15

B) Methyl 2-(((*tert*-butoxycarbonyl)amino)methyl)-5-cyanobenzofuran-7-carboxylate

A mixture of methyl 5-cyano-2-hydroxy-3-iodobenzoate (2.1 g, 6.93 mmol), *tert*-
 20 butyl prop-2-yn-1-ylcarbamate (1.24 g, 7.97 mmol), TEA (11.6 mL, 83 mmol), and
 copper(I) iodide (0.132 g, 0.693 mmol) in DMF (15 mL) was purged with a nitrogen
 stream for 5 mins. Bis(triphenylphosphine)palladium(II) chloride (0.29 g, 0.416 mmol)
 was added and the resulting mixture was heated at 80 °C for 2 h. The reaction mixture
 was cooled down and diluted with ethyl acetate and saturated aqueous NaHCO₃ solution.

The organic layer was separated, washed with brine, dried over MgSO₄, and filtered. The filtrate was concentrated *in vacuo*. The residue was dissolved in DCM and purified by flash chromatography (ISCO 80g column, 0 - 40% ethyl acetate in hexanes) to give the title compound (1.8 g, 79 % yield) as a light brown solid. ¹H NMR (400 MHz, Chloroform-d) δ 8.21 (d, *J* = 1.6 Hz, 1H), 8.04 (d, *J* = 1.6 Hz, 1H), 7.29 (s, 1H), 6.76 (s, 1H), 4.56 (br d, *J* = 6.1 Hz, 2H), 4.05 (s, 3H), 1.49 (s, 9H); MS (ESI+) *m/z* = 275.2 (M-55+H)⁺.



10 **C) Methyl 2-(aminomethyl)-5-cyanobenzofuran-7-carboxylate**

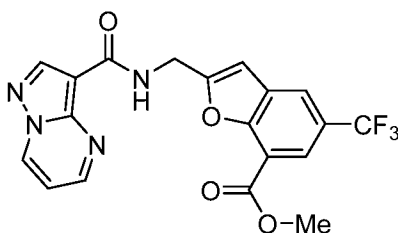
To a solution of methyl 2-(((*tert*-butoxycarbonyl)amino)methyl)-5-cyanobenzofuran-7-carboxylate (0.3 g, 0.91 mmol) in DCM (3 mL) was added TFA (1.05 mL, 13.6 mmol). The reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated *in vacuo* to give the title compound (0.3 g, 86% yield, TFA salt) as a light brown solid. MS (ESI+) *m/z* = 231.1 (M+H)⁺.

D) Methyl 5-cyano-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate

To a suspension of pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (14 mg, 0.087 mmol) and BOP (39 mg, 0.087 mmol) in DMF (1 mL) was added methyl 2-(aminomethyl)-5-cyanobenzofuran-7-carboxylate, TFA salt (25 mg, 0.073 mmol) and DIPEA (0.05 mL, 0.29 mmol). The reaction mixture turned into a clear solution and was stirred at room temperature for 20 hours. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in DMF, filtered and purified by preparative HPLC (Method B). Fractions containing the desired product were combined and dried *via* centrifugal evaporation to give the title compound (7.7 mg, 27%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.29 (d, *J* = 7.0 Hz, 1H), 8.84 (d, *J* = 4.0 Hz, 1H), 8.62 (s, 1H), 8.53 (br t, *J*

= 5.9 Hz, 1H), 8.38 (s, 1H), 8.14 (s, 1H), 7.28 (dd, $J = 6.9, 4.2$ Hz, 1H), 6.99 (s, 1H), 4.86 (d, $J = 5.9$ Hz, 2H), 3.94 (s, 3H); MS (ESI+) $m/z = 376.1$ (M+H)⁺.

EXAMPLE 106



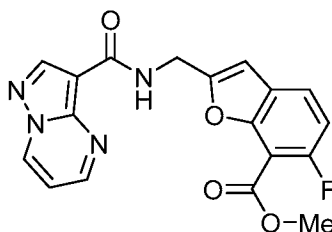
5

Methyl 2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)-5-(trifluoromethyl)benzofuran-7-carboxylate

2-((Pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)-5-(trifluoromethyl)benzofuran-7-carboxylic acid (20 mg, 0.049 mmol, Example 180) was dissolved in DMF (198 μ l) and DIPEA (34.6 μ l, 0.198 mmol) and methanol (4.76 mg, 0.148 mmol) were added. BOP (32.8 mg, 0.074 mmol) was added and the reaction was stirred at room temperature overnight. The reaction was diluted with DMF, filtered, and purified *via* preparative HPLC (method B) to give the title compound (12.1 mg, 58% yield). ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.31 (br d, $J = 6.7$ Hz, 1H), 8.83 (br d, $J = 2.1$ Hz, 1H), 8.63 (s, 1H), 8.57 (br t, $J = 5.5$ Hz, 1H), 8.30 (s, 1H), 8.02 (s, 1H), 7.29 (br dd, $J = 6.3, 4.4$ Hz, 1H), 7.00 (s, 1H), 4.85 (br d, $J = 5.8$ Hz, 2H), 3.93 (s, 3H); MS (ESI+) $m/z = 419.1$ (M+H)⁺.

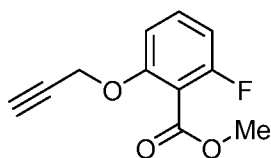
15

EXAMPLE 107



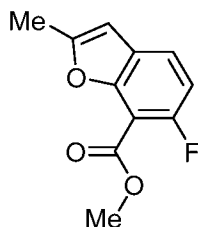
20

Methyl 6-fluoro-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate



A) Methyl 2-fluoro-6-(prop-2-yn-1-yloxy)benzoate

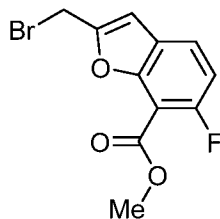
To a solution of methyl 2-fluoro-6-hydroxybenzoate (3.6 g, 21.2 mmol) and 3-bromoprop-1-yne (2.77 g, 23.3 mmol) in DMF (25 mL) was added K₂CO₃ (4.39 g, 31.7 mmol). The reaction mixture was stirred at rt for 5 h. The reaction mixture was diluted with ethyl acetate and saturated aqueous NaHCO₃ solution. The organic layer was separated, washed with brine, dried over MgSO₄, and filtered. The filtrate was concentrated *in vacuo*. The residue was dissolved in DCM and purified by flash chromatography (80g column, 0 - 20% ethyl acetate in hexanes) to give the title compound (3.4 g, 77%) as oil. ¹H NMR (400 MHz, Chloroform-d) δ 7.37 (td, *J* = 8.5, 6.5 Hz, 1H), 6.91 (d, *J* = 8.5 Hz, 1H), 6.80 (t, *J* = 8.7 Hz, 1H), 4.77 (d, *J* = 2.4 Hz, 2H), 3.95 (s, 3H), 2.55 (t, *J* = 2.4 Hz, 1H); MS (ESI+) *m/z* = 209.1 (M+H)⁺.



B) Methyl 6-fluoro-2-methylbenzofuran-7-carboxylate

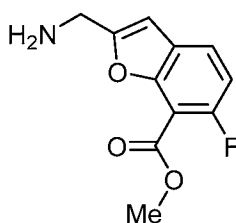
A mixture of methyl 2-fluoro-6-(prop-2-yn-1-yloxy)benzoate (3.3 g, 15.9 mmol) and cesium fluoride (3.61 g, 23.8 mmol) in *N,N*-diethylaniline (20.3 ml, 127 mmol) was heated at 230 °C for 6 h and then at 200 °C overnight. The reaction mixture was cooled down and diluted with ethyl acetate and saturated aqueous NaHCO₃ solution. The organic layer was separated, washed with 1N aqueous HCl solution followed by brine, dried over MgSO₄, and filtered. The filtrate was concentrated *in vacuo*. The residue was dissolved in DCM and purified by flash chromatography (80g column, 0 - 16% ethyl acetate in hexanes) to give the title compound (1.1 g, 33%) as light brown solid. ¹H NMR (400

MHz, Chloroform-d) δ 7.53 (dd, $J = 8.5, 5.0$ Hz, 1H), 7.03 (dd, $J = 11.0, 8.5$ Hz, 1H), 6.40 (d, $J = 1.1$ Hz, 1H), 4.04 (s, 3H), 2.52 (s, 3H); MS (ESI+) $m/z = 209.2$ (M+H)⁺.



5 **C) Methyl 2-(bromomethyl)-6-fluorobenzofuran-7-carboxylate**

To a mixture of methyl 6-fluoro-2-methylbenzofuran-7-carboxylate (1.1 g, 5.28 mmol) and NBS (1.08 g, 6.08 mmol) in CCl₄ (25 mL) was added AIBN (0.087 g, 0.528 mmol). The resulting mixture was heated at 70 °C overnight. The reaction mixture was diluted with ethyl acetate and saturated aqueous NaHCO₃ solution. The organic layer was separated, washed with brine, dried over MgSO₄, and filtered. The filtrate was concentrated *in vacuo*. The residue was dissolved in DCM and purified by flash chromatography (40g column, 0 - 20% ethyl acetate in hexanes) to give the title compound (0.96 g, 63%) as light brown solid. ¹H NMR (400 MHz, DMSO-d₆) δ 7.90 (dd, $J = 8.6, 5.2$ Hz, 1H), 7.33 - 7.25 (m, 1H), 7.14 (s, 1H), 4.94 (s, 2H), 3.96 - 3.92 (m, 3H); MS (ESI+) $m/z = 289$ (M+H)⁺.



20 **D) Methyl 2-(aminomethyl)-6-fluorobenzofuran-7-carboxylate**

To a solution of methyl 2-(bromomethyl)-6-fluorobenzofuran-7-carboxylate (0.95 g, 3.31 mmol) in DMF (15 mL) was added K₂CO₃ (0.46 g, 3.31 mmol) and sodium azide (0.24 g, 3.64 mmol). The reaction mixture was stirred at rt for 24 h. The reaction mixture was diluted with ethyl acetate and saturated aqueous NaHCO₃ solution. The organic layer was separated, washed with brine, dried over MgSO₄, and filtered. The filtrate was concentrated *in vacuo*. To the crude intermediate (methyl 2-(azidomethyl)-6-

fluorobenzofuran-7-carboxylate) was added MeOH (15 mL) and Pd/C (0.68 g, 0.32 mmol). The reaction mixture was evacuated and then filled with hydrogen (balloon). The reaction mixture was stirred under a hydrogen atmosphere at room temperature for 2 hours. The reaction mixture was filtered through a celite pad. The filtrate was concentrated *in vacuo*. The residue was dissolved in DCM and purified by flash chromatography (40g column, 0 - 15% MeOH in DCM) to give the title compound (0.21 g, 29%) as light yellow oil. ¹H NMR (400 MHz, DMSO-d₆) δ 7.81 (dd, *J* = 8.6, 5.2 Hz, 1H), 7.23 (dd, *J* = 11.3, 8.6 Hz, 1H), 6.80 (s, 1H), 3.93 (s, 3H), 3.87 (s, 2H); MS (ESI+) *m/z* = 447.3 (2M+H)⁺.

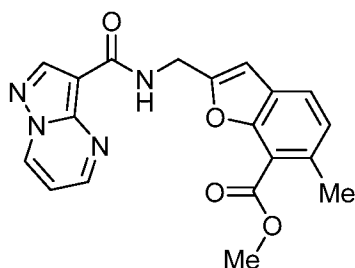
10

E) Methyl 6-fluoro-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl) benzofuran-7-carboxylate

A mixture of pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (0.184 g, 1.13 mmol) and BOP (0.54 g, 1.22 mmol) in DMF (5 mL) was stirred at room temperature for 10 min.

15 A solution of methyl 2-(aminomethyl)-6-fluorobenzofuran-7-carboxylate (0.21 g, 0.94 mmol) in THF (2 mL) and DIPEA (0.49 mL, 2.82 mmol) was then added. The reaction mixture was stirred at room temperature for 24 hours. The reaction mixture was diluted with ethyl acetate and saturated aqueous NaHCO₃ solution. The organic layer was separated, washed with brine, dried over MgSO₄, and filtered. The filtrate was concentrated *in vacuo*. The residue was dissolved in DCM and purified by flash chromatography (24g column, 0-60% ethyl acetate in DCM) to give the title compound (0.225 g, 72%) as a white solid. ¹H NMR (500 MHz, DMSO-d₆) δ 9.27 (br d, *J* = 6.1 Hz, 1H), 8.82 (br d, *J* = 3.1 Hz, 1H), 8.61 (s, 1H), 8.46 (br t, *J* = 5.3 Hz, 1H), 7.80 (dd, *J* = 8.5, 5.2 Hz, 1H), 7.40 - 7.15 (m, 2H), 6.86 (s, 1H), 4.78 (br d, *J* = 5.8 Hz, 2H), 3.91 (s, 25 3H); MS (ESI+) *m/z* = 369.2 (M+H)⁺.

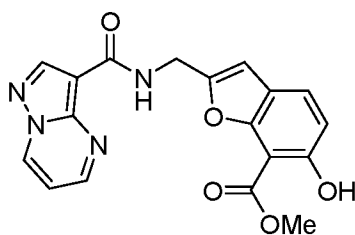
EXAMPLE 108



Methyl 6-methyl-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate

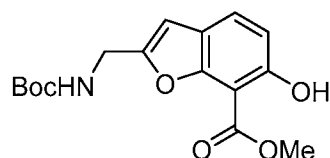
- 5 To a solution of 6-methyl-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido) methyl) benzofuran-7-carboxylic acid (30 mg, 0.086 mmol, Example 182) and BOP (37.9 mg, 0.086 mmol) in DMF (1.5 mL) was added methanol (27.4 mg, 0.856 mmol) and DIPEA (0.060 mL, 0.343 mmol). The reaction mixture was stirred at room temperature for 4 hours. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in
- 10 DMF, filtered and purified by preparative LC/MS (Method B). Fractions containing the desired product were combined and dried *via* centrifugal evaporation to give the title compound (5 mg, 16%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.27 (br d, *J* = 6.8 Hz, 1H), 8.82 (br d, *J* = 3.0 Hz, 1H), 8.61 (s, 1H), 8.48 - 8.38 (m, 1H), 7.61 (d, *J* = 7.9 Hz, 1H), 7.27 (dd, *J* = 6.8, 4.3 Hz, 1H), 7.16 (d, *J* = 8.0 Hz, 1H), 6.78 (s, 1H), 4.77 (d, *J* = 5.9 Hz,
- 15 2H), 3.90 (s, 3H), 2.48 (s, 3H); MS (ESI+) *m/z* = 365.0 (M+H)⁺.

EXAMPLE 109



Methyl 6-hydroxy-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate

20



A) Methyl 2-(((tert-butoxycarbonyl)amino)methyl)-6-hydroxybenzofuran-7-carboxylate

To a solution of *tert*-butyl prop-2-yn-1-ylcarbamate (68.0 mg, 0.438 mmol),
 5 methyl 2,6-dihydroxy-3-iodobenzoate (112.1 mg, 0.381 mmol) (*Bioorg. Med. Chem. Lett.*
2003, *13*, 4015-4017), and copper(I) iodide (7.26 mg, 0.038 mmol) in DMF (477 μ L) was
 added Et₃N (638 μ L, 4.57 mmol). The mixture was sparged with N₂ for 3 min and then
 bis(triphenylphosphine)palladium(II) chloride (13.38 mg, 0.019 mmol) was added. The
 reaction mixture was sparged with N₂ for an additional 1 min, sealed, and heated to 80 °C
 10 for 2 h. The reaction mixture was cooled to room temperature and concentrated *in vacuo*.
 The residue was dissolved in DCM and purified by flash chromatography (ISCO 12 g
 column, 0 - 50% EtOAc in hexanes) to give the title compound (10.4 mg, 8%). ¹H NMR
 (400 MHz, Chloroform-d) δ 11.16 (s, 1H), 7.58 (d, *J*=8.6 Hz, 1H), 6.91 (d, *J*=8.6 Hz,
 1H), 6.56 (s, 1H), 4.99 (br s, 1H), 4.48 (br d, *J*=5.7 Hz, 2H), 4.08 (s, 3H), 1.50 (s, 9H);
 15 MS (ESI+) *m/z* = 344.3 (M+Na)⁺.

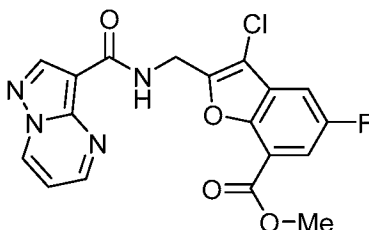
B) Methyl 6-hydroxy-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate

To a solution of methyl 2-(((*tert*-butoxycarbonyl)amino)methyl)-6-
 20 hydroxybenzofuran-7-carboxylate (10.4 mg, 0.032 mmol) in DCM (485 μ L) was added
 TFA (162 μ L). The reaction mixture was stirred for 3 h and then concentrated *in vacuo* to
 obtain a residue that was used without further purification.

To this residue was added pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (7.49 mg,
 0.046 mmol) and ((1H-benzo[*d*][1,2,3]triazol-1-yl)oxy)tris(dimethylamino) phosphonium
 25 hexafluorophosphate(V) (20.3 mg, 0.046 mmol). DMF (0.21 mL) and DIPEA (21.8 μ L,
 0.125 mmol) were added and the reaction mixture was stirred at room temperature for 16
 h. The reaction mixture was diluted with water and a precipitate formed. The slurry was
 filtered and the filter cake was rinsed with water. The solid was collected and placed on
 high vacuum to give the title compound (8.5 mg, 55%). ¹H NMR (400 MHz, DMSO-*d*₆) δ

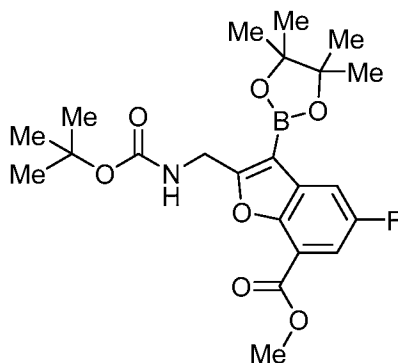
10.70 (s, 1H), 9.34 (dd, $J=7.0, 1.6$ Hz, 1H), 8.84 (dd, $J=4.2, 1.6$ Hz, 1H), 8.63 (s, 1H), 8.44 (t, $J=5.9$ Hz, 1H), 7.67 (d, $J=8.5$ Hz, 1H), 7.29 (dd, $J=6.9, 4.2$ Hz, 1H), 6.88 (d, $J=8.6$ Hz, 1H), 6.74 (s, 1H), 4.75 (d, $J=5.8$ Hz, 2H), 3.94 (s, 3H); MS (ESI+) $m/z = 367.0$ (M+H)⁺.

5

EXAMPLE 110

Methyl 3-chloro-5-fluoro-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate

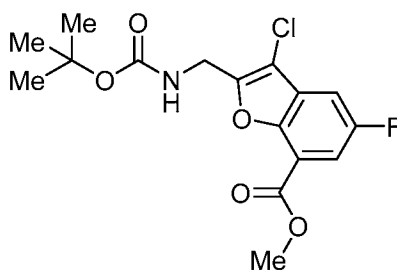
10



A) Methyl 2-(((*tert*-butoxycarbonyl)amino)methyl)-5-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-7-carboxylate

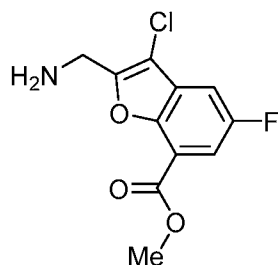
A mixture of methyl 2-(((*tert*-butoxycarbonyl)amino)methyl)-5-fluorobenzofuran-7-carboxylate (0.66 g, 2.041 mmol, Step B of Example 35), 4,4'-di-*tert*-butyl-2,2'-bipyridine (0.055 g, 0.20 mmol), and bis(pinacolato)diboron (0.62 g, 2.45 mmol) in hexane (30 mL) was sonicated and purged with a nitrogen stream for 5 min. Next, (1,5-cyclooctadiene) (methoxy) iridium (I) dimer (0.081 g, 0.122 mmol) was added. The resulting mixture was heated at 80 °C under a nitrogen atmosphere overnight. The reaction mixture was cooled down and filtered through a celite pad. The pad was washed

with ethyl acetate. The filtrate was concentrated *in vacuo*. The residue was dissolved in DCM and purified by flash chromatography (ISCO column 40 g, 0 - 30% ethyl acetate in hexanes) to give the title compound (0.52 g, 57%) as a white solid. ¹H NMR (400 MHz, Chloroform-d) 7.79 (dd, *J* = 8.1, 2.7 Hz, 1H), 7.64 (dd, *J* = 9.6, 2.7 Hz, 1H), 5.99 - 5.62 (m, 1H), 4.95 - 4.64 (m, 2H), 4.02 (s, 3H), 1.48 (s, 9H), 1.41 (s, 12H); MS (ESI+) *m/z* = 450.4 (M+H)⁺.



B) Methyl 2-(((*tert*-butoxycarbonyl)amino)methyl)-3-chloro-5-fluorobenzofuran-7-carboxylate

To a solution of methyl 2-(((*tert*-butoxycarbonyl)amino)methyl)-5-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-7-carboxylate (0.52 g, 1.16 mmol) in MeOH (15 mL) was added copper(II) chloride (0.31 g, 2.31 mmol). The reaction mixture was heated at 50 °C for 4 hours and then stirred at room temperature overnight. The reaction mixture was filtered through a celite pad and the pad was washed with ethyl acetate. The filtrate was concentrated *in vacuo*. The residue was dissolved in DCM and purified by flash chromatography (ISCO column 40 g, 0 - 20% ethyl acetate in hexanes) to give the title compound (0.29 g, 70%) as a white solid. ¹H NMR (400 MHz, Chloroform-d) δ 7.71 (dd, *J* = 9.4, 2.7 Hz, 1H), 7.43 (dd, *J* = 7.3, 2.7 Hz, 1H), 5.33 - 4.96 (m, 1H), 4.59 (br d, *J* = 5.1 Hz, 2H), 4.02 (s, 3H), 1.49 (s, 9H); MS (ESI+) *m/z* = 302.1 (M+H)⁺.



C) Methyl 2-(aminomethyl)-3-chloro-5-fluorobenzofuran-7-carboxylate

To a solution of methyl 2-(((*tert*-butoxycarbonyl)amino)methyl)-3-chloro-5-fluorobenzofuran-7-carboxylate (0.29 g, 0.81 mmol) in DCM (5 mL) was added TFA (0.94 mL, 12.2 mmol). The reaction mixture was stirred at room temperature overnight. The reaction mixture was concentrated *in vacuo* to give the crude title compound (TFA salt) as a white solid (0.3 g, 95%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.56 (br s, 2H), 7.90 (dd, *J* = 7.6, 2.7 Hz, 1H), 7.82 (dd, *J* = 9.5, 2.7 Hz, 1H), 4.38 (s, 2H), 3.97 (s, 3H); MS (ESI+) *m/z* = 241.1 (M-16+H)⁺.

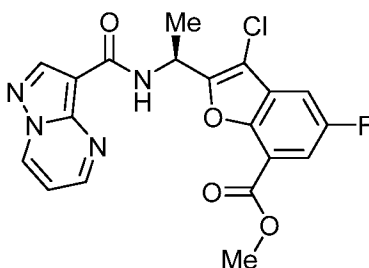
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D) Methyl 3-chloro-5-fluoro-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate

A mixture of pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (163 mg, 1.0 mmol) and BOP (516 mg, 1.17 mmol) in DMF (7 mL) was stirred at room temperature for 10 minutes. A solution of methyl 2-(aminomethyl)-3-chloro-5-fluorobenzofuran-7-carboxylate, TFA salt (310 mg, 0.834 mmol) in THF (2 mL) and DIPEA (0.874 mL, 5.00 mmol) were then added. The reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was diluted with ethyl acetate and saturated aqueous NaHCO₃ solution. The organic layer was separated, washed with brine and 1 N aqueous HCl solution successively, dried over MgSO₄, and filtered. The filtrate was concentrated *in vacuo* to give the title compound as a light tan solid (315 mg, 94%). A portion of the sample was dissolved in DMF and purified by preparative HPLC (Method B). Fractions containing the desired product were combined and dried *via* centrifugal evaporation to give the title compound. ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.26 (br d, *J* = 6.9 Hz, 1H), 8.83 (br d, *J* = 3.5 Hz, 1H), 8.60 (s, 1H), 8.54 - 8.38 (m, 1H), 7.83 - 7.55 (m, 2H), 7.39 - 7.15 (m, 1H), 4.88 (br d, *J* = 5.7 Hz, 2H), 3.88 (s, 3H); MS (ESI+) *m/z* = 402.9 (M+H)⁺.

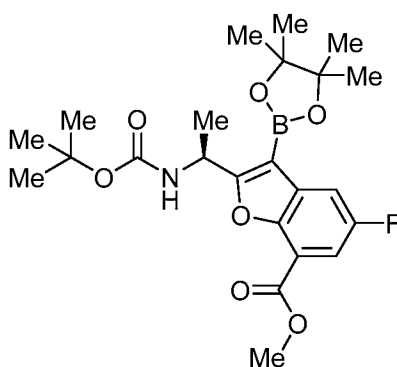
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EXAMPLE 111



Methyl (*S*)-3-chloro-5-fluoro-2-(1-(pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)ethyl)benzofuran-7-carboxylate

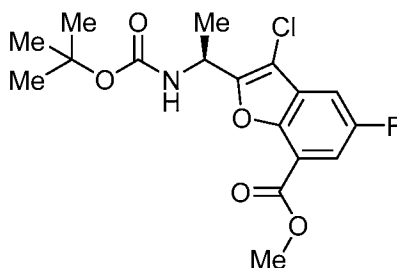
5



A) Methyl (*S*)-2-(1-((*tert*-butoxycarbonyl)amino)ethyl)-5-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-7-carboxylate

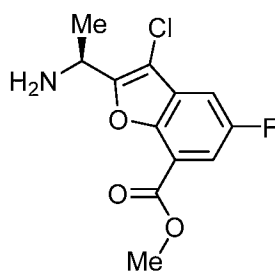
A mixture of methyl (*S*)-2-(1-((*tert*-butoxycarbonyl)amino)ethyl)-5-fluorobenzofuran-7-carboxylate (0.8 g, 2.371 mmol, Step C of Example 46), 4,4'-di-*tert*-butyl-2,2'-bipyridine (0.064 g, 0.237 mmol), bis(pinacolato)diboron (0.723 g, 2.85 mmol) in hexane (30 mL) was sonicated and purged with a nitrogen stream for 5 min. (1,5-Cyclooctadiene)(methoxy) iridium(I) dimer (0.094 g, 0.142 mmol) was then added. The resulting mixture was heated at 80 °C under a nitrogen atmosphere overnight. The reaction mixture was cooled down, filtered through a celite pad and the pad was washed with ethyl acetate. The filtrate was concentrated *in vacuo*. The residue was dissolved in DCM and purified by flash chromatography (ISCO column 40 g, 0 - 20% ethyl acetate in hexanes) to give the title compound (0.26 g, 24 %) as a white solid. ¹H NMR (400 MHz, CHLOROFORM-*d*) δ 7.80 (dd, *J* = 8.2, 2.8 Hz, 1H), 7.62 (dd, *J* = 9.5, 2.8 Hz, 1H), 6.27

(br d, $J = 8.2$ Hz, 1H), 5.47 - 5.19 (m, 1H), 4.01 (s, 3H), 1.55 (d, $J = 7.0$ Hz, 3H), 1.45 (s, 9H), 1.43 - 1.38 (m, 12H); MS (ESI+) $m/z = 408.3$ (M-55+H)⁺.



5 **B) Methyl (*S*)-2-(1-((*tert*-butoxycarbonyl)amino)ethyl)-3-chloro-5-fluorobenzofuran-7-carboxylate**

To a solution of methyl (*S*)-2-(1-((*tert*-butoxycarbonyl)amino)ethyl)-5-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-7-carboxylate (0.26 g, 0.561 mmol) in MeOH (8 mL) was added copper(II) chloride (0.15 g, 1.12 mmol). The reaction mixture was heated at 50 °C overnight. The reaction mixture was filtered through a celite pad and the pad was washed with ethyl acetate. The filtrate was concentrated *in vacuo*.
 10 The residue was dissolved in DCM and purified by flash chromatography (ISCO column 24 g, 0 - 15% ethyl acetate in hexanes) to give the title compound (0.1 g, 48 %) as a white solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.67 (dd, $J = 9.4, 2.7$ Hz, 1H), 7.40 (dd, $J = 7.4, 2.7$ Hz, 1H), 5.29 - 5.08 (m, 2H), 4.01 (s, 3H), 1.59 (d, $J = 6.8$ Hz, 3H), 1.45 (s, 9H);
 15 MS (ESI+) $m/z = 316.2$ (M-55+H)⁺.



20 **C) Methyl (*S*)-2-(1-aminoethyl)-3-chloro-5-fluorobenzofuran-7-carboxylate**

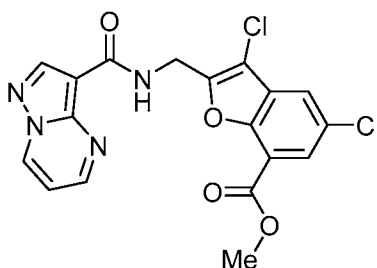
To a solution of methyl (*S*)-2-(1-((*tert*-butoxycarbonyl)amino)ethyl)-3-chloro-5-fluorobenzofuran-7-carboxylate (100 mg, 0.269 mmol) in DCM (3 mL) was added TFA (0.21 mL, 2.69 mmol). The reaction mixture was stirred at rt for 2 h. The reaction mixture was concentrated *in vacuo* and dried on high vacuum overnight to give the title compound (TFA salt) as a white solid (100 mg, 96%); MS (ESI+) $m/z = 255$ (M-16+H)⁺.

D) Methyl (*S*)-3-chloro-5-fluoro-2-(1-(pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)ethyl)benzofuran-7-carboxylate

The reaction mixture of pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (55.0 mg, 0.337 mmol) and BOP (161 mg, 0.363 mmol) in DMF (2 mL) was stirred at rt for 15 min, followed by addition of a solution of methyl (*S*)-2-(1-aminoethyl)-3-chloro-5-fluorobenzofuran-7-carboxylate TFA salt (100 mg, 0.259 mmol) in THF (2 mL) and DIPEA (0.27 mL, 1.556 mmol). The reaction mixture turned into clear solution after addition of amine and was stirred at rt for 3 h. The reaction mixture was diluted with ethyl acetate and saturated NaHCO₃ solution. The organic layer was separated, washed with brine, and dried over MgSO₄. The organic layer was filtered and the filtrate was concentrated *in vacuo* to give the title compound as white solid (82 mg, 80%). A portion of the residue was dissolved in DMF, filtered and purified by preparative HPLC (Method B). Fractions containing the desired product were combined and dried *via* centrifugal evaporation to give the title compound (11.1 mg, 43%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.31 (d, $J=7.3$ Hz, 1H), 8.87 (br d, $J=3.1$ Hz, 1H), 8.60 (s, 1H), 8.49 (br d, $J=7.6$ Hz, 1H), 7.74 (dd, $J=7.6, 2.4$ Hz, 1H), 7.69 (dd, $J=9.5, 2.4$ Hz, 1H), 7.30 (dd, $J=6.7, 4.3$ Hz, 1H), 5.57 (br t, $J=7.3$ Hz, 1H), 3.90 (s, 3H), 1.67 (d, $J=7.0$ Hz, 3H); MS (ESI+) $m/z = 417.2$ (M+H)⁺.

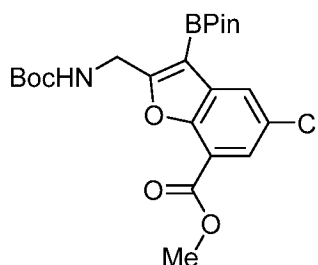
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EXAMPLE 112



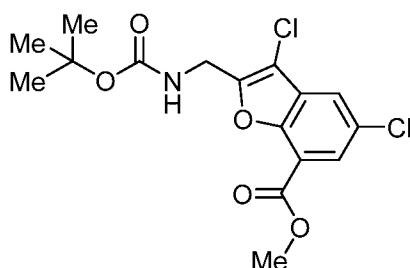
Methyl 3,5-dichloro-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate

5



A) Methyl 2-(((*tert*-butoxycarbonyl)amino)methyl)-5-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-7-carboxylate

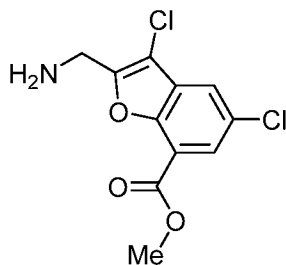
A mixture of methyl 2-(((*tert*-butoxycarbonyl)amino)methyl)-5-chlorobenzofuran-7-carboxylate (1.3 g, 3.83 mmol, Step B of Example 48), 4,4'-di-*tert*-butyl-2,2'-bipyridine (0.103 g, 0.383 mmol), and bis(pinacolato)diboron (1.17 g, 4.59 mmol) in hexane (50 mL) was sonicated and purged with a nitrogen stream for 5 min. Then, (1,5-cyclooctadiene) (methoxy) iridium (I) dimer (0.152 g, 0.230 mmol) was added. The resulting mixture was heated at 80 °C under a nitrogen atmosphere overnight. The reaction mixture was cooled down, filtered through a celite pad, and the pad was washed with ethyl acetate. The filtrate was concentrated *in vacuo*. The residue was dissolved in DCM and purified by flash chromatography (ISCO column 40 g, 0 - 20% ethyl acetate in hexanes) to give the title compound (1.25 g, 70%) as a white solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.06 (d, *J* = 2.2 Hz, 1H), 7.90 (d, *J* = 2.2 Hz, 1H), 5.91 - 5.66 (m, 1H), 4.72 (br d, *J* = 4.7 Hz, 2H), 4.01 (s, 3H), 1.48 (s, 9H), 1.41 (s, 12H); MS (ESI⁺) *m/z* = 410.3 (M-55+H)⁺.



B) Methyl 2-(((*tert*-butoxycarbonyl)amino)methyl)-3,5-dichlorobenzofuran-7-carboxylate

5 To a solution of methyl 2-(((*tert*-butoxycarbonyl)amino)methyl)-5-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-7-carboxylate (0.56 g, 1.20 mmol) in MeOH (20 mL) was added copper(II) chloride (0.323 g, 2.4 mmol). The reaction mixture was heated at 50 °C overnight. The reaction mixture was filtered through a celite pad and the pad was washed with ethyl acetate. The filtrate was
 10 concentrated *in vacuo*. The residue was dissolved in DCM and purified by flash chromatography (ISCO column 40 g, 0 - 20% ethyl acetate in hexanes) to give the title compound (0.36 g, 80%) as a white solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.97 (d, *J* = 2.2 Hz, 1H), 7.73 (d, *J* = 2.2 Hz, 1H), 5.20 - 4.96 (m, 1H), 4.59 (br d, *J* = 4.9 Hz, 2H), 4.02 (s, 3H), 1.49 (s, 9H); MS (ESI+) *m/z* = 396.1 (M+Na)⁺.

15



C) Methyl 2-(aminomethyl)-3,5-dichlorobenzofuran-7-carboxylate

To a solution of methyl 2-(((*tert*-butoxycarbonyl)amino)methyl)-3,5-dichlorobenzofuran-7-carboxylate (0.36 g, 0.96 mmol) in DCM (6 mL) was added TFA
 20 (0.9 mL, 11.5 mmol). The reaction mixture was stirred at room temperature for 2 hours.

The reaction mixture was concentrated *in vacuo* to give the crude title compound (TFA salt, 0.37 g, 99%) and as a white solid. MS (ESI+) $m/z = 257 (M+H)^+$.

D) Methyl 3,5-dichloro-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate

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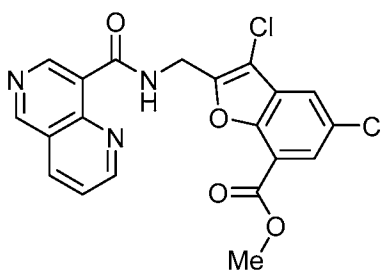
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A reaction mixture of pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (0.187 g, 1.14 mmol) and BOP (0.55 g, 1.24 mmol) in DMF (7 mL) was stirred at room temperature for 15 minutes. A solution of methyl 2-(aminomethyl)-3,5-dichlorobenzofuran-7-carboxylate, TFA salt (0.37 g, 0.953 mmol) in THF (7 mL) and DIPEA (0.67 mL, 3.81 mmol) were then added. The reaction mixture turned into a clear solution after addition of the amine and was stirred at room temperature for 16 hours. The reaction mixture was diluted with ethyl acetate and saturated aqueous NaHCO₃ solution. The organic layer was separated, washed with brine, dried over MgSO₄, and filtered. The filtrate was concentrated *in vacuo* to give a solid. The solid was triturated with MeOH and the solid was isolated *via* filtration to give the title compound as a white solid (0.39 g, 93%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.34 (dd, $J = 7.0, 1.6$ Hz, 1H), 8.85 (dd, $J = 4.2, 1.7$ Hz, 1H), 8.62 (s, 1H), 8.54 (t, $J = 5.9$ Hz, 1H), 7.95 (d, $J = 2.2$ Hz, 1H), 7.87 (d, $J = 2.2$ Hz, 1H), 7.30 (dd, $J = 7.0, 4.2$ Hz, 1H), 4.88 (d, $J = 5.9$ Hz, 2H), 3.88 (s, 3H); MS (ESI+) $m/z = 419.1 (M+H)^+$.

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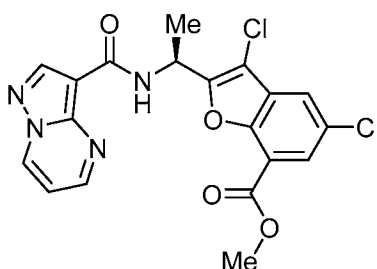
EXAMPLE 113



methyl 2-((1,6-naphthyridine-8-carboxamido)methyl)-3,5-dichlorobenzofuran-7-carboxylate

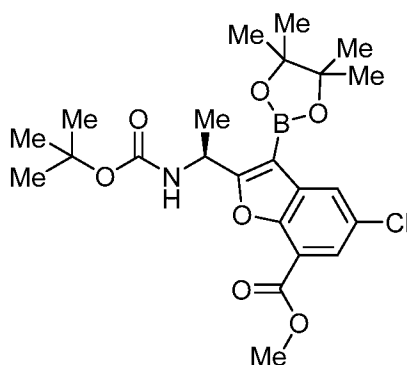
A mixture of 1,6-naphthyridine-8-carboxylic acid, HCl (10 mg, 0.047 mmol), methyl 2-(aminomethyl)-3,5-dichlorobenzofuran-7-carboxylate, TFA (18.43 mg, 0.047 mmol, Step C of Example 112), HATU (18.05 mg, 0.047 mmol) and Hunig's Base (0.033 mL, 0.190 mmol) in DMF (0.5 mL) was stirred at rt for 24 h. The reaction was quenched with 1:1 DMF/AcOH and purified by preparative HPLC (Method B) to give the title compound (2.7 mg, 6.20 μ mol, 13.06 % yield). ^1H NMR (500 MHz, DMSO- d_6) δ 11.15 - 11.04 (m, 1H), 9.61 (s, 1H), 9.36 (s, 1H), 9.30 (br d, $J=2.4$ Hz, 1H), 8.80 (br d, $J=8.2$ Hz, 1H), 7.96 (s, 1H), 7.87 (br s, 2H), 4.97 (br d, $J=5.5$ Hz, 2H), 3.86 (s, 3H); MS (ESI+) m/z = 430.2 (M+H) $^+$.

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EXAMPLE 114

Methyl (S)-3,5-dichloro-2-(1-(pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)ethyl)benzofuran-7-carboxylate

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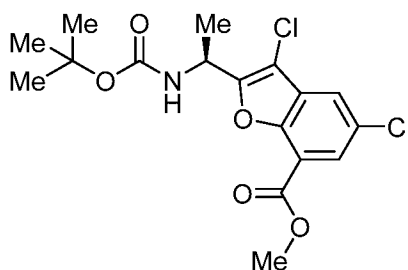


A) Methyl (S)-2-(1-((*tert*-butoxycarbonyl)amino)ethyl)-5-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-7-carboxylate

A mixture of methyl (*S*)-2-(1-((*tert*-butoxycarbonyl)amino)ethyl)-5-chlorobenzofuran-7-carboxylate (1.7 g, 4.80 mmol, Step B of Example 79), 4,4'-di-*tert*-butyl-2,2'-bipyridine (0.129 g, 0.480 mmol), and bis(pinacolato)diboron (1.464 g, 5.77 mmol) in hexane (50 mL) was sonicated and purged with a nitrogen stream for 5 min.

5 (1,5-Cyclooctadiene)(methoxy) iridium(I) dimer (0.191 g, 0.288 mmol) was then added. The resulting mixture was heated at 80 °C under a nitrogen atmosphere overnight. The reaction mixture was filtered through a celite pad and the pad was washed with ethyl acetate. The filtrate was concentrated *in vacuo*. The residue was dissolved in DCM and purified by flash chromatography (ISCO column 80 g, 0 - 20% ethyl acetate in hexanes)

10 to give the title compound (1.2 g, 52 %) as a white solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.07 (d, *J* = 2.2 Hz, 1H), 7.89 (d, *J* = 2.2 Hz, 1H), 6.41 - 6.13 (m, 1H), 5.46 - 5.21 (m, 1H), 4.01 (s, 3H), 1.55 (d, *J* = 7.0 Hz, 3H), 1.45 (s, 9H), 1.44 - 1.39 (m, 12H); MS (ESI+) *m/z* = 480.5 (M+H)⁺.



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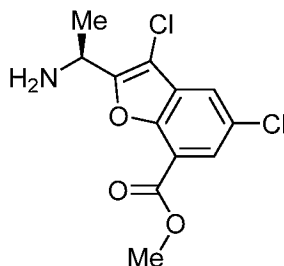
B) Methyl (*S*)-2-(1-((*tert*-butoxycarbonyl)amino)ethyl)-3,5-dichlorobenzofuran-7-carboxylate

To a solution of methyl (*S*)-2-(1-((*tert*-butoxycarbonyl)amino)ethyl)-5-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-7-carboxylate (0.7 g, 1.46 mmol) in methanol (20 mL) was added copper(II) chloride (0.392 g, 2.92 mmol). The resulting reaction mixture was heated at 50 °C overnight. The reaction mixture was filtered through a celite pad and the pad was washed with ethyl acetate. The filtrate was concentrated *in vacuo*. The residue was dissolved in DCM and purified by flash

20 chromatography (ISCO column 40 g, 0 - 20% ethyl acetate in hexanes) to give the title compound (0.48 g, 85%) as a white solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.96 (d,

25

$J = 2.2$ Hz, 1H), 7.72 (d, $J = 2.2$ Hz, 1H), 5.32 - 5.19 (m, 1H), 5.18 - 4.98 (m, 1H), 4.03 (s, 3H), 1.65 - 1.57 (m, 3H), 1.46 (s, 9H); MS (ESI+) $m/z = 332.1$ (M-55+H)⁺.



5 **C) Methyl (*S*)-2-(1-aminoethyl)-3,5-dichlorobenzofuran-7-carboxylate**

To a solution of methyl (*S*)-2-(1-((*tert*-butoxycarbonyl)amino)ethyl)-3,5-dichlorobenzofuran-7-carboxylate (0.48 g, 1.24 mmol) in DCM (6 mL) was added TFA (1.14 mL, 14.8 mmol). The reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated *in vacuo* and dried on high vacuum overnight to give the title compound (TFA salt, 0.48 g, 97%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.64 (br s, 2H), 8.09 (d, $J = 2.1$ Hz, 1H), 7.97 (d, $J = 2.2$ Hz, 1H), 4.86 (br d, $J = 5.9$ Hz, 1H), 3.97 (s, 3H), 1.66 (d, $J = 6.9$ Hz, 3H); MS (ESI) $m/z = 271.0$ (M-17+H)⁺.

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15 **D) Methyl (*S*)-3,5-dichloro-2-(1-(pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)ethyl)benzofuran-7-carboxylate**

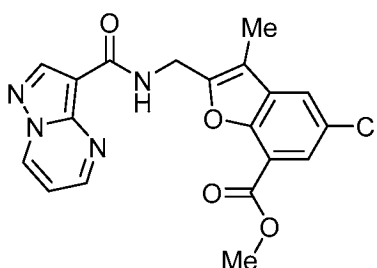
A mixture of pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (142 mg, 0.873 mmol) and BOP (416 mg, 0.94 mmol) in DMF (4 mL) was stirred at room temperature for 15 minutes. A solution of methyl (*S*)-2-(1-aminoethyl)-3,5-dichlorobenzofuran-7-carboxylate TFA salt (270 mg, 0.671 mmol) in THF (2 mL) and DIPEA (0.70 mL, 4.03 mmol) were then added. The reaction mixture turned into a clear solution after addition of the amine and was stirred at room temperature for 2 hours. The reaction mixture was diluted with ethyl acetate and saturated aqueous NaHCO₃ solution. The organic layer was separated, washed with brine, dried over MgSO₄, and filtered. The filtrate was concentrated *in vacuo* to give the crude title compound as a white solid (200 mg, 70%). A portion of the material was purified by preparative HPLC (Method A). Fractions

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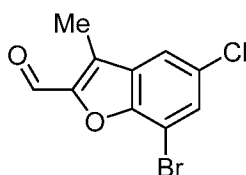
containing the desired product were combined and dried *via* centrifugal evaporation to give the title compound as a TFA salt. ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.27 (dd, *J* = 6.9, 1.1 Hz, 1H), 8.93 - 8.81 (m, 1H), 8.58 (s, 1H), 8.47 (br d, *J* = 7.6 Hz, 1H), 7.84 (d, *J* = 2.1 Hz, 1H), 7.79 (d, *J* = 2.1 Hz, 1H), 7.28 (dd, *J* = 7.0, 4.3 Hz, 1H), 5.56 (br t, *J* = 7.2 Hz, 1H), 3.89 (s, 3H), 1.67 (br d, *J* = 7.0 Hz, 3H); MS (ESI⁺): *m/z* = 433.2 (M+H)⁺.

EXAMPLE 115



Methyl 5-chloro-3-methyl-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate

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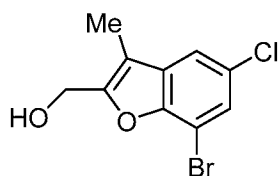


A) 7-Bromo-5-chloro-3-methylbenzofuran-2-carbaldehyde

To a solution of 1-(3-bromo-5-chloro-2-hydroxyphenyl)ethan-1-one (3.5 g, 14.03 mmol) in THF (70 mL) were added 1,1-dichloroethene (2.242 mL, 28.1 mmol) and potassium *tert*-butoxide (6.30 g, 56.1 mmol) slowly at ice bath temperature. The resulting reaction mixture was stirred at rt for 18 h. The reaction mixture was diluted with DCM and 1 N HCl solution. The organic layer was separated and washed with brine, dried over MgSO₄ and filtered. The filtrate was concentrated *in vacuo*. To the residue was added DCE (20 mL) and sulfuric acid (0.748 mL, 14.03 mmol). The reaction mixture was stirred at rt for 2 h. Then to the reaction mixture was added water and more DCM. The resulting mixture was stirred for 5 min vigorously, then poured into the separational funnel. The

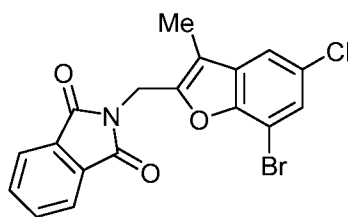
20

organic layer was separated, washed with brine, dried over MgSO₄ and filtered. The filtrate was concentrated *in vacuo*. The residue was dissolved in DCM and purified by silica gel column chromatography (80 g column, 0 - 20% ethyl acetate in hexanes) to give 7-bromo-5-chloro-3-methylbenzofuran-2-carbaldehyde (1.8 g, 47% yield) as a yellow solid. ¹H NMR (400 MHz, Chloroform-d) δ 10.10 (s, 1H), 7.70 (d, *J* = 1.9 Hz, 1H), 7.64 (d, *J* = 2.0 Hz, 1H), 2.61 (s, 3H); MS (ESI+) *m/z* = 273.1, 275.1 (M+H)⁺.



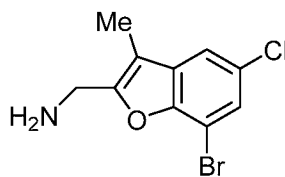
B) (7-Bromo-5-chloro-3-methylbenzofuran-2-yl)methanol

To a solution of 7-bromo-5-chloro-3-methylbenzofuran-2-carbaldehyde (0.6 g, 2.194 mmol) in THF (6 mL) and MeOH (10 mL) was added sodium borohydride (0.166 g, 4.39 mmol). The reaction mixture was stirred at rt for 1 h. The reaction mixture was quenched with water and the resulting mixture was diluted with ethyl acetate. The organic layer was separated, washed with brine, dried over MgSO₄, and filtered. The filtrate was concentrated *in vacuo* to give (7-bromo-5-chloro-3-methylbenzofuran-2-yl)methanol (0.5 g, 83% yield) as a light yellow solid. ¹H NMR (400 MHz, Chloroform-d) δ 7.47 (d, *J* = 1.9 Hz, 1H), 7.43 (d, *J* = 2.0 Hz, 1H), 4.80 (br d, *J* = 4.9 Hz, 2H), 2.25 (s, 3H), 2.03 - 1.90 (m, 1H); MS (ESI+) *m/z* = 256.9 (M-17+H)⁺.



C) 2-((7-Bromo-5-chloro-3-methylbenzofuran-2-yl)methyl)isoindoline-1,3-dione

To a solution of (7-bromo-5-chloro-3-methylbenzofuran-2-yl)methanol (0.5 g, 1.815 mmol) in THF (15 mL) were added isoindoline-1,3-dione (0.320 g, 2.178 mmol) and triphenylphosphine (0.547 g, 2.087 mmol). The resulting reaction mixture was cooled to ice bath temperature and to the mixture was added DEAD (0.35 mL, 2.18 mmol) dropwise. The resulting mixture was allowed to warm up to rt and stirred at rt for 4 h. The reaction mixture was diluted with ethyl acetate and saturated NaHCO₃ solution. The organic layer was separated, washed with brine, 1 N HCl solution successively. The organic layer was separated, dried over MgSO₄, and filtered. The filtrate was concentrated *in vacuo*. The residue was dissolved in DCM and purified by silica gel column chromatography (40 g column, 0 - 30% ethyl acetate in DCM) to give 2-((7-bromo-5-chloro-3-methylbenzofuran-2-yl)methyl)isoindoline-1,3-dione (0.3 g, 41% yield) as a light brown solid. ¹H NMR (400 MHz, Chloroform-d) δ 7.90 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.75 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.44 - 7.38 (m, 2H), 5.01 (s, 2H), 2.37 (s, 3H).

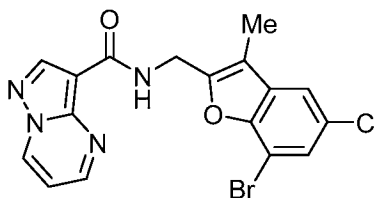


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D) (7-Bromo-5-chloro-3-methylbenzofuran-2-yl)methanamine

To a suspension of 2-((7-bromo-5-chloro-3-methylbenzofuran-2-yl)methyl)isoindoline-1,3-dione (0.3 g, 0.741 mmol) in ethanol (7 mL) was added hydrazine (0.035 mL, 1.112 mmol). The reaction mixture was stirred at rt for 16 h. The reaction mixture was diluted with ethyl acetate and filtered to remove solid impurity. The filtrate was diluted with ethyl acetate and saturated NaHCO₃ solution. The organic layer was separated, washed with brine, dried over MgSO₄ and filtered. The filtrate was concentrated *in vacuo* to give (7-bromo-5-chloro-3-methylbenzofuran-2-yl)methanamine (0.16 g, 79%) as a light brown solid. MS (ESI+) *m/z* = 257.0, 259.0 (M-17+H)⁺.

25



E) N-((7-Bromo-5-chloro-3-methylbenzofuran-2-yl)methyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide

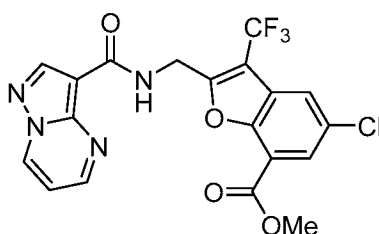
The reaction mixture of pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (116 mg, 0.710 mmol) and BOP (314 mg, 0.710 mmol) in DMF (3 mL) was stirred at rt for 10 min, followed by addition of a solution of (7-bromo-5-chloro-3-methylbenzofuran-2-yl)methanamine (150 mg, 0.546 mmol) in DMF (2 mL) and DIPEA (0.286 mL, 1.639 mmol). The reaction mixture was stirred at rt for 2 h. The reaction mixture was diluted with ethyl acetate and saturated NaHCO₃ solution. The organic layer was separated, washed with brine, dried over MgSO₄ and filtered. The filtrate was concentrated *in vacuo*. The crude residue was purified *via* silica gel column chromatography (24 g column, 0-40% EtOAc in DCM) to give *N*-((7-bromo-5-chloro-3-methylbenzofuran-2-yl)methyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (105 mg, 60% purity, 27 % yield) as a pale yellow solid. Analytical sample was purified with preparative HPLC (Method B). ¹H NMR (400 MHz, DMSO-d₆) δ 9.32 (dd, *J* = 7.0, 1.7 Hz, 1H), 8.83 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.62 (s, 1H), 8.47 (t, *J* = 5.8 Hz, 1H), 7.72 (d, *J* = 2.0 Hz, 1H), 7.62 (d, *J* = 2.0 Hz, 1H), 7.28 (dd, *J* = 7.0, 4.2 Hz, 1H), 4.77 (d, *J* = 5.9 Hz, 2H), 2.28 (s, 3H); MS (ESI+) *m/z* = 419.1, 421.1 (M+H)⁺.

F) Methyl 5-chloro-3-methyl-2-((pyrazolo[1,5-a]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate

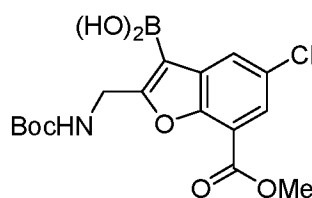
The reaction mixture of *N*-((7-bromo-5-chloro-3-methylbenzofuran-2-yl)methyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (50 mg, 0.119 mmol), palladium(II) acetate (4.01 mg, 0.018 mmol), 1,3-bis(diphenylphosphino)propane (9.9 mg, 0.024 mmol) and TEA (0.166 mL, 1.191 mmol) in MeOH (4 mL) and DMF (1 mL) was vacated and then filled with nitrogen. The reaction mixture was vacated, filled with nitrogen again. The reaction mixture was heated under CO atmosphere (balloon) at 70 °C over

night. The reaction mixture was filtered through a celite pad and the filtrate was concentrated *in vacuo*. The residue was diluted with ethyl acetate and saturated NaHCO₃ solution. The organic layer was separated, dried over MgSO₄ and filtered. The filtrate was concentrated *in vacuo*. The residue was taken up in DMF, filtered, and purified with preparative HPLC (Method B) to give methyl 5-chloro-3-methyl-2-((pyrazolo[1,5-
 5 a]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate (2.4 mg, 4.9% yield). ¹H NMR (500 MHz, DMSO-d₆) δ 9.28 (d, J = 7.0 Hz, 1H), 8.82 (br d, J = 4.0 Hz, 1H), 8.60 (s, 1H), 8.41 (br s, 1H), 7.94 (d, J = 1.9 Hz, 1H), 7.75 (d, J = 1.9 Hz, 1H), 7.27 (dd, J = 6.9, 4.3 Hz, 1H), 4.80 (d, J = 5.8 Hz, 2H), 3.90 (s, 3H), 2.30 (s, 3H); MS (ESI+) m/z =
 10 398.9 (M+H)⁺.

EXAMPLE 116



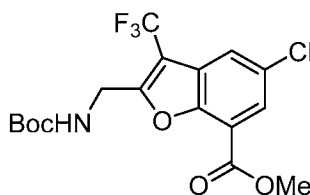
**Methyl 5-chloro-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)-3-
 15 (trifluoromethyl)benzofuran-7-carboxylate**



A) (2-(((*tert*-Butoxycarbonyl)amino)methyl)-7-(methoxycarbonyl)-5-chlorobenzofuran-3-yl)boronic acid

To a suspension of methyl 2-(((*tert*-butoxycarbonyl)amino)methyl)-5-chloro-3-
 20 (4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-7-carboxylate (108.9 mg, 0.234 mmol, Step A of Example 112) in acetone (1.2 mL) and water (1.2 mL) was added ammonium acetate (90 mg, 1.169 mmol), followed by sodium periodate (250 mg, 1.169 mmol). The reaction mixture was stirred for 3 h and then concentrated *in vacuo*. The

slurry was sonicated with water and filtered. The filter cake was rinsed with water, collected, and dried on high vacuum to give the title compound (82.3 mg, 92%). ¹H NMR (400 MHz, Chloroform-d) δ 8.16 (d, J=2.2 Hz, 1H), 7.92 (d, J=2.2 Hz, 1H), 6.94 (br s, 2H), 5.54 (br t, J=6.0 Hz, 1H), 4.49 (d, J=6.7 Hz, 2H), 4.01 (s, 3H), 1.44 (s, 9H); MS (ESI+) m/z = 327.9 (M-tBu+H)⁺.



B) Methyl 2-(((tert-butoxycarbonyl)amino)methyl)-5-chloro-3-(trifluoromethyl)benzofuran-7-carboxylate

A solution of (2-(((tert-butoxycarbonyl)amino)methyl)-7-(methoxycarbonyl)-5-chlorobenzofuran-3-yl)boronic acid (82.3 mg, 0.215 mmol), 3,3-dimethyl-1-(trifluoromethyl)-1,3-dihydro-1H-benzo[d][1,2]iodoxole (142 mg, 0.429 mmol), 1,10-phenanthroline (3.87 mg, 0.021 mmol), and potassium carbonate (59.3 mg, 0.429 mmol) in diglyme (2.1 mL) was sparged with N₂ for 5 min. Copper(I) iodide (2.04 mg, 0.011 mmol) was added and the reaction mixture was sparged with N₂ for an additional 5 min, sealed, and heated to 35 °C. The reaction mixture was cooled to room temperature and diluted with water and extracted with EtOAc. The organic layers were combined, washed with a 10% aqueous solution of LiCl, washed with brine, dried over MgSO₄, filtered, and concentrated *in vacuo*. The residue was dissolved in MeCN and purified by flash chromatography (ISCO 12 g column, 0 - 25% EtOAc in hexanes) to give the title compound (36.0 mg, 41%). ¹H NMR (400 MHz, Chloroform-d) δ 7.81 (s, 1H), 7.61 (s, 1H), 5.18 (br s, 1H), 4.66 (br s, 2H), 3.99 (s, 3H), 2.48 (s, 3H), 1.46 (s, 9H); MS (ESI+) m/z = 332.1 (M-tBu+H)⁺.

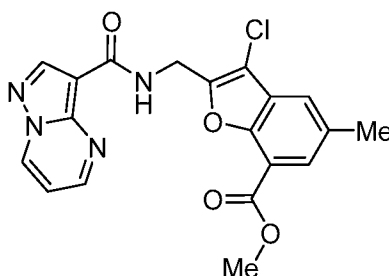
C) Methyl 5-chloro-2-((pyrazolo[1,5-a]pyrimidine-3-carboxamido)methyl)-3-(trifluoromethyl)benzofuran-7-carboxylate

To a solution of methyl 2-(((tert-butoxycarbonyl)amino)methyl)-5-chloro-3-(trifluoromethyl)benzofuran-7-carboxylate (36.0 mg, 0.088 mmol) in DCM (0.66 mL)

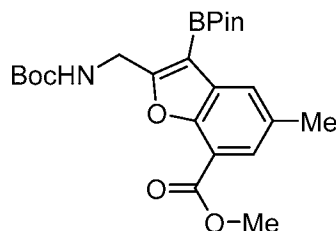
was added TFA (0.22 mL). The reaction mixture was stirred for 20 min and then concentrated *in vacuo* to obtain a residue that was used without further purification.

To this residue was added pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (32.6 mg, 0.200 mmol) and ((1H-benzo[*d*][1,2,3]triazol-1-yl)oxy)tris(dimethylamino)phosphonium hexafluorophosphate(V) (88 mg, 0.200 mmol). DMF (1.5 mL) and DIPEA (96 μ L, 0.553 mmol) and the reaction mixture was stirred at room temperature for 2.5 hours. The reaction mixture was diluted with water and extracted with EtOAc. The organic layers were combined, washed with a 10% aqueous solution of LiCl, washed with brine, dried over MgSO₄, filtered, and concentrated *in vacuo*. A third of the obtained residue was dissolved in 2 mL MeOH, filtered through a syringe filter, and purified by preparative LC/MS (Method B). Fractions containing the desired product were combined and dried *via* centrifugal evaporation to give the title compound (3.3 mg, 5%). The remaining obtained residue contained additional semipure title compound (72.8 mg) that was used without further purification. ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.32 (br d, *J*=5.8 Hz, 1H), 8.85 (br d, *J*=2.7 Hz, 1H), 8.66 - 8.55 (m, 2H), 7.96 (s, 1H), 7.89 (br d, *J*=1.8 Hz, 1H), 7.30 (br dd, *J*=6.9, 4.4 Hz, 1H), 4.98 (br d, *J*=5.5 Hz, 2H), 3.78 (s, 3H); MS (ESI+) *m/z* = 453.0 (M+H)⁺.

EXAMPLE 117



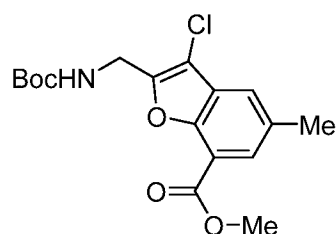
Methyl 3-chloro-5-methyl-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate



A) Methyl 2-(((tert-butoxycarbonyl)amino)methyl)-5-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-7-carboxylate

A vial was charged with methyl 2-(((tert-butoxycarbonyl)amino)methyl)-5-methylbenzofuran-7-carboxylate (3.2 g, 102 mmol, Step B of Example 85), 4,4'-di-tert-butyl-2,2'-bipyridine (0.269 g, 1.002 mmol), bis(pinacolato)diboron (2.90 g, 11.42 mmol) and (1,5-cyclooctadiene)(methoxy) iridium (I) dimer (0.4 g, 0.60 mmol) in hexane (45 ml). The reaction mixture was purged with nitrogen and heated to 80 °C for 5 hours. The reaction mixture was filtered and concentrated *in vacuo*. The crude product mixture was purified by a silica gel ISCO 120 g column eluting with 0-20% ethyl acetate in hexanes over a 15 minute gradient. The appropriate fractions were isolated and concentrated *in vacuo* to afford the product (2.5 g, 56% yield) as a solid. ¹H NMR (400 MHz, Chloroform-d) δ 8.00 - 7.78 (m, 1H), 7.76 - 7.59 (m, 1H), 4.97 - 4.52 (m, 2H), 4.22 - 3.79 (m, 3H), 2.78 - 2.25 (m, 3H), 1.60 - 1.35 (m, 21H); MS (ESI+) m/z = 390 (M-55+H)⁺.

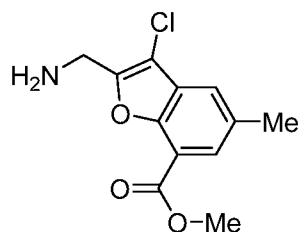
15



B) Methyl 2-(((tert-butoxycarbonyl)amino)methyl)-3-chloro-5-methylbenzofuran-7-carboxylate

A vial was charged with methyl 2-(((tert-butoxycarbonyl)amino)methyl)-5-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-7-carboxylate (300 mg, 0.674 mmol), copper(II) chloride (181 mg, 1.347 mmol) and MeOH (3 mL). The reaction mixture was heated to 50 °C for 16 hours. The solution was filtered through celite and concentrated *in vacuo*. The crude product mixture was purified by a silica gel

ISCO 24 g column eluting with 0-20% ethyl acetate/hexane over a 15 minute gradient. The appropriate fractions were isolated and concentrated *in vacuo* to afford the title compound (1.12 g, 69.8 % yield) as a solid. ¹H NMR (400MHz, Chloroform-d) δ 8.04 (d, *J* = 0.6 Hz, 1H), 7.84 (d, *J* = 6.5 Hz, 1H), 7.27 (dd, *J* = 6.5, 0.8 Hz, 1H), 3.97 (s, 3H),
 5 3.74 - 3.65 (m, 2H), 2.48 (s, 3H), 1.57 - 1.50 (m, 9H); MS (ESI+) *m/z* = 298.0 (M-55+H)⁺.



C) Methyl 2-(aminomethyl)-3-chlorobenzofuran-7-carboxylate, TFA

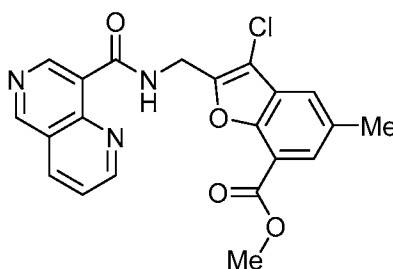
10 A vial was charged methyl 2-(((*tert*-butoxycarbonyl)amino)methyl)-3-chlorobenzofuran-7-carboxylate (1.12 g, 3.17 mmol), DCM (20 mL) and TFA (2 mL). The reaction solution was stirred at RT for 2 hours. The reaction mixture was concentrated *in vacuo* to afford the crude product (0.98 g, 85% yield) as a solid. ¹H NMR (400 MHz, Chloroform-d) δ 7.86 - 7.81 (m, 1H), 7.61 - 7.54 (m, 1H), 4.31 (s, 2H), 3.97
 15 (s, 3H), 2.48 (s, 3H); MS (ESI+) *m/z* = 237.0 (M-16)⁺.

D) Methyl 3-chloro-5-methyl-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate

20 A flask was charged with a suspension of pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (88 mg, 0.537 mmol) and BOP (238 mg, 0.537 mmol) in DMF (2 mL). To the reaction mixture was added methyl 2-(aminomethyl)-3-chloro-5-methylbenzofuran-7-carboxylate, TFA (158 mg, 0.430 mmol) and DIPEA (0.300 mL, 1.719 mmol). The reaction mixture was stirred at rt for 16 hours. The solution was quenched with water and the precipitate was collected by vacuum filtration. The crude material was purified *via*
 25 preparative HPLC (Method B) to yield the title compound (156 mg, 35 % yield. ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.32 (d, *J* = 6.1 Hz, 1H), 8.85 (br d, *J* = 2.7 Hz, 1H), 8.62 (s,

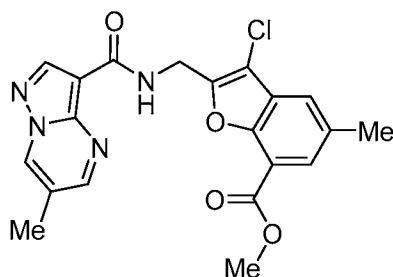
1H), 8.51 (br t, $J = 5.5$ Hz, 1H), 7.75 (s, 1H), 7.65 (s, 1H), 7.29 (dd, $J = 7.0, 4.3$ Hz, 1H), 4.86 (d, $J = 5.8$ Hz, 2H), 3.86 (s, 3H), 2.49 - 2.46 (m, 3H); MS (ESI+) $m/z = 399.0$ (M+H)⁺.

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EXAMPLE 118

methyl 2-((1,6-naphthyridine-8-carboxamido)methyl)-3-chloro-5-methylbenzofuran-7-carboxylate

A mixture of 1,6-naphthyridine-8-carboxylic acid, HCl (7 mg, 0.033 mmol),
 10 methyl 2-(aminomethyl)-3-chloro-5-methylbenzofuran-7-carboxylate, TFA (12.22 mg,
 0.033 mmol, Step C Example 117), HATU (12.64 mg, 0.033 mmol) and Hunig's Base
 (0.023 mL, 0.133 mmol) in DMF (0.5 mL) was stirred at rt for 3 h. The reaction was
 quenched with 1:1 DMF/AcOH and purified by preparative LC/MS (Method B) to give
 the title compound (2.5 mg, 5.84 μ mol, 17.57 % yield). ¹H NMR (500 MHz, DMSO-d₆) δ
 15 11.06 (br s, 1H), 9.60 (s, 1H), 9.36 (s, 1H), 9.33 - 9.26 (m, 1H), 8.79 (br d, $J = 7.3$ Hz, 1H),
 7.87 (dd, $J = 8.2, 4.3$ Hz, 1H), 7.75 (s, 1H), 7.70 - 7.60 (m, 1H), 4.95 (br d, $J = 5.5$ Hz, 2H),
 3.85 (s, 3H); MS (ESI+) $m/z = 410.1$ (M+H)⁺.

EXAMPLE 119

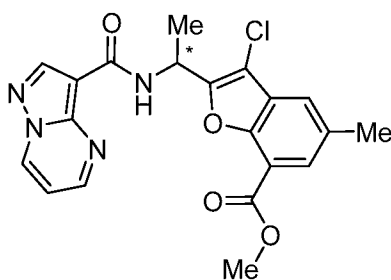
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Methyl 3-chloro-5-methyl-2-((6-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate

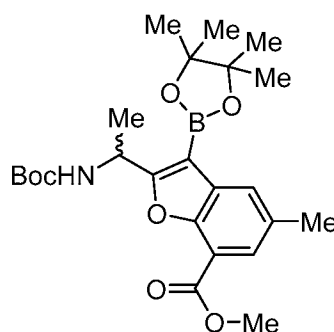
To a suspension of 6-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (20 mg, 0.113 mmol) and BOP (62.4 mg, 0.141 mmol) in DMF (2 mL) was added methyl 2-(aminomethyl)-3-chloro-5-methylbenzofuran-7-carboxylate, TFA (41.5 mg, 0.113 mmol, Step C of Example 264) and DIPEA (0.079 mL, 0.452 mmol). The reaction mixture turned into clear solution and was stirred at rt for 16 hours. The reaction was quenched with water, the precipitate that formed was filtered, and then dissolved in 2 mL of DMF for purification. The crude material was purified *via* preparative HPLC (Method B) to afford the product (15.4 mg, 33 % yield). ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.13 (s, 1H), 8.73 (s, 1H), 8.54 - 8.50 (m, 1H), 8.50 - 8.45 (m, 1H), 7.73 (s, 1H), 7.64 - 7.61 (m, 1H), 4.84 (br d, J = 5.8 Hz, 2H), 3.85 (s, 3H), 2.48 - 2.43 (m, 3H), 2.40 - 2.35 (m, 3H); MS (ESI+) *m/z* = 413.1 (M+H)⁺.

15

Example 120



Methyl-3-chloro-5-methyl-2-(1-(pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)ethyl)benzofuran-7-carboxylate

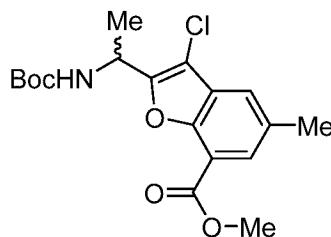


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A) Methyl 2-(1-((*tert*-butoxycarbonyl)amino)ethyl)-5-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-7-carboxylate

A vial was charged with methyl 2-(1-((*tert*-butoxycarbonyl)amino)ethyl)-5-methylbenzofuran-7-carboxylate (2 g, 6.00 mmol, Step A of Example 96), 4,4'-*tert*-butyl-2,2'-bipyridine (0.161 g, 0.6 mmol), bis(pinacolato)diboron (1.74 g, 6.84 mmol) and
 5 butyl-2,2'-bipyridine (0.161 g, 0.6 mmol), bis(pinacolato)diboron (1.74 g, 6.84 mmol) and (1,5-cyclooctadiene)(methoxy)iridium (I) dimer (0.24 g, 0.360 mmol) in hexanes (45 ml). The reaction mixture was purged with nitrogen and heated to 80 °C for 16 hours. The reaction mixture was filtered and concentrated *in vacuo*. The crude product mixture was purified by a silica gel ISCO 80 g column eluting with 0 - 20% ethyl acetate in hexanes
 10 over a 15 minute gradient. The appropriate fractions were isolated and concentrated *in vacuo* to afford the product (1.21 g, 44 % yield) as a solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.97 - 7.79 (m, 1H), 7.79 - 7.66 (m, 1H), 6.46 - 6.08 (m, 1H), 5.61 - 5.21 (m, 1H), 3.86 (s, 3H), 2.50 (s, 3H), 1.55 (d, *J* = 6.9 Hz, 3H), 1.50 - 1.32 (m, 21H); MS (ESI+) *m/z* = 404.1 (M-55+H)⁺.

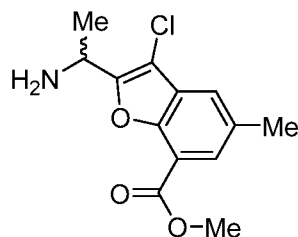
15



B) Methyl 2-(1-((*tert*-butoxycarbonyl)amino)ethyl)-3-chloro-5-methylbenzofuran-7-carboxylate

A vial was charged with methyl 2-(1-((*tert*-butoxycarbonyl)amino)ethyl)-5-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-7-carboxylate (1.2 g,
 20 2.61 mmol), copper(II) chloride (0.70 g, 5.22 mmol) and MeOH (10 mL). The reaction mixture was heated to 50 °C for 3 hours. The solution was filtered through celite and concentrated *in vacuo*. The crude product mixture was purified by a silica gel ISCO 40g column eluting with 0-30% ethyl acetate in hexanes over a 15 minute gradient. The
 25 appropriate fractions were isolated and concentrated *in vacuo* to afford the title compound (0.697, 72 % yield) as a solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.84 - 7.80 (m, 1H),

7.57 - 7.51 (m, 1H), 4.15 (q, $J = 7.1$ Hz, 1H), 4.02 - 4.01 (m, 3H), 2.54 - 2.51 (m, 3H), 1.62 - 1.58 (m, 3H), 1.49 - 1.45 (m, 9H); MS (ESI+) $m/z = 312.0$ (M-55+H)⁺.



C) Methyl 2-(aminomethyl)-3-chlorobenzofuran-7-carboxylate, TFA

5 A vial was charged methyl 2-(1-((*tert*-butoxycarbonyl)amino)ethyl)-3-chloro-5-methylbenzofuran-7-carboxylate (0.7 g, 1.9 mmol), DCM (20 mL) and TFA (2 mL). The reaction solution was stirred at room temperature for 2 hours. The reaction mixture was concentrated *in vacuo* to afford crude methyl 2-(aminomethyl)-3-chlorobenzofuran-7-carboxylate, TFA (0.72 g, 100 % yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.94 - 7.59 (m, 2H), 4.83 (q, $J = 6.9$ Hz, 1H), 4.10 - 3.72 (m, 3H), 2.54 - 2.51 (m, 3H), 1.85 - 1.52 (m, 3H); MS (ESI+) $m/z = 251.0$ (M-16)⁺.

10

D) Methyl-3-chloro-5-methyl-2-(1-(pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)ethyl)benzofuran-7-carboxylate

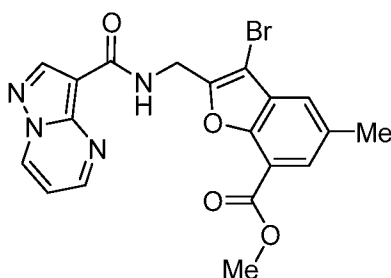
15 The above product was added to a mixture of pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (338 mg, 2.075 mmol), BOP (1.25 g, 2.83 mmol) and DIPEA (1.32 mL, 7.54 mmol) in DMF (10 mL). The reaction mixture was stirred at room temperature for 16 hours. The solution was diluted with water, and a precipitate formed which was isolated *via* filtration. This crude product was purified by a silica gel ISCO 24 g column eluting with 0-10% methanol in DCM over a 15 minute gradient. The appropriate fractions were isolated and concentrated *in vacuo* to afford the title compound (0.643 g, 83 % yield) as a solid. The racemic product mixture was separated using chiral SFC (Method L) to give the first eluting enantiomer as the title compound (245 mg, 32%) ¹H NMR (400 MHz, Methanol-*d*₄) δ 9.09 (dd, $J = 7.0, 1.7$ Hz, 1H), 8.84 (dd, $J = 4.2, 1.7$ Hz, 1H), 8.58 (s, 1H), 7.81 (d, $J = 1.8$ Hz, 1H), 7.60 (dd, $J = 1.8, 0.8$ Hz, 1H), 7.23 (dd, $J =$

20

25

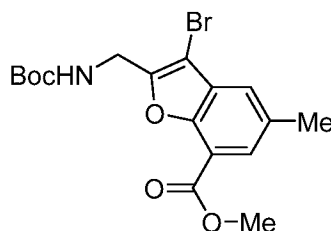
7.1, 4.2 Hz, 1H), 5.72 (d, $J = 7.1$ Hz, 1H), 3.97 (s, 3H), 2.50 (s, 3H), 1.76 (d, $J = 7.0$ Hz, 3H); MS (ESI+) $m/z = 413.2$ (M+H)⁺; Chiral purity > 99.8 % ee.

EXAMPLE 121



5

Methyl 3-bromo-5-methyl-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate



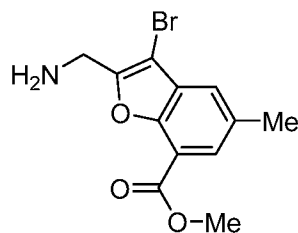
10

A) Methyl-3-bromo-2-(((*tert*-butoxycarbonyl)amino)methyl)-5-methylbenzofuran-7-carboxylate

A vial was charged methyl 2-(((*tert*-butoxycarbonyl)amino)methyl)-5-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-7-carboxylate (400 mg, 0.9 mmol, Step A of Example 117), copper(II) bromide (410 mg, 1.796 mmol) and MeOH (5 mL). The reaction mixture was heated to 50 °C for 16 hours. The solution was filtered through celite and concentrated *in vacuo*. The crude product mixture was purified by a silica gel ISCO 24 g column eluting with 0-20% ethyl acetate in hexanes over a 15 minute gradient. The appropriate fractions were isolated and concentrated *in vacuo* to afford the title compound (177 mg, 50 % yield) as a solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.75 (d, $J = 1.3$ Hz, 1H), 7.55 - 7.51 (m, 1H), 6.61 (s, 1H), 4.52 (br d, $J = 5.8$ Hz, 2H),

20

4.01 (s, 3H), 2.48 (s, 3H), 1.49 (s, 9H); MS (ESI+) $m/z = 341.9$ (M-55)⁺.



B) Methyl 2-(aminomethyl)-3-bromo-5-methylbenzofuran-7-carboxylate

5 A vial was charged methyl 2-(((*tert*-butoxycarbonyl)amino)methyl)-3-bromobenzofuran-7-carboxylate (177 mg, 0.44 mmol), DCM (10 mL) and TFA (1 mL). The reaction solution was stirred at room temperature for 2 hours. The reaction mixture was concentrated *in vacuo* to afford methyl 2-(aminomethyl)-3-bromo-5-methylbenzofuran-7-carboxylate (183 mg, 49 % yield) as a solid. ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.87 - 7.72 (m, 1H), 7.53 - 7.44 (m, 1H), 4.58 - 4.42 (m, 2H), 4.04 - 3.84 (m, 3H), 2.63 - 2.35 (m, 3H); MS (ESI+) $m/z = 281.0$ (M-16)⁺.

10

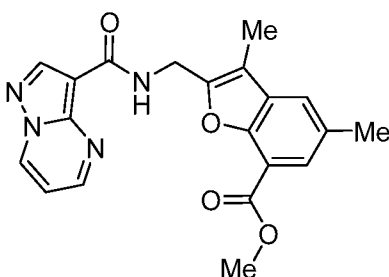
C) Methyl 3-bromo-5-methyl-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate

15 A flask was charged with a suspension of pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (91 mg, 0.555 mmol) BOP (245 mg, 0.555 mmol), methyl 2-(aminomethyl)-3-bromo-5-methylbenzofuran-7-carboxylate, TFA salt (183 mg, 0.444 mmol) and DIPEA (0.310 mL, 1.776 mmol) in DMF (5 mL). The reaction mixture was stirred at room temperature for 16 hours. The solution was quenched with water and a precipitate formed

20 which was collected by vacuum filtration. The crude material was purified *via* preparative HPLC (Method B) to yield the title compound (156 mg, 35 % yield). ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.28 (br d, $J = 6.7$ Hz, 1H), 8.84 (br d, $J = 4.0$ Hz, 1H), 8.62 (s, 1H), 8.58 - 8.49 (m, 1H), 7.74 (s, 1H), 7.57 (s, 1H), 7.28 (dd, $J = 6.9, 4.1$ Hz, 1H), 4.84 (br d, $J = 5.8$ Hz, 2H), 3.85 (s, 3H), 2.48 - 2.45 (m, 3H); MS (ESI+) $m/z =$

25 443.1 (M+H)⁺.

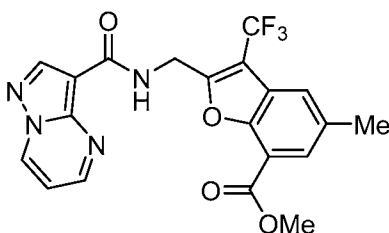
EXAMPLE 122



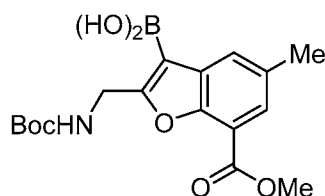
Methyl 3,5-dimethyl-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate

- 5 A vial was charged with methyl 3-bromo-5-methyl-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate (50 mg, 0.113 mmol, Example 121), methylboronic acid (13.50 mg, 0.226 mmol), Pd(OAc)₂ (2.53 mg, 0.011 mmol), tricyclohexylphosphine (3.16 mg, 0.011 mmol) and a potassium phosphate tribasic aqueous solution (0.112 mL, 0.338 mmol, 3M) in toluene (2 mL). The solution
- 10 was degassed and heated to 100°C for 16 hours. The reaction mixture was filtered and concentrated *in vacuo*. The crude material was purified *via* preparative HPLC (Method B) to yield the title compound (2.2 mg, 5 % yield). ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.25 (d, *J* = 7.0 Hz, 1H), 8.81 (br d, *J* = 3.1 Hz, 1H), 8.60 (s, 1H), 8.46 (br s, 1H), 7.63 (s, 2H), 7.26 (dd, *J* = 7.0, 4.3 Hz, 1H), 4.75 (br d, *J* = 5.8 Hz, 2H), 3.85 (s, 3H), 2.43 (s, 3H),
- 15 2.26 (s, 3H); MS (ESI⁺) *m/z* = 379.2 (M+H)⁺.

EXAMPLE 123

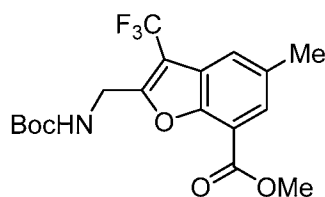


- 20 **Methyl 5-methyl-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)-3-(trifluoromethyl)benzofuran-7-carboxylate**



A) (2-(((*tert*-Butoxycarbonyl)amino)methyl)-7-(methoxycarbonyl)-5-methylbenzofuran-3-yl)boronic acid

To a suspension of methyl 2-(((*tert*-butoxycarbonyl)amino)methyl)-5-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-7-carboxylate (220.1 mg, 0.494 mmol, Step A of Example 117) in acetone (2.5 mL) and water (2.5 mL) was added ammonium acetate (190 mg, 2.471 mmol), followed by sodium periodate (529 mg, 2.471 mmol). The reaction mixture was stirred for 15 h and then concentrated *in vacuo*. The slurry was sonicated with water and filtered. The filter cake was rinsed with water, collected, and dried on high vacuum to give the title compound (174.4 mg, 97%). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.95 (s, 1H), 7.76 (d, *J*=1.3 Hz, 1H), 7.00 (br s, 2H), 5.56 (br t, *J*=6.6 Hz, 1H), 4.47 (d, *J*=6.6 Hz, 2H), 3.99 (s, 3H), 2.48 (s, 3H), 1.42 (s, 9H); MS (ESI+) *m/z* = 386.1 (M+Na)⁺.



B) Methyl 2-(((*tert*-butoxycarbonyl)amino)methyl)-5-methyl-3-(trifluoromethyl)benzofuran-7-carboxylate

A solution of (2-(((*tert*-butoxycarbonyl)amino)methyl)-7-(methoxycarbonyl)-5-methylbenzofuran-3-yl)boronic acid (100 mg, 0.275 mmol), 3,3-dimethyl-1-(trifluoromethyl)-1,3-dihydro-1H-benzo[*d*][1,2]iodoxole (109 mg, 0.330 mmol), 1,10-phenanthroline (4.96 mg, 0.028 mmol), and potassium carbonate (76 mg, 0.551 mmol) in diglyme (2754 μ L) was sparged with N₂ for 5 min. Copper(I) iodide (2.62 mg, 0.014 mmol) was added and the reaction mixture was sparged with N₂ for an additional 5 min, sealed, and heated to 35 °C. The reaction mixture was cooled to room temperature and diluted with water and extracted with EtOAc. The organic layers were combined, washed

with a 10% aqueous solution of LiCl, washed with brine, dried over MgSO₄, filtered, and concentrated *in vacuo*. The residue was dissolved in MeCN and purified by flash chromatography (Gold C18 ISCO 50 g column, 5 - 95% MeCN in water with TFA) to give the title compound (65.2 mg, 61%). ¹H NMR (400 MHz, Chloroform-d) δ 7.81 (s, 1H), 7.61 (s, 1H), 5.18 (br s, 1H), 4.66 (br s, 2H), 3.99 (s, 3H), 2.48 (s, 3H), 1.46 (s, 9H); MS (ESI+) m/z = 332.1 (M-*t*Bu+H)⁺.

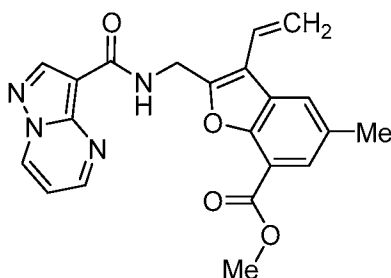
C) Methyl 5-methyl-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)-3-(trifluoromethyl)benzofuran-7-carboxylate

10 To a solution of methyl 2-(((*tert*-butoxycarbonyl)amino)methyl)-5-methyl-3-(trifluoromethyl)benzofuran-7-carboxylate (65.2 mg, 0.168 mmol) in DCM (1.3 mL) was added TFA (0.42 mL). The reaction mixture was stirred for 20 min and then concentrated *in vacuo* to obtain a residue that was used without further purification.

To this residue was added pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (30.1 mg, 0.185 mmol) and ((1H-benzo[*d*][1,2,3]triazol-1-yl)oxy)tris(dimethylamino)phosphonium hexafluorophosphate(V) (82 mg, 0.185 mmol). DMF (1.7 mL) and DIPEA (88 μL, 0.504 mmol) were added and the reaction mixture was stirred at room temperature for 15 hours. An additional portion of pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (6 mg, 0.037 mmol), ((1H-benzo[*d*][1,2,3]triazol-1-yl)oxy)tris(dimethylamino)phosphonium hexafluorophosphate(V) (16 mg, 0.054 mmol), and DIPEA (18 μL, 0.188 mmol) were added and the reaction mixture was stirred for 20 min. The reaction mixture was diluted with water and extracted with EtOAc. The organic layers were combined, washed with a 10% aqueous solution of LiCl, washed with brine, dried over MgSO₄, filtered, and concentrated *in vacuo*. A fourth of the obtained residue was dissolved in 2 mL MeOH, filtered through a syringe filter, and purified by preparative LC/MS (Method B). Fractions containing the desired product were combined and dried *via* centrifugal evaporation to give the title compound (11.4 mg, 16%). The remaining obtained residue contained additional semipure title compound (71.0 mg) that was used without further purification. ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.32 (br d, *J*=7.0 Hz, 1H), 8.85 (br d, *J*=2.4 Hz, 1H), 8.64 - 8.55 (m, 2H), 7.77 (s, 1H), 7.72 (s, 1H), 7.33 -

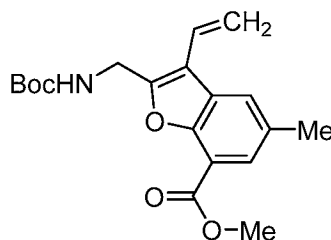
7.25 (m, 1H), 4.96 (br d, $J=5.2$ Hz, 2H), 3.76 (s, 3H), 2.47 (s, 3H); MS (ESI+) m/z = 433.1 (M+H)⁺.

EXAMPLE 124



5

Methyl 5-methyl-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)-3-vinylbenzofuran-7-carboxylate



10

A) Methyl 2-(((*tert*-butoxycarbonyl)amino)methyl)-5-methyl-3-vinylbenzofuran-7-carboxylate

A vial was charged with methyl 2-(((*tert*-butoxycarbonyl)amino)methyl)-5-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-7-carboxylate (300 mg, 0.674 mmol, Step A of Example 117), bromoethene (1.347 mL, 1.347 mmol), 1,1'-bis(*di-tert*-butylphosphino)ferrocene palladium dichloride (43.9 mg, 0.067 mmol) and a potassium phosphate tribasic aqueous solution (0.674 mL, 2.021 mmol, 3M) in toluene (5 mL). The solution was degassed and heated to 50 °C for 1 hour.

The reaction solution was diluted with ethyl acetate, washed with saturated sodium bicarbonate, water, and saturated sodium chloride, dried with anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product mixture was purified by a silica gel ISCO 40 g column eluting with 0-20% ethyl acetate / hexane over a 15 minute

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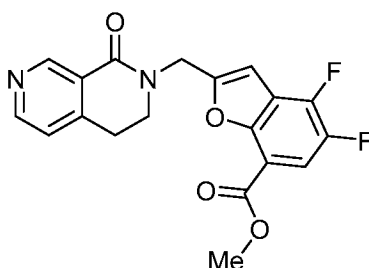
gradient. The appropriate fractions were isolated and concentrated *in vacuo* to afford the title compound (85 mg, 36.5 % yield) as a solid. ¹H NMR (400 MHz, Chloroform-d) δ 7.85 - 7.68 (m, 2H), 7.05 - 6.72 (m, 1H), 5.98 - 5.68 (m, 1H), 5.56 - 5.39 (m, 1H), 5.26 - 5.01 (m, 1H), 4.75 - 4.40 (m, 2H), 4.06 - 3.82 (m, 3H), 2.66 - 2.39 (m, 3H), 1.56 - 1.36 (m, 9H); MS (ESI+) m/z = 290.1 (M-55)⁺.

B) Methyl 5-methyl-2-((pyrazolo[1,5-a]pyrimidine-3-carboxamido)methyl)-3-vinylbenzofuran-7-carboxylate

A vial was charged methyl 2-(((*tert*-butoxycarbonyl)amino)methyl)-5-methyl-3-vinylbenzofuran-7-carboxylate (85 mg, 0.25 mmol), DCM (5 mL) and TFA (0.5 mL). The reaction solution was stirred at room temperature for 2 hours. The reaction mixture was concentrated *in vacuo* to afford methyl-2-(aminomethyl)-5-methyl-3-vinylbenzofuran-7-carboxylate, TFA (88 mg, 0.25 mmol, 100 % yield) as a solid. To a solution of methyl 2-(aminomethyl)-5-methyl-3-vinylbenzofuran-7-carboxylate, TFA (88 mg, 0.25 mmol) in DMF (5 mL) was added pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (30.3 mg, 0.186 mmol), BOP (123 mg, 0.279 mmol) and DIPEA (0.097 mL, 0.558 mmol). The reaction mixture was stirred at RT for 16 hours. The solution was quenched with water and the precipitated product was collected by vacuum filtration. The crude material was purified *via* preparative HPLC (Method B) to yield the title compound (11.6 mg, 16 % yield). ¹H NMR (500 MHz, DMSO-d₆) δ 9.32 - 9.22 (m, 1H), 8.87 - 8.78 (m, 1H), 8.64 - 8.57 (m, 1H), 8.52 - 8.44 (m, 1H), 8.00 - 7.96 (m, 1H), 7.68 (s, 1H), 7.30 - 7.25 (m, 1H), 7.10 - 7.02 (m, 1H), 5.94 (d, *J* = 17.7 Hz, 1H), 5.47 (d, *J* = 11.9 Hz, 1H), 4.86 (br d, *J* = 5.5 Hz, 2H), 3.88 - 3.82 (m, 3H), 2.48 - 2.43 (m, 3H); MS (ESI+) m/z = 391.2 (M+H)⁺.

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EXAMPLE 125

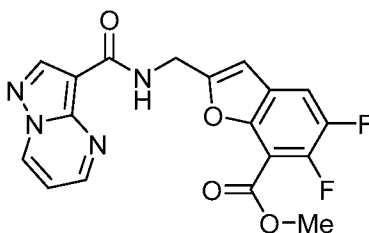


Methyl 4,5-difluoro-2-((1-oxo-3,4-dihydro-2,7-naphthyridin-2(1H)-yl)methyl)benzofuran-7-carboxylate

5 3,4-Dihydro-1*H*-pyrano[3,4-*c*]pyridin-1-one, HCl (22.99 mg, 0.124 mmol) and methyl 2-(aminomethyl)-4,5-difluorobenzofuran-7-carboxylate, TFA (40 mg, 0.113 mmol, Step E in Example 138) were taken up in Pyridine (1 mL). The reaction was sealed and heated at 125 °C for 18 hours. The reaction mixture was diluted with saturated NaHCO₃ solution, diluted with water, and extracted with ethyl acetate. The organic layers
10 were separated, combined, and concentrated *in vacuo*. The residue was dissolved in MeOH, filtered, and purified *via* HPLC (method B) to give the title compound (2.3 mg, 5%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.95 (s, 1H), 8.61 (d, *J* = 4.9 Hz, 1H), 7.81 (dd, *J* = 11.3, 7.9 Hz, 1H), 7.38 (d, *J* = 4.9 Hz, 1H), 7.18 (s, 1H), 4.93 (s, 2H), 3.86 (s, 3H), 3.76 (t, *J* = 6.6 Hz, 2H), 3.10 (t, *J* = 6.6 Hz, 2H); MS (ESI+) *m/z* = 373.0 (M+H)⁺.

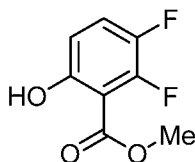
15

EXAMPLE 126



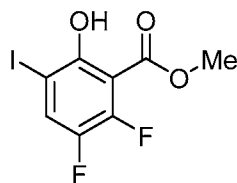
Methyl 5,6-difluoro-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate

20



A) Methyl 2,3-difluoro-6-hydroxybenzoate

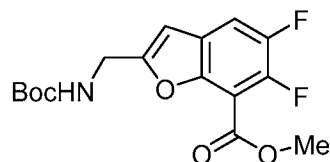
To a solution of 2,3-difluoro-6-hydroxybenzoic acid (2 g, 11.49 mmol) in thionyl chloride (2.52 mL, 34.5 mmol) was added a few drops of DMF. The reaction mixture was stirred at rt over night. The reaction was then concentrated *in vacuo* and azeotroped three times with toluene to remove excess thionyl chloride. To the residue were added DCM (10 mL), MeOH (10 mL) and TEA (6.40 mL, 45.9 mmol). The reaction mixture was stirred at rt for 5 h. The solvents were removed under reduced pressure and the residue was diluted with ethyl acetate and brine. The organic layer was separated, washed with brine, dried over MgSO₄ and filtered. The filtrate was concentrated *in vacuo*. to give methyl 2,3-difluoro-6-hydroxybenzoate (1.85 g, 86% yield) as a light brown solid. ¹H NMR (400 MHz, CHLOROFORM-d) δ 10.78 (d, *J* = 1.2 Hz, 1H), 7.66 (dd, *J* = 10.4, 9.0 Hz, 1H), 6.80 (dd, *J* = 11.4, 6.7 Hz, 1H), 3.98 (s, 3H).



B) Methyl 2,3-difluoro-6-hydroxy-5-iodobenzoate

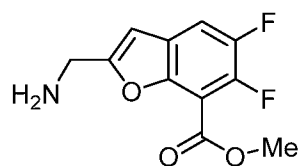
To a solution of methyl 2,3-difluoro-6-hydroxybenzoate (1.8 g, 9.57 mmol) in DMF (20 mL) were added sodium iodide (1.793 g, 11.96 mmol) and chloramine T trihydrate (3.23 g, 11.48 mmol) slowly. The reaction mixture was stirred at rt over night. The reaction mixture was diluted with ethyl acetate and 1 N aqueous HCl solution. The organic layer was separated and washed with brine, Na₂S₂O₃ solution, dried over MgSO₄, and filtered. The filtrate was concentrated *in vacuo* to give a light yellow oil. The crude residue was dissolved in DCM and purified by silica gel column chromatography (40 g column, 0 – 20% ethyl acetate in hexanes) to give methyl 2,3-difluoro-6-hydroxy-5-iodobenzoate (1.5 g, 50%) as a white solid. ¹H NMR (400 MHz, Chloroform-d) δ 11.70

(d, $J=2.0$ Hz, 1H), 10.78 (d, $J=1.4$ Hz, 1H), 7.74 (dd, $J=10.0, 8.8$ Hz, 1H), 7.66 (dd, $J=10.4, 9.0$ Hz, 1H), 6.80 (dd, $J=11.4, 6.6$ Hz, 1H), 4.01 (s, 3H), 3.98 (s, 3H).



5 **C) Methyl 2-(((tert-butoxycarbonyl)amino)methyl)-5,6-difluorobenzofuran-7-carboxylate**

To the reaction mixture of methyl 2,3-difluoro-6-hydroxy-5-iodobenzoate (1.5 g, 4.78 mmol), tert-butyl prop-2-yn-1-ylcarbamate (0.815 g, 5.25 mmol) in DMF (12 mL) were added TEA (5.33 mL, 38.2 mmol) and copper(I) iodide (0.091 g, 0.478 mmol). The
 10 reaction mixture was purged with nitrogen stream for 5 min, then bis(triphenylphosphine)palladium(II) chloride (0.335 g, 0.478 mmol) was added. The resulting mixture was heated at 80 °C under nitrogen stream for 2 h. The reaction mixture was cooled down, diluted with ethyl acetate and 1N aqueous HCl solution. The organic layer was separated, washed with brine, Na₂S₂O₃ solution, dried over MgSO₄,
 15 and filtered. The filtrate was concentrated *in vacuo*. The crude residue was dissolved in DCM and purified by silica gel column chromatography (40 g column, 0 – 20% ethyl acetate in hexanes) to give methyl 2-(((tert-butoxycarbonyl)amino)methyl)-5,6-difluorobenzofuran-7-carboxylate (0.8 g, 49.1%) as a light yellow solid. ¹H NMR (400 MHz, CHLOROFORM-*d*) δ7.79 (dd, $J=11.1, 7.7$ Hz, 1H), 6.81 (s, 1H), 5.23
 20 - 5.00 (m, 1H), 4.53 (br d, $J=5.8$ Hz, 2H), 4.01 (s, 3H), 1.49 (s, 9H).



D) Methyl 2-(aminomethyl)-5,6-difluorobenzofuran-7-carboxylate

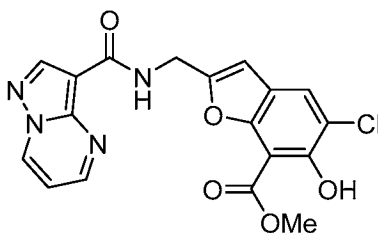
To a solution of methyl 2-(((tert-butoxycarbonyl)amino)methyl)-5,6-difluorobenzofuran-7-carboxylate (0.42 g, 1.231 mmol) in DCM (5 mL) was added TFA

(0.948 mL, 12.31 mmol). The reaction mixture was stirred at rt for 2 h. The reaction was then concentrated *in vacuo* and azeotroped three times with toluene to remove excess TFA. The crude product was placed under high vacuum overnight to give methyl 2-(aminomethyl)-5,6-difluorobenzofuran-7-carboxylate TFA salt (0.43 g, 98 % yield) as a brown solid. ¹H NMR (400 MHz, Methanol-d₄) δ 7.95 (dd, *J* = 11.3, 7.8 Hz, 1H), 7.24 (t, *J* = 0.7 Hz, 1H), 4.45 (s, 2H), 4.02 (s, 3H); MS (ESI+) *m/z* = 242.1 (M+H)⁺.

E) Methyl 5,6-difluoro-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate

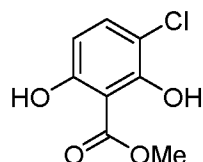
To a suspension of pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (185 mg, 1.135 mmol) in DMF (10 mL) was added BOP (540 mg, 1.222 mmol). The reaction mixture was stirred at rt for 20 min, then a solution of methyl 2-(aminomethyl)-5,6-difluorobenzofuran-7-carboxylate TFA salt (310 mg, 0.873 mmol) in THF (3 mL) and DIPEA (0.610 mL, 3.49 mmol) were added. The resulting mixture was stirred at rt for 1 h. The reaction mixture turned into clear solution after addition of DIPEA and solid crashed out after 10 min. After 1 h, the reaction mixture was diluted with water and filtered to give light brown solid as the pure product methyl 5,6-difluoro-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate (300 mg, 85 % yield). The solid was not soluble in DMF. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.35 (br d, *J* = 6.6 Hz, 1H), 8.85 (br d, *J* = 2.6 Hz, 1H), 8.64 (s, 1H), 8.56 (br t, *J* = 5.5 Hz, 1H), 7.84 (br dd, *J* = 11.4, 7.9 Hz, 1H), 7.31 (br dd, *J* = 6.3, 4.5 Hz, 1H), 7.05 (s, 1H), 4.83 (br d, *J* = 5.6 Hz, 2H), 3.91 (s, 3H); MS (ESI+) *m/z* = 387.2 (M+H)⁺.

EXAMPLE 127



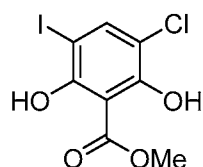
25

Methyl 5-chloro-6-hydroxy-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate



5 **A) Methyl 3-chloro-2,6-dihydroxybenzoate**

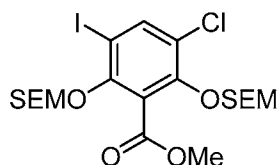
To a flask charged with methyl 2,6-dihydroxybenzoate (1.5 g, 8.92 mmol) was added sulfuryl chloride, 1 M in DCM (13.38 mL, 13.38 mmol) under N₂. The mixture was cooled to 0 °C and Et₂O (1.391 mL, 13.38 mmol) was added. The reaction mixture was warmed to room temperature and stirred for 70 min. Additional portions of sulfuryl chloride, 1 M in DCM (4.5 mL, 4.5 mmol) and Et₂O (0.47 mL, 4.5 mmol) were added and the reaction mixture was stirred for 30 min. Additional portions of sulfuryl chloride, 1 M in DCM (2.3 mL, 2.3 mmol) and Et₂O (0.24 mL, 2.3 mmol) were added and the reaction mixture was stirred for 15 min. The reaction mixture was concentrated *in vacuo* to give the title compound (1.7856 g, 99%). ¹H NMR (400 MHz, CHLOROFORM-*d*) δ 10.31 (br s, 1H), 9.51 (br s, 1H), 7.44 (d, *J*=9.0 Hz, 1H), 6.51 (d, *J*=8.9 Hz, 1H), 4.14 (s, 3H).



20 **B) Methyl 3-chloro-2,6-dihydroxy-5-iodobenzoate**

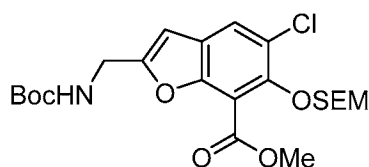
To a suspension of methyl 3-chloro-2,6-dihydroxybenzoate (1.7856 g, 8.81 mmol) in AcOH (5.04 mL) was added NIS (2.97 g, 13.22 mmol). The headspace was flushed with N₂ and the vessel was sealed and heated to 65 °C for 30 min. The reaction mixture was cooled to rt, quenched with a saturated aqueous solutions of NaHCO₃ and Na₂S₂O₃, and extracted with EtOAc. The organic layers were combined, washed with brine, dried over MgSO₄, filtered, and concentrated *in vacuo*. The residue was dissolved in DCM and

purified by flash chromatography (ISCO 80 g column, 0 - 40% EtOAc in hexanes) to give the title compound (1.6310 g, 56%). ¹H NMR (400 MHz, CHLOROFORM-d) δ 10.47 (s, 1H), 10.20 (br s, 1H), 7.91 (s, 1H), 4.17 (s, 3H).



5 **C) Methyl 3-chloro-5-iodo-2,6-bis((2-(trimethylsilyl)ethoxy)methoxy)benzoate**

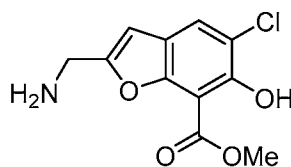
To a solution of methyl 3-chloro-2,6-dihydroxy-5-iodobenzoate (1.7366 g, 5.29 mmol) in DCM (26.4 mL) was added Hunig's Base (5.54 mL, 31.7 mmol) at 0 °C. SEMCl (2.344 mL, 13.22 mmol) was added and the reaction vessel was flushed with N₂, sealed, and warmed to room temperature and stirred for 5 h. An additional portion of SEMCl (0.47 mL, 2.65 mmol) was added and the reaction mixture was stirred for 1.5 h. The reaction mixture was quenched with water and extracted with EtOAc. The organic layers were combined, washed with brine, dried over MgSO₄, filtered, and concentrated *in vacuo*. The residue was dissolved in DCM and purified by flash chromatography (ISCO 80 g column, 0 - 10% EtOAc in hexanes) to give the title compound (3.0224 g, 97%). ¹H NMR (400 MHz, CHLOROFORM-d) δ 7.88 (s, 1H), 5.19 (s, 2H), 5.15 (s, 2H), 3.93 (s, 3H), 3.91 - 3.81 (m, 4H), 1.05 - 0.99 (m, 4H), 0.06 (s, 9H), 0.05 (s, 9H).



20 **D) Methyl 2-(((tert-butoxycarbonyl)amino)methyl)-5-chloro-6-((2-(trimethylsilyl)ethoxy)methoxy)benzofuran-7-carboxylate**

To a solution of *tert*-butyl prop-2-yn-1-ylcarbamate (916 mg, 5.90 mmol) and methyl 3-chloro-5-iodo-2,6-bis((2-(trimethylsilyl)ethoxy)methoxy)benzoate (3.0224 g, 5.13 mmol) in DMF (477 μl) was added Et₃N (638 μl, 4.57 mmol). The mixture was sparged with N₂ for 13 min and then copper(I) iodide (98 mg, 0.513 mmol) and

bis(triphenylphosphine)palladium(II) chloride (180 mg, 0.257 mmol) was added. The reaction mixture was sparged with N₂ for an additional 3 min, sealed, and heated to 80 °C for 2.5 h. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. The residue was dissolved in DCM and purified by flash chromatography (ISCO 120 g column, 0 - 30% EtOAc in hexanes) to give the title compound (1.3544 g, 54%). ¹H NMR (400 MHz, Chloroform-d) δ 7.66 (s, 1H), 6.57 (s, 1H), 5.22 (s, 2H), 5.00 (br d, *J*=2.9 Hz, 1H), 4.45 (br d, *J*=5.9 Hz, 2H), 4.03 (s, 3H), 3.94 - 3.87 (m, 2H), 1.48 (s, 9H), 1.02 (d, *J*=17.2 Hz, 2H), 0.06 (s, 9H); MS (ESI+) *m/z* = 524.0 (M+K)⁺.



10

E) Methyl 2-(aminomethyl)-5-chloro-6-hydroxybenzofuran-7-carboxylate

To a solution of methyl 2-(((*tert*-butoxycarbonyl)amino)methyl)-5-chloro-6-((2-(trimethylsilyl)ethoxy)methoxy)benzofuran-7-carboxylate (184 mg, 0.379 mmol) in DCM (2839 μL) was added TFA (946 μL). The reaction mixture was stirred for 2 h and then concentrated *in vacuo* and placed on high vacuum. The residue was dissolved in MeCN and purified by flash chromatography (Gold C18 ISCO 50 g column, 5 - 95% MeCN in water with TFA) to give the title compound (39.5 mg, 28%) as the TFA salt. ¹H NMR (400 MHz, Methanol-d₄) δ 7.85 (s, 1H), 6.78 (s, 1H), 4.11 (d, *J*=0.7 Hz, 2H), 4.09 (s, 3H); MS (ESI+) *m/z* = 238.9 (M-NH₂)⁺.

20

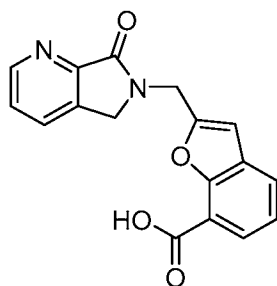
F) Methyl 5-chloro-6-hydroxy-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate

To a flask charged with methyl 2-(aminomethyl)-5-chloro-6-hydroxybenzofuran-7-carboxylate, TFA (39.5 mg, 0.107 mmol), pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (22.7 mg, 0.139 mmol) and ((1H-benzo[*a*][1,2,3]triazol-1-yl)oxy)tris(dimethylamino)phosphonium hexafluorophosphate(V) (61.4 mg, 0.139 mmol) was added DMF (1.1 mL) and DIPEA (67 μL, 0.385 mmol) and the reaction mixture was

25

stirred at room temperature for 45 min. The reaction mixture was diluted with water and extracted with EtOAc. The organic layers were combined, washed with a 10% aqueous solution of LiCl, washed with brine, dried over MgSO₄, filtered, and concentrated *in vacuo*. A third of the obtained residue was dissolved in 2 mL MeOH, filtered through a syringe filter, and purified by preparative LC/MS (Method B). Fractions containing the desired product were combined and dried *via* centrifugal evaporation to give the title compound (2.0 mg, 5%). The remaining obtained residue contained additional semipure title compound (72.8 mg) that was used without further purification. ¹H NMR (500 MHz, DMSO-d₆) δ 9.26 (br d, *J*=6.7 Hz, 1H), 8.80 (br s, 1H), 8.59 (s, 1H), 8.46 (br s, 1H), 7.91 (s, 1H), 7.25 (br dd, *J*=6.7, 4.3 Hz, 1H), 6.71 (s, 1H), 4.72 (br d, *J*=5.5 Hz, 2H), 3.94 (s, 3H); MS (ESI+) *m/z* = 401.0 (M+H)⁺.

EXAMPLE 128



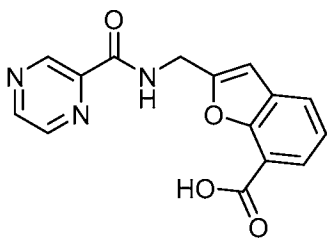
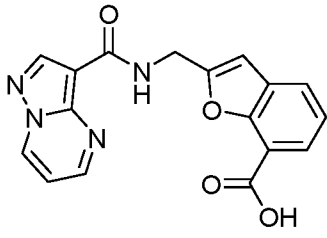
15 2-((7-Oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)methyl)benzofuran-7-carboxylic acid

Methyl 2-((3-oxo-1,3-dihydro-2H-pyrrolo[3,4-c]pyridin-2-yl)methyl)benzofuran-7-carboxylate (1.39 g, 4.31 mmol, Example 2) was taken up in THF (17.25 ml), methanol (8.62 ml), and water (17.25 ml). LiOH (1.03 g, 43.1 mmol) was added and reaction stirred was at room temperature for 1 hour. The solvent was removed under reduced pressure and water was added. The pH value of the mixture was adjusted to 4-5 with acetic acid and the aqueous layer turned cloudy. The aqueous layer was extracted with EtOAc. The combined organic extracts were dried with sodium sulfate, filtered, and concentrated *in vacuo* to give 2-((3-oxo-1,3-dihydro-2H-pyrrolo[3,4-c]pyridin-2-yl)methyl)benzofuran-7-carboxylic acid (590 mg, 1.91 mmol, 44.4 % yield). ¹H NMR (400 MHz, Methanol-d₄) δ 8.98 (s, 1H), 8.72 (d, *J* = 5.3 Hz, 1H), 7.89 (dd, *J* = 7.6, 1.2

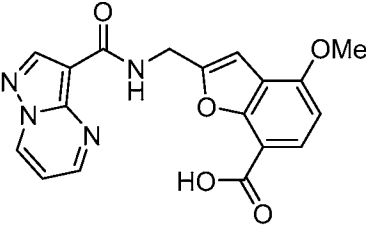
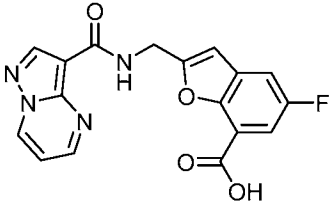
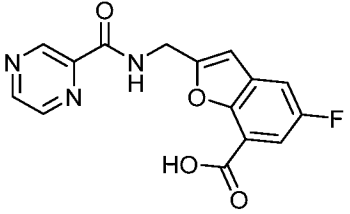
Hz, 1H), 7.80 (dd, $J = 7.7, 1.2$ Hz, 1H), 7.71 - 7.66 (m, 1H), 7.31 (t, $J = 7.7$ Hz, 1H), 6.90 (s, 1H), 5.04 (s, 2H), 4.77 (s, 2H); MS (ESI+) $m/z = 309.3$ (M+H)⁺.

EXAMPLES 129- 184

5 The following acids were synthesized from the corresponding methyl esters according to the hydrolysis procedure outlined in Example 128.

Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺
130		2-((Pyrazine-2-carboxamido)methyl)benzofuran-7-carboxylic acid	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.36 (s, 1H), 8.73 (d, $J = 5.2$ Hz, 1H), 7.88 - 7.77 (m, 3H), 7.62 (d, $J = 5.2$ Hz, 1H), 7.32 (t, $J = 7.6$ Hz, 1H), 6.88 (s, 1H), 6.73 (d, $J = 7.3$ Hz, 1H), 5.43 (s, 2H)	298.1
131		2-((pyrazolo[1,5-a]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylic acid	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.25 (br d, $J = 6.7$ Hz, 1H), 8.81 (br d, $J = 3.1$ Hz, 1H), 8.61 (s, 1H), 8.59 - 8.53 (m, 1H), 7.82 (br d, $J = 7.3$ Hz, 1H), 7.80 - 7.75 (m, 1H), 7.31 (br t, $J = 7.6$ Hz, 1H), 7.29 - 7.24 (m, 1H), 6.84 (s, 1H), 4.79 (br d, $J = 5.5$ Hz, 2H), 3.67 (br s, 2H)	337.0

Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺
132		2-((1,6-naphthyridine-8-carboxamido)methyl)benzofuran-7-carboxylic acid	¹ H NMR (500 MHz, DMSO-d ₆) δ 10.97 (br s, 1H), 9.60 (s, 1H), 9.36 (s, 1H), 9.34 - 9.26 (m, 1H), 8.79 (br d, <i>J</i> =8.2 Hz, 1H), 7.98 - 7.82 (m, 2H), 7.80 (br d, <i>J</i> =7.6 Hz, 1H), 7.33 (br t, <i>J</i> =7.6 Hz, 1H), 6.95 (s, 1H), 4.91 (br d, <i>J</i> =5.5 Hz, 2H)	348.1
133		3-Chloro-2-((pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylic acid	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.30 - 9.26 (m, 1H), 8.85 - 8.81 (m, 1H), 8.61 (s, 1H), 8.53 (br t, <i>J</i> = 5.6 Hz, 1H), 7.84 (d, <i>J</i> = 7.3 Hz, 1H), 7.71 (d, <i>J</i> = 7.6 Hz, 1H), 7.41 (t, <i>J</i> = 7.6 Hz, 1H), 7.27 (dd, <i>J</i> = 7.0, 4.3 Hz, 1H), 4.85 (d, <i>J</i> = 5.8 Hz, 2H)	371.1
134		4-Methyl-2-((pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylic acid	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.29 - 9.23 (m, 1H), 8.82 (d, <i>J</i> = 2.7 Hz, 1H), 8.62 (s, 1H), 8.57 - 8.51 (m, 1H), 7.70 (d, <i>J</i> = 7.6 Hz, 1H), 7.27 (dd, <i>J</i> = 6.9, 4.1 Hz, 1H), 7.13 (d, <i>J</i> = 7.9 Hz, 1H), 6.88 (s, 1H), 4.79 (br d, <i>J</i> = 5.8 Hz, 2H), 2.48 (s, 3H)	351.0

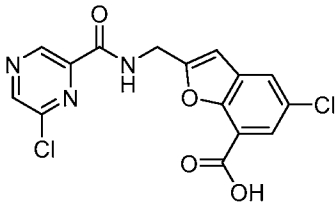
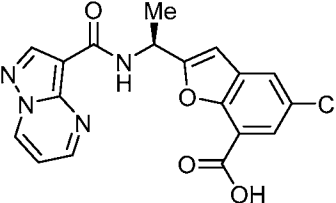
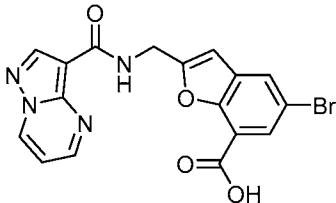
Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺
135		4-Methoxy-2-((pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylic acid	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.22 (br d, <i>J</i> = 7.0 Hz, 1H), 8.80 (br d, <i>J</i> = 3.4 Hz, 1H), 8.60 (s, 1H), 8.54 (br t, <i>J</i> = 5.6 Hz, 1H), 7.81 (d, <i>J</i> = 8.5 Hz, 1H), 7.25 (dd, <i>J</i> = 7.0, 4.3 Hz, 1H), 6.88 (d, <i>J</i> = 8.5 Hz, 1H), 6.77 (s, 1H), 4.75 (br d, <i>J</i> = 5.8 Hz, 2H), 3.92 (s, 3H)	367.1
136		5-Fluoro-2-((pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylic acid	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.34 (dd, <i>J</i> = 7.0, 1.6 Hz, 1H), 8.84 (dd, <i>J</i> = 4.2, 1.6 Hz, 1H), 8.64 (s, 1H), 8.53 (t, <i>J</i> = 5.9 Hz, 1H), 7.69 (dd, <i>J</i> = 8.4, 2.7 Hz, 1H), 7.52 (dd, <i>J</i> = 9.7, 2.7 Hz, 1H), 7.30 (dd, <i>J</i> = 7.0, 4.2 Hz, 1H), 6.85 (s, 1H), 4.80 (d, <i>J</i> = 5.8 Hz, 2H)	355.2
137		5-fluoro-2-((pyrazine-2-carboxamido)methyl)benzofuran-7-carboxylic acid	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.60 (br t, <i>J</i> = 5.8 Hz, 1H), 9.22 (s, 1H), 8.90 (br d, <i>J</i> = 2.1 Hz, 1H), 8.77 (s, 1H), 7.74 - 7.57 (m, 1H), 7.50 (br d, <i>J</i> = 9.8 Hz, 1H), 6.82 (s, 1H), 4.71 (br d, <i>J</i> = 5.8 Hz, 2H)	316.2

Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺
138		5-Chloro-2-((pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylic acid	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.32 (br d, <i>J</i> = 6.7 Hz, 1H), 8.84 (br d, <i>J</i> = 3.4 Hz, 1H), 8.64 (s, 1H), 8.53 (br t, <i>J</i> = 5.5 Hz, 1H), 7.76 (s, 1H), 7.62 (s, 1H), 7.38 - 7.20 (m, 1H), 6.78 (s, 1H), 4.79 (br d, <i>J</i> = 5.5 Hz, 2H)	371.0
139		5-Chloro-2-((5-methoxypyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylic acid	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.97 (d, <i>J</i> = 7.5 Hz, 1H), 8.38 (s, 1H), 8.19 (br t, <i>J</i> = 5.5 Hz, 1H), 7.86 (s, 1H), 7.69 (s, 1H), 6.86 (s, 1H), 6.70 (d, <i>J</i> = 7.5 Hz, 1H), 4.79 (d, <i>J</i> = 5.8 Hz, 2H), 4.03 (s, 3H)	401.1
140		5-Chloro-2-((1-oxo-3,4-dihydro-2,7-naphthyridin-2(1 <i>H</i>)-yl)methyl)benzofuran-7-carboxylic acid	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.94 (br s, 1H), 8.60 (br d, <i>J</i> = 4.0 Hz, 1H), 7.86 (d, <i>J</i> = 1.6 Hz, 1H), 7.69 (d, <i>J</i> = 1.8 Hz, 1H), 7.49 (br d, <i>J</i> = 5.0 Hz, 1H), 6.90 (s, 1H), 4.89 (s, 2H), 3.73 (t, <i>J</i> = 6.6 Hz, 2H), 3.11 (t, <i>J</i> = 6.6 Hz, 2H)	357.2

Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺
141		2-((1,6-naphthyridine-8-carboxamido)methyl)-5-chlorobenzofuran-7-carboxylic acid	¹ H NMR (500 MHz, DMSO-d ₆) δ 10.90 (br t, <i>J</i> =5.5 Hz, 1H), 9.54 (s, 1H), 9.29 (s, 1H), 9.27 - 9.21 (m, 1H), 8.73 (br d, <i>J</i> =8.2 Hz, 1H), 7.86 (s, 1H), 7.81 (dd, <i>J</i> =8.1, 4.4 Hz, 1H), 7.65 (d, <i>J</i> =1.8 Hz, 1H), 6.89 (s, 1H), 4.85 (br d, <i>J</i> =5.5 Hz, 2H)	382.0
142		5-Chloro-2-((1-methyl-6-oxo-1,6-dihydropyrimidine-5-carboxamido)methyl)benzofuran-7-carboxylic acid	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.61 (br t, <i>J</i> =5.3 Hz, 1H), 8.75 (s, 1H), 8.70 (s, 1H), 7.92 (s, 1H), 7.71 (s, 1H), 6.82 (s, 1H), 4.75 (br d, <i>J</i> =5.8 Hz, 2H), 3.53 (s, 3H)	362.0
143		5-Chloro-2-((1-propyl-6-oxo-1,6-dihydropyrimidine-5-carboxamido)methyl)benzofuran-7-carboxylic acid	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.62 - 9.53 (m, 1H), 8.76 (s, 1H), 8.69 (s, 1H), 7.90 (s, 1H), 7.70 (s, 1H), 6.82 (s, 1H), 4.73 (br d, <i>J</i> =5.8 Hz, 2H), 3.97 (br t, <i>J</i> =7.2 Hz, 2H), 1.79 - 1.64 (m, 2H), 0.88 (br t, <i>J</i> =7.3 Hz, 3H)	390.3
144		2-((3H-Imidazo[4,5-c]pyridine-7-carboxamido)methyl)-5-chlorobenzofuran-7-carboxylic acid	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.75 (br s, 1H), 9.09 (s, 1H), 8.90 (s, 1H), 8.54 (br s, 1H), 7.85 (s, 1H), 7.68 (s, 1H), 6.86 (s, 1H), 4.83 (br d, <i>J</i> =4.9 Hz, 2H)	371.2

Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺
147		5-Chloro-2-((1-methyl-1 <i>H</i> -imidazo[4,5- <i>c</i>]pyridine-7-carboxamido)methyl)benzofuran-7-carboxylic acid	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.81 - 9.70 (m, 1H), 9.18 (s, 1H), 8.95 (s, 1H), 8.63 (s, 1H), 7.92 (d, <i>J</i> = 2.0 Hz, 1H), 7.72 (d, <i>J</i> = 2.0 Hz, 1H), 6.89 (s, 1H), 4.91 (d, <i>J</i> = 5.6 Hz, 2H), 4.04 (s, 3H)	385.0
148		5-Chloro-2-((thiazolo[5,4- <i>c</i>]pyridine-7-carboxamido)methyl)benzofuran-7-carboxylic acid	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.79 (s, 1H), 9.74 (br s, 1H), 9.50 (s, 1H), 9.03 (s, 1H), 7.34 (m, 3H), 6.62 (s, 1H), 4.70 (br d, <i>J</i> = 5.2 Hz, 2H)	388.0
149		5-Chloro-2-((4-methoxypyrimidine-5-carboxamido)methyl)benzofuran-7-carboxylic acid	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.01 (br t, <i>J</i> = 5.3 Hz, 1H), 8.90 (s, 1H), 8.87 - 8.83 (m, 1H), 7.73 (s, 1H), 7.60 (s, 1H), 6.78 (s, 1H), 4.68 (br d, <i>J</i> = 5.8 Hz, 2H), 4.06 (s, 3H)	362.1
150		5-Chloro-2-((4-hydroxypyrimidine-5-carboxamido)methyl)benzofuran-7-carboxylic acid	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.71 (br s, 1H), 8.65 (s, 1H), 8.43 (s, 1H), 7.90 (d, <i>J</i> = 1.5 Hz, 1H), 7.70 (d, <i>J</i> = 1.5 Hz, 1H), 6.81 (s, 1H), 4.72 (br d, <i>J</i> = 5.5 Hz, 2H)	346.2

Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺
151		5-Chloro-2-((4-ethoxypyrimidin-5-carboxamido)methyl)benzofuran-7-carboxylic acid	¹ H NMR (500 MHz, DMSO-d ₆) δ 8.84 (s, 1H), 8.82 - 8.73 (m, 2H), 7.81 (s, 1H), 7.67 (s, 1H), 6.82 (s, 1H), 4.70 (br d, <i>J</i> = 5.6 Hz, 2H), 4.54 (q, <i>J</i> = 6.9 Hz, 2H), 1.36 (t, <i>J</i> = 7.0 Hz, 3H)	376.2
152		5-Chloro-2-((pyrazine-2-carboxamido)methyl)benzofuran-7-carboxylic acid	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.60 (br t, <i>J</i> = 5.6 Hz, 1H), 9.20 (s, 1H), 8.88 (d, <i>J</i> = 2.1 Hz, 1H), 8.75 (s, 1H), 7.91 (d, <i>J</i> = 1.5 Hz, 1H), 7.70 (d, <i>J</i> = 1.5 Hz, 1H), 6.83 (s, 1H), 4.71 (br d, <i>J</i> = 6.1 Hz, 2H)	332.0
153		5-Chloro-2-((6-methylpyrazine-2-carboxamido)methyl)benzofuran-7-carboxylic acid	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.46 (br t, <i>J</i> = 6.0 Hz, 1H), 9.01 (s, 1H), 8.79 (s, 1H), 7.92 (d, <i>J</i> = 1.8 Hz, 1H), 7.71 (d, <i>J</i> = 1.8 Hz, 1H), 6.82 (s, 1H), 4.71 (br d, <i>J</i> = 6.1 Hz, 2H), 2.61 (s, 3H)	346.1
154		5-Chloro-2-((6-methoxypyrazine-2-carboxamido)methyl)benzofuran-7-carboxylic acid	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.31 (br t, <i>J</i> = 5.8 Hz, 1H), 8.73 (s, 1H), 8.48 (s, 1H), 7.85 (d, <i>J</i> = 1.9 Hz, 1H), 7.68 (d, <i>J</i> = 2.0 Hz, 1H), 6.82 (s, 1H), 4.72 (d, <i>J</i> = 6.0 Hz, 2H), 4.05 (s, 3H)	362.1

Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺
155		5-Chloro-2-((6-chloropyrazine-2-carboxamido)methyl)benzofuran-7-carboxylic acid	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.59 (br t, <i>J</i> = 5.8 Hz, 1H), 9.15 (s, 1H), 9.01 (s, 1H), 7.74 (s, 1H), 7.61 (d, <i>J</i> = 1.5 Hz, 1H), 6.77 (s, 1H), 4.70 - 4.65 (m, 2H)	366.2
156		(<i>S</i>)-5-Chloro-2-(1-(pyrazolo[1,5- <i>a</i>]pyrimidin-3-carboxamido)ethyl)benzofuran-7-carboxylic acid	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.28 - 9.16 (m, 1H), 8.86 - 8.73 (m, 1H), 8.60 (s, 1H), 8.37 (br d, <i>J</i> = 8.0 Hz, 1H), 7.85 (d, <i>J</i> = 1.2 Hz, 1H), 7.68 (s, 1H), 7.33 - 7.13 (m, 1H), 6.87 (s, 1H), 5.47 (br t, <i>J</i> = 7.4 Hz, 1H), 1.65 (d, <i>J</i> = 6.9 Hz, 3H)	384.9
157		5-Bromo-2-((pyrazolo[1,5- <i>a</i>]pyrimidin-3-carboxamido)methyl)benzofuran-7-carboxylic acid	¹ H NMR (400 MHz, DMSO-d ₆) δ 13.49 (br s, 1H), 9.34 (dd, <i>J</i> = 7.0, 1.7 Hz, 1H), 8.84 (dd, <i>J</i> = 4.2, 1.7 Hz, 1H), 8.64 (s, 1H), 8.53 (t, <i>J</i> = 5.9 Hz, 1H), 8.06 (d, <i>J</i> = 2.1 Hz, 1H), 7.84 (d, <i>J</i> = 2.1 Hz, 1H), 7.30 (dd, <i>J</i> = 7.0, 4.2 Hz, 1H), 6.84 (s, 1H), 4.81 (d, <i>J</i> = 5.7 Hz, 2H)	417.1

Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺
158		5-Methyl-2-((pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylic acid	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.26 (br d, <i>J</i> = 6.7 Hz, 1H), 8.81 (br d, <i>J</i> = 2.7 Hz, 1H), 8.61 (s, 1H), 8.53 (br t, <i>J</i> = 5.8 Hz, 1H), 7.59 (br d, <i>J</i> = 5.5 Hz, 2H), 7.27 (dd, <i>J</i> = 7.0, 4.3 Hz, 1H), 6.76 (s, 1H), 4.76 (br d, <i>J</i> = 5.8 Hz, 2H), 2.39 (s, 3H)	351.0
159		5-Methyl-2-((6-methylpyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylic acid	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.09 (s, 1H), 8.71 (s, 1H), 8.52 (s, 1H), 8.41 (br t, <i>J</i> = 5.6 Hz, 1H), 7.63 - 7.57 (m, 2H), 6.76 (s, 1H), 4.77 (d, <i>J</i> = 5.8 Hz, 2H), 2.44 - 2.37 (m, 6H)	365.2
160		2-((3 <i>H</i> -Imidazo[4,5- <i>c</i>]pyridine-7-carboxamido)methyl)-5-methylbenzofuran-7-carboxylic acid	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.72 (br d, <i>J</i> = 5.8 Hz, 1H), 9.09 (s, 1H), 8.92 (s, 1H), 8.55 (br s, 1H), 7.62 (br s, 2H), 6.82 (s, 1H), 4.82 (br d, <i>J</i> = 4.0 Hz, 2H), 2.41 (s, 3H)	351.2

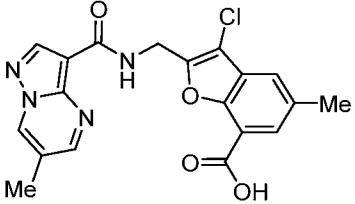
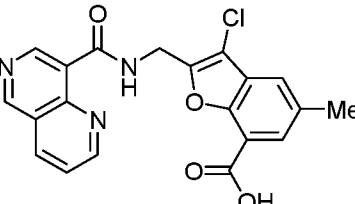
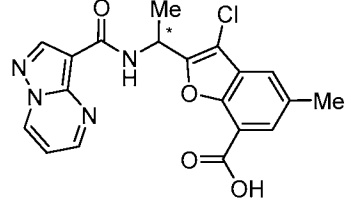
Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺
161		5-Methyl-2-(1-(pyrazolo[1,5-a]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylic acid (racemic)	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.39 - 9.15 (m, 1H), 8.96 - 8.73 (m, 1H), 8.69 - 8.52 (m, 1H), 8.46 - 8.22 (m, 1H), 7.71 - 7.49 (m, 2H), 7.32 - 7.18 (m, 1H), 6.87 - 6.74 (m, 1H), 5.56 - 5.38 (m, 1H), 2.45 - 2.28 (m, 3H), 1.80 - 1.49 (m, 3H)	365.1
162		2-(5-Methyl-2-((pyrazolo[1,5-a]pyrimidine-3-carboxamido)methyl)benzofuran-7-yl)acetic acid	¹ H NMR (400 MHz, Methanol-d ₄) δ 9.10 (dd, <i>J</i> = 7.0, 1.7 Hz, 1H), 8.81 (dd, <i>J</i> = 4.2, 1.7 Hz, 1H), 8.62 (s, 1H), 7.26 (s, 1H), 7.24 - 7.19 (m, 1H), 7.01 (s, 1H), 6.67 (s, 1H), 4.83 (br d, <i>J</i> = 5.0 Hz, 2H), 3.86 (s, 2H), 2.41 (s, 3H)	365.1
163		2-((4-Methoxypyrimidine-5-carboxamido)methyl)-5-methylbenzofuran-7-carboxylic acid	¹ H NMR (500 MHz, DMSO-d ₆) δ 8.97 (br s, 1H), 8.94 - 8.88 (m, 1H), 8.88 - 8.82 (m, 1H), 7.63 (br d, <i>J</i> = 9.2 Hz, 3H), 4.68 (br d, <i>J</i> = 5.8 Hz, 2H), 4.06 (s, 3H), 2.42 (s, 3H)	342.0
164		2-((4-Hydroxypyrimidine-5-carboxamido)methyl)-5-methylbenzofuran-7-carboxylic acid	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.79 (br s, 1H), 8.65 (s, 1H), 8.42 (s, 1H), 7.61 (br d, <i>J</i> = 7.0 Hz, 2H), 6.75 (s, 1H), 4.70 (br d, <i>J</i> = 5.8 Hz, 2H), 2.40 (s, 3H)	328.3

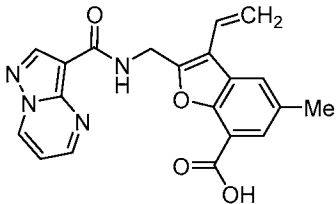
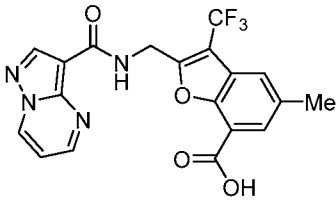
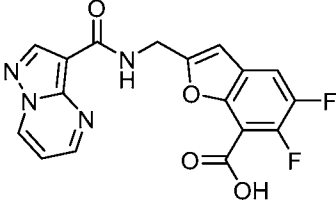
Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺
165		5-Cyclopropyl-2-((pyrazolo[1,5-a]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylic acid	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.30 (d, <i>J</i> = 6.1 Hz, 1H), 8.82 (br d, <i>J</i> = 3.1 Hz, 1H), 8.62 (s, 1H), 8.49 (br t, <i>J</i> = 5.8 Hz, 1H), 7.50 (s, 2H), 7.28 (dd, <i>J</i> = 7.0, 4.3 Hz, 1H), 6.75 (s, 1H), 4.77 (br d, <i>J</i> = 5.8 Hz, 2H), 2.08 - 2.01 (m, 1H), 0.97 (br d, <i>J</i> = 6.7 Hz, 2H), 0.67 (br d, <i>J</i> = 4.3 Hz, 2H)	377.2
166		2-((Pyrazolo[1,5-a]pyrimidine-3-carboxamido)methyl)-5-vinylbenzofuran-7-carboxylic acid	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.30 (br d, <i>J</i> = 7.0 Hz, 1H), 8.83 (br d, <i>J</i> = 3.7 Hz, 1H), 8.63 (s, 1H), 8.53 (br t, <i>J</i> = 5.6 Hz, 1H), 7.93 (s, 1H), 7.90 - 7.83 (m, 1H), 7.31 - 7.25 (m, 1H), 6.89 - 6.80 (m, 2H), 5.83 (d, <i>J</i> = 17.7 Hz, 1H), 5.28 (d, <i>J</i> = 11.0 Hz, 1H), 4.79 (br d, <i>J</i> = 5.5 Hz, 2H)	363.1
167		5-Methoxy-2-((pyrazolo[1,5-a]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylic acid	¹ H NMR (400 MHz, DMSO-d ₆) δ 9.34 (br d, <i>J</i> = 6.9 Hz, 1H), 8.83 (br s, 1H), 8.64 (s, 1H), 8.49 (br s, 1H), 7.38 (d, <i>J</i> = 2.6 Hz, 1H), 7.31 (d, <i>J</i> = 2.6 Hz, 2H), 6.77 (s, 1H), 4.77 (d, <i>J</i> = 5.8 Hz, 2H), 3.80 (s, 3H)	367.3

Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺
168		5-Cyano-2-((pyrazolo[1,5-a]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylic acid	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.28 (br d, <i>J</i> = 7.0 Hz, 1H), 8.82 (br d, <i>J</i> = 4.0 Hz, 1H), 8.61 (s, 1H), 8.52 (br t, <i>J</i> = 5.7 Hz, 1H), 8.33 (s, 1H), 8.09 (s, 1H), 7.28 (dd, <i>J</i> = 6.8, 4.2 Hz, 1H), 6.97 (s, 1H), 4.85 (d, <i>J</i> = 5.8 Hz, 2H)	362.0
169		6-Fluoro-2-((pyrazolo[1,5-a]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylic acid	¹ H NMR (400 MHz, DMSO-d ₆) δ 13.77 (s, 1H), 9.34 (dd, <i>J</i> = 7.0, 1.7 Hz, 1H), 8.84 (dd, <i>J</i> = 4.2, 1.7 Hz, 1H), 8.64 (s, 1H), 8.49 (t, <i>J</i> = 5.8 Hz, 1H), 7.74 (dd, <i>J</i> = 8.6, 5.2 Hz, 1H), 7.30 (dd, <i>J</i> = 7.0, 4.2 Hz, 1H), 7.20 (dd, <i>J</i> = 10.9, 8.6 Hz, 1H), 6.84 (s, 1H), 4.78 (d, <i>J</i> = 5.9 Hz, 2H)	355.0
170		6-Methyl-2-((pyrazolo[1,5-a]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylic acid	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.27 (br d, <i>J</i> = 6.2 Hz, 1H), 8.81 (br d, <i>J</i> = 3.8 Hz, 1H), 8.61 (s, 1H), 8.42 (br s, 1H), 7.50 (d, <i>J</i> = 7.9 Hz, 1H), 7.27 (dd, <i>J</i> = 6.6, 4.5 Hz, 1H), 7.10 (d, <i>J</i> = 7.8 Hz, 1H), 6.74 (s, 1H), 4.76 (br d, <i>J</i> = 5.7 Hz, 2H), 2.52 (s, 3H)	351.0

Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺
171		6-Hydroxy-2-((pyrazolo[1,5-a]pyrimidin-3-yl)methyl)benzofuran-7-carboxylic acid	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.30 (br d, <i>J</i> =7.0 Hz, 1H), 8.82 (br d, <i>J</i> =3.4 Hz, 1H), 8.62 (s, 1H), 8.39 (br t, <i>J</i> =5.3 Hz, 1H), 7.38 (d, <i>J</i> =8.5 Hz, 1H), 7.27 (dd, <i>J</i> =6.7, 4.3 Hz, 1H), 6.64 (d, <i>J</i> =8.2 Hz, 1H), 6.59 (s, 1H), 4.70 (br d, <i>J</i> =5.5 Hz, 2H)	353.0
172		3-Chloro-5-fluoro-2-((pyrazolo[1,5-a]pyrimidin-3-yl)methyl)benzofuran-7-carboxylic acid	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.29 (br d, <i>J</i> = 5.8 Hz, 1H), 8.83 (br d, <i>J</i> = 2.7 Hz, 1H), 8.60 (s, 1H), 8.54 (br t, <i>J</i> = 5.5 Hz, 1H), 7.72 - 7.51 (m, 2H), 7.28 (dd, <i>J</i> = 6.7, 4.3 Hz, 1H), 4.85 (br d, <i>J</i> = 5.8 Hz, 2H)	389.1
173		(<i>S</i>)-3-Chloro-5-fluoro-2-(1-(pyrazolo[1,5-a]pyrimidin-3-yl)ethyl)benzofuran-7-carboxylic acid	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.26 (d, <i>J</i> = 7.0 Hz, 1H), 8.84 (br d, <i>J</i> = 3.1 Hz, 1H), 8.59 (s, 1H), 8.52 (br d, <i>J</i> = 7.6 Hz, 1H), 7.69 - 7.57 (m, 2H), 7.28 (dd, <i>J</i> = 7.0, 4.3 Hz, 1H), 5.54 (br t, <i>J</i> = 7.3 Hz, 1H), 1.66 (d, <i>J</i> = 7.0 Hz, 3H)	403.0

Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺
174		3,5-Dichloro-2-((pyrazolo[1,5- <i>a</i>]pyrimidin-3-carboxamido)methyl)benzofuran-7-carboxylic acid	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.32 (dd, <i>J</i> = 7.0, 1.6 Hz, 1H), 8.84 (dd, <i>J</i> = 4.1, 1.5 Hz, 1H), 8.61 (s, 1H), 8.51 (br t, <i>J</i> = 5.7 Hz, 1H), 7.75 (s, 2H), 7.29 (dd, <i>J</i> = 7.0, 4.2 Hz, 1H), 4.85 (d, <i>J</i> = 5.8 Hz, 2H)	407.0
175		(<i>S</i>)-3,5-Dichloro-2-(1-(pyrazolo[1,5- <i>a</i>]pyrimidin-3-carboxamido)ethyl)benzofuran-7-carboxylic acid	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.27 (br d, <i>J</i> = 7.0 Hz, 1H), 8.86 (br d, <i>J</i> = 3.7 Hz, 1H), 8.59 (s, 1H), 8.53 (br d, <i>J</i> = 7.6 Hz, 1H), 7.77 (s, 2H), 7.28 (dd, <i>J</i> = 6.9, 4.4 Hz, 1H), 5.55 (br t, <i>J</i> = 7.2 Hz, 1H), 1.66 (br d, <i>J</i> = 7.0 Hz, 3H)	418.9
176		3-Chloro-5-methyl-2-((pyrazolo[1,5- <i>a</i>]pyrimidin-3-carboxamido)methyl)benzofuran-7-carboxylic acid	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 9.01 (dd, <i>J</i> = 7.0, 1.7 Hz, 1H), 8.77 (dd, <i>J</i> = 4.2, 1.7 Hz, 1H), 8.60 (s, 1H), 7.79 - 7.73 (m, 2H), 7.48 (d, <i>J</i> = 1.0 Hz, 1H), 7.18 (dd, <i>J</i> = 7.0, 4.2 Hz, 1H), 4.96 - 4.91 (m, 2H), 2.49 (s, 3H)	385.0

Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺
177		3-Chloro-5-methyl-2-((6-methylpyrazolo[1,5-a]pyrimidin-3-carboxamido)methyl)benzofuran-7-carboxylic acid	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.13 (s, 1H), 8.72 (s, 1H), 8.51 (s, 1H), 8.47 (br t, <i>J</i> = 5.5 Hz, 1H), 7.71 (s, 1H), 7.60 (s, 1H), 4.83 (br d, <i>J</i> = 5.5 Hz, 2H), 2.45 (s, 3H), 2.38 (s, 3H)	398.9
178		2-((1,6-naphthyridine-8-carboxamido)methyl)-3-chloro-5-methylbenzofuran-7-carboxylic acid	¹ H NMR (500 MHz, DMSO-d ₆) δ 11.04 (br t, <i>J</i> = 4.9 Hz, 1H), 9.52 (s, 1H), 9.30 (s, 1H), 9.25 (br d, <i>J</i> = 3.1 Hz, 1H), 8.70 (br d, <i>J</i> = 8.2 Hz, 1H), 7.77 (dd, <i>J</i> = 7.9, 4.3 Hz, 1H), 7.61 (s, 1H), 7.44 (s, 1H), 4.88 (br d, <i>J</i> = 5.5 Hz, 2H), 2.39 (s, 3H)	396.1
179		3-Chloro-5-methyl-2-(1-(pyrazolo[1,5-a]pyrimidin-3-carboxamido)ethyl)benzofuran-7-carboxylic acid	¹ H NMR (400 MHz, Methanol-d ₄) δ 9.06 (dd, <i>J</i> = 7.0, 1.6 Hz, 1H), 8.80 (dd, <i>J</i> = 4.1, 1.5 Hz, 1H), 8.57 (s, 1H), 7.80 (d, <i>J</i> = 1.8 Hz, 1H), 7.56 (dd, <i>J</i> = 1.7, 0.8 Hz, 1H), 7.21 (dd, <i>J</i> = 7.0, 4.3 Hz, 1H), 5.72 (q, <i>J</i> = 7.1 Hz, 1H), 2.49 (s, 3H), 1.75 (d, <i>J</i> = 7.0 Hz, 3H)	399.1

Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺
180		5-Methyl-2-((pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)-3-vinylbenzofuran-7-carboxylate	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 9.05 - 9.00 (m, 1H), 8.79 - 8.75 (m, 1H), 8.62 - 8.56 (m, 1H), 7.90 - 7.84 (m, 1H), 7.82 - 7.79 (m, 2H), 7.78 - 7.75 (m, 1H), 7.21 - 7.16 (m, 1H), 7.12 - 7.02 (m, 1H), 5.93 - 5.86 (m, 1H), 5.52 - 5.47 (m, 1H), 4.97 - 4.91 (m, 2H), 2.50 (s, 3H)	377.1
182		5-Methyl-2-((pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)-3-(trifluoromethyl)benzofuran-7-carboxylic acid	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.29 (d, <i>J</i> =7.0 Hz, 1H), 8.83 (br d, <i>J</i> =3.0 Hz, 1H), 8.59 (s, 1H), 8.55 (br t, <i>J</i> =5.4 Hz, 1H), 7.77 (s, 1H), 7.69 (s, 1H), 7.28 (dd, <i>J</i> =6.9, 4.2 Hz, 1H), 4.97 (br d, <i>J</i> =5.5 Hz, 2H), 2.48 (s, 3H)	419.1
183		5,6-Difluoro-2-((pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylic acid	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.34 (dd, <i>J</i> = 7.0, 1.6 Hz, 1H), 8.84 (dd, <i>J</i> = 4.3, 1.7 Hz, 1H), 8.64 (s, 1H), 8.55 (t, <i>J</i> = 6.0 Hz, 1H), 7.76 (dd, <i>J</i> = 11.5, 7.9 Hz, 1H), 7.30 (dd, <i>J</i> = 7.0, 4.2 Hz, 1H), 7.02 (s, 1H), 4.82 (d, <i>J</i> = 5.9 Hz, 2H)	373.1

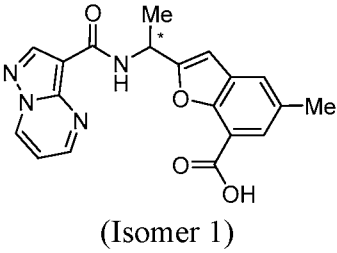
Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺
184		5-Chloro-6-hydroxy-2-((pyrazolo[1,5- <i>a</i>]pyrimidin-3-carboxamido)methyl)benzofuran-7-carboxylic acid	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.27 (br d, <i>J</i> =7.0 Hz, 1H), 8.79 (br s, 1H), 8.59 (s, 1H), 8.44 (br s, 1H), 7.80 (s, 1H), 7.25 (br d, <i>J</i> =4.3 Hz, 1H), 6.66 (s, 1H), 4.71 (br d, <i>J</i> =5.5 Hz, 2H)	386.9

EXAMPLES 185- 186

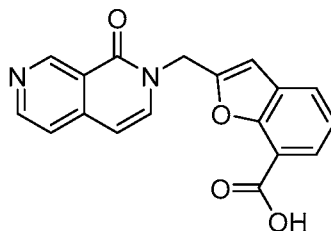
The following acids were synthesized from the corresponding racemic methyl esters according to the hydrolysis procedure outlined in Example 128 and resolved

5 according to the methods listed.

Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺	Method
185		5-Fluoro-2-(1-(pyrazolo[1,5- <i>a</i>]pyrimidin-3-carboxamido)ethyl)benzofuran-7-carboxylic acid (Isomer 1)	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.25 (dd, <i>J</i> = 7.0, 1.2 Hz, 1H), 8.81 (dd, <i>J</i> = 4.0, 1.2 Hz, 1H), 8.61 (s, 1H), 8.41 (d, <i>J</i> = 8.2 Hz, 1H), 7.68 (dd, <i>J</i> = 8.2, 2.4 Hz, 1H), 7.51 (dd, <i>J</i> = 9.6, 2.6 Hz, 1H), 7.26 (dd, <i>J</i> = 7.0, 4.3 Hz, 1H), 6.91 (s, 1H), 5.46 (br t, <i>J</i> = 7.3 Hz, 1H), 1.64 (d, <i>J</i> = 7.0 Hz, 3H)	369.2	Method G

Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺	Method
186	 (Isomer 1)	5-Methyl-2-(1-(pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)ethyl)benzofuran-7-carboxylic acid	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 9.17 - 8.99 (m, 1H), 8.91 - 8.66 (m, 1H), 8.60 (s, 1H), 7.69 (s, 1H), 7.56 (s, 1H), 7.32 - 7.11 (m, 1H), 6.73 (s, 1H), 5.57 (br d, <i>J</i> = 6.0 Hz, 1H), 2.44 (s, 3H), 1.75 (br d, <i>J</i> = 6.1 Hz, 3H)	365.1	Method L

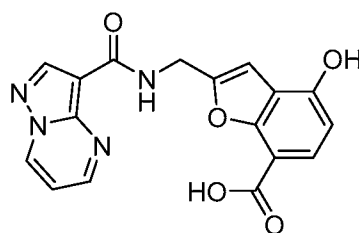
EXAMPLE 187

5 **2-((1-Oxo-2,7-naphthyridin-2(1H)-yl)methyl)benzofuran-7-carboxylic acid**

2,7-Naphthyridin-1(2H)-one (15 mg, 0.103 mmol, Step A of Example 7) was taken up in dry DMF (1.0 mL) and cooled to 0 °C. Sodium hydride (6.16 mg, 0.154 mmol) (60% dispersion in mineral oil) was added and after 30 minutes, methyl 2-(bromomethyl)benzofuran-7-carboxylate (38.7 mg, 0.144 mmol, Step D of Example 7) was added. Once the addition was complete, the reaction was allowed to warm to room temperature. The reaction was stirred at room temperature for 30 minutes, after which time, LCMS indicated that some of the methyl ester had been cleaved. The reaction was quenched with a few drops of ammonium chloride solution, filtered, and purified *via* preparative HPLC (Method B) to give 2-((1-oxo-2,7-naphthyridin-2(1H)-yl)methyl)benzofuran-7-carboxylic acid (16.9 mg, 0.046 mmol, 45.2 % yield). ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.36 (s, 1H), 8.73 (d, *J* = 5.2 Hz, 1H), 7.88 - 7.77 (m, 3H), 7.62

(d, $J = 5.2$ Hz, 1H), 7.32 (t, $J = 7.6$ Hz, 1H), 6.88 (s, 1H), 6.73 (d, $J = 7.3$ Hz, 1H), 5.43 (s, 2H); MS (ESI+) $m/z = 321.0$ (M+H)⁺.

EXAMPLE 188



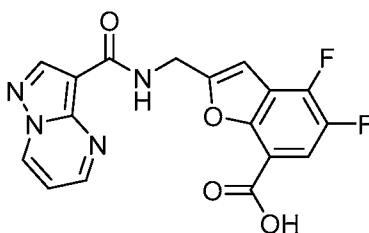
5

4-Hydroxy-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylic acid

To a solution of methyl 4-methoxy-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate (10 mg, 0.026 mmol, Example 33) in DCM (1 mL) at 0 °C was added tribromoborane (5.07 μ l, 0.053 mmol). The reaction mixture was stirred at room temperature for 4 hours. The reaction mixture was acidified with 1 N aqueous HCl solution to pH 2-3 and extracted with DCM. The organic layer was dried over sodium sulfate, filtered, concentrated, and purified with prep HPLC, Method C, to give the product (5.1 mg, 38% yield). ¹H NMR (400 MHz, Chloroform-*d*) δ 9.01 (dd, $J = 7.0, 1.8$ Hz, 1H), 8.78 (dd, $J = 4.1, 1.6$ Hz, 1H), 8.62 (s, 1H), 7.80 (d, $J = 8.5$ Hz, 1H), 7.19 (dd, $J = 7.1, 4.3$ Hz, 1H), 6.86 (s, 1H), 6.64 (d, $J = 8.5$ Hz, 1H), 5.41 (s, 2H); MS (ESI+) $m/z = 353.1$ (M+H)⁺.

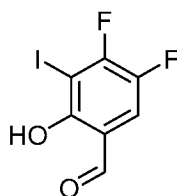
15

EXAMPLE 189



20

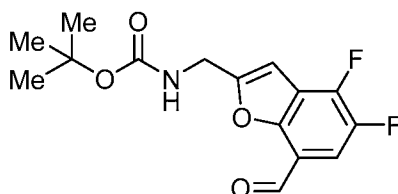
4,5-Difluoro-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylic acid



A) 4,5-Difluoro-2-hydroxy-3-iodobenzaldehyde

To a solution of 4,5-difluoro-2-hydroxybenzaldehyde (3.0 g, 19.0 mmol) in *N,N*-
 5 dimethylformamide (30 mL) was added sodium iodide (3.41 g, 22.8 mmol), followed by
 chloramine T trihydrate (5.88 g, 20.9 mmol) slowly. The resulting mixture was stirred at
 room temperature overnight. The reaction was not complete by LCMS, so the reaction
 mixture was stirred at room temperature for another 24 hours. The reaction mixture was
 diluted with ethyl acetate and 1 N aqueous HCl solution. The organic layer was separated,
 10 washed with brine followed by Na₂S₂O₃ solution, dried over MgSO₄, and filtered. The
 filtrate was concentrated *in vacuo* to give light a yellow solid. The residue was dissolved
 in DCM and purified by flash chromatography (80g column, 0 - 15% ethyl acetate in
 hexanes) to give the title compound (3.0 g, 56% yield) as a white solid. ¹H NMR (400
 MHz, CHLOROFORM-*d*) δ 12.02 (d, *J* = 1.9 Hz, 1H), 9.74 (s, 1H), 7.56 - 7.39 (m, 1H).

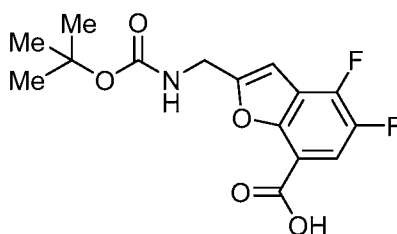
15



B) *tert*-Butyl ((4,5-difluoro-7-formylbenzofuran-2-yl)methyl)carbamate

A mixture of 4,5-difluoro-2-hydroxy-3-iodobenzaldehyde (3.0 g, 10.6 mmol),
tert-butyl prop-2-yn-1-ylcarbamate (1.89 g, 12.2 mmol), TEA (17.7 mL, 127 mmol), and
 20 copper(I) iodide (0.16 g, 0.85 mmol) in DMF (20 mL) was purged with a nitrogen stream
 for 5 mins. Bis(triphenylphosphine)palladium(II) chloride (0.37 g, 0.53 mmol) was then
 added. The resulting mixture was heated at 80 °C for 2 hours. The reaction mixture was
 cooled down and diluted with ethyl acetate and saturated aqueous NaHCO₃ solution. The
 organic layer was separated, washed with brine followed by saturated aqueous NH₄Cl

solution, dried over MgSO₄, and filtered. The filtrate was concentrated *in vacuo* to give an oil. The oil was dissolved in DCM and purified by flash chromatography (80g column, 0 - 25% ethyl acetate in hexanes) to give the title compound (2.44 g, 74% yield) as a white solid. ¹H NMR (400 MHz, Chloroform-d) δ 10.39 (d, *J* = 2.0 Hz, 1H), 7.65 (dd, *J* = 10.4, 7.6 Hz, 1H), 6.84 (s, 1H), 5.19 - 4.99 (m, 1H), 4.54 (br d, *J* = 6.0 Hz, 2H), 1.50 (s, 9H).



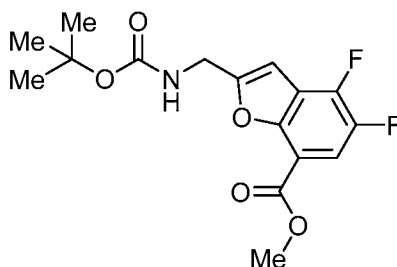
C) 2-(((*tert*-Butoxycarbonyl)amino)methyl)-4,5-difluorobenzofuran-7-carboxylic acid

10

To a solution of *tert*-butyl ((4,5-difluoro-7-formylbenzofuran-2-yl)methyl) carbamate (2.4 g, 7.71 mmol) in *tert*-butanol (24 mL) was added 2-methyl-2-butene (2.0 M solution in THF) (19.3 mL, 38.5 mmol) and a solution of potassium dihydrogen phosphate (4.20 g, 30.8 mmol) in water (24 mL). A solution of sodium chlorite (1.74 g, 15.4 mmol) in water (2 mL) was then added slowly. The reaction mixture was stirred at room temperature for 3 hours. To the reaction mixture was added water and then acetic acid was added to adjust the pH to 4-5. The resulting mixture was extracted with ethyl acetate. The organic layer was separated, washed with brine, dried over MgSO₄, and filtered. The filtrate was concentrated *in vacuo*. A solid crashed out from the residue upon standing. To the residue was added MeOH and the resulting precipitate was filtered to give the crude title compound (0.8 g) as a pale yellow solid. The filtrate was concentrated *in vacuo*. The residue was dissolved in DCM and purified by flash chromatography (ISCO 40g column, 0 - 50% ethyl acetate in DCM) to give a white solid. The combined yield of the title compound was 2.2 g or 87% yield. ¹H NMR (400 MHz, DMSO-d₆) δ 7.78 (dd, *J* = 11.5, 7.9 Hz, 1H), 7.60 - 7.52 (m, 1H), 6.92 (s, 1H), 4.34 (br d, *J* = 5.7 Hz, 2H), 1.41 (s, 9H); MS (ESI+) *m/z* = 272.1 (M-55+H)⁺.

20

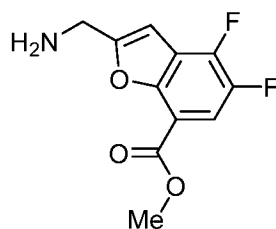
25



D) Methyl 2-(((*tert*-butoxycarbonyl)amino)methyl)-4,5-difluorobenzofuran-7-carboxylate

To a solution of 2-(((*tert*-butoxycarbonyl)amino)methyl)-4,5-difluorobenzofuran-7-carboxylic acid (1.3 g, 3.97 mmol) in DMF (12 mL) was added BOP (2.11 g, 4.77 mmol). The reaction mixture was stirred at rt for 5 min. Methanol (5 mL, 3.97 mmol) and DIPEA (1.4 mL, 7.94 mmol) were the added. The reaction mixture was stirred at rt overnight. The reaction mixture was diluted with ethyl acetate and saturated aqueous NaHCO₃ solution. The organic layer was separated, washed with brine, dried over MgSO₄, and filtered. The filtrate was concentrated *in vacuo*. The residue was triturated with MeOH and filtered to give the title compound as a white solid (0.85 g, 63%). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.79 (dd, *J* = 11.1, 7.7 Hz, 1H), 6.80 (s, 1H), 5.58 - 4.93 (m, 1H), 4.53 (br d, *J* = 6.0 Hz, 2H), 4.01 (s, 3H), 1.49 (s, 9H); MS (ESI+) *m/z* = 286.2 (M-55+H)⁺.

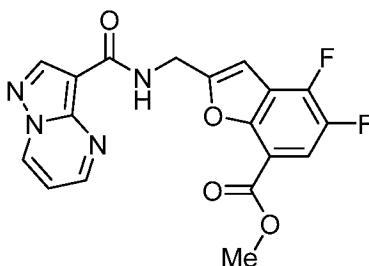
15



E) Methyl 2-(aminomethyl)-4,5-difluorobenzofuran-7-carboxylate

To a solution of methyl 2-(((*tert*-butoxycarbonyl)amino)methyl)-4,5-difluorobenzofuran-7-carboxylate (0.9 g, 2.64 mmol) in DCE (10 mL) was added TFA (2.44 mL, 31.6 mmol). The reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated *in vacuo* and dried on high vacuum overnight to give the crude title compound (TFA salt) as a white solid (0.98 g, 99%). ¹H NMR (400

MHz, DMSO- d_6) δ 8.54 (br s, 1H), 7.96 (dd, J = 11.4, 7.9 Hz, 1H), 4.38 (br s, 2H), 3.95 (s, 3H); MS (ESI+) m/z = 225.2 (M-17+H) $^+$.



5 **F) Methyl 4,5-difluoro-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate**

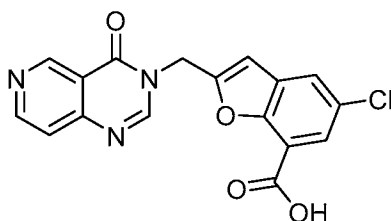
A suspension of pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (248 mg, 1.52 mmol) and BOP (672 mg, 1.52 mmol) in DMF (8 mL) was stirred at room temperature for 10 minutes. A solution of methyl 2-(aminomethyl)-4,5-difluorobenzofuran-7-
 10 carboxylate, TFA (450 mg, 1.27 mmol) in THF (4 mL) and DIPEA (0.9 mL, 5.1 mmol) were added. The reaction mixture turned into a clear solution after addition of the amine and was stirred at room temperature for 1.5 h. During this time a solid crashed out. To the reaction mixture was added water and the solid was filtered to give the crude title
 15 compound (440 mg, 85%). ^1H NMR (400 MHz, DMSO- d_6) δ 9.35 (dd, J = 7.0, 1.6 Hz, 1H), 8.85 (dd, J = 4.2, 1.7 Hz, 1H), 8.64 (s, 1H), 8.56 (t, J = 6.0 Hz, 1H), 7.84 (dd, J = 11.4, 7.8 Hz, 1H), 7.31 (dd, J = 7.0, 4.2 Hz, 1H), 7.05 (s, 1H), 4.83 (d, J = 5.8 Hz, 2H), 3.91 (s, 3H); MS (ESI+) m/z = 387.3 (M+H) $^+$.

20 **G) 4,5-Difluoro-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylic acid**

To a suspension of methyl 4,5-difluoro-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate (380 mg, 0.984 mmol) in THF (6 mL) and MeOH (6 mL) was added 2M LiOH aqueous solution (4.92 mL, 9.84 mmol). The resulting mixture was stirred at room temperature for 24 hours. To the reaction mixture
 25 was added water and then acetic acid was added to adjust the pH to 4-5. A white solid

crashed out and the mixture was filtered to give the title compound as a white solid (340 mg, 88%). ¹H NMR (400 MHz, DMSO-d₆) δ 9.34 (dd, *J* = 7.0, 1.7 Hz, 1H), 8.84 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.64 (s, 1H), 8.55 (t, *J* = 6.1 Hz, 1H), 7.77 (dd, *J* = 11.5, 7.9 Hz, 1H), 7.30 (dd, *J* = 7.0, 4.2 Hz, 1H), 7.02 (s, 1H), 4.82 (d, *J* = 5.9 Hz, 2H); MS (ESI+) *m/z* = 373.2 (M+H)⁺.

EXAMPLE 190



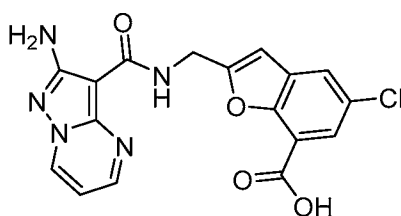
5-Chloro-2-((4-oxopyrido[4,3-*d*]pyrimidin-3(4*H*)-yl)methyl)benzofuran-7-carboxylic acid

10

4-Aminonicotinic acid (65.1 mg, 0.471 mmol) and *N,N*-dimethylformamide dimethyl acetal (0.221 mL, 1.649 mmol) were taken up in DMF (0.5 mL) in a microwave vial. The vial was sealed and heated at 110 °C for 20 min. The reaction mixture was cooled and concentrated *in vacuo*. To the residue was added 1 mL of acetic acid and 2-(aminomethyl)-5-chlorobenzofuran-7-carboxylic acid, TFA (80 mg, 0.236 mmol). The mixture was heated at 110 °C for another 20 minutes in a microwave reactor. The reaction mixture was cooled and concentrated *in vacuo*. To the residue was added MeOH, and a solid crashed out. The mixture was filtered to give a grey solid as the title compound (34 mg, 41% yield). ¹H NMR (500 MHz, DMSO-d₆) δ 9.33 (s, 1H), 8.86 (br d, *J* = 5.5 Hz, 1H), 8.74 (s, 1H), 7.85 (s, 1H), 7.69 (s, 1H), 7.63 (d, *J* = 5.6 Hz, 1H), 6.96 (s, 1H), 5.45 (s, 2H); MS (ESI+) *m/z* = 356.2 (M+H)⁺.

20

EXAMPLE 191



2-((2-Aminopyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)-5-chlorobenzofuran-7-carboxylic acid

5 A vial was charged with methyl 2-((2-((*tert*-butoxycarbonyl)amino)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)-5-chlorobenzofuran-7-carboxylate (35 mg, 0.070 mmol, Step D of Example 63) in methanol (4 mL) and tetrahydrofuran (2 mL). To the solution was added lithium hydroxide (0.047 mL, 0.140 mmol, 3M) and the reaction was stirred at room temperature for 3 hours. The solution was concentrated *in vacuo* and the

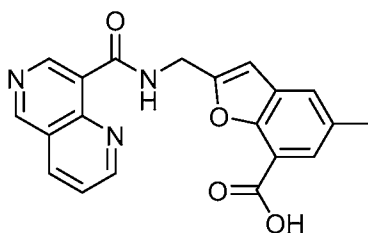
10 residue acidified with 1N HCl. The product precipitate, 2-((2-((*tert*-butoxycarbonyl)amino)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)-5-chlorobenzofuran-7-carboxylic acid, was filtered, pumped dried by vacuum and used as is in next step.

The above product was dissolved in DCM (5 mL) and TFA (0.5 mL) was added.

15 The solution was stirred at room temperature for 2 hours. The solution was concentrated *in vacuo*, dissolved in 2 mL of DMF and purified via preparative HPLC (Method A) to yield the title compound (7.8 mg, 28.8 % yield). ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.97 - 8.88 (m, 1H), 8.55 - 8.47 (m, 1H), 8.29 - 8.19 (m, 1H), 7.95 - 7.87 (m, 1H), 7.74 - 7.67 (m, 1H), 7.05 - 6.95 (m, 1H), 6.84 - 6.73 (m, 1H), 6.57 - 6.43 (m, 2H), 4.85 - 4.72 (m,

20 2H); MS (ESI+) *m/z* = 386.1 (M+H)⁺.

EXAMPLE 192

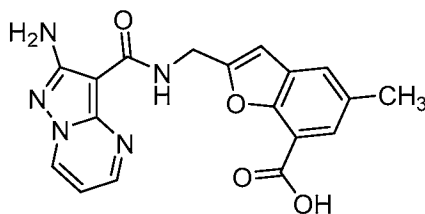


2-((1,6-naphthyridine-8-carboxamido)methyl)-5-methylbenzofuran-7-carboxylic acid

A mixture of 1,6-naphthyridine-8-carboxylic acid, HCl (10 mg, 0.047 mmol), methyl 2-(aminomethyl)-5-methylbenzofuran-7-carboxylate, TFA (15.82 mg, 0.047 mmol, Step C of Example 85), HATU (18.05 mg, 0.047 mmol) and Hunig's Base (0.033 mL, 0.190 mmol) in THF (0.5 mL) was stirred at rt for 48 h. The solvent was evaporated and the residue was suspended in Water (0.500 mL) and THF (0.5 mL). Lithium hydroxide dihydrate (19.47 mg, 0.475 mmol) was added and the reaction was stirred at rt for 48 h. The solvent was evaporated and the residue was dissolved in 1:1 DMF/AcOH and purified by preparative LC/MS (Method B) to give the title compound (2.7 mg, 7.28 μ mol, 15.33 % yield). ^1H NMR (500 MHz, DMSO- d_6) δ 10.97 (br s, 1H), 9.59 (s, 1H), 9.36 (s, 1H), 9.33 - 9.28 (m, 1H), 8.78 (br d, $J=8.2$ Hz, 1H), 7.86 (br dd, $J=8.1, 4.1$ Hz, 1H), 7.55 (br d, $J=10.1$ Hz, 2H), 6.83 (s, 1H), 4.87 (br d, $J=5.5$ Hz, 2H), 2.39 (s, 3H); MS (ESI+) $m/z = 362.0$ (M+H) $^+$.

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EXAMPLE 194



2-((2-Aminopyrazolo[1,5-a]pyrimidine-3-carboxamido)methyl)-5-methylbenzofuran-7-carboxylic acid

20

A vial was charged with methyl 2-((2-((tert-butoxycarbonyl)amino)pyrazolo[1,5-a]pyrimidine-3-carboxamido)methyl)-5-methylbenzofuran-7-carboxylate (45 mg, 0.094 mmol, Step A of Example 93) in methanol (4 mL) and tetrahydrofuran (2 mL). To the solution was added lithium hydroxide (0.063 mL, 0.188 mmol, 3M) and the reaction was stirred at room temperature for 3 hours. The solution was concentrated *in vacuo* and the residue acidified with 1N HCl. The product precipitate 2-((2-((tert-

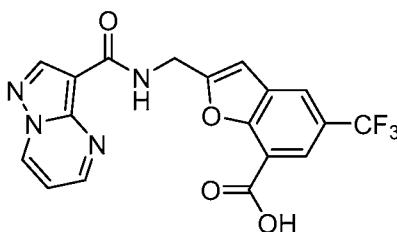
25

butoxycarbonyl)amino)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)-5-methylbenzofuran-7-carboxylic acid was filtered, pumped dried by vacuum and used as is in next step

The above product was dissolved in DCM (5 mL) and TFA (0.5 mL) was added.

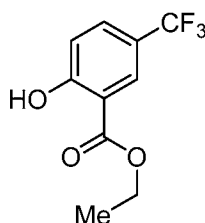
- 5 The solution was stirred at RT for 2 hours. The solution was concentrated *in vacuo*, dissolved in 2 mL of DMF and purified via preparative HPLC (Method B) to yield the title compound (14 mg, 40.8 % yield). ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.91 - 8.84 (m, 1H), 8.49 - 8.44 (m, 1H), 8.21 - 8.15 (m, 1H), 7.60 - 7.51 (m, 2H), 6.99 - 6.92 (m, 1H), 6.73 - 6.67 (m, 1H), 6.52 - 6.44 (m, 1H), 4.77 - 4.66 (m, 2H), 2.35 (s, 3H); MS (ESI+) m/z = 366.1 (M+H)⁺.
- 10

EXAMPLE 195



2-((Pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)-5-(trifluoromethyl)benzofuran-7-carboxylic acid

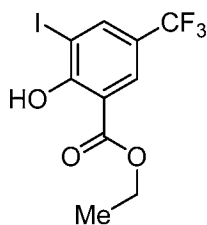
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A) Ethyl 2-hydroxy-5-(trifluoromethyl)benzoate

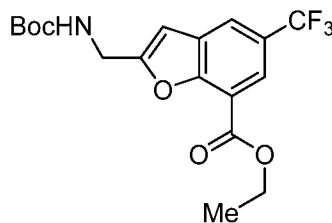
- To a solution of 2-hydroxy-5-(trifluoromethyl)benzonitrile (3.45 g, 18.4 mmol) in ethanol (35 mL) was added sulfuric acid (6.9 mL, 130 mmol). The reaction mixture was heated at 85 °C overnight. After 16 hours, additional sulfuric acid (6.9 mL, 130 mmol) and the reaction mixture was heated at 92 °C for another 72 hours. The reaction mixture was cooled down and the mixture was poured into ice. The resulting mixture was
- 20

extracted with ethyl acetate. The organic layer was separated and washed with brine, dried over MgSO₄ and filtered. The filtrate was concentrated *in vacuo*. The residue was dissolved in DCM and purified by ISCO (80 g column, 0 - 30% ethyl acetate in hexanes) to give ethyl 2-hydroxy-5-(trifluoromethyl)benzoate (1.2 g, 28% yield). ¹H NMR (400 MHz, Chloroform-d) δ 11.20 (s, 1H), 8.14 (d, *J* = 1.8 Hz, 1H), 7.69 (dd, *J* = 8.8, 2.3 Hz, 1H), 7.08 (d, *J* = 8.8 Hz, 1H), 4.47 (q, *J* = 7.1 Hz, 2H), 1.46 (t, *J* = 7.1 Hz, 3H); MS (ESI+) *m/z* = 335.1 (M+H)⁺.



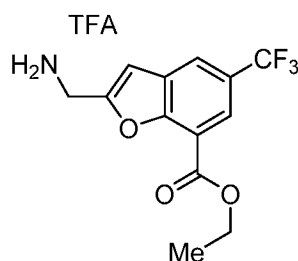
10 **B) Ethyl 2-hydroxy-3-iodo-5-(trifluoromethyl)benzoate**

To a solution of ethyl 2-hydroxy-5-(trifluoromethyl)benzoate (1.2 g, 5.12 mmol) in *N,N*-dimethylformamide (20 mL) was added sodium iodide (0.92 g, 6.15 mmol) followed by chloramine T trihydrate (1.59 g, 5.64 mmol) slowly. The resulting mixture was stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate and 1 N aqueous HCl solution. The organic layer was separated and washed with brine, Na₂S₂O₃ solution, dried over MgSO₄, and filtered. The filtrate was concentrated *in vacuo* to give a light yellow oil. The crude residue was dissolved in DCM and purified by silica gel column chromatography (80 g column, 0 – 10% ethyl acetate in hexanes) to give ethyl 2-hydroxy-3-iodo-5-(trifluoromethyl)benzoate (0.83 g, 45%). ¹H NMR (400 MHz, CHLOROFORM-d) δ 12.11 (s, 1H), 8.18 (d, *J* = 2.0 Hz, 1H), 8.15 (d, *J* = 1.5 Hz, 1H), 4.50 (q, *J* = 7.1 Hz, 2H), 1.47 (t, *J* = 7.1 Hz, 3H).



C) Ethyl 2-(((*tert*-butoxycarbonyl)amino)methyl)-5-(trifluoromethyl)benzofuran-7-carboxylate

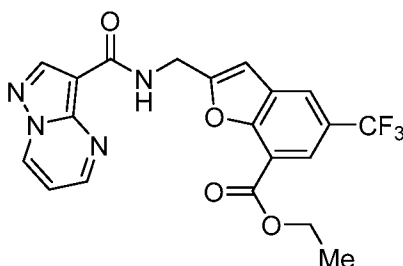
The reaction mixture of ethyl 2-hydroxy-3-iodo-5-(trifluoromethyl)benzoate (0.83 g, 2.31 mmol), *tert*-butyl prop-2-yn-1-ylcarbamate (0.43 g, 2.77 mmol), TEA (4.82 mL, 34.6 mmol), and copper(I) iodide (0.044 g, 0.23 mmol) in DMF (10 mL) was purged with a nitrogen stream for 5 mins, then bis(triphenylphosphine) palladium(II) chloride (0.097 g, 0.14 mmol) was added. The resulting mixture was sealed and heated at 80 °C for 2 hours. The reaction mixture was cooled down and diluted with ethyl acetate and saturated aqueous NaHCO₃ solution. The organic layer was separated and washed with brine, dried over MgSO₄, and filtered. The filtrate was concentrated *in vacuo*. The crude residue was dissolved in DCM and purified by silica gel column chromatography (40 g column, 0 – 25% ethyl acetate in hexanes) to give ethyl 2-(((*tert*-butoxycarbonyl)amino)methyl)-5-(trifluoromethyl) benzofuran-7-carboxylate (0.80 g, 90% yield). ¹H NMR (400 MHz, Chloroform-*d*) δ 8.19 (d, *J* = 1.3 Hz, 1H), 8.00 (s, 1H), 6.76 (s, 1H), 5.22 - 5.06 (m, 1H), 4.60 - 4.54 (m, 2H), 4.52 - 4.46 (m, 2H), 1.50 - 1.45 (m, 12H); MS (ESI+) *m/z* = 332.3 (M+H-*t*Bu)⁺.



D) Ethyl 2-(aminomethyl)-5-(trifluoromethyl)benzofuran-7-carboxylate•TFA

Ethyl 2-(((*tert*-butoxycarbonyl)amino)methyl)-5-(trifluoromethyl)benzofuran-7-carboxylate (400 mg, 1.03 mmol) was taken up in DCM (3.9 mL) and cooled to 0 °C. TFA (1.3 mL) was added and the reaction was stirred at room temperature for 2 hours. The reaction was then concentrated *in vacuo* and azeotroped three times with toluene to remove excess TFA. The crude product was placed under high vacuum overnight to give ethyl 2-(aminomethyl)-5-(trifluoromethyl)benzofuran-7-carboxylate as a TFA salt (418

mg, 1.08 mmol, 100 % yield). ^1H NMR (400 MHz, Chloroform- d) δ 8.18 (d, J = 1.3 Hz, 1H), 8.05 (s, 1H), 6.98 (s, 1H), 4.46 (s, 2H), 4.42 (q, J = 7.1 Hz, 2H), 1.42 (t, J = 7.1 Hz, 3H); MS (ESI+) m/z = 575.4 (2M+H) $^+$.



5

E) Ethyl 2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)-5-(trifluoromethyl)benzofuran-7-carboxylate

Pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (212 mg, 1.30 mmol) was dissolved in DMF (2.2 mL). DIPEA (760 μl , 4.34 mmol) and ethyl 2-(aminomethyl)-5-(trifluoromethyl)benzofuran-7-carboxylate, TFA salt (418 mg, 1.09 mmol) were added. BOP (720 mg, 1.63 mmol) was then added and the reaction was stirred at room temperature overnight. After 16 hours, the reaction was diluted with water and extracted with EtOAc and DCM (solubility of product in organic solvent is poor). Organics were dried over sodium sulfate, filtered, and concentrated in vacuo. The crude residue was purified *via* silica gel column chromatography (24 g column, 0-100% EtOAc in hexanes, product elutes at ~60% EtOAc) to give ethyl 2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)-5-(trifluoromethyl)benzofuran-7-carboxylate (472 mg, 0.873 mmol, 80 % yield) as a pale yellow solid. MS (ESI+) m/z = 433.3 (M+H) $^+$.

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F) 2-((Pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)-5-(trifluoromethyl)benzofuran-7-carboxylic acid

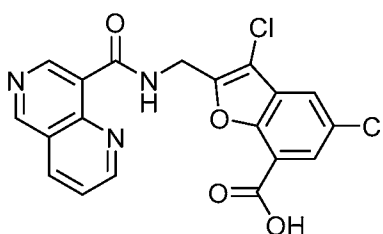
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Ethyl 2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)-5-(trifluoromethyl)benzofuran-7-carboxylate (472 mg, 1.09 mmol) was taken up in THF (3.3 mL), methanol (2.2 mL), and water (4.4 mL). LiOH (261 mg, 10.9 mmol) was added and the reaction was stirred at room temperature for 1 hour. The solvent was then

removed under reduced pressure and water was added. The pH value of the mixture was adjusted to 4-5 with acetic acid and a precipitate formed. The precipitate was filtered to give 2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)-5-

(trifluoromethyl)benzofuran-7-carboxylic acid (210 mg, 0.519 mmol, 47.6 % yield). ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.30 (br d, *J* = 6.4 Hz, 1H), 8.83 (br d, *J* = 3.1 Hz, 1H), 8.62 (s, 1H), 8.59 - 8.52 (m, 1H), 8.10 (s, 1H), 7.93 (s, 1H), 7.28 (br dd, *J* = 6.3, 4.4 Hz, 1H), 6.92 (s, 1H), 4.82 (br d, *J* = 5.5 Hz, 2H); MS (ESI+) *m/z* = 405.1 (M+H)⁺.

EXAMPLE 196



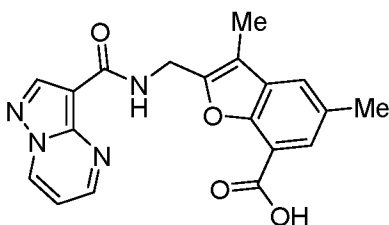
10

2-((1,6-naphthyridine-8-carboxamido)methyl)-3,5-dichlorobenzofuran-7-carboxylic acid

A mixture of 1,6-naphthyridine-8-carboxylic acid, HCl (10 mg, 0.047 mmol), methyl 2-(aminomethyl)-3,5-dichlorobenzofuran-7-carboxylate, TFA (18.43 mg, 0.047 mmol, Example 113), HATU (18.05 mg, 0.047 mmol) and Hunig's Base (0.033 mL, 0.190 mmol) in THF (0.5 mL) was stirred at rt for 3 h. To the reaction, lithium hydroxide hydrate (38.9 mg, 0.950 mmol) and water (0.500 mL) were added. The reaction was stirred at rt for 12 h. The solvent was evaporated and the residue was dissolved in 1:1 DMF/AcOH. The suspension was filtered and purified by preparative LC/MS (Method B) to give the title compound (3.1 mg, 7.37 μmol, 15.51 % yield). ¹H NMR (500 MHz, DMSO-*d*₆) δ 11.10 (br s, 1H), 11.06 (br s, 1H), 9.58 (s, 1H), 9.34 (s, 1H), 9.29 (br s, 1H), 9.05 (br d, *J* = 4.0 Hz, 1H), 8.63 (br d, *J* = 7.6 Hz, 1H), 8.77 (br d, *J* = 8.2 Hz, 1H), 8.26 (s, 1H), 8.03 - 7.38 (m, 4H), 4.99 - 4.83 (m, 2H); MS (ESI+) *m/z* = 415.9 (M+H)⁺.

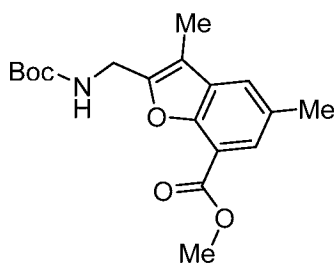
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EXAMPLE 197

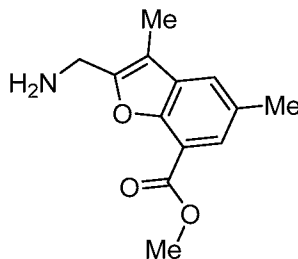


3,5-Dimethyl-2-((pyrazolo[1,5-a]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylic acid

5



A) Methyl 2-(((tert-butoxycarbonyl)amino)methyl)-3,5-dimethylbenzofuran-7-carboxylate



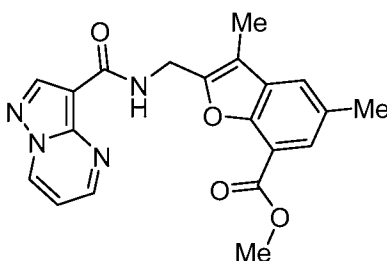
10 A vial was charged with methyl 2-(((tert-butoxycarbonyl)amino)methyl)-5-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-7-carboxylate (850 mg, 1.909 mmol, Step A of Example 117), methyl iodide (0.239 mL, 3.82 mmol), 1,1'-bis(di-tert-butylphosphino)ferrocene palladium dichloride (124 mg, 0.191 mmol) and potassium phosphate tribasic aqueous solution (1.909 mL, 5.73 mmol, 3M) in toluene (5

15 mL). The solution was degassed and heated to 50 °C for 1 hour. LCMS of the reaction showed 30% of the title product and 70% of the des-boronated material. The reaction solution was cooled, diluted with ethyl acetate, washed with saturated sodium bicarbonate, water, and saturated sodium chloride, dried with anhydrous sodium sulfate,

filtered, and concentrated *in vacuo*. The crude product mixture was purified via preparative HPLC (Method C) to yield the title compound (197 mg, 31 % yield). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.81 - 7.68 (m, 1H), 7.47 (dd, *J* = 1.7, 0.7 Hz, 1H), 4.58 - 4.36 (m, 2H), 4.02 (s, 3H), 2.48 (s, 3H), 2.34 (s, 3H), 1.56 - 1.33 (m, 9H); MS (ESI+) *m/z* = 278.1 (M-55)+.

B) Methyl 2-(aminomethyl)-3,5-dimethylbenzofuran-7-carboxylate, TFA

A flask was charged with methyl 2-(((tert-butoxycarbonyl)amino)methyl)-3,5-dimethylbenzofuran-7-carboxylate (197 mg, 0.591 mmol), DCM (5 mL) and TFA (0.5 mL). The reaction solution was stirred at room temperature for 2 hours. The solution was concentrated *in vacuo* to give methyl 3-allyl-2-(aminomethyl)-5-methylbenzofuran-7-carboxylate, TFA (202 mg, 98 % yield), which was used in the next step without further purification. ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.79 - 7.70 (m, 1H), 7.67 - 7.58 (m, 1H), 6.94 - 6.86 (m, 1H), 4.35 - 4.26 (m, 2H), 3.93 (s, 3H), 2.49 (s, 3H), 2.35 (s, 3H); MS (ESI+) *m/z* = 217.0 (M-16)+.



C) Methyl 3,5-dimethyl-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate

To a vial was added pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (95 mg, 0.582 mmol), methyl 2-(aminomethyl)-3,5-dimethylbenzofuran-7-carboxylate, TFA (202 mg, 0.582 mmol), and DIEA (0.406 mL, 2.327 mmol) in acetonitrile (2 mL). To the solution was added BOP (386 mg, 0.872 mmol) and the reaction stirred at room temperature for 16 hours. The reaction was quenched with water. The resulting product precipitate was filtered and dissolved in 2 mL of DMF, and purified *via* preparative HPLC (Method B) to yield the title compound (150 mg, 68.2 % yield). ¹H NMR (400 MHz, Chloroform-*d*) δ

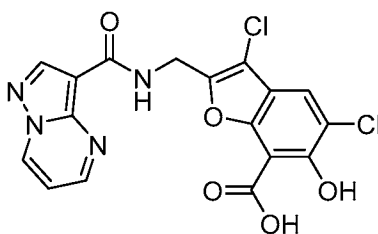
8.80 - 8.75 (m, 1H), 8.73 - 8.70 (m, 1H), 8.67 - 8.64 (m, 1H), 8.48 - 8.36 (m, 1H), 7.76 - 7.73 (m, 1H), 7.50 - 7.46 (m, 1H), 7.03 - 6.98 (m, 1H), 4.89 (d, $J=5.7$ Hz, 2H), 4.02 - 3.95 (m, 3H), 2.49 (s, 3H), 2.35 (s, 3H); MS (ESI+) $m/z = 379.1$ (M+H)⁺.

5 **D) 3,5-Dimethyl-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylic acid, TFA**

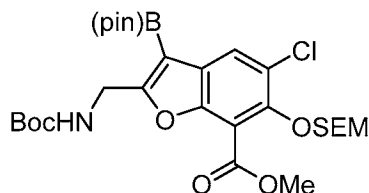
A flask was charged with methyl 3,5-dimethyl-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate (24 mg, 0.063 mmol), lithium hydroxide (0.063 mL, 0.127 mmol, 2M) in methanol (2 mL) and tetrahydrofuran (2 mL). The
10 reaction solution was stirred at room temperature for 3 hours. The reaction was concentrated *in vacuo* and acidified with 1N HCl. The product was extracted with DCM, the organic phase was dried with anhydrous sodium sulfate and concentrated *in vacuo*. The crude product mixture was purified *via* preparative HPLC (Method C) to yield the
15 title compound (10 mg, 0.020 mmol, 31.3 % yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.88 - 7.84 (m, 1H), 7.83 - 7.77 (m, 2H), 7.70 - 7.64 (m, 1H), 7.25 - 7.19 (m, 1H), 6.97 - 6.89 (m, 1H), 6.84 - 6.75 (m, 1H), 4.12 - 3.99 (m, 2H), 1.72 (s, 3H), 1.57 (s, 3H); MS (ESI+) $m/z = 365$ (M+H)⁺.

EXAMPLE 201

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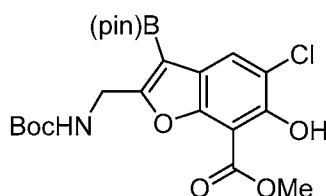


3,5-Dichloro-6-hydroxy-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylic acid



A) Methyl 2-(((*tert*-butoxycarbonyl)amino)methyl)-5-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6-((2-(trimethylsilyl)ethoxy)methoxy)benzofuran-7-carboxylate

5 To a vial charged with methyl 2-(((*tert*-butoxycarbonyl)amino)methyl)-5-chloro-6-((2-(trimethylsilyl)ethoxy)methoxy)benzofuran-7-carboxylate (200.5 mg, 0.413 mmol, Step D in Example 127), bis(pinacolato)diboron (119 mg, 0.470 mmol), and 4,4'-di-*tert*-butyl-2,2'-bipyridine (11.1 mg, 0.041 mmol) was added hexanes (1.85 mL). The mixture was sparged with N₂ for 3 min and then (1,5-cyclooctadiene)(methoxy)iridium(I) dimer
10 (16.41 mg, 0.025 mmol) was added. The reaction mixture was sparged with N₂ for an additional 30 seconds, sealed, and heated to 80 °C for 6 h. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. The residue was dissolved in DCM and purified by flash chromatography (ISCO 12 g column, 0 - 30% EtOAc in hexanes) to give the title compound (115.7 mg, 46%). ¹H NMR (400 MHz, Chloroform-
15 d) δ 7.99 (s, 1H), 5.67 (br s, 1H), 5.20 (s, 2H), 4.64 (br d, *J*=4.7 Hz, 2H), 4.00 (s, 3H), 3.95 - 3.87 (m, 2H), 1.47 (s, 9H), 1.39 (s, 12H), 1.06 - 0.96 (m, 2H), 0.05 (s, 9H); MS (ESI+) *m/z* = 612.1 (M+H)⁺.

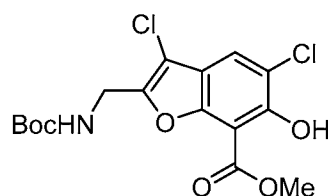


20

B) Methyl 2-(((*tert*-butoxycarbonyl)amino)methyl)-5-chloro-6-hydroxy-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-7-carboxylate

A solution of methyl 2-(((*tert*-butoxycarbonyl)amino)methyl)-5-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6-((2-(trimethylsilyl)ethoxy)

methoxy)benzofuran-7-carboxylate (115.7 mg, 0.189 mmol) and copper(II) chloride (50.8 mg, 0.378 mmol) in MeOH was heated to 50 °C under N₂ for 80 min. The reaction mixture was cooled to room temperature and water was added. The resultant slurry was filtered and the filter cake was rinsed with water. The solid was collected and dried on high vacuum to give the title compound (76.4 mg, 84%). ¹H NMR (400 MHz, Chloroform-d) δ 11.75 (s, 1H), 8.08 (s, 1H), 5.70 (br s, 1H), 4.66 (br d, *J*=5.3 Hz, 2H), 4.09 (s, 3H), 1.49 (s, 9H), 1.40 (s, 12H); MS (ESI+) *m/z* = 520.0 (M+K)⁺.

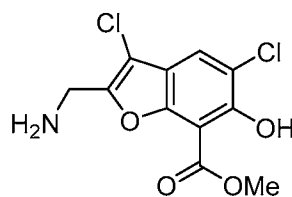


10

C) Methyl 2-(((*tert*-butoxycarbonyl)amino)methyl)-3,5-dichloro-6-hydroxybenzofuran-7-carboxylate

A solution of methyl 2-(((*tert*-butoxycarbonyl)amino)methyl)-5-chloro-6-hydroxy-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-7-carboxylate (76.4 mg, 0.159 mmol) and copper(II) chloride (42.6 mg, 0.317 mmol) in MeOH was heated to 50 °C under N₂ for 22 h. The reaction mixture was cooled to room temperature and water was added. The resultant slurry was filtered and the filter cake was rinsed with water. The solid was collected and dried on high vacuum to give the title compound (56.0 mg, 90%). ¹H NMR (400 MHz, Chloroform-d) δ 11.86 (s, 1H), 7.75 (s, 1H), 4.93 (br s, 1H), 4.55 (br d, *J*=2.5 Hz, 2H), 4.11 (s, 3H), 1.50 (s, 9H); MS (ESI+) *m/z* = 390.1 (M+H)⁺.

20



D) Methyl 2-(aminomethyl)-3,5-dichloro-6-hydroxybenzofuran-7-carboxylate

To a solution of methyl 2-(((*tert*-butoxycarbonyl)amino)methyl)-3,5-dichloro-6-hydroxybenzofuran-7-carboxylate (56.0 mg, 0.144 mmol) in DCM (807 μ L) was added
5 TFA (269 μ L). The reaction mixture was stirred for 3 h and then concentrated *in vacuo* and placed on high vacuum. The residue was dissolved in DMSO and purified by flash chromatography (Gold C18 ISCO 50 g column, 5 - 95% MeCN in water with TFA) to give the title compound (30.3 mg, 52%) as the TFA salt. $^1\text{H NMR}$ (400 MHz, Methanol- d_4) δ 7.83 (s, 1H), 4.92 - 4.83 (m, 2H), 4.11 (s, 3H); MS (ESI+) $m/z = 272.9$ (M-NH $_2$) $^+$.

10

E) Methyl 3,5-dichloro-6-hydroxy-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate

To a flask charged with methyl 2-(aminomethyl)-3,5-dichloro-6-hydroxybenzofuran-7-carboxylate, TFA (30.3 mg, 0.075 mmol), pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (15.9 mg, 0.097 mmol) and ((1H-benzo[*d*][1,2,3]triazol-1-yl)oxy)tris(dimethylamino)phosphonium hexafluorophosphate(V) (43.1 mg, 0.097 mmol) was added DMF (0.75 mL) and DIPEA (47 μ L, 0.270 mmol) and the reaction mixture was stirred at room temperature for 3 h. Additional portions of pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (4 mg, 0.025 mmol), ((1H-benzo[*d*][1,2,3]triazol-1-yl)oxy)tris(dimethylamino)
20 phosphonium hexafluorophosphate(V) (10 mg, 0.023 mmol), and DIPEA (10 μ L, 0.058 mmol) were added and the reaction mixture was stirred for 30 min. The reaction mixture was diluted with water and a precipitate formed. The slurry was filtered and the filter cake was rinsed with water. The solid was collected and placed on high vacuum to give the
25 title compound (9.8 mg, 29%). The filtrate was extracted with EtOAc. The organic layers were combined, washed with a 10% aqueous solution of LiCl, washed with brine, dried over MgSO $_4$, filtered, and concentrated *in vacuo*. The residue was dissolved in DCM and purified by flash chromatography (ISCO 4 g column, 0 - 10% MeOH in DCM) to give additional semipure title compound (25.0 mg) that was used without further purification.
30 $^1\text{H NMR}$ (400 MHz, DMSO- d_6) δ 11.35 (br s, 1H), 9.33 (dd, $J=7.0, 1.7$ Hz, 1H), 8.84 (dd,

$J=4.1, 1.5$ Hz, 1H), 8.62 (s, 1H), 8.47 (t, $J=5.8$ Hz, 1H), 7.90 (s, 1H), 7.29 (dd, $J=7.0, 4.2$ Hz, 1H), 4.81 (d, $J=5.9$ Hz, 2H), 3.93 (s, 3H); MS (ESI+) $m/z = 435.0$ (M+H)⁺.

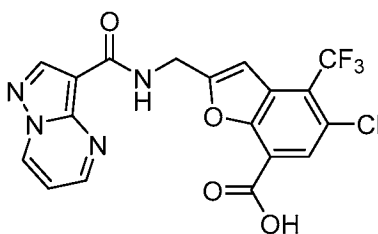
F) 3,5-Dichloro-6-hydroxy-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylic acid

5

Semipure methyl 3,5-dichloro-6-hydroxy-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate (25 mg) was suspended in THF (460 μ L), water (460 μ L), and MeOH (230 μ L). Lithium hydroxide monohydrate (12.1 mg, 0.287 mmol) was added and the reaction mixture was stirred for 2.5 h. The reaction mixture was transferred to a vial and rinsed with 2.5 mL of a 1:2:2 (v/v/v) solution of MeOH, THF, and water. The vial was flushed with N₂, sealed, and heated to 160 °C for 15 min. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. The residue was dissolved in 2 mL DMSO, filtered through a syringe filter, and purified by preparative LC/MS (Method A). Fractions containing the desired product were combined and dried *via* centrifugal evaporation to give the title compound (5.4 mg, 21%) as the TFA salt. ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.30 (br d, $J=6.7$ Hz, 1H), 8.82 (br s, 1H), 8.61 (s, 1H), 8.41 (br s, 1H), 7.64 (s, 1H), 7.27 (br s, 1H), 4.77 (br d, $J=5.2$ Hz, 2H); MS (ESI+) $m/z = 420.9$ (M+H)⁺.

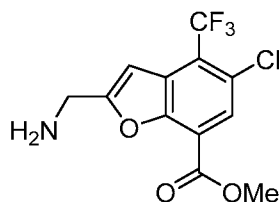
20

EXAMPLE 202



5-Chloro-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)-4-(trifluoromethyl)benzofuran-7-carboxylic acid

25



A) Methyl 2-(aminomethyl)-5-chloro-4-(trifluoromethyl)benzofuran-7-carboxylate

To a biphasic mixture of methyl 2-(aminomethyl)-5-chlorobenzofuran-7-carboxylate, TFA (50 mg, 0.141 mmol, Step C of Example 48) and sodium trifluoromethanesulfinate (66.2 mg, 0.424 mmol) in DCM (561 μ L) and water (224 μ L) was slowly added *tert*-butyl hydroperoxide, 70% in water (98 μ L, 0.707 mmol) at 0 $^{\circ}$ C. The reaction mixture was warmed to room temperature and stirred for 2 h. The reaction mixture was cooled to 0 $^{\circ}$ C and additional portions of sodium trifluoromethanesulfinate (66.2 mg, 0.424 mmol) and *tert*-butyl hydroperoxide, 70% in water (98 μ L, 0.707 mmol) were added. The reaction mixture was warmed to room temperature and stirred for 14 h. The reaction mixture was quenched with a saturated aqueous solution of NaHCO₃ and extracted with EtOAc. The organic layers were combined and washed with brine, dried over MgSO₄, filtered, and concentrated *in vacuo*. The residue was dissolved in DCM and purified by flash chromatography (ISCO 4 g column, 0 - 10% MeOH in DCM) to give the title compound (17.8 mg, 41%). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.98 (s, 1H), 6.90 (br s, 1H), 4.04 (m, 5H); MS (ESI+) *m/z* = 307.9 (M+H)⁺.

B) Methyl 5-chloro-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)-4-(trifluoromethyl)benzofuran-7-carboxylate

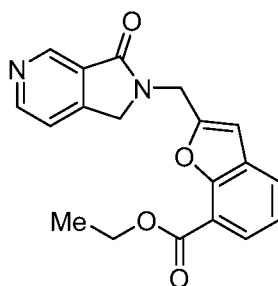
To a flask charged with methyl 2-(aminomethyl)-5-chloro-4-(trifluoromethyl)benzofuran-7-carboxylate (17.8 mg, 0.058 mmol), pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (10.4 mg, 0.064 mmol), and ((1H-benzo[*d*][1,2,3]triazol-1-yl)oxy)tris(dimethylamino)phosphonium hexafluorophosphate(V) (28.1 mg, 0.064 mmol) was added DMF (0.58 mL) and DIPEA (30 μ L, 0.174 mmol) and the reaction mixture was stirred at room temperature for 1.5 h. The reaction mixture was diluted with water and extracted with EtOAc. The organic layers were combined, washed with a 10%

aqueous solution of LiCl, washed with brine, dried over MgSO₄, filtered, and concentrated *in vacuo*. The residue was dissolved in DCM and purified by flash chromatography (ISCO 4 g column, 0 - 10% MeOH in DCM) to give the title compound (15.2 mg, 58%). ¹H NMR (500 MHz, DMSO-d₆) δ 9.33 (br d, *J*=7.0 Hz, 1H), 8.84 (br d, *J*=3.7 Hz, 1H), 8.64 (s, 1H), 8.58 (br t, *J*=5.6 Hz, 1H), 7.95 (s, 1H), 7.30 (dd, *J*=6.7, 4.3 Hz, 1H), 7.01 (br s, 1H), 4.87 (br d, *J*=5.8 Hz, 2H), 3.94 (s, 3H); MS (ESI+) *m/z* = 453.1 (M+H)⁺.

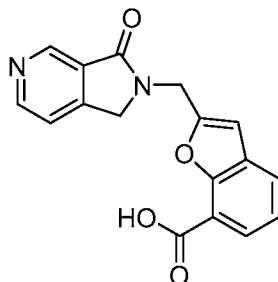
10 **C) 5-Chloro-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)-4-(trifluoromethyl)benzofuran-7-carboxylic acid**

Methyl 5-chloro-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)-4-(trifluoromethyl)benzofuran-7-carboxylate (15.2 mg, 0.034 mmol) was suspended in THF (537 μL), water (537 μL), and MeOH (269 μL). Lithium hydroxide monohydrate (7.0 mg, 0.168 mmol) was added and the reaction mixture was stirred for 8 h. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in 2 mL DMSO, filtered through a syringe filter, and purified by preparative LC/MS (Method B). Fractions containing the desired product were combined and dried *via* centrifugal evaporation to give the title compound (2.3 mg, 15%). ¹H NMR (500 MHz, DMSO-d₆) δ 9.33 - 9.24 (m, 1H), 8.86 - 8.78 (m, 1H), 8.62 (s, 1H), 8.55 - 8.44 (m, 1H), 7.68 (s, 1H), 7.27 (dd, *J*=7.0, 4.2 Hz, 1H), 6.88 (br d, *J*=2.2 Hz, 1H), 4.83 (br d, *J*=5.7 Hz, 2H); MS (ESI+) *m/z* = 439.1 (M+H)⁺.

EXAMPLE 203



Ethyl 2-((3-oxo-1,3-dihydro-2*H*-pyrrolo[3,4-*c*]pyridin-2-yl)methyl)benzofuran-7-carboxylate



5 **A) 2-((3-Oxo-1,3-dihydro-2*H*-pyrrolo[3,4-*c*]pyridin-2-yl)methyl)benzofuran-7-carboxylic acid**

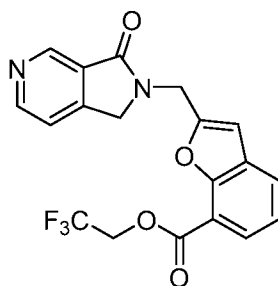
Methyl 2-((3-oxo-1,3-dihydro-2*H*-pyrrolo[3,4-*c*]pyridin-2-yl)methyl)benzofuran-7-carboxylate (347 mg, 1.08 mmol, Example 2) was taken up in THF (4.31 mL), methanol (2.15 mL), and water (4.31 mL). LiOH (258 mg, 10.8 mmol) was added and the reaction stirred at room temperature. After 1 hour, the solvent was removed under reduced pressure and water was added. The pH of the reaction mixture was adjusted to 4-5 with acetic acid and the aqueous layer turned cloudy. The resulting precipitate was extracted with EtOAc. The combined organic extracts were dried with sodium sulfate, filtered, and concentrated *in vacuo* to give 2-((3-oxo-1,3-dihydro-2*H*-pyrrolo[3,4-*c*]pyridin-2-yl)methyl)benzofuran-7-carboxylic acid (97 mg, 0.315 mmol, 29.2 % yield). ¹H NMR (400 MHz, Methanol-*d*₄) δ 8.98 (s, 1H), 8.72 (d, *J* = 5.3 Hz, 1H), 7.89 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.80 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.71 - 7.66 (m, 1H), 7.31 (t, *J* = 7.7 Hz, 1H), 6.90 (s, 1H), 5.04 (s, 2H), 4.77 (s, 2H); MS (ESI+) *m/z* = 309.3 (M+H)⁺.

20 **B) Ethyl 2-((3-oxo-1,3-dihydro-2*H*-pyrrolo[3,4-*c*]pyridin-2-yl)methyl)benzofuran-7-carboxylate**

2-((3-Oxo-1,3-dihydro-2*H*-pyrrolo[3,4-*c*]pyridin-2-yl)methyl)benzofuran-7-carboxylic acid (10 mg, 0.032 mmol) was dissolved in DMF (162 μl) and DIPEA (23 μl, 0.130 mmol) and ethanol (14.9 mg, 0.162 mmol) were added. BOP (21.5 mg, 0.049 mmol) was added and the reaction was stirred at room temperature for 2 hours. The

reaction was then diluted with 1.5 mL DMF, filtered, and purified *via* HPLC (Method A) to give ethyl 2-((3-oxo-1,3-dihydro-2*H*-pyrrolo[3,4-*c*]pyridin-2-yl)methyl)benzofuran-7-carboxylate (3.7 mg, 10.9 μ mol, 33.6 % yield). ^1H NMR (500 MHz, DMSO- d_6) δ 8.94 (s, 1H), 8.76 (br d, $J = 4.9$ Hz, 1H), 7.88 (br d, $J = 7.6$ Hz, 1H), 7.82 (d, $J = 7.6$ Hz, 1H), 7.69 (br d, $J = 4.6$ Hz, 1H), 7.35 (t, $J = 7.6$ Hz, 1H), 7.01 (s, 1H), 4.98 (s, 2H), 4.68 (s, 2H), 4.31 (q, $J = 7.1$ Hz, 2H), 1.27 (t, $J = 7.0$ Hz, 3H); MS (ESI+) $m/z = 337.2$ (M+H) $^+$.

EXAMPLE 204

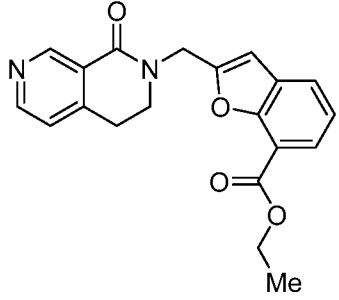
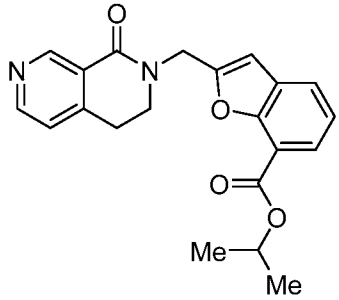
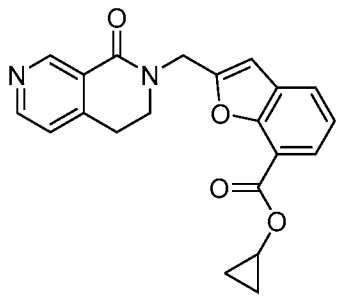


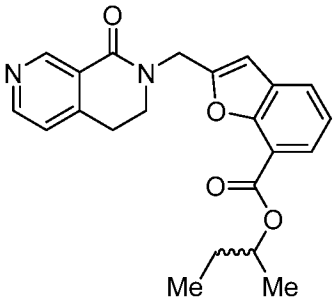
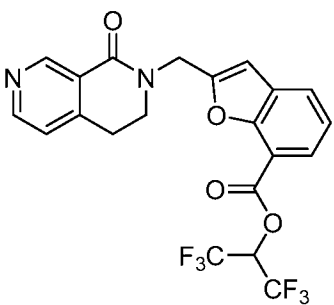
10 2,2,2-Trifluoroethyl 2-((3-oxo-1,3-dihydro-2*H*-pyrrolo[3,4-*c*]pyridin-2-yl)methyl)benzofuran-7-carboxylate

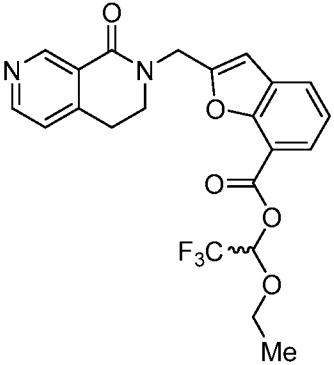
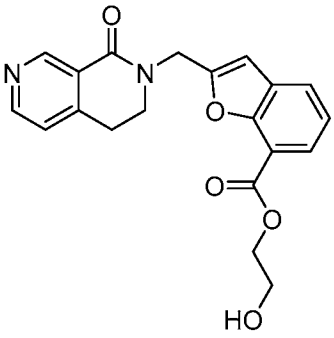
2-((3-Oxo-1,3-dihydro-2*H*-pyrrolo[3,4-*c*]pyridin-2-yl)methyl)benzofuran-7-carboxylic acid (15 mg, 0.049 mmol, Step A of Example 203) was dissolved in DMF (243 μ l). DIPEA (34.0 μ l, 0.195 mmol) and 2,2,2-trifluoroethan-1-ol (24.3 mg, 0.243 mmol) were added. BOP (32.3 mg, 0.073 mmol) was added and the reaction was stirred at room temperature for 1 hour. The reaction was diluted with 1.5 mL DMF, filtered, and purified *via* HPLC (Method B) to give 2,2,2-trifluoroethyl 2-((3-oxo-1,3-dihydro-2*H*-pyrrolo[3,4-*c*]pyridin-2-yl)methyl)benzofuran-7-carboxylate (2.6 mg, 6.59 μ mol, 13.6 % yield). ^1H NMR (500 MHz, DMSO- d_6) δ 8.94 (s, 1H), 8.76 (d, $J = 4.9$ Hz, 1H), 7.97 (d, $J = 7.6$ Hz, 1H), 7.88 (d, $J = 7.6$ Hz, 1H), 7.67 (d, $J = 4.9$ Hz, 1H), 7.41 (t, $J = 7.6$ Hz, 1H), 7.05 (s, 1H), 5.06 - 4.94 (m, 4H), 4.67 (s, 2H); MS (ESI+) $m/z = 391.0$ (M+H) $^+$.

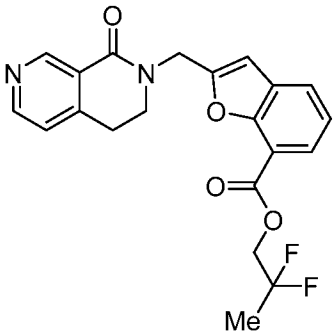
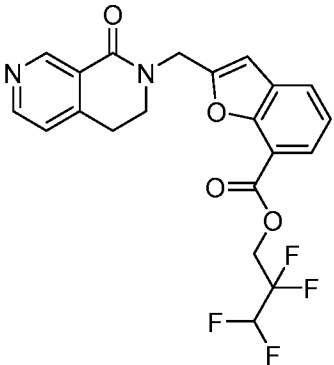
EXAMPLES 205-306

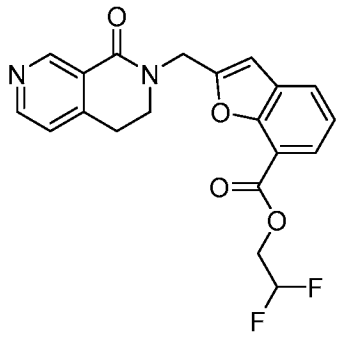
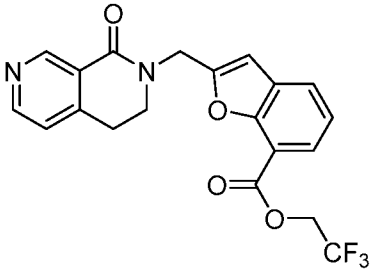
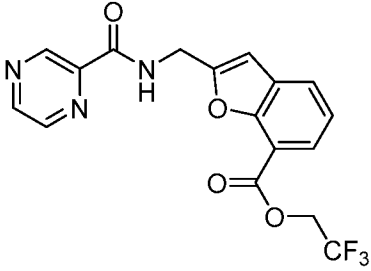
The following examples were synthesized from the corresponding esters according to the procedure outlined in Example 204.

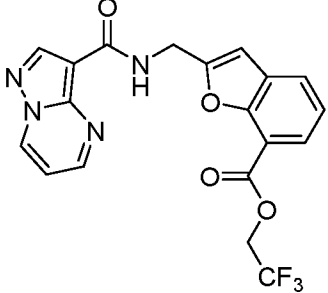
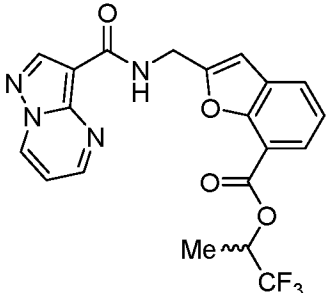
Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺
205		Ethyl 2-((1-oxo-3,4-dihydro-2,7-naphthyridin-2(1H)-yl)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO-d ₆) δ 8.95 (s, 1H), 8.61 (d, <i>J</i> = 4.9 Hz, 1H), 7.87 (d, <i>J</i> = 7.6 Hz, 1H), 7.81 (d, <i>J</i> = 7.3 Hz, 1H), 7.40 - 7.30 (m, 2H), 6.97 (s, 1H), 4.93 (s, 2H), 4.31 (q, <i>J</i> = 7.0 Hz, 2H), 3.74 (t, <i>J</i> = 6.6 Hz, 2H), 3.07 (t, <i>J</i> = 6.6 Hz, 2H), 1.26 (t, <i>J</i> = 7.2 Hz, 3H)	351.0
206		Isopropyl 2-((1-oxo-3,4-dihydro-2,7-naphthyridin-2(1H)-yl)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO-d ₆) δ 8.96 (s, 1H), 8.59 (br d, <i>J</i> = 4.8 Hz, 1H), 7.85 (d, <i>J</i> = 7.6 Hz, 1H), 7.77 (d, <i>J</i> = 7.5 Hz, 1H), 7.39 - 7.29 (m, 2H), 6.95 (s, 1H), 5.15 (dt, <i>J</i> = 12.4, 6.2 Hz, 1H), 4.93 (s, 2H), 3.72 (t, <i>J</i> = 6.6 Hz, 2H), 3.05 (t, <i>J</i> = 6.6 Hz, 2H), 1.26 (d, <i>J</i> = 6.2 Hz, 6H)	365.0
207		Cyclopropyl 2-((1-oxo-3,4-dihydro-2,7-naphthyridin-2(1H)-yl)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO-d ₆) δ 8.96 (s, 1H), 8.60 (br d, <i>J</i> = 4.9 Hz, 1H), 7.87 (d, <i>J</i> = 7.3 Hz, 1H), 7.77 (d, <i>J</i> = 7.3 Hz, 1H), 7.39 - 7.30 (m, 2H), 6.96 (s, 1H), 4.92 (s, 2H), 4.32 (tt, <i>J</i> = 6.1, 3.2 Hz, 1H), 3.69 (t, <i>J</i> = 6.7 Hz, 2H), 3.05 (t, <i>J</i> = 6.6 Hz, 2H), 0.77 - 0.67 (m, 4H)	363.0

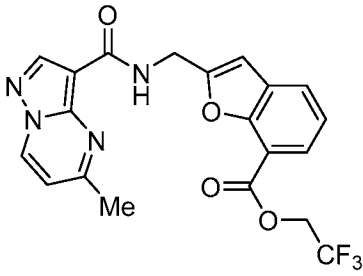
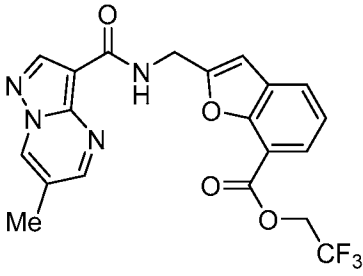
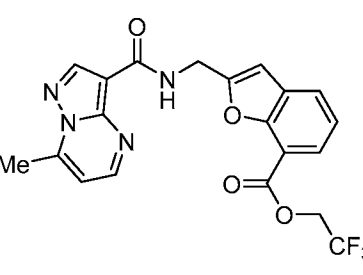
Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺
208		<p>Sec-butyl 2-((1-oxo-3,4-dihydro-2,7-naphthyridin-2(1H)-yl)methyl)benzofuran-7-carboxylate (racemic)</p>	<p>¹H NMR (500 MHz, DMSO-d₆) δ 8.97 (s, 1H), 8.60 (d, <i>J</i> = 4.9 Hz, 1H), 7.86 (d, <i>J</i> = 7.2 Hz, 1H), 7.79 (d, <i>J</i> = 7.6 Hz, 1H), 7.39 - 7.30 (m, 2H), 6.97 (s, 1H), 5.07 - 5.00 (m, 1H), 4.94 (q, <i>J</i> = 15.9 Hz, 2H), 3.71 (t, <i>J</i> = 6.6 Hz, 2H), 3.05 (t, <i>J</i> = 6.6 Hz, 2H), 1.68 - 1.52 (m, 2H), 1.24 (d, <i>J</i> = 6.3 Hz, 3H), 0.84 (t, <i>J</i> = 7.4 Hz, 3H)</p>	379.0
209		<p>1,1,1-Trifluoropropan-2-yl 2-((1-oxo-3,4-dihydro-2,7-naphthyridin-2(1H)-yl)methyl)benzofuran-7-carboxylate</p>	<p>¹H NMR (500 MHz, DMSO-d₆) δ 8.95 (s, 1H), 8.61 (d, <i>J</i> = 4.9 Hz, 1H), 8.04 (d, <i>J</i> = 7.6 Hz, 1H), 7.93 (d, <i>J</i> = 7.6 Hz, 1H), 7.45 (t, <i>J</i> = 7.6 Hz, 1H), 7.36 (d, <i>J</i> = 4.9 Hz, 1H), 7.12 - 7.07 (m, 1H), 7.06 (s, 1H), 4.94 (s, 2H), 3.72 (t, <i>J</i> = 6.6 Hz, 2H), 3.04 (t, <i>J</i> = 6.6 Hz, 2H)</p>	473.1

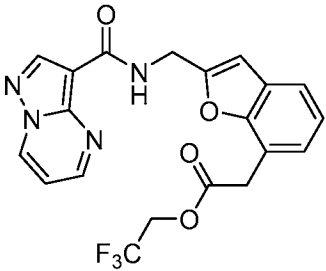
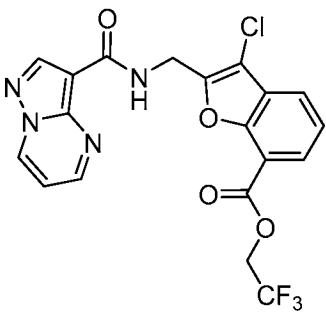
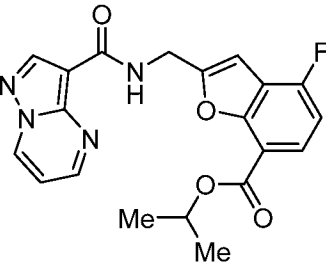
Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺
210		1-Ethoxy-2,2,2-trifluoroethyl 2-((1-oxo-3,4-dihydro-2,7-naphthyridin-2(1H)-yl)methyl)benzofuran-7-carboxylate (racemic)	¹ H NMR (500 MHz, DMSO-d ₆) δ 8.95 (s, 1H), 8.61 (d, <i>J</i> = 4.9 Hz, 1H), 7.98 (d, <i>J</i> = 7.3 Hz, 1H), 7.88 (d, <i>J</i> = 7.6 Hz, 1H), 7.42 (t, <i>J</i> = 7.8 Hz, 1H), 7.37 (d, <i>J</i> = 4.9 Hz, 1H), 7.03 (s, 1H), 6.65 - 6.59 (m, 1H), 4.93 (s, 2H), 3.98 - 3.86 (m, 2H), 3.74 (t, <i>J</i> = 6.6 Hz, 2H), 3.06 (t, <i>J</i> = 6.6 Hz, 2H), 1.16 (t, <i>J</i> = 7.0 Hz, 3H)	449.1
211		2-Hydroxyethyl 2-((1-oxo-3,4-dihydro-2,7-naphthyridin-2(1H)-yl)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO-d ₆) δ 8.94 (br s, 1H), 8.60 (br s, 1H), 7.87 (d, <i>J</i> = 7.7 Hz, 1H), 7.85 (br d, <i>J</i> = 7.6 Hz, 1H), 7.41 - 7.32 (m, 2H), 6.96 (s, 1H), 4.92 (s, 2H), 4.30 (t, <i>J</i> = 4.9 Hz, 2H), 3.82 - 3.69 (m, 4H), 3.07 (br t, <i>J</i> = 6.5 Hz, 2H)	367.1

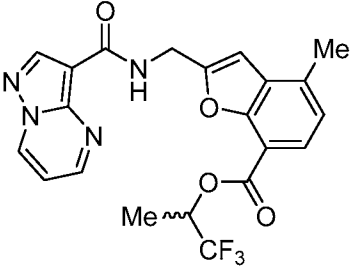
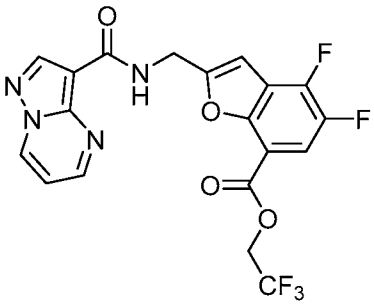
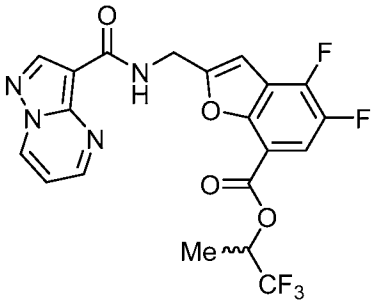
Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺
212		2,2-Difluoropropyl 2-((1-oxo-3,4-dihydro-2,7-naphthyridin-2(1H)-yl)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO-d ₆) δ 8.94 (br s, 1H), 8.58 (br s, 1H), 7.91 (d, <i>J</i> = 7.7 Hz, 1H), 7.85 (d, <i>J</i> = 7.6 Hz, 1H), 7.37 (t, <i>J</i> = 7.7 Hz, 1H), 7.34 (br d, <i>J</i> = 4.6 Hz, 1H), 6.98 (s, 1H), 4.91 (s, 2H), 4.55 (t, <i>J</i> = 12.9 Hz, 2H), 3.69 (br t, <i>J</i> = 6.6 Hz, 2H), 3.08 - 2.99 (m, 2H), 1.69 (br t, <i>J</i> = 19.2 Hz, 3H)	401.1
213		2,2,3,3-Tetrafluoropropyl 2-((1-oxo-3,4-dihydro-2,7-naphthyridin-2(1H)-yl)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO-d ₆) δ 8.96 (s, 1H), 8.59 (br d, <i>J</i> = 4.8 Hz, 1H), 7.94 (d, <i>J</i> = 7.7 Hz, 1H), 7.88 (d, <i>J</i> = 7.7 Hz, 1H), 7.39 (t, <i>J</i> = 7.7 Hz, 1H), 7.34 (d, <i>J</i> = 4.9 Hz, 1H), 7.00 (s, 1H), 6.73 - 6.46 (m, 1H), 4.93 (s, 2H), 4.86 (br t, <i>J</i> = 13.7 Hz, 2H), 3.72 (br t, <i>J</i> = 6.6 Hz, 2H), 3.05 (br t, <i>J</i> = 6.5 Hz, 2H)	437.0

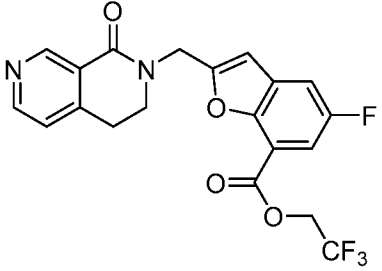
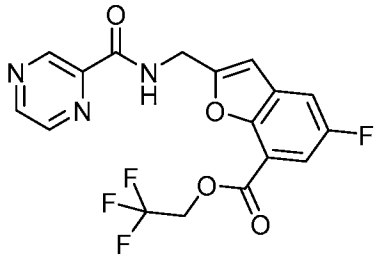
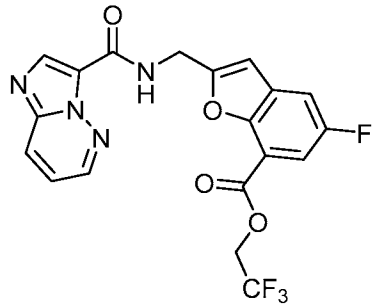
Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺
214		2,2-Difluoroethyl 2-((1-oxo-3,4-dihydro-2,7-naphthyridin-2(1H)-yl)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO-d ₆) δ 8.94 (br s, 1H), 8.58 (br s, 1H), 7.91 (d, <i>J</i> = 7.7 Hz, 1H), 7.84 (d, <i>J</i> = 7.7 Hz, 1H), 7.42 - 7.31 (m, 2H), 6.96 (s, 1H), 6.48 - 6.17 (m, 1H), 4.91 (s, 2H), 4.58 (td, <i>J</i> = 15.2, 2.9 Hz, 2H), 3.73 (t, <i>J</i> = 6.6 Hz, 2H), 3.05 (t, <i>J</i> = 6.6 Hz, 2H)	386.9
215		2,2,2-Trifluoroethyl 2-((1-oxo-3,4-dihydro-2,7-naphthyridin-2(1H)-yl)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO-d ₆) δ 8.94 (s, 1H), 8.57 (br d, <i>J</i> = 4.6 Hz, 1H), 7.91 (d, <i>J</i> = 7.7 Hz, 1H), 7.83 (d, <i>J</i> = 7.6 Hz, 1H), 7.36 (t, <i>J</i> = 7.7 Hz, 1H), 7.32 (d, <i>J</i> = 4.8 Hz, 1H), 6.96 (s, 1H), 4.96 (q, <i>J</i> = 9.0 Hz, 2H), 4.90 (s, 2H), 3.72 (t, <i>J</i> = 6.6 Hz, 2H), 3.03 (t, <i>J</i> = 6.6 Hz, 2H)	405.0
216		2,2,2-Trifluoroethyl 2-((pyrazine-2-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.37 (br s, 1H), 9.20 (s, 1H), 8.86 (s, 1H), 8.72 (s, 1H), 7.92 (d, <i>J</i> = 7.6 Hz, 1H), 7.84 (d, <i>J</i> = 7.7 Hz, 1H), 7.38 (t, <i>J</i> = 7.7 Hz, 1H), 6.87 (s, 1H), 4.97 (q, <i>J</i> = 8.9 Hz, 2H), 4.74 (d, <i>J</i> = 6.0 Hz, 2H)	380.1

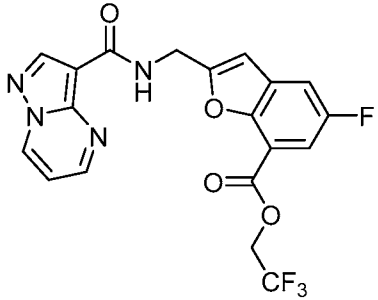
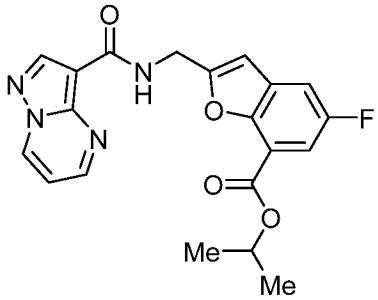
Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺
217		2,2,2-Trifluoroethyl 2-((pyrazolo[1,5- <i>a</i>] pyrimidine-3- carboxamido)methyl)benzofuran-7- carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.23 (br d, <i>J</i> = 6.9 Hz, 1H), 8.79 (br d, <i>J</i> = 3.6 Hz, 1H), 8.59 (s, 1H), 8.48 (br t, <i>J</i> = 5.4 Hz, 1H), 7.92 (d, <i>J</i> = 7.6 Hz, 1H), 7.84 (d, <i>J</i> = 7.6 Hz, 1H), 7.38 (t, <i>J</i> = 7.7 Hz, 1H), 7.25 (dd, <i>J</i> = 6.8, 4.3 Hz, 1H), 6.90 (s, 1H), 4.98 (q, <i>J</i> = 8.9 Hz, 2H), 4.80 (d, <i>J</i> = 5.8 Hz, 2H)	419.0
218		1,1,1- Trifluoropropan-2-yl 2-((pyrazolo[1,5- <i>a</i>] pyrimidine-3- carboxamido)methyl)benzofuran-7- carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.26 (br d, <i>J</i> = 7.1 Hz, 1H), 8.79 (br d, <i>J</i> = 3.9 Hz, 1H), 8.60 (s, 1H), 8.50 - 8.41 (m, 1H), 7.92 (d, <i>J</i> = 7.6 Hz, 1H), 7.83 (d, <i>J</i> = 7.7 Hz, 1H), 7.38 (t, <i>J</i> = 7.7 Hz, 1H), 7.26 (dd, <i>J</i> = 6.7, 4.2 Hz, 1H), 6.90 (s, 1H), 5.70 (dt, <i>J</i> = 13.4, 6.7 Hz, 1H), 4.81 (br d, <i>J</i> = 5.8 Hz, 2H), 1.49 (d, <i>J</i> = 6.6 Hz, 3H)	433.2

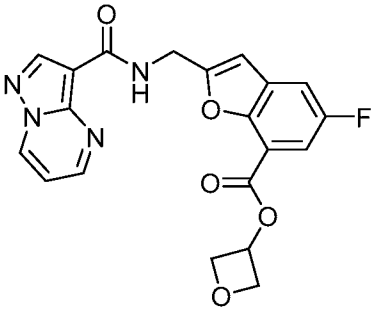
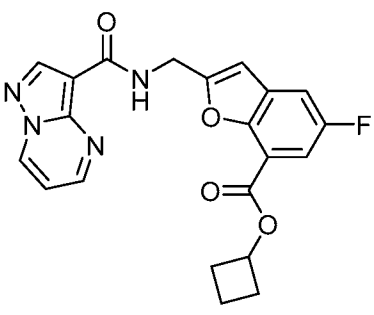
Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺
219		2,2,2-Trifluoroethyl 2-((5-methyl pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.10 (d, <i>J</i> = 7.2 Hz, 1H), 8.56 - 8.47 (m, 2H), 7.94 (d, <i>J</i> = 7.7 Hz, 1H), 7.86 (d, <i>J</i> = 7.7 Hz, 1H), 7.40 (t, <i>J</i> = 7.7 Hz, 1H), 7.15 (d, <i>J</i> = 7.1 Hz, 1H), 6.91 (s, 1H), 5.02 (q, <i>J</i> = 8.9 Hz, 2H), 4.82 (br d, <i>J</i> = 5.7 Hz, 2H), 2.66 (s, 3H)	433.1
220		2,2,2-Trifluoroethyl 2-((6-methyl pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.13 (br s, 1H), 8.71 (s, 1H), 8.53 (s, 1H), 8.42 (br t, <i>J</i> = 5.5 Hz, 1H), 7.93 (d, <i>J</i> = 7.7 Hz, 1H), 7.86 (d, <i>J</i> = 7.6 Hz, 1H), 7.39 (t, <i>J</i> = 7.7 Hz, 1H), 6.90 (s, 1H), 5.02 (q, <i>J</i> = 8.9 Hz, 2H), 4.82 (d, <i>J</i> = 5.8 Hz, 2H), 2.40 (s, 3H)	433.1
221		2,2,2-Trifluoroethyl 2-((7-methyl pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.72 (d, <i>J</i> = 4.3 Hz, 1H), 8.66 (s, 1H), 8.63 - 8.55 (m, 1H), 7.95 (br d, <i>J</i> = 7.6 Hz, 1H), 7.87 (br d, <i>J</i> = 7.6 Hz, 1H), 7.41 (br t, <i>J</i> = 7.8 Hz, 1H), 7.26 (br d, <i>J</i> = 4.0 Hz, 1H), 6.91 (s, 1H), 5.09 - 5.00 (m, 2H), 4.87 - 4.79 (m, 2H), 2.83 (s, 3H)	433.1

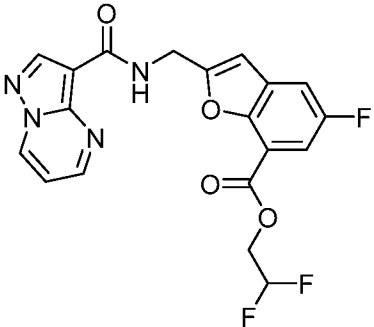
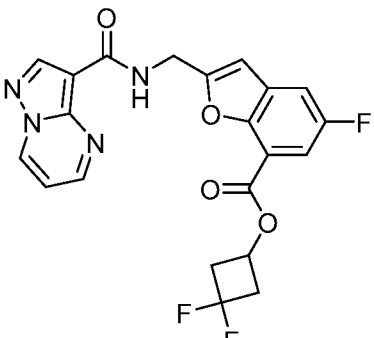
Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺
222		2,2,2-Trifluoroethyl 2-(2-((pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-yl)acetate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.26 (d, <i>J</i> = 6.9 Hz, 1H), 8.85 - 8.74 (m, 1H), 8.60 (s, 1H), 8.42 (br s, 1H), 7.60 - 7.47 (m, 1H), 7.27 (dd, <i>J</i> = 7.0, 4.2 Hz, 1H), 7.21 - 7.14 (m, 2H), 6.79 (s, 1H), 4.84 - 4.63 (m, 4H), 4.06 (s, 2H)	433.2
223		2,2,2-Trifluoroethyl 3-chloro-2-((pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.30 (d, <i>J</i> = 5.8 Hz, 1H), 8.82 (d, <i>J</i> = 3.1 Hz, 1H), 8.60 (s, 1H), 8.53 (br t, <i>J</i> = 5.6 Hz, 1H), 7.98 (d, <i>J</i> = 7.3 Hz, 1H), 7.93 (d, <i>J</i> = 7.6 Hz, 1H), 7.54 (t, <i>J</i> = 7.6 Hz, 1H), 7.31 - 7.27 (m, 1H), 4.99 (q, <i>J</i> = 8.9 Hz, 2H), 4.88 (d, <i>J</i> = 5.8 Hz, 2H)	453.1
224		Isopropyl 4-fluoro-2-((pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.29 (dd, <i>J</i> = 7.0, 1.2 Hz, 1H), 8.82 (dd, <i>J</i> = 4.1, 1.4 Hz, 1H), 8.62 (s, 1H), 8.54 (br t, <i>J</i> = 6.0 Hz, 1H), 7.84 (dd, <i>J</i> = 8.5, 5.5 Hz, 1H), 7.35 - 7.10 (m, 2H), 6.96 (s, 1H), 5.13 (dt, <i>J</i> = 12.4, 6.3 Hz, 1H), 4.83 (d, <i>J</i> = 6.1 Hz, 2H), 1.26 (d, <i>J</i> = 6.1 Hz, 6H)	397.0

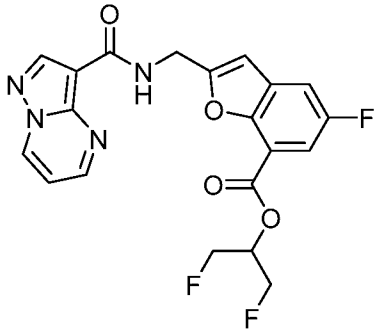
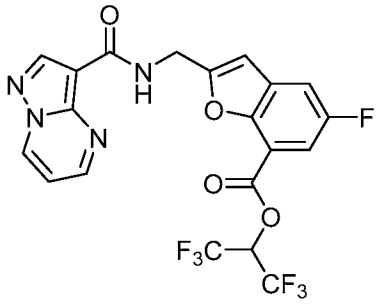
Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺
225		1,1,1-Trifluoropropan-2-yl 4-methyl-2-((pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.23 (br d, <i>J</i> = 5.7 Hz, 1H), 8.94 - 8.72 (m, 1H), 8.60 (s, 1H), 8.51 (br s, 1H), 7.73 (d, <i>J</i> = 7.8 Hz, 1H), 7.28 (br s, 1H), 7.19 (d, <i>J</i> = 7.8 Hz, 1H), 6.93 (s, 1H), 5.66 (dt, <i>J</i> = 13.3, 6.6 Hz, 1H), 4.80 (br d, <i>J</i> = 5.5 Hz, 2H), 2.54 (s, 3H), 1.46 (d, <i>J</i> = 6.5 Hz, 3H)	447.1
226		2,2,2-Trifluoroethyl 4,5-difluoro-2-((pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.27 (br d, <i>J</i> = 6.8 Hz, 1H), 8.81 (br d, <i>J</i> = 3.2 Hz, 1H), 8.61 (s, 1H), 8.51 (br t, <i>J</i> = 5.6 Hz, 1H), 7.84 (dd, <i>J</i> = 11.1, 7.7 Hz, 1H), 7.28 (dd, <i>J</i> = 6.9, 4.2 Hz, 1H), 7.07 (s, 1H), 5.01 (q, <i>J</i> = 8.9 Hz, 2H), 4.83 (d, <i>J</i> = 5.8 Hz, 2H)	455.2
227		1,1,1-Trifluoropropan-2-yl 4,5-difluoro-2-((pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.29 (d, <i>J</i> = 7.0 Hz, 1H), 8.82 (br d, <i>J</i> = 4.0 Hz, 1H), 8.61 (s, 1H), 8.55 - 8.38 (m, 1H), 7.84 (dd, <i>J</i> = 11.1, 7.7 Hz, 1H), 7.28 (dd, <i>J</i> = 6.9, 4.2 Hz, 1H), 7.08 (s, 1H), 5.81 - 5.60 (m, 1H), 4.84 (d, <i>J</i> = 5.9 Hz, 2H), 1.49 (d, <i>J</i> = 6.6 Hz, 3H)	469.3

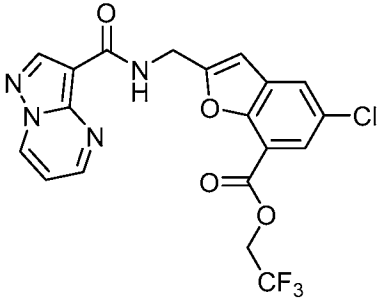
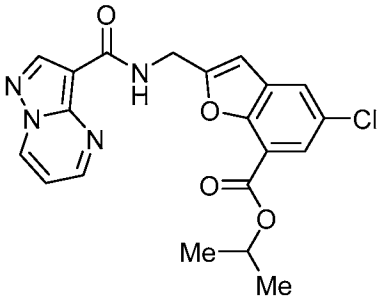
Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺
228		2,2,2-Trifluoroethyl 5-fluoro-2-((1-oxo-3,4-dihydro-2,7-naphthyridin-2(1H)-yl)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO-d ₆) δ 8.95 (s, 1H), 8.61 (br d, <i>J</i> = 4.9 Hz, 1H), 7.83 (dd, <i>J</i> = 8.2, 2.4 Hz, 1H), 7.60 (dd, <i>J</i> = 9.5, 2.4 Hz, 1H), 7.37 (d, <i>J</i> = 4.9 Hz, 1H), 7.03 (s, 1H), 5.03 (q, <i>J</i> = 9.1 Hz, 2H), 4.93 (s, 2H), 3.74 (t, <i>J</i> = 6.6 Hz, 2H), 3.06 (t, <i>J</i> = 6.6 Hz, 2H)	423.2
229		2,2,2-Trifluoroethyl 5-fluoro-2-((pyrazine-2-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.57 (br t, <i>J</i> = 5.6 Hz, 1H), 9.23 (s, 1H), 8.91 (d, <i>J</i> = 2.1 Hz, 1H), 8.77 (s, 1H), 7.81 (dd, <i>J</i> = 8.2, 2.4 Hz, 1H), 7.59 (dd, <i>J</i> = 9.5, 2.4 Hz, 1H), 6.90 (s, 1H), 5.04 (q, <i>J</i> = 9.1 Hz, 2H), 4.73 (br d, <i>J</i> = 5.8 Hz, 2H)	398.2
230		2,2,2-Trifluoroethyl 5-fluoro-2-((imidazo[1,2- <i>b</i>]pyridazine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.22 (br t, <i>J</i> = 5.6 Hz, 1H), 8.78 (br d, <i>J</i> = 3.1 Hz, 1H), 8.52 - 8.13 (m, 2H), 7.81 (dd, <i>J</i> = 8.2, 2.4 Hz, 1H), 7.59 (dd, <i>J</i> = 9.5, 2.4 Hz, 1H), 7.49 (dd, <i>J</i> = 9.2, 4.6 Hz, 1H), 6.95 (s, 1H), 5.02 (q, <i>J</i> = 8.9 Hz, 2H), 4.85 (br d, <i>J</i> = 5.8 Hz, 2H)	437.2

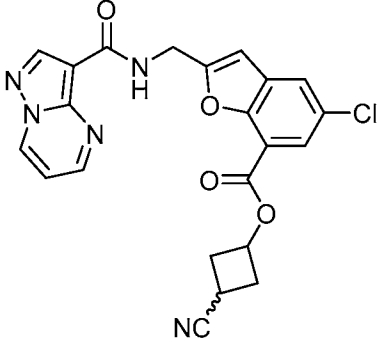
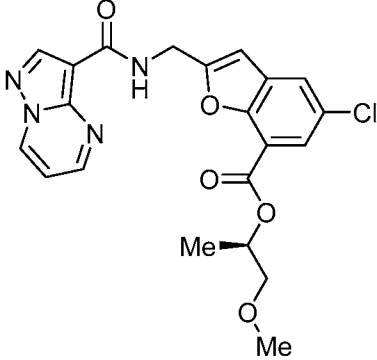
Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺
231		2,2,2-Trifluoroethyl 5-fluoro-2-((pyrazolo[1,5-a]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.30 (br d, <i>J</i> = 6.7 Hz, 1H), 8.85 (br d, <i>J</i> = 3.1 Hz, 1H), 8.72 - 8.54 (m, 2H), 7.83 (br d, <i>J</i> = 6.7 Hz, 1H), 7.62 (br d, <i>J</i> = 8.9 Hz, 1H), 7.32 (br dd, <i>J</i> = 6.3, 4.4 Hz, 1H), 6.94 (s, 1H), 5.04 (br d, <i>J</i> = 8.9 Hz, 2H), 4.83 (br d, <i>J</i> = 5.5 Hz, 2H)	437.3
232		Isopropyl 5-fluoro-2-((pyrazolo[1,5-a]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.27 (br d, <i>J</i> = 6.8 Hz, 1H), 8.81 (br d, <i>J</i> = 3.8 Hz, 1H), 8.61 (s, 1H), 8.52 - 8.40 (m, 1H), 7.69 (dd, <i>J</i> = 8.3, 2.3 Hz, 1H), 7.51 (dd, <i>J</i> = 9.6, 2.4 Hz, 1H), 7.27 (dd, <i>J</i> = 6.9, 4.4 Hz, 1H), 6.88 (s, 1H), 5.17 (dt, <i>J</i> = 12.4, 6.1 Hz, 1H), 4.82 (d, <i>J</i> = 5.9 Hz, 1H), 1.30 (d, <i>J</i> = 6.2 Hz, 6H)	397.3

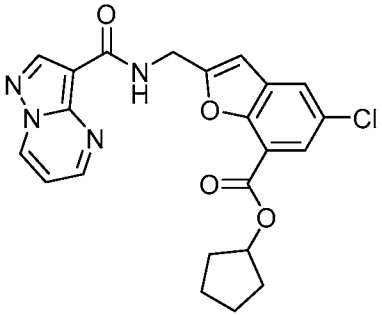
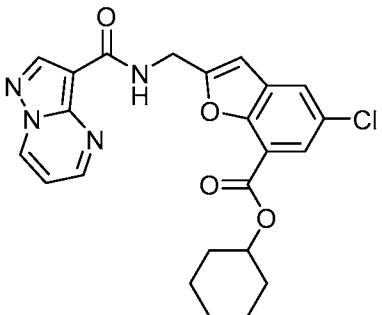
Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺
233		Oxetan-3-yl 5-fluoro-2-((pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.33 (br d, <i>J</i> = 6.4 Hz, 1H), 8.85 (br d, <i>J</i> = 3.1 Hz, 1H), 8.65 (s, 1H), 8.58 (br t, <i>J</i> = 5.5 Hz, 1H), 7.80 (dd, <i>J</i> = 8.4, 2.3 Hz, 1H), 7.65 (dd, <i>J</i> = 9.8, 2.1 Hz, 1H), 7.31 (dd, <i>J</i> = 7.0, 4.3 Hz, 1H), 6.93 (s, 1H), 5.68 (br t, <i>J</i> = 5.5 Hz, 1H), 5.01 - 4.78 (m, 4H), 4.73 - 4.54 (m, 2H)	411.3
234		Cyclobutyl 5-fluoro-2-((pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.20 (br d, <i>J</i> = 6.6 Hz, 1H), 8.79 (br d, <i>J</i> = 2.9 Hz, 1H), 8.59 (s, 1H), 8.52 (br t, <i>J</i> = 5.5 Hz, 1H), 7.67 (dd, <i>J</i> = 8.2, 2.4 Hz, 1H), 7.50 (dd, <i>J</i> = 9.6, 2.4 Hz, 1H), 7.25 (dd, <i>J</i> = 6.9, 4.1 Hz, 1H), 6.87 (s, 1H), 5.15 (br t, <i>J</i> = 7.3 Hz, 1H), 4.81 (br d, <i>J</i> = 5.9 Hz, 2H), 2.32 (br d, <i>J</i> = 7.5 Hz, 2H), 2.17 - 2.03 (m, 2H), 1.82 - 1.53 (m, 2H)	409.3

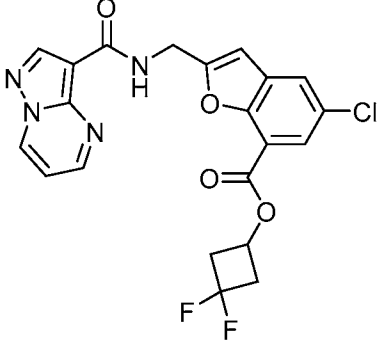
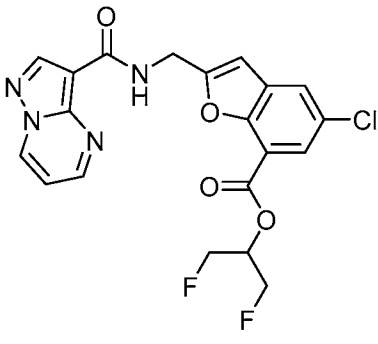
Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺
235		2,2-Difluoroethyl 5-fluoro-2-((pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.23 (br d, <i>J</i> = 6.6 Hz, 1H), 8.81 (br d, <i>J</i> = 2.8 Hz, 1H), 8.60 (s, 1H), 8.52 (br s, 1H), 7.75 (dd, <i>J</i> = 8.2, 2.4 Hz, 1H), 7.57 (dd, <i>J</i> = 9.5, 2.4 Hz, 1H), 7.26 (dd, <i>J</i> = 6.9, 4.2 Hz, 1H), 6.90 (s, 1H), 6.51 - 6.19 (m, 1H), 4.80 (br d, <i>J</i> = 5.9 Hz, 2H), 4.62 (td, <i>J</i> = 15.0, 3.0 Hz, 2H)	419.3
236		3,3-Difluorocyclobutyl 5-fluoro-2-((pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.33 (br d, <i>J</i> = 6.7 Hz, 1H), 8.83 (br d, <i>J</i> = 3.4 Hz, 1H), 8.63 (s, 1H), 8.53 (br t, <i>J</i> = 5.6 Hz, 1H), 7.77 (dd, <i>J</i> = 8.2, 2.4 Hz, 1H), 7.61 (dd, <i>J</i> = 9.8, 2.4 Hz, 1H), 7.30 (dd, <i>J</i> = 6.7, 4.3 Hz, 1H), 6.91 (s, 1H), 5.26 - 5.05 (m, 1H), 4.84 (br d, <i>J</i> = 5.8 Hz, 2H), 3.24 - 3.05 (m, 2H), 2.89 (qd, <i>J</i> = 14.4, 4.9 Hz, 2H)	445.3

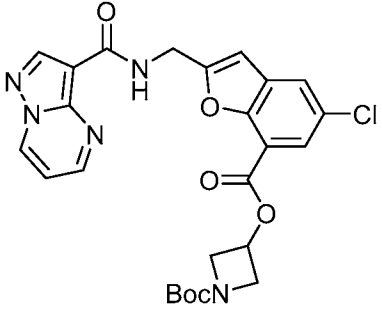
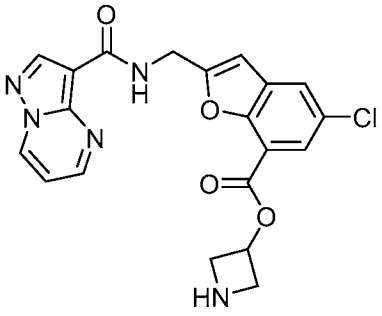
Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺
237		1,3-Difluoropropan-2-yl 5-fluoro-2-((pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.24 (br d, <i>J</i> = 6.6 Hz, 1H), 8.90 - 8.75 (m, 1H), 8.60 (s, 1H), 8.50 (br s, 1H), 7.84 - 7.69 (m, 1H), 7.58 (dd, <i>J</i> = 9.5, 2.2 Hz, 1H), 7.26 (dd, <i>J</i> = 6.8, 4.2 Hz, 1H), 6.90 (s, 1H), 5.70 - 5.46 (m, 1H), 4.89 - 4.74 (m, 4H), 4.69 (br d, <i>J</i> = 5.5 Hz, 2H)	433.3
238		1,1,1,3,3,3-Hexafluoropropan-2-yl 5-fluoro-2-((pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.35 - 9.23 (m, 1H), 8.80 (d, <i>J</i> = 3.1 Hz, 1H), 8.61 (s, 1H), 8.54 (br t, <i>J</i> = 5.8 Hz, 1H), 7.88 (dd, <i>J</i> = 8.2, 2.4 Hz, 1H), 7.64 (dd, <i>J</i> = 9.3, 2.6 Hz, 1H), 7.28 (dd, <i>J</i> = 7.0, 4.3 Hz, 1H), 7.11 - 7.01 (m, 1H), 6.94 (s, 1H), 4.80 (d, <i>J</i> = 5.8 Hz, 2H)	505.3

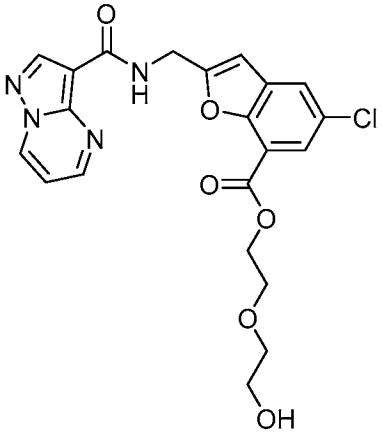
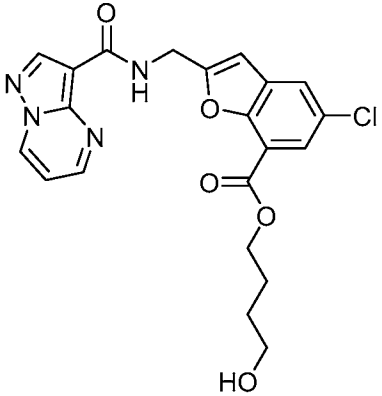
Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺
239		2,2,2-Trifluoroethyl 5-chloro-2- ((pyrazolo[1,5- <i>a</i>]pyrimidine-3- carboxamido)methyl)benzofuran-7- carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.28 (br d, <i>J</i> = 6.9 Hz, 1H), 8.82 (br d, <i>J</i> = 3.7 Hz, 1H), 8.61 (s, 1H), 8.49 (br t, <i>J</i> = 5.6 Hz, 1H), 8.02 (d, <i>J</i> = 1.6 Hz, 1H), 7.76 (d, <i>J</i> = 1.6 Hz, 1H), 7.28 (dd, <i>J</i> = 6.9, 4.3 Hz, 1H), 6.90 (s, 1H), 5.02 (q, <i>J</i> = 9.0 Hz, 2H), 4.82 (d, <i>J</i> = 5.9 Hz, 2H)	453.1
240		Isopropyl 5-chloro- 2-((pyrazolo[1,5- <i>a</i>]pyrimidine-3- carboxamido)methyl)benzofuran-7- carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.27 (d, <i>J</i> = 6.9 Hz, 1H), 8.82 (br d, <i>J</i> = 3.1 Hz, 1H), 8.61 (s, 1H), 8.48 (br t, <i>J</i> = 5.7 Hz, 1H), 7.93 (d, <i>J</i> = 1.9 Hz, 1H), 7.70 (d, <i>J</i> = 1.9 Hz, 1H), 7.28 (dd, <i>J</i> = 6.9, 4.2 Hz, 1H), 6.87 (s, 1H), 5.17 (dt, <i>J</i> = 12.4, 6.1 Hz, 1H), 4.83 (d, <i>J</i> = 5.9 Hz, 2H), 1.31 (d, <i>J</i> = 6.2 Hz, 6H)	413.3

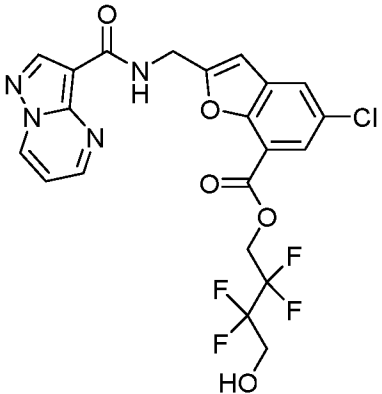
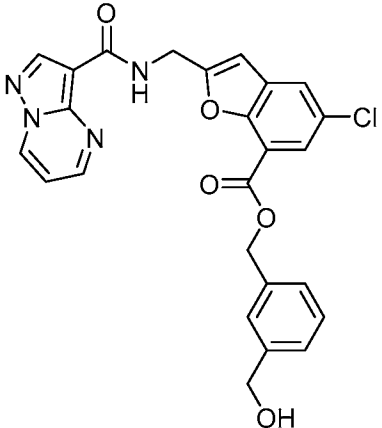
Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺
241		3-Cyanocyclobutyl 5-chloro-2- ((pyrazolo[1,5- <i>a</i>]pyrimidine-3- carboxamido)methyl)benzofuran-7- carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.37 - 9.27 (m, 1H), 8.84 (d, <i>J</i> = 3.1 Hz, 1H), 8.64 (s, 1H), 8.53 (br t, <i>J</i> = 6.0 Hz, 1H), 7.98 (d, <i>J</i> = 2.1 Hz, 1H), 7.79 (d, <i>J</i> = 2.1 Hz, 1H), 7.29 (dd, <i>J</i> = 6.9, 4.1 Hz, 1H), 6.88 (s, 1H), 5.16 (t, <i>J</i> = 7.3 Hz, 1H), 4.83 (br d, <i>J</i> = 5.8 Hz, 2H), 3.25 - 3.08 (m, 1H), 2.84 (br dd, <i>J</i> = 7.6, 1.8 Hz, 2H), 2.58 - 2.53 (m, 2H)	450.3
242		<i>(R)</i> -1- Methoxypropan-2-yl 5-chloro-2- ((pyrazolo[1,5- <i>a</i>]pyrimidine-3- carboxamido)methyl)benzofuran-7- carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.24 (br d, <i>J</i> = 6.8 Hz, 1H), 8.81 (br d, <i>J</i> = 2.9 Hz, 1H), 8.61 (s, 1H), 8.49 (br s, 1H), 7.93 (d, <i>J</i> = 1.9 Hz, 1H), 7.70 (d, <i>J</i> = 1.9 Hz, 1H), 7.27 (dd, <i>J</i> = 6.9, 4.2 Hz, 1H), 6.87 (s, 1H), 5.24 (td, <i>J</i> = 6.4, 3.9 Hz, 1H), 4.81 (br d, <i>J</i> = 5.9 Hz, 2H), 3.50 - 3.42 (m, 5H), 1.25 (d, <i>J</i> = 6.5 Hz, 3H)	443.0

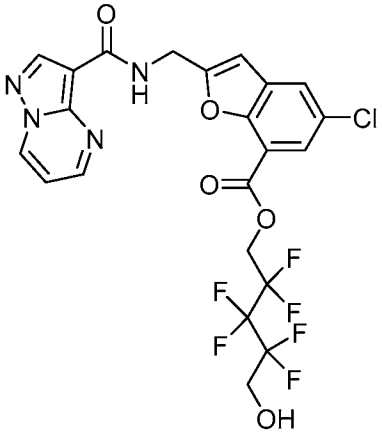
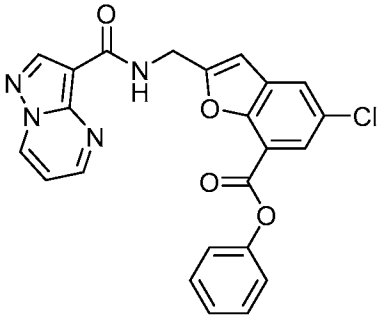
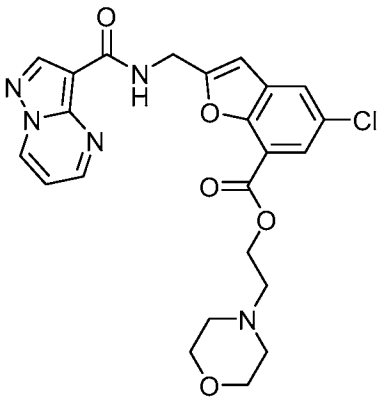
Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺
243		Cyclopentyl 5-chloro-2-((pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.23 (br d, <i>J</i> = 6.9 Hz, 1H), 8.79 (br d, <i>J</i> = 4.0 Hz, 1H), 8.60 (s, 1H), 8.47 (br t, <i>J</i> = 5.6 Hz, 1H), 7.91 (s, 1H), 7.67 (s, 1H), 7.26 (dd, <i>J</i> = 6.6, 4.5 Hz, 1H), 6.87 (s, 1H), 5.34 (br s, 1H), 4.81 (d, <i>J</i> = 5.8 Hz, 2H), 1.95 - 1.80 (m, 2H), 1.79 - 1.69 (m, 2H), 1.64 (br d, <i>J</i> = 4.0 Hz, 2H), 1.50 (br s, 2H)	439.3
244		Cyclohexyl 5-chloro-2-((pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.25 (br d, <i>J</i> = 6.6 Hz, 1H), 8.80 (br d, <i>J</i> = 3.7 Hz, 1H), 8.60 (s, 1H), 8.46 (br t, <i>J</i> = 5.6 Hz, 1H), 7.93 (s, 1H), 7.70 (s, 1H), 7.27 (dd, <i>J</i> = 6.5, 4.5 Hz, 1H), 6.88 (s, 1H), 4.99 (br s, 1H), 4.82 (br d, <i>J</i> = 5.8 Hz, 2H), 1.80 (br s, 2H), 1.66 (br d, <i>J</i> = 3.2 Hz, 2H), 1.57 - 1.15 (m, 6H)	453.4

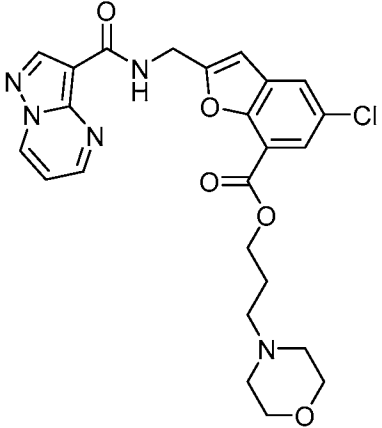
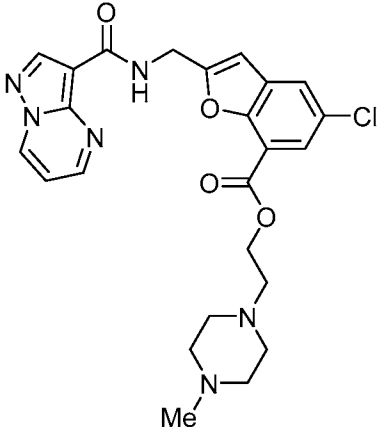
Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺
245		3,3-Difluorocyclobutyl 5-chloro-2-((pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.29 (d, <i>J</i> = 6.7 Hz, 1H), 8.81 (br d, <i>J</i> = 3.4 Hz, 1H), 8.61 (s, 1H), 8.54 (br t, <i>J</i> = 5.8 Hz, 1H), 7.98 (d, <i>J</i> = 1.5 Hz, 1H), 7.77 (d, <i>J</i> = 1.5 Hz, 1H), 7.28 (dd, <i>J</i> = 7.0, 4.3 Hz, 1H), 6.88 (s, 1H), 5.14 (br dd, <i>J</i> = 7.2, 4.4 Hz, 1H), 4.82 (br d, <i>J</i> = 5.8 Hz, 2H), 3.22 - 3.07 (m, 2H), 2.87 (br dd, <i>J</i> = 14.8, 4.4 Hz, 2H)	461.3
246		1,3-Difluoropropan-2-yl 5-chloro-2-((pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.26 (br d, <i>J</i> = 6.7 Hz, 1H), 8.81 (br d, <i>J</i> = 3.7 Hz, 1H), 8.62 (s, 1H), 8.56 (br t, <i>J</i> = 5.8 Hz, 1H), 7.77 (d, <i>J</i> = 1.2 Hz, 1H), 7.27 (dd, <i>J</i> = 6.9, 4.1 Hz, 1H), 6.89 (s, 1H), 5.63 - 5.44 (m, 1H), 4.85 - 4.74 (m, 4H), 4.73 - 4.62 (m, 2H)	449.3

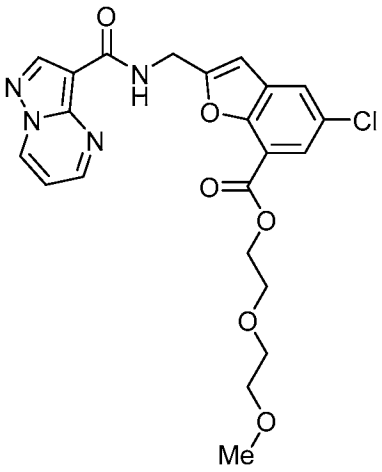
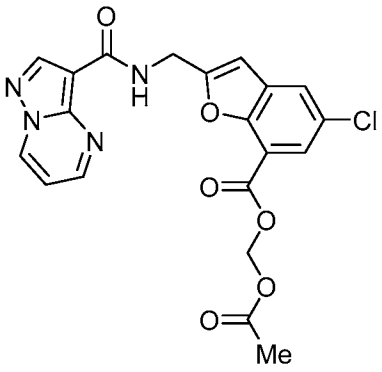
Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺
247		<p>Tert-butyl 3-((5-chloro-2-((pyrazolo[1,5-a]pyrimidine-3-carboxamido)methyl)benzofuran-7-carbonyloxy)azetidine-1-carboxylate</p>	<p>¹H NMR (400 MHz, CHLOROFORM-d) δ 8.81 (dd, <i>J</i> = 7.0, 1.7 Hz, 1H), 8.76 - 8.69 (m, 2H), 8.49 (br t, <i>J</i> = 5.9 Hz, 1H), 7.90 (d, <i>J</i> = 2.1 Hz, 1H), 7.72 (d, <i>J</i> = 2.1 Hz, 1H), 7.04 (dd, <i>J</i> = 7.0, 4.2 Hz, 1H), 6.76 (s, 1H), 5.44 (ddd, <i>J</i> = 6.8, 4.3, 2.4 Hz, 1H), 4.93 (d, <i>J</i> = 6.0 Hz, 2H), 4.40 (ddd, <i>J</i> = 10.1, 6.9, 1.0 Hz, 2H), 4.19 - 4.13 (m, 2H), 1.49 (s, 9H)</p>	526.2
248		<p>Azetidin-3-yl 5-chloro-2-((pyrazolo[1,5-a]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate</p>	<p>¹H NMR (500 MHz, DMSO-d₆) δ 9.34 - 9.19 (m, 1H), 8.91 - 8.74 (m, 1H), 8.63 (d, <i>J</i> = 1.2 Hz, 1H), 8.52 (br s, 1H), 8.01 (s, 1H), 7.85 (s, 1H), 7.37 - 7.18 (m, 1H), 6.91 (s, 1H), 5.52 (br t, <i>J</i> = 5.9 Hz, 1H), 4.83 (br d, <i>J</i> = 5.8 Hz, 2H), 4.45 (br dd, <i>J</i> = 12.3, 6.9 Hz, 2H), 4.26 (br dd, <i>J</i> = 11.7, 4.7 Hz, 2H)</p>	426.1

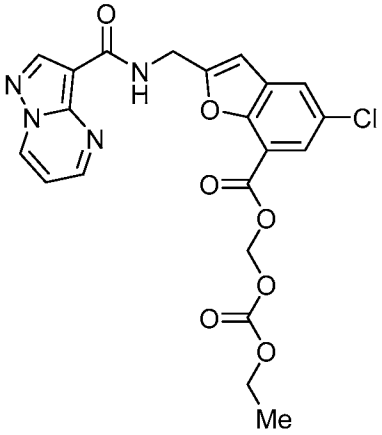
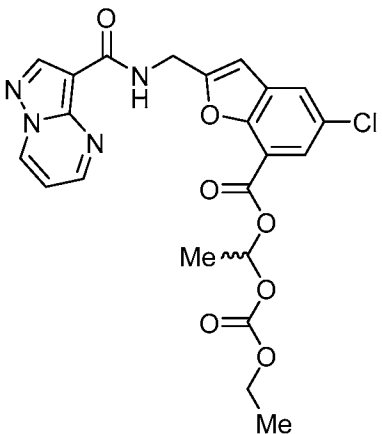
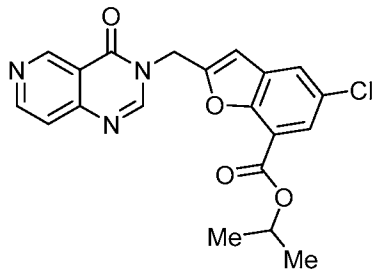
Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺
249		2-(2-(2-Hydroxyethoxy)ethyl 5-chloro-2-((pyrazolo[1,5-a]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.26 (d, <i>J</i> = 7.0 Hz, 1H), 8.91 - 8.78 (m, 1H), 8.61 (s, 1H), 8.55 (br t, <i>J</i> = 5.8 Hz, 1H), 7.94 (d, <i>J</i> = 2.1 Hz, 1H), 7.72 (d, <i>J</i> = 2.1 Hz, 1H), 7.27 (dd, <i>J</i> = 7.0, 4.3 Hz, 1H), 6.85 (s, 1H), 4.79 (br d, <i>J</i> = 5.8 Hz, 2H), 4.50 - 4.38 (m, 2H), 3.77 - 3.70 (m, 2H), 3.65 - 3.53 (m, 4H)	459.2
250 I		4-Hydroxybutyl 5-chloro-2-((pyrazolo[1,5-a]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.34 - 9.20 (m, 1H), 8.81 (br d, <i>J</i> = 2.7 Hz, 1H), 8.61 (s, 1H), 8.53 (br t, <i>J</i> = 5.8 Hz, 1H), 7.93 (d, <i>J</i> = 2.1 Hz, 1H), 7.70 (d, <i>J</i> = 2.1 Hz, 1H), 7.27 (dd, <i>J</i> = 7.0, 4.3 Hz, 1H), 6.85 (s, 1H), 4.79 (br d, <i>J</i> = 5.8 Hz, 2H), 4.55 (t, <i>J</i> = 5.0 Hz, 1H), 4.31 (t, <i>J</i> = 6.4 Hz, 2H), 3.40 (q, <i>J</i> = 6.1 Hz, 2H), 1.76 - 1.67 (m, 2H), 1.60 - 1.49 (m, 2H)	443.3

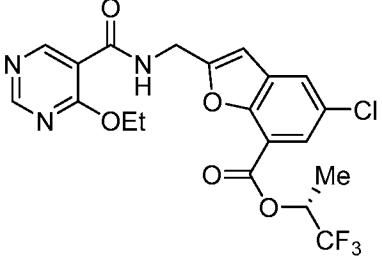
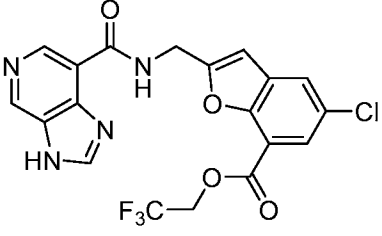
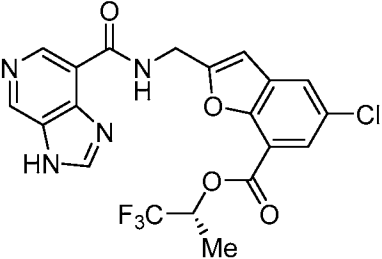
Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺
251		2,2,3,3-Tetrafluoro-4-hydroxybutyl 5-chloro-2-((pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.19 (br d, <i>J</i> = 6.8 Hz, 1H), 8.75 (br d, <i>J</i> = 3.5 Hz, 1H), 8.55 (s, 1H), 8.46 (br t, <i>J</i> = 5.8 Hz, 1H), 7.94 (s, 1H), 7.70 (d, <i>J</i> = 1.5 Hz, 1H), 7.21 (dd, <i>J</i> = 6.8, 4.3 Hz, 1H), 6.84 (s, 1H), 4.87 (br t, <i>J</i> = 14.8 Hz, 2H), 4.76 (d, <i>J</i> = 5.9 Hz, 2H), 3.87 (td, <i>J</i> = 14.6, 5.8 Hz, 2H)	515.3
252		3-(Hydroxymethyl)benzyl 5-chloro-2-((pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.29 (dd, <i>J</i> = 7.0, 1.2 Hz, 1H), 8.83 - 8.69 (m, 1H), 8.62 (s, 1H), 8.54 (br t, <i>J</i> = 5.8 Hz, 1H), 7.96 (d, <i>J</i> = 2.1 Hz, 1H), 7.74 (d, <i>J</i> = 2.1 Hz, 1H), 7.46 (s, 1H), 7.41 - 7.21 (m, 4H), 6.86 (s, 1H), 5.41 (s, 2H), 4.82 (br d, <i>J</i> = 5.8 Hz, 2H), 4.50 (d, <i>J</i> = 5.5 Hz, 2H)	491.2

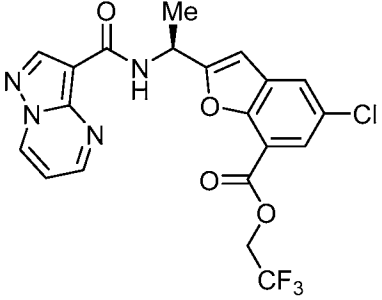
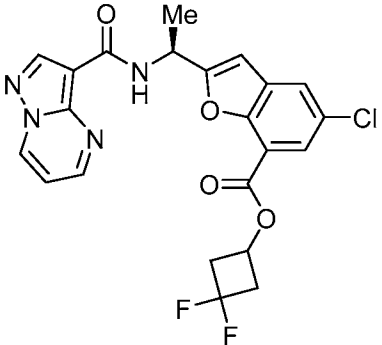
Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺
253		2,2,3,3,4,4-Hexafluoro-5-hydroxypentyl 5-chloro-2-((pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.24 (dd, <i>J</i> = 7.0, 1.2 Hz, 1H), 8.82 - 8.72 (m, 1H), 8.59 (s, 1H), 8.57 - 8.53 (m, 1H), 8.01 (d, <i>J</i> = 2.1 Hz, 1H), 7.73 (d, <i>J</i> = 2.1 Hz, 1H), 7.26 (dd, <i>J</i> = 6.7, 4.3 Hz, 1H), 6.88 (s, 1H), 4.99 (br t, <i>J</i> = 14.3 Hz, 2H), 4.78 (br d, <i>J</i> = 5.8 Hz, 2H), 3.98 - 3.84 (m, 2H)	565.2
254		Phenyl 5-chloro-2-((pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.24 (br d, <i>J</i> = 6.4 Hz, 1H), 8.72 (br s, 1H), 8.63 - 8.53 (m, 2H), 8.03 (br s, 1H), 7.90 (br s, 1H), 7.49 - 7.39 (m, 2H), 7.36 - 7.19 (m, 4H), 6.90 (s, 1H), 4.81 (br d, <i>J</i> = 5.2 Hz, 2H)	447.2
255		2-Morpholinoethyl 5-chloro-2-((pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.18 (br d, <i>J</i> = 6.9 Hz, 1H), 8.78 (br d, <i>J</i> = 3.8 Hz, 1H), 8.58 (s, 1H), 8.50 (br t, <i>J</i> = 5.8 Hz, 1H), 7.90 (s, 1H), 7.71 (d, <i>J</i> = 1.8 Hz, 1H), 7.24 (dd, <i>J</i> = 6.7, 4.3 Hz, 1H), 6.86 (s, 1H), 4.77 (br d, <i>J</i> = 5.8 Hz, 2H), 4.41 (t, <i>J</i> = 5.5 Hz, 2H), 3.50 - 3.44 (m, 4H), 2.67 (t, <i>J</i> = 5.5 Hz, 2H), 2.44 - 2.39 (m, 4H)	484.1

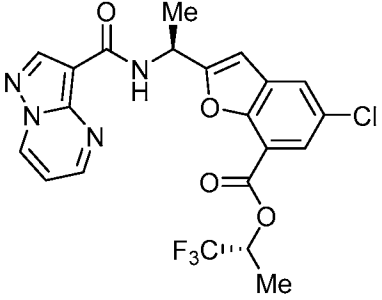
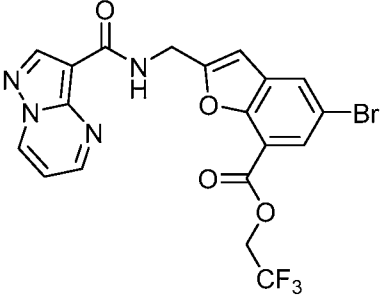
Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺
256		3-Morpholinopropyl 5-chloro-2-((pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.20 (br d, <i>J</i> = 7.0 Hz, 1H), 8.79 (br d, <i>J</i> = 4.0 Hz, 1H), 8.58 (s, 1H), 8.49 (br t, <i>J</i> = 5.6 Hz, 1H), 7.91 (s, 1H), 7.71 (s, 1H), 7.25 (dd, <i>J</i> = 6.8, 4.3 Hz, 1H), 6.86 (s, 1H), 4.78 (d, <i>J</i> = 5.8 Hz, 2H), 4.34 (t, <i>J</i> = 6.2 Hz, 2H), 3.50 - 3.44 (m, 4H), 2.39 (br t, <i>J</i> = 7.0 Hz, 2H), 2.29 (br s, 4H), 1.84 (quin, <i>J</i> = 6.6 Hz, 2H)	498.3
257		2-(4-Methylpiperazin-1-yl)ethyl 5-chloro-2-((pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.26 (br d, <i>J</i> = 7.1 Hz, 1H), 8.81 (br d, <i>J</i> = 2.7 Hz, 1H), 8.60 (s, 1H), 8.46 (br t, <i>J</i> = 5.7 Hz, 1H), 7.93 (d, <i>J</i> = 1.9 Hz, 1H), 7.72 (d, <i>J</i> = 2.0 Hz, 1H), 7.27 (dd, <i>J</i> = 6.9, 4.1 Hz, 1H), 6.87 (s, 1H), 4.80 (br d, <i>J</i> = 5.8 Hz, 2H), 4.41 (t, <i>J</i> = 5.6 Hz, 2H), 2.68 (br t, <i>J</i> = 5.6 Hz, 2H), 2.44 (br s, 4H), 2.25 (br s, 4H), 2.09 (s, 3H)	497.1

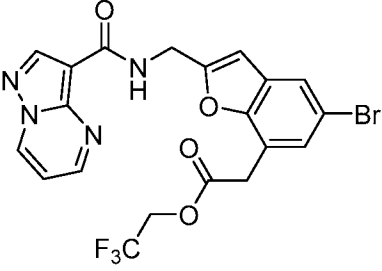
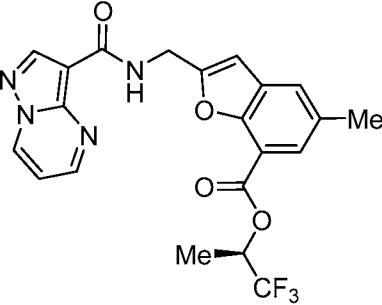
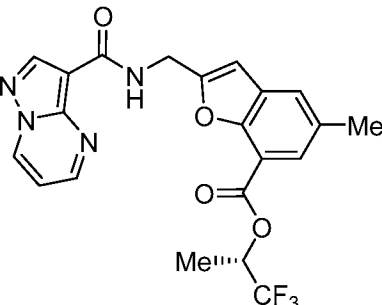
Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺
258		2-(2-Methoxyethoxy)ethyl 15-chloro-2-((pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.26 (d, <i>J</i> = 5.8 Hz, 1H), 8.81 (br d, <i>J</i> = 3.1 Hz, 1H), 8.61 (s, 1H), 8.54 (br t, <i>J</i> = 5.8 Hz, 1H), 7.94 (d, <i>J</i> = 2.1 Hz, 1H), 7.72 (d, <i>J</i> = 2.1 Hz, 1H), 7.27 (dd, <i>J</i> = 6.9, 4.1 Hz, 1H), 6.86 (s, 1H), 4.79 (br d, <i>J</i> = 5.8 Hz, 2H), 4.46 - 4.37 (m, 2H), 3.75 - 3.70 (m, 2H), 3.55 - 3.52 (m, 2H), 3.40 - 3.35 (m, 2H), 3.16 (s, 3H)	473.3
259		Acetoxymethyl 5-chloro-2-((pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.27 (br d, <i>J</i> = 6.7 Hz, 1H), 8.85 - 8.79 (m, 1H), 8.61 (s, 1H), 8.56 (br t, <i>J</i> = 5.8 Hz, 1H), 8.00 (d, <i>J</i> = 2.1 Hz, 1H), 7.73 (d, <i>J</i> = 1.8 Hz, 1H), 7.27 (dd, <i>J</i> = 7.0, 4.3 Hz, 1H), 6.87 (s, 1H), 5.94 (s, 2H), 4.79 (br d, <i>J</i> = 5.8 Hz, 2H), 2.07 (s, 3H)	443.2

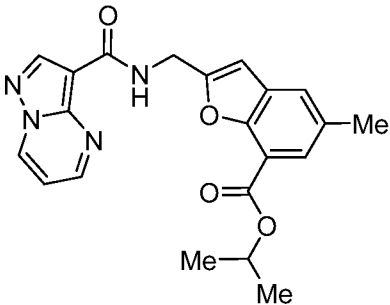
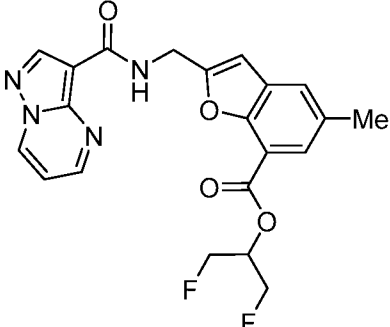
Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺
260		((Ethoxycarbonyl)oxy)methyl 5-chloro-2-((pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.29 - 9.21 (m, 1H), 8.82 - 8.79 (m, 1H), 8.59 (d, <i>J</i> = 1.4 Hz, 1H), 8.50 (br s, 1H), 7.98 (t, <i>J</i> = 2.1 Hz, 1H), 7.74 (t, <i>J</i> = 1.8 Hz, 1H), 7.26 (t, <i>J</i> = 4.6, 1H), 6.87 (s, 1H), 5.97 (s, 2H), 4.80 (br d, <i>J</i> = 5.6 Hz, 2H), 4.17 (q, <i>J</i> = 7.0, 2H), 1.21 (t, <i>J</i> = 7.0 Hz, 3H)	473.0
261		1-((Ethoxycarbonyl)oxy)ethyl 5-chloro-2-((pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate (racemic)	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.26 (br d, <i>J</i> = 6.7 Hz, 1H), 8.81 (br d, <i>J</i> = 3.4 Hz, 1H), 8.60 (s, 1H), 8.56 (br t, <i>J</i> = 5.6 Hz, 1H), 7.99 (s, 1H), 7.72 (s, 1H), 7.26 (dd, <i>J</i> = 6.7, 4.3 Hz, 1H), 6.90-6.85 (m, 2H), 4.79 (br d, <i>J</i> = 5.8 Hz, 2H), 4.17 - 4.07 (m, 2H), 1.55 (d, <i>J</i> = 5.2 Hz, 3H), 1.17 (t, <i>J</i> = 7.2 Hz, 3H)	487.3
262		Isopropyl 5-chloro-2-((4-oxopyrido[4,3- <i>d</i>]pyrimidin-3(4 <i>H</i>)-yl)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.33 (s, 1H), 8.88 (d, <i>J</i> = 5.5 Hz, 1H), 8.80 (s, 1H), 7.99 (d, <i>J</i> = 1.8 Hz, 1H), 7.72 (d, <i>J</i> = 1.8 Hz, 1H), 7.65 (d, <i>J</i> = 5.5 Hz, 1H), 7.07 (s, 1H), 5.50 (s, 2H), 5.27 - 5.03 (m, 1H), 1.25 (d, <i>J</i> = 6.1 Hz, 6H)	398.2

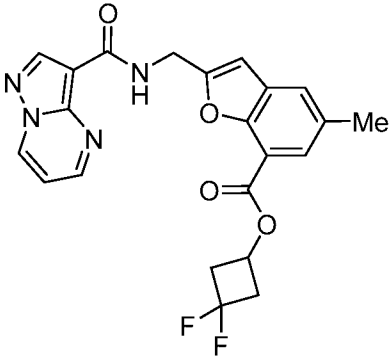
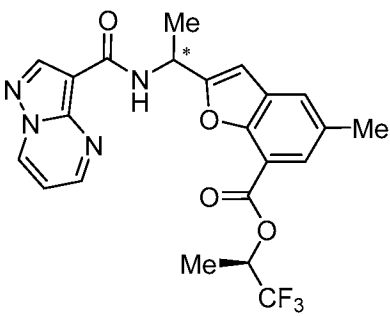
Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺
263		(R)-1,1,1-trifluoropropan-2-yl 5-chloro-2-((4-ethoxypyrimidine-5-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO-d ₆) δ 8.87 (s, 1H), 8.84 (s, 1H), 8.80 - 8.70 (m, 1H), 8.04 (d, <i>J</i> =1.9 Hz, 1H), 7.76 (d, <i>J</i> =1.9 Hz, 1H), 6.92 (s, 1H), 5.74 (dt, <i>J</i> =13.3, 6.6 Hz, 1H), 4.74 (br d, <i>J</i> =5.7 Hz, 3H), 4.55 (q, <i>J</i> =7.0 Hz, 3H), 1.53 (d, <i>J</i> =6.6 Hz, 4H), 1.37 (t, <i>J</i> =7.0 Hz, 3H)	472.3
264		2,2,2-Trifluoroethyl 2-((3H-imidazo[4,5-c]pyridine-7-carboxamido)methyl)-5-chlorobenzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.70 (br d, <i>J</i> = 3.1 Hz, 1H), 9.11 (s, 1H), 8.93 (s, 1H), 8.55 (br s, 1H), 8.04 (s, 1H), 7.78 (s, 1H), 6.96 (s, 1H), 5.03 (q, <i>J</i> = 8.9 Hz, 2H), 4.87 (br d, <i>J</i> = 5.0 Hz, 2H)	453.1
265		(R)-1,1,1-Trifluoropropan-2-yl 2-((3H-imidazo[4,5-c]pyridine-7-carboxamido)methyl)-5-chlorobenzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.71 (br s, 1H), 9.20 (s, 1H), 8.96 (s, 1H), 8.63 (s, 1H), 8.04 (d, <i>J</i> = 2.0 Hz, 1H), 7.76 (d, <i>J</i> = 2.1 Hz, 1H), 6.97 (s, 1H), 5.72 (dt, <i>J</i> = 13.3, 6.7 Hz, 1H), 4.88 (br d, <i>J</i> = 5.6 Hz, 2H)	467.1

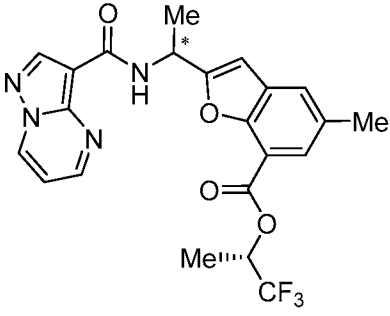
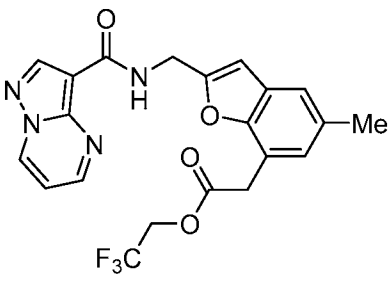
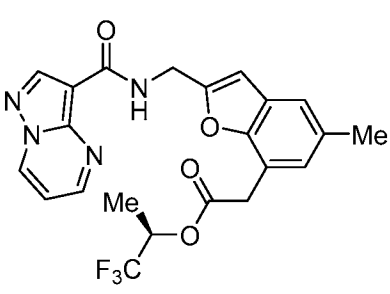
Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺
266		2,2,2-Trifluoroethyl (<i>S</i>)-5-chloro-2-(1-(pyrazolo[1,5- <i>a</i>]pyrimidin-3-carboxamido)ethyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.31 (d, <i>J</i> = 6.1 Hz, 1H), 8.82 (br d, <i>J</i> = 3.4 Hz, 1H), 8.62 (s, 1H), 8.39 (br d, <i>J</i> = 7.9 Hz, 1H), 8.04 (d, <i>J</i> = 1.8 Hz, 1H), 7.77 (d, <i>J</i> = 1.8 Hz, 1H), 7.29 (dd, <i>J</i> = 7.0, 4.3 Hz, 1H), 6.94 (s, 1H), 5.50 (br t, <i>J</i> = 7.3 Hz, 1H), 5.04 (q, <i>J</i> = 8.9 Hz, 2H), 1.66 (d, <i>J</i> = 6.7 Hz, 3H)	467.3
267		3,3-Difluorocyclobutyl (<i>S</i>)-5-chloro-2-(1-(pyrazolo[1,5- <i>a</i>]pyrimidin-3-carboxamido)ethyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.31 (br d, <i>J</i> = 7.0 Hz, 1H), 8.82 (br d, <i>J</i> = 3.4 Hz, 1H), 8.62 (s, 1H), 8.37 (br d, <i>J</i> = 8.2 Hz, 1H), 8.00 (s, 1H), 7.78 (s, 1H), 7.29 (dd, <i>J</i> = 6.7, 4.3 Hz, 1H), 6.93 (s, 1H), 5.53 (br t, <i>J</i> = 7.2 Hz, 1H), 5.16 (br dd, <i>J</i> = 7.6, 4.9 Hz, 1H), 3.25 - 3.05 (m, 2H), 2.84 (br dd, <i>J</i> = 13.3, 9.6 Hz, 2H), 1.67 (br d, <i>J</i> = 6.7 Hz, 3H)	475.3

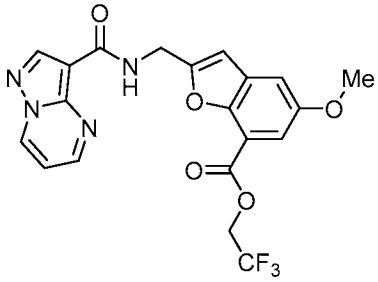
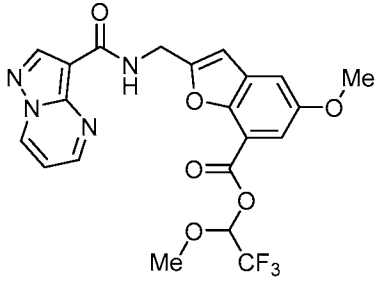
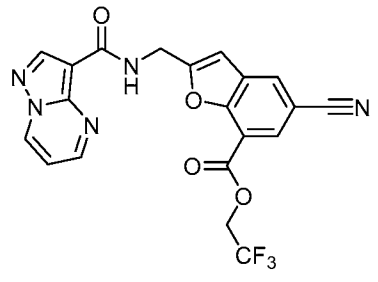
Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺
268		(R)-1,1,1-Trifluoropropan-2-yl 5-chloro-2-((S)-1-(pyrazolo[1,5-a]pyrimidine-3-carboxamido)ethyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.32 (br d, <i>J</i> = 6.7 Hz, 1H), 8.81 (br d, <i>J</i> = 3.1 Hz, 1H), 8.62 (s, 1H), 8.37 (br d, <i>J</i> = 8.2 Hz, 1H), 8.04 (d, <i>J</i> = 1.5 Hz, 1H), 7.77 (d, <i>J</i> = 1.8 Hz, 1H), 7.29 (dd, <i>J</i> = 6.9, 4.4 Hz, 1H), 6.94 (s, 1H), 5.85 - 5.61 (m, 1H), 5.51 (br t, <i>J</i> = 7.3 Hz, 1H), 1.66 (br d, <i>J</i> = 7.0 Hz, 3H), 1.49 (br d, <i>J</i> = 6.4 Hz, 3H)	481.2
269		2,2,2-Trifluoroethyl 5-bromo-2-((pyrazolo[1,5-a]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.32 (br d, <i>J</i> = 6.7 Hz, 1H), 8.84 (br d, <i>J</i> = 3.4 Hz, 1H), 8.64 (s, 1H), 8.58 (br t, <i>J</i> = 5.8 Hz, 1H), 8.19 (s, 1H), 7.90 (d, <i>J</i> = 1.5 Hz, 1H), 7.31 (dd, <i>J</i> = 6.9, 4.1 Hz, 1H), 6.92 (s, 1H), 5.04 (q, <i>J</i> = 8.9 Hz, 2H), 4.83 (br d, <i>J</i> = 5.8 Hz, 2H)	497.1

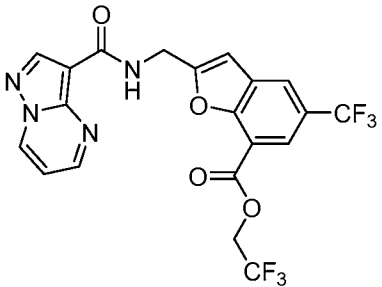
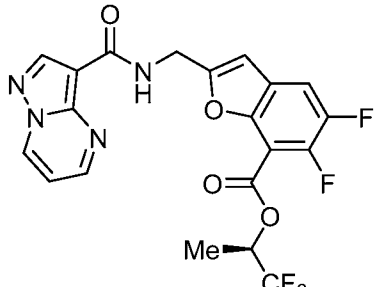
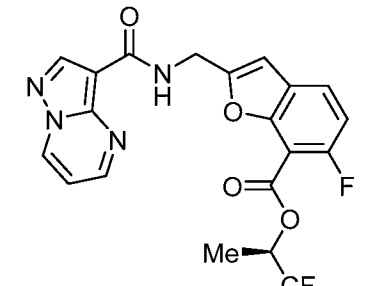
Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺
270		2,2,2-Trifluoroethyl 2-(5-bromo-2-((pyrazolo[1,5-a]pyrimidine-3-carboxamido)methyl)benzofuran-7-yl)acetate	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.22 (br d, <i>J</i> = 7.0 Hz, 1H), 8.79 (br d, <i>J</i> = 3.1 Hz, 1H), 8.59 (s, 1H), 8.53 (br t, <i>J</i> = 5.8 Hz, 1H), 7.72 (d, <i>J</i> = 1.2 Hz, 1H), 7.35 (s, 1H), 7.26 (dd, <i>J</i> = 6.7, 4.3 Hz, 1H), 6.77 (s, 1H), 4.72 (br d, <i>J</i> = 5.8 Hz, 2H), 4.67 (q, <i>J</i> = 9.1 Hz, 2H), 4.05 (s, 2H)	513.1
271		(R)-1,1,1-Trifluoropropan-2-yl 5-methyl-2-((pyrazolo[1,5-a]pyrimidine-3-carboxamido)methyl)-benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.31 (br d, <i>J</i> = 7.0 Hz, 1H), 8.82 (br d, <i>J</i> = 2.7 Hz, 1H), 8.63 (s, 1H), 8.50 (br s, 1H), 7.73 (s, 1H), 7.64 (s, 1H), 7.31 - 7.26 (m, 1H), 6.83 (s, 1H), 5.77 - 5.68 (m, 1H), 4.80 (br d, <i>J</i> = 5.2 Hz, 2H), 2.43 (s, 3H), 1.48 (br d, <i>J</i> = 6.4 Hz, 3H)	447.2
272		(S)-1,1,1-Trifluoropropan-2-yl 5-methyl-2-((pyrazolo[1,5-a]pyrimidine-3-carboxamido)methyl)-benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.31 (br d, <i>J</i> = 6.7 Hz, 1H), 8.82 (br d, <i>J</i> = 2.1 Hz, 1H), 8.80 - 8.59 (m, 1H), 8.50 (br t, <i>J</i> = 5.5 Hz, 1H), 7.73 (s, 1H), 7.64 (s, 1H), 7.32 - 7.26 (m, 1H), 6.83 (s, 1H), 5.77 - 5.67 (m, 1H), 4.80 (br d, <i>J</i> = 5.2 Hz, 2H), 2.43 (s, 3H), 1.48 (br d, <i>J</i> = 6.4 Hz, 3H)	447.1

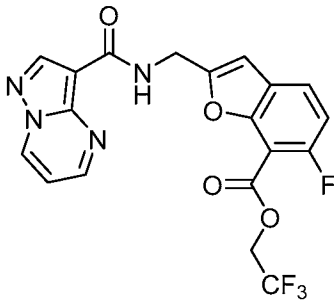
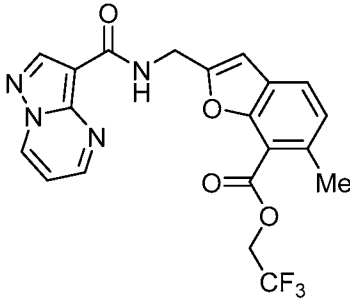
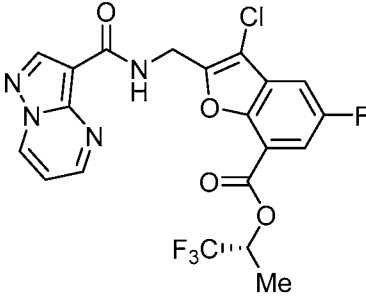
Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺
273		Isopropyl 5-methyl-2-((pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)-benzofuran-7-carboxylate	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ 9.08 (dd, <i>J</i> = 7.0, 1.7 Hz, 1H), 8.78 (dd, <i>J</i> = 4.2, 1.7 Hz, 1H), 8.61 (s, 1H), 8.54 - 8.48 (m, 1H), 7.66 (d, <i>J</i> = 1.2 Hz, 1H), 7.58 (dd, <i>J</i> = 1.6, 0.7 Hz, 1H), 7.21 (dd, <i>J</i> = 7.0, 4.2 Hz, 1H), 6.74 (s, 1H), 5.26 (dt, <i>J</i> = 12.5, 6.2 Hz, 1H), 4.87 (d, <i>J</i> = 0.6 Hz, 2H), 2.45 (s, 3H), 1.38 (d, <i>J</i> = 6.2 Hz, 6H)	393.1
274		1,3-Difluoropropan-2-yl 5-methyl-2-((pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)-benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.30 - 9.24 (m, 1H), 8.81 (br d, <i>J</i> = 3.1 Hz, 1H), 8.64 - 8.59 (m, 1H), 8.55 - 8.46 (m, 1H), 7.74 - 7.67 (m, 1H), 7.67 - 7.61 (m, 1H), 7.30 - 7.23 (m, 1H), 6.86 - 6.75 (m, 1H), 5.61 - 5.47 (m, 1H), 4.84 - 4.74 (m, 4H), 4.74 - 4.62 (m, 2H), 2.42 (s, 3H)	429.2

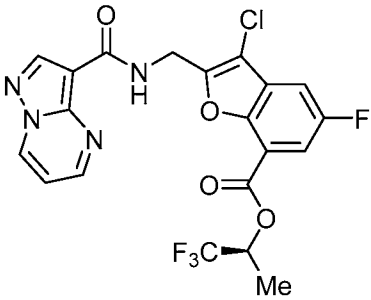
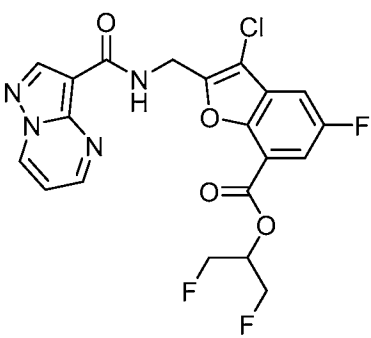
Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺
275		3,3-Difluorocyclobutyl 5-methyl-2- ((pyrazolo[1,5- <i>a</i>]pyrimidine-3- carboxamido)methyl)-benzofuran-7- carboxylate	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.29 (br d, <i>J</i> = 6.7 Hz, 1H), 8.81 (br d, <i>J</i> = 3.7 Hz, 1H), 8.62 (s, 1H), 8.51 (br t, <i>J</i> = 5.8 Hz, 1H), 7.68 (s, 1H), 7.64 (s, 1H), 6.81 (s, 1H), 5.12 (br s, 1H), 4.80 (br d, <i>J</i> = 5.8 Hz, 2H), 3.18 - 3.08 (m, 2H), 2.82 (qd, <i>J</i> = 14.3, 4.7 Hz, 2H), 2.41 (s, 3H)	441.0
276		(<i>R</i>)-1,1,1- Trifluoropropan-2-yl 5-methyl-2-(1- (pyrazolo[1,5- <i>a</i>]pyrimidine-3- carboxamido)ethyl)b enzofuran-7- carboxylate	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.25 (br d, <i>J</i> = 7.0 Hz, 1H), 8.81 - 8.75 (m, 1H), 8.60 (s, 1H), 8.35 - 8.30 (m, 1H), 7.73 (s, 1H), 7.64 (s, 1H), 7.26 (dd, <i>J</i> = 6.9, 4.2 Hz, 1H), 6.85 (s, 1H), 5.73 - 5.66 (m, 1H), 5.54 - 5.44 (m, 1H), 2.43 (s, 3H), 1.66 (d, <i>J</i> = 7.0 Hz, 3H), 1.51 - 1.47 (m, 3H)	461.3

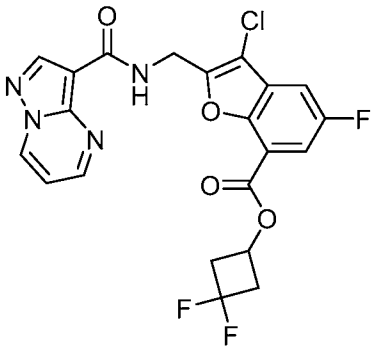
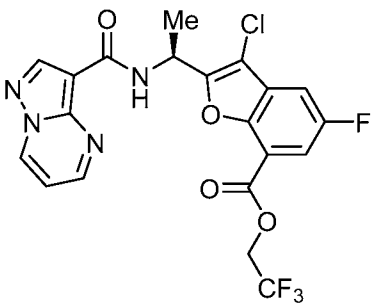
Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺
277		<p>(<i>S</i>)-1,1,1-Trifluoropropan-2-yl 5-methyl-2-(1-(pyrazolo[1,5-<i>a</i>]pyrimidine-3-carboxamido)ethyl)benzofuran-7-carboxylate</p>	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.25 (br d, <i>J</i> = 7.0 Hz, 1H), 8.81 - 8.75 (m, 1H), 8.60 (s, 1H), 8.35 - 8.30 (m, 1H), 7.73 (s, 1H), 7.64 (s, 1H), 7.26 (dd, <i>J</i> = 6.9, 4.2 Hz, 1H), 6.85 (s, 1H), 5.73 - 5.66 (m, 1H), 5.54 - 5.44 (m, 1H), 2.43 (s, 3H), 1.66 (d, <i>J</i> = 7.0 Hz, 3H), 1.51 - 1.47 (m, 3H)	461.3
278		<p>2,2,2-Trifluoroethyl 2-(5-methyl-2-((pyrazolo[1,5-<i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-yl)acetate</p>	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.21 (d, <i>J</i> = 6.1 Hz, 1H), 8.78 (br d, <i>J</i> = 2.7 Hz, 1H), 8.59 (s, 1H), 8.49 (br t, <i>J</i> = 5.6 Hz, 1H), 7.28 (s, 1H), 7.25 (dd, <i>J</i> = 7.0, 4.3 Hz, 1H), 6.97 (s, 1H), 6.69 (s, 1H), 4.78 - 4.61 (m, 4H), 3.97 (s, 2H), 2.33 (s, 3H)	447.2
279		<p>(<i>R</i>)-1,1,1-Trifluoropropan-2-yl 2-(5-methyl-2-((pyrazolo[1,5-<i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-yl)acetate</p>	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.31 (br d, <i>J</i> = 6.4 Hz, 1H), 8.82 (br d, <i>J</i> = 3.1 Hz, 1H), 8.62 (s, 1H), 8.44 (br t, <i>J</i> = 5.3 Hz, 1H), 7.29 (br s, 2H), 6.99 (s, 1H), 6.70 (s, 1H), 5.50 - 5.31 (m, 1H), 4.73 (br d, <i>J</i> = 5.8 Hz, 2H), 3.98 (s, 2H), 2.35 (s, 3H), 1.30 (br d, <i>J</i> = 6.4 Hz, 3H)	461.2

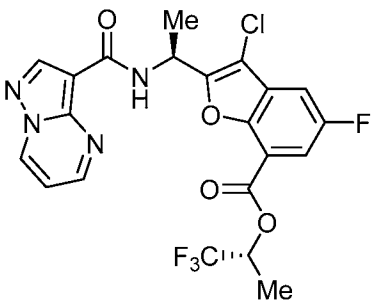
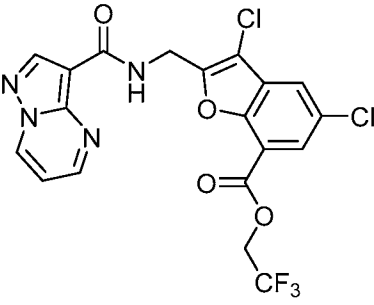
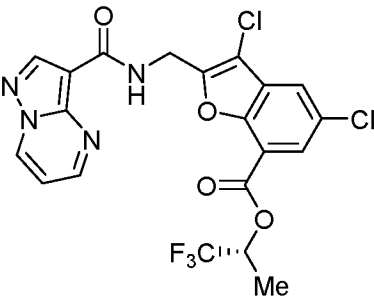
Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺
280		2,2,2-Trifluoroethyl 5-methoxy-2-((pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.32 (br s, 1H), 8.84 (br s, 1H), 8.65 (s, 1H), 8.55 (br s, 1H), 7.53 (d, <i>J</i> = 2.1 Hz, 1H), 7.42 - 7.23 (m, 2H), 6.86 (s, 1H), 5.03 (q, <i>J</i> = 8.9 Hz, 2H), 4.80 (br d, <i>J</i> = 4.9 Hz, 2H), 3.84 (s, 3H)	448.9
281		2,2,2-Trifluoro-1-methoxyethyl 5-methoxy-2-((pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate (racemate)	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.33 (d, <i>J</i> = 7.0 Hz, 1H), 8.82 (br d, <i>J</i> = 2.7 Hz, 1H), 8.63 (s, 1H), 8.50 (br t, <i>J</i> = 5.6 Hz, 1H), 7.55 (d, <i>J</i> = 2.4 Hz, 1H), 7.35 (d, <i>J</i> = 2.4 Hz, 1H), 7.30 (dd, <i>J</i> = 7.0, 4.3 Hz, 1H), 6.84 (s, 1H), 6.56 (br d, <i>J</i> = 3.7 Hz, 1H), 4.79 (br d, <i>J</i> = 6.1 Hz, 2H), 3.84 (s, 3H), 3.65 (s, 3H)	479.3
282		2,2,2-Trifluoroethyl 5-cyano-2-((pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.30 (br d, <i>J</i> = 7.1 Hz, 1H), 8.82 (br d, <i>J</i> = 3.0 Hz, 1H), 8.62 (s, 1H), 8.56 - 8.49 (m, 1H), 8.45 (s, 1H), 8.18 (s, 1H), 7.29 (br dd, <i>J</i> = 6.8, 4.4 Hz, 1H), 7.02 (s, 1H), 5.05 (br d, <i>J</i> = 8.8 Hz, 2H), 4.86 (br d, <i>J</i> = 6.1 Hz, 2H)	444.2

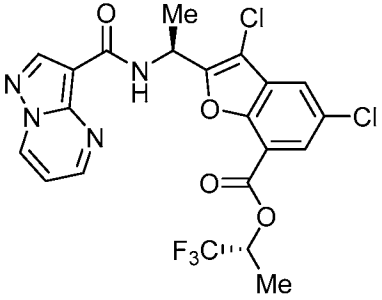
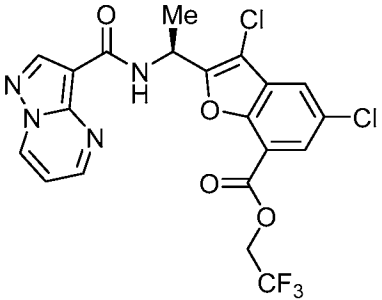
Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺
283		2,2,2-Trifluoroethyl 2-((pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)-5-(trifluoromethyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.26 (br d, <i>J</i> = 6.1 Hz, 1H), 8.80 (br d, <i>J</i> = 3.8 Hz, 1H), 8.60 (s, 1H), 8.52 (br s, 1H), 8.35 (s, 1H), 8.04 (s, 1H), 7.33 - 7.22 (m, 1H), 7.04 (s, 1H), 5.04 (q, <i>J</i> = 8.7 Hz, 2H), 4.85 (br d, <i>J</i> = 5.8 Hz, 2H)	487.2
284		<i>(R)</i> -1,1,1-Trifluoropropan-2-yl 5,6-difluoro-2-((pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.33 (br d, <i>J</i> = 6.7 Hz, 1H), 8.82 (br d, <i>J</i> = 3.1 Hz, 1H), 8.62 (s, 1H), 8.53 (br t, <i>J</i> = 5.6 Hz, 1H), 7.85 (br dd, <i>J</i> = 10.8, 7.8 Hz, 1H), 7.29 (dd, <i>J</i> = 6.6, 4.4 Hz, 1H), 7.09 (s, 1H), 5.85 - 5.59 (m, 1H), 4.83 (br d, <i>J</i> = 5.8 Hz, 2H), 1.47 (br d, <i>J</i> = 6.4 Hz, 3H)	469.3
285		<i>(R)</i> -1,1,1-Trifluoropropan-2-yl 6-fluoro-2-((pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.23 (d, <i>J</i> = 6.1 Hz, 1H), 8.79 (d, <i>J</i> = 3.1 Hz, 1H), 8.60 (s, 1H), 8.52 (br t, <i>J</i> = 5.8 Hz, 1H), 7.87 (dd, <i>J</i> = 8.5, 5.2 Hz, 1H), 7.35 - 7.18 (m, 2H), 6.89 (s, 1H), 5.84 - 5.62 (m, 1H), 4.76 (br d, <i>J</i> = 4.0 Hz, 2H), 1.45 (d, <i>J</i> = 6.4 Hz, 3H)	451.2

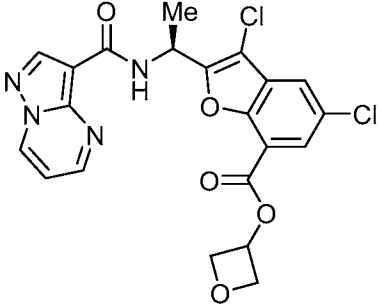
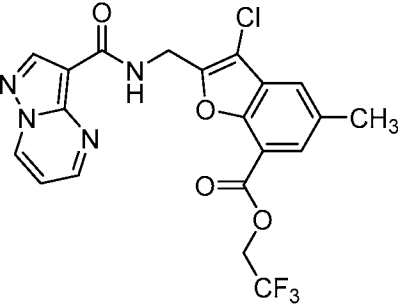
Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺
286		2,2,2-Trifluoroethyl 6-fluoro-2-((pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500MHz, DMSO-d ₆) δ 9.29 (br d, <i>J</i> = 6.9 Hz, 1H), 8.81 (br d, <i>J</i> = 3.8 Hz, 1H), 8.61 (s, 1H), 8.45 (br s, 1H), 7.89 (dd, <i>J</i> = 8.6, 5.2 Hz, 1H), 7.38 -7.15 (m, 2H), 6.90 (s, 1H), 5.05 (q, <i>J</i> = 8.9 Hz, 2H), 4.79 (br d, <i>J</i> = 5.8 Hz, 2H)	437.3
287		2,2,2-Trifluoroethyl 6-methyl-2-((pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.24 (br d, <i>J</i> = 5.9 Hz, 1H), 8.79 (br d, <i>J</i> = 2.9 Hz, 1H), 8.60 (s, 1H), 8.43 (br t, <i>J</i> = 5.4 Hz, 1H), 7.69 (d, <i>J</i> = 7.9 Hz, 1H), 7.26 (dd, <i>J</i> = 6.9, 4.2 Hz, 1H), 7.21 (d, <i>J</i> = 7.9 Hz, 1H), 6.81 (s, 1H), 5.00 (q, <i>J</i> = 9.0 Hz, 2H), 4.75 (d, <i>J</i> = 5.8 Hz, 2H), 2.52 (s, 3H)	433.1
288		<i>(R)</i> -1,1,1-Trifluoropropan-2-yl 3-chloro-5-fluoro-2-((pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.31 (dd, <i>J</i> = 6.9, 1.4 Hz, 1H), 8.82 (dd, <i>J</i> = 4.0, 1.2 Hz, 1H), 8.60 (s, 1H), 8.56 - 8.45 (m, 1H), 7.82 (dd, <i>J</i> = 7.6, 2.7 Hz, 1H), 7.70 (dd, <i>J</i> = 9.5, 2.4 Hz, 1H), 7.29 (dd, <i>J</i> = 7.0, 4.3 Hz, 1H), 5.85 - 5.54 (m, 1H), 4.87 (dd, <i>J</i> = 5.8, 1.8 Hz, 2H), 1.42 (d, <i>J</i> = 6.7 Hz, 3H)	485.3

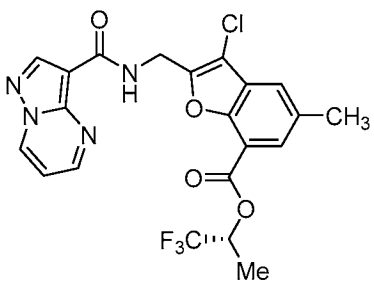
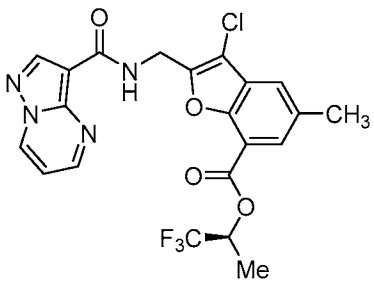
Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺
289		(S)-1,1,1-Trifluoropropan-2-yl 3-chloro-5-fluoro-2-((pyrazolo[1,5-a]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.28 (d, <i>J</i> = 6.1 Hz, 1H), 8.81 (br d, <i>J</i> = 2.7 Hz, 1H), 8.62 - 8.47 (m, 2H), 7.81 (dd, <i>J</i> = 7.6, 2.4 Hz, 1H), 7.70 (dd, <i>J</i> = 9.2, 2.4 Hz, 1H), 7.28 (dd, <i>J</i> = 7.0, 4.3 Hz, 1H), 5.81 - 5.56 (m, 1H), 4.91 - 4.75 (m, 2H), 1.40 (d, <i>J</i> = 6.7 Hz, 3H)	485.3
290		1,3-Difluoropropan-2-yl 3-chloro-5-fluoro-2-((pyrazolo[1,5-a]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.32 (dd, <i>J</i> = 7.0, 1.2 Hz, 1H), 8.83 (br d, <i>J</i> = 2.7 Hz, 1H), 8.61 (s, 1H), 8.55 (br t, <i>J</i> = 5.8 Hz, 1H), 7.80 (dd, <i>J</i> = 7.6, 2.4 Hz, 1H), 7.72 (dd, <i>J</i> = 9.5, 2.7 Hz, 1H), 7.29 (dd, <i>J</i> = 7.0, 4.3 Hz, 1H), 5.74 - 5.39 (m, 1H), 4.88 (d, <i>J</i> = 5.8 Hz, 2H), 4.80 - 4.54 (m, 4H)	467.3

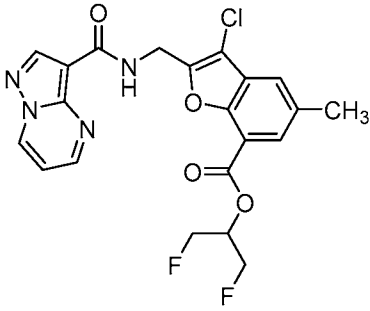
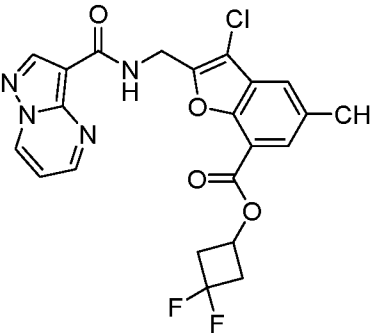
Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺
291		3,3-Difluorocyclobutyl 3-chloro-5-fluoro-2-((pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.32 (dd, <i>J</i> = 7.0, 1.2 Hz, 1H), 8.83 (dd, <i>J</i> = 4.0, 1.5 Hz, 1H), 8.68 - 8.49 (m, 2H), 7.77 (dd, <i>J</i> = 7.6, 2.4 Hz, 1H), 7.72 (dd, <i>J</i> = 9.5, 2.4 Hz, 1H), 7.29 (dd, <i>J</i> = 6.7, 4.3 Hz, 1H), 5.12 (br dd, <i>J</i> = 7.3, 4.3 Hz, 1H), 4.88 (d, <i>J</i> = 6.1 Hz, 2H), 3.06 (td, <i>J</i> = 7.6, 4.3 Hz, 2H), 2.81 (br dd, <i>J</i> = 14.8, 4.4 Hz, 2H)	479.3
292		2,2,2-Trifluoroethyl (<i>S</i>)-3-chloro-5-fluoro-2-(1-(pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)ethyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.28 (br d, <i>J</i> = 6.4 Hz, 1H), 8.82 (br d, <i>J</i> = 3.1 Hz, 1H), 8.58 (s, 1H), 8.44 (br d, <i>J</i> = 7.6 Hz, 1H), 7.81 (dd, <i>J</i> = 7.5, 2.3 Hz, 1H), 7.72 (dd, <i>J</i> = 9.2, 2.4 Hz, 1H), 7.29 (dd, <i>J</i> = 6.9, 4.4 Hz, 1H), 5.56 (br t, <i>J</i> = 7.2 Hz, 1H), 5.03 (q, <i>J</i> = 8.9 Hz, 2H), 1.67 (br d, <i>J</i> = 7.0 Hz, 3H)	485.0

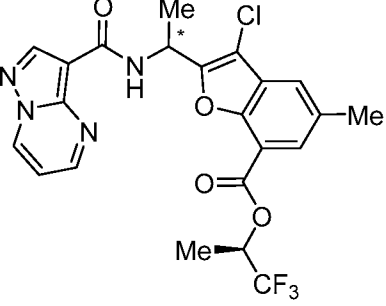
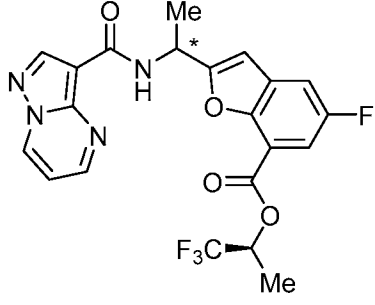
Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺
293		<p>(<i>R</i>)-1,1,1-Trifluoropropan-2-yl 3-chloro-5-fluoro-2-((<i>S</i>)-1-(pyrazolo[1,5-<i>a</i>]pyrimidine-3-carboxamido)ethyl)benzofuran-7-carboxylate</p>	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.29 (br d, <i>J</i> = 6.4 Hz, 1H), 8.81 (br d, <i>J</i> = 3.1 Hz, 1H), 8.58 (s, 1H), 8.42 (br d, <i>J</i> = 7.6 Hz, 1H), 7.81 (dd, <i>J</i> = 7.6, 2.1 Hz, 1H), 7.72 (dd, <i>J</i> = 9.3, 2.3 Hz, 1H), 7.29 (dd, <i>J</i> = 6.7, 4.3 Hz, 1H), 5.82 - 5.67 (m, 1H), 5.57 (br t, <i>J</i> = 7.2 Hz, 1H), 1.66 (br d, <i>J</i> = 7.0 Hz, 3H), 1.46 (br d, <i>J</i> = 6.7 Hz, 3H)	499.3
294		<p>2,2,2-Trifluoroethyl 3,5-dichloro-2-((pyrazolo[1,5-<i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate</p>	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.30 (d, <i>J</i> = 7.0 Hz, 1H), 8.82 (br d, <i>J</i> = 3.1 Hz, 1H), 8.60 (s, 1H), 8.55 (s, 1H), 8.02 (d, <i>J</i> = 1.8 Hz, 1H), 7.88 (d, <i>J</i> = 1.8 Hz, 1H), 7.29 (dd, <i>J</i> = 6.7, 4.3 Hz, 1H), 4.99 (br d, <i>J</i> = 9.2 Hz, 2H), 4.87 (br d, <i>J</i> = 5.8 Hz, 2H)	487.1
295		<p>(<i>R</i>)-1,1,1-Trifluoropropan-2-yl 3,5-dichloro-2-((pyrazolo[1,5-<i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate</p>	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.23 (br d, <i>J</i> = 6.7 Hz, 1H), 8.80 (br d, <i>J</i> = 2.9 Hz, 1H), 8.58 (s, 1H), 8.53 - 8.43 (m, 1H), 7.96 (s, 1H), 7.85 (s, 1H), 7.26 (dd, <i>J</i> = 6.8, 4.3 Hz, 1H), 5.79 - 5.50 (m, 1H), 4.87 (br d, <i>J</i> = 5.7 Hz, 2H), 1.43 (br d, <i>J</i> = 6.6 Hz, 3H)	501.1

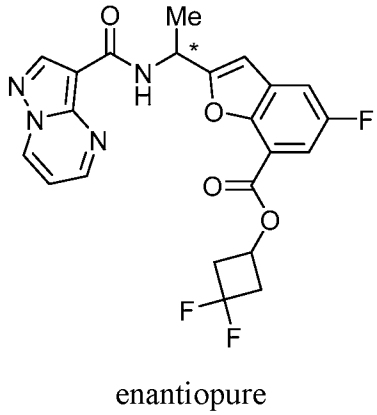
Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺
296		<p>(<i>R</i>)-1,1,1-Trifluoropropan-2-yl 3,5-dichloro-2-((<i>S</i>)-1-(pyrazolo[1,5-<i>a</i>]pyrimidine-3-carboxamido)ethyl)benzofuran-7-carboxylate</p>	<p>¹H NMR (500 MHz, DMSO-<i>d</i>₆) δ 9.31 (d, <i>J</i> = 6.7 Hz, 1H), 8.82 (br d, <i>J</i> = 3.4 Hz, 1H), 8.59 (s, 1H), 8.42 (br d, <i>J</i> = 7.6 Hz, 1H), 8.02 (d, <i>J</i> = 1.5 Hz, 1H), 7.89 (d, <i>J</i> = 1.5 Hz, 1H), 7.30 (dd, <i>J</i> = 6.7, 4.3 Hz, 1H), 5.84 - 5.68 (m, 1H), 5.58 (br t, <i>J</i> = 7.3 Hz, 1H), 1.67 (br d, <i>J</i> = 7.0 Hz, 3H), 1.47 (d, <i>J</i> = 6.4 Hz, 3H)</p>	515.1
297		<p>2,2,2-Trifluoroethyl (<i>S</i>)-3,5-dichloro-2-(1-(pyrazolo[1,5-<i>a</i>]pyrimidine-3-carboxamido)ethyl)benzofuran-7-carboxylate</p>	<p>¹H NMR (500 MHz, DMSO-<i>d</i>₆) δ 9.30 (d, <i>J</i> = 6.7 Hz, 1H), 8.82 (br d, <i>J</i> = 3.4 Hz, 1H), 8.59 (s, 1H), 8.44 (br d, <i>J</i> = 7.3 Hz, 1H), 8.01 (s, 1H), 7.89 (d, <i>J</i> = 1.5 Hz, 1H), 7.30 (dd, <i>J</i> = 6.9, 4.4 Hz, 1H), 5.57 (br t, <i>J</i> = 7.2 Hz, 1H), 5.16 - 4.96 (m, 2H), 1.67 (br d, <i>J</i> = 7.0 Hz, 3H)</p>	500.9

Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺
298		Oxetan-3-yl (<i>S</i>)-3,5-dichloro-2-(1-(pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)ethyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.29 (br d, <i>J</i> = 5.8 Hz, 1H), 8.84 (br d, <i>J</i> = 2.7 Hz, 1H), 8.59 (s, 1H), 8.48 (br d, <i>J</i> = 7.6 Hz, 1H), 7.97 (d, <i>J</i> = 2.1 Hz, 1H), 7.92 (d, <i>J</i> = 1.8 Hz, 1H), 7.29 (dd, <i>J</i> = 7.0, 4.3 Hz, 1H), 5.68 (br t, <i>J</i> = 5.3 Hz, 1H), 5.58 (br t, <i>J</i> = 7.3 Hz, 1H), 4.95 - 4.77 (m, 2H), 4.70 - 4.54 (m, 2H), 1.68 (br d, <i>J</i> = 7.0 Hz, 3H)	475.1
299		2,2,2-Trifluoroethyl 3-chloro-5-methyl-2-((pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.25 (d, <i>J</i> = 7.0 Hz, 1H), 8.80 (br d, <i>J</i> = 3.1 Hz, 1H), 8.59 (s, 1H), 8.53 (br t, <i>J</i> = 5.8 Hz, 1H), 7.75 (s, 1H), 7.70 (s, 1H), 7.27 (dd, <i>J</i> = 7.0, 4.3 Hz, 1H), 4.95 (q, <i>J</i> = 9.1 Hz, 2H), 4.84 (d, <i>J</i> = 5.8 Hz, 2H), 2.48 - 2.44 (m, 3H)	467.2

Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺
300		(R)-1,1,1-Trifluoropropan-2-yl 3-chloro-5-methyl-2-((pyrazolo[1,5-a]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.24 (br d, <i>J</i> = 6.1 Hz, 1H), 8.79 (br d, <i>J</i> = 2.7 Hz, 1H), 8.58 (s, 1H), 8.55 - 8.51 (m, 1H), 7.73 (s, 1H), 7.70 - 7.67 (m, 1H), 7.27 (dd, <i>J</i> = 7.0, 4.3 Hz, 1H), 5.71 - 5.62 (m, 1H), 4.84 (br d, <i>J</i> = 4.3 Hz, 2H), 2.48 - 2.44 (m, 3H), 1.40 (d, <i>J</i> = 6.7 Hz, 3H)	481.2
301		(S)-1,1,1-Trifluoropropan-2-yl 3-chloro-5-methyl-2-((pyrazolo[1,5-a]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.31 (d, <i>J</i> = 6.1 Hz, 1H), 8.81 (d, <i>J</i> = 3.1 Hz, 1H), 8.60 (s, 1H), 8.50 (br t, <i>J</i> = 5.6 Hz, 1H), 7.75 (s, 1H), 7.72 - 7.69 (m, 1H), 7.29 (dd, <i>J</i> = 7.0, 4.3 Hz, 1H), 5.74 - 5.66 (m, 1H), 4.86 (br d, <i>J</i> = 5.5 Hz, 2H), 2.48 (s, 3H), 1.42 (d, <i>J</i> = 6.7 Hz, 3H)	481.2

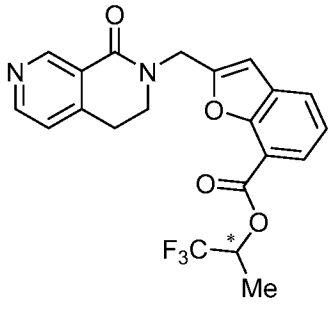
Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺
302		1,3-Difluoropropan-2-yl 3-chloro-5-methyl-2-((pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ 9.12 (dd, <i>J</i> = 7.0, 1.7 Hz, 1H), 8.88 (dd, <i>J</i> = 4.2, 1.8 Hz, 1H), 8.75 (s, 1H), 7.95 (d, <i>J</i> = 1.8 Hz, 1H), 7.73 (dd, <i>J</i> = 1.8, 0.8 Hz, 1H), 7.31 (dd, <i>J</i> = 7.0, 4.3 Hz, 1H), 5.64 (tquin, <i>J</i> = 19.5, 4.6 Hz, 1H), 5.08 (s, 2H), 4.93 - 4.89 (m, 2H), 4.81 - 4.77 (m, 4H), 2.64 (s, 3H)	463.1
303		3,3-Difluorocyclobutyl 3-chloro-5-methyl-2-((pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.27 (br d, <i>J</i> = 7.0 Hz, 1H), 8.81 (br s, 1H), 8.54 (br t, <i>J</i> = 5.6 Hz, 1H), 7.77 - 7.72 (m, 1H), 7.68 - 7.64 (m, 1H), 7.28 (br d, <i>J</i> = 4.6 Hz, 1H), 5.14 - 5.06 (m, 1H), 4.88 - 4.82 (m, 2H), 3.12 - 2.99 (m, 2H), 2.84 - 2.69 (m, 2H), 2.48 - 2.43 (m, 3H)	475.3

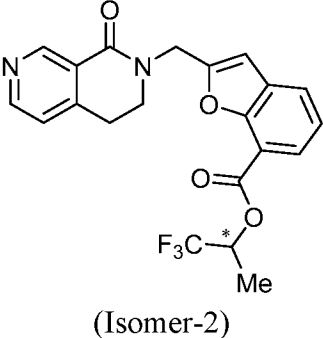
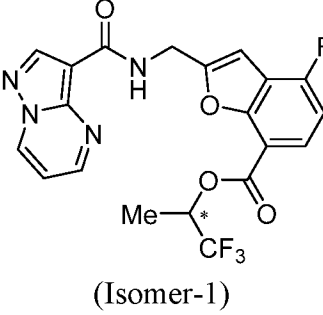
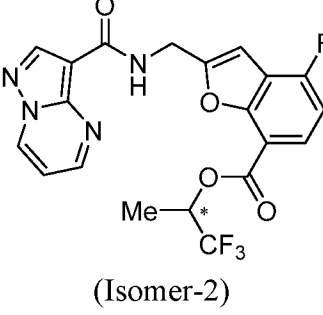
Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺
304		(R)-1,1,1-Trifluoropropan-2-yl 3-chloro-5-methyl-2-(1-(pyrazolo[1,5-a]pyrimidine-3-carboxamido)ethyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.23 (d, <i>J</i> = 6.4 Hz, 1H), 8.78 (br d, <i>J</i> = 3.4 Hz, 1H), 8.57 (s, 1H), 8.44 (br d, <i>J</i> = 7.6 Hz, 1H), 7.78 - 7.72 (m, 1H), 7.70 - 7.67 (m, 1H), 7.27 (dd, <i>J</i> = 7.0, 4.3 Hz, 1H), 5.76 - 5.66 (m, 1H), 5.62 - 5.51 (m, 1H), 2.45 (s, 3H), 1.68 - 1.59 (m, 3H), 1.48 - 1.41 (m, 3H)	495.3
305	 <p style="text-align: center;">enantiopure</p>	(S)-1,1,1-Trifluoropropan-2-yl 5-fluoro-2-(1-(pyrazolo[1,5-a]pyrimidine-3-carboxamido)ethyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.30 (br d, <i>J</i> = 6.4 Hz, 1H), 8.81 (br d, <i>J</i> = 3.1 Hz, 1H), 8.62 (s, 1H), 8.38 (br d, <i>J</i> = 8.2 Hz, 1H), 7.81 (dd, <i>J</i> = 8.2, 2.4 Hz, 1H), 7.59 (dd, <i>J</i> = 9.5, 2.4 Hz, 1H), 7.29 (dd, <i>J</i> = 6.7, 4.3 Hz, 1H), 6.94 (s, 1H), 5.81 - 5.65 (m, 1H), 5.56 - 5.40 (m, 1H), 1.66 (br d, <i>J</i> = 7.0 Hz, 3H), 1.48 (d, <i>J</i> = 6.7 Hz, 3H)	465.1

Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺
306	 <p>enantiopure</p>	3,3-Difluorocyclobutyl 5-fluoro-2-(1-(pyrazolo[1,5-a]pyrimidine-3-carboxamido)ethyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.22 (br d, <i>J</i> = 6.7 Hz, 1H), 8.78 (br d, <i>J</i> = 2.7 Hz, 1H), 8.59 (s, 1H), 8.39 (br d, <i>J</i> = 8.2 Hz, 1H), 7.73 (dd, <i>J</i> = 8.1, 2.6 Hz, 1H), 7.56 (dd, <i>J</i> = 9.5, 2.4 Hz, 1H), 7.25 (dd, <i>J</i> = 6.7, 4.3 Hz, 1H), 6.92 (s, 1H), 5.49 (br t, <i>J</i> = 7.3 Hz, 1H), 5.13 (br dd, <i>J</i> = 7.5, 4.4 Hz, 1H), 3.16 - 3.00 (m, 2H), 2.85 - 2.67 (m, 2H), 1.65 (br d, <i>J</i> = 6.7 Hz, 3H)	459.3

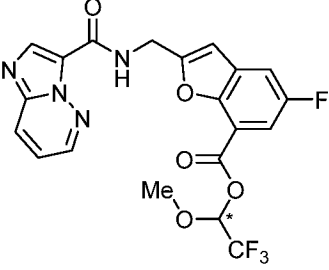
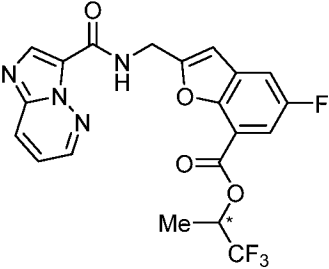
EXAMPLES 307- 352

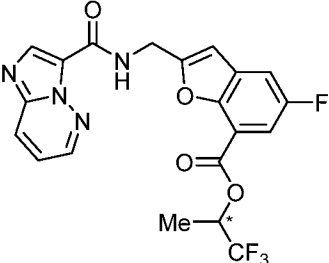
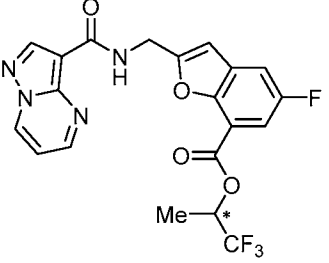
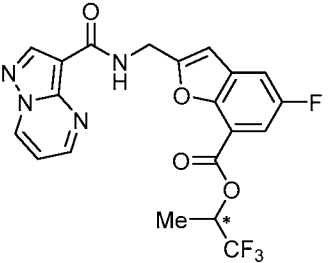
The following esters were synthesized from the acids according to the procedure outlined in Example 204 and asymmetrically resolved according to the methods listed.

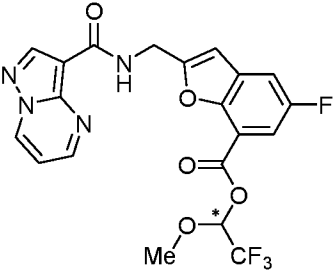
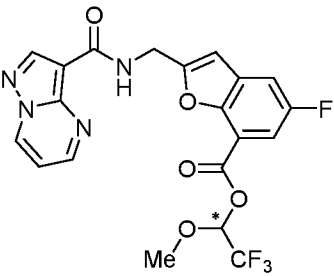
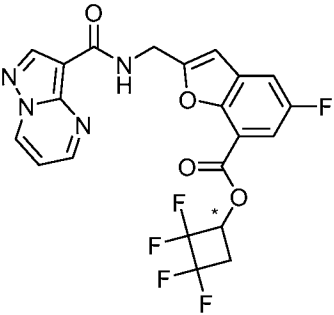
Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺	Method
307	 <p>(Isomer-1)</p>	1,1,1-Trifluoropropan-2-yl 2-((1-oxo-3,4-dihydro-2,7-naphthyridin-2(1H)-yl)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO-d ₆) δ 8.97 (s, 1H), 8.63 (br d, <i>J</i> = 4.6 Hz, 1H), 7.97 (d, <i>J</i> = 7.6 Hz, 1H), 7.87 (d, <i>J</i> = 7.6 Hz, 1H), 7.51 - 7.31 (m, 2H), 7.04 (s, 1H), 5.75 (dt, <i>J</i> = 13.4, 6.7 Hz, 1H), 5.05 - 4.79 (m, 2H), 3.75 (br t, <i>J</i> = 6.6 Hz, 2H), 3.07 (br t,	419.3	Method F

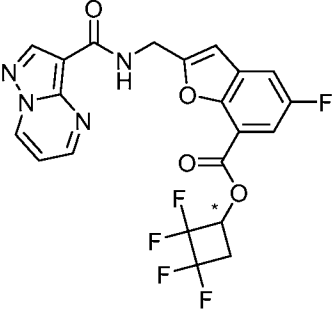
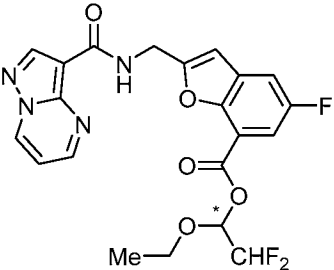
Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺	Method
			<i>J</i> = 6.6 Hz, 2H), 1.48 (d, <i>J</i> = 6.4 Hz, 3H)		
308	 <p>(Isomer-2)</p>	1,1,1-Trifluoropropan-2-yl 2-((1-oxo-3,4-dihydro-2,7-naphthyridin-2(1H)-yl)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO-d ₆) δ 8.97 (s, 1H), 8.63 (br d, <i>J</i> = 4.6 Hz, 1H), 7.97 (d, <i>J</i> = 7.6 Hz, 1H), 7.87 (d, <i>J</i> = 7.6 Hz, 1H), 7.51 - 7.31 (m, 2H), 7.04 (s, 1H), 5.75 (dt, <i>J</i> = 13.4, 6.7 Hz, 1H), 5.05 - 4.79 (m, 2H), 3.75 (br t, <i>J</i> = 6.6 Hz, 2H), 3.07 (br t, <i>J</i> = 6.6 Hz, 2H), 1.48 (d, <i>J</i> = 6.4 Hz, 3H)	419.3	Method F
309	 <p>(Isomer-1)</p>	1,1,1-Trifluoropropan-2-yl 4-fluoro-2-((pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.36 - 9.26 (m, 1H), 8.82 (d, <i>J</i> = 3.1 Hz, 1H), 8.62 (s, 1H), 8.54 (br t, <i>J</i> = 5.8 Hz, 1H), 7.91 (dd, <i>J</i> = 8.5, 5.2 Hz, 1H), 7.37 - 7.19 (m, 2H), 7.00 (s, 1H), 5.79 - 5.63 (m, 1H), 4.83 (br d, <i>J</i> = 5.5 Hz, 2H), 1.47 (d, <i>J</i> = 6.7 Hz, 3H)	451.1	Method F
310	 <p>(Isomer-2)</p>	1,1,1-Trifluoropropan-2-yl 4-fluoro-2-((pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.36 - 9.26 (m, 1H), 8.82 (d, <i>J</i> = 3.1 Hz, 1H), 8.62 (s, 1H), 8.54 (br t, <i>J</i> = 5.8 Hz, 1H), 7.91 (dd, <i>J</i> = 8.5, 5.2 Hz, 1H), 7.37 - 7.19 (m, 2H), 7.00 (s, 1H), 5.79 - 5.63 (m, 1H), 4.83 (br d, <i>J</i> = 5.5	451.1	Method F

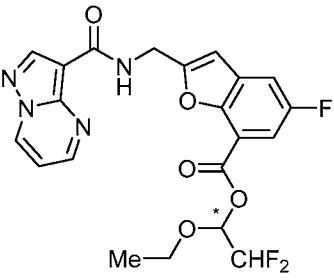
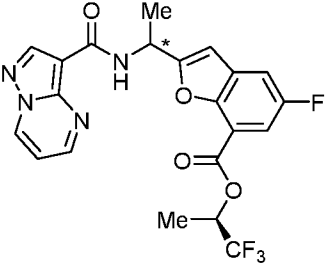
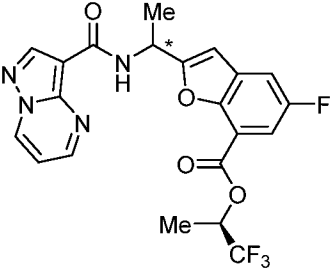
Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺	Method
			Hz, 2H), 1.47 (d, <i>J</i> = 6.7 Hz, 3H)		
311		1,1,1-Trifluoropropan-2-yl 4-chloro-2-((pyrazolo[1,5- α]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.39 - 9.24 (m, 1H), 8.86 - 8.77 (m, 1H), 8.63 (s, 1H), 8.55 (br t, <i>J</i> = 5.8 Hz, 1H), 7.85 (d, <i>J</i> = 8.2 Hz, 1H), 7.51 (d, <i>J</i> = 8.2 Hz, 1H), 7.30 (dd, <i>J</i> = 6.9, 4.1 Hz, 1H), 6.94 (s, 1H), 5.81 - 5.63 (m, 1H), 4.85 (br d, <i>J</i> = 5.8 Hz, 2H), 1.48 (d, <i>J</i> = 6.4 Hz, 3H)	467.0	Method M
312		1,1,1-Trifluoropropan-2-yl 4-chloro-2-((pyrazolo[1,5- α]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.39 - 9.24 (m, 1H), 8.86 - 8.77 (m, 1H), 8.63 (s, 1H), 8.55 (br t, <i>J</i> = 5.8 Hz, 1H), 7.85 (d, <i>J</i> = 8.2 Hz, 1H), 7.51 (d, <i>J</i> = 8.2 Hz, 1H), 7.30 (dd, <i>J</i> = 6.9, 4.1 Hz, 1H), 6.94 (s, 1H), 5.81 - 5.63 (m, 1H), 4.85 (br d, <i>J</i> = 5.8 Hz, 2H), 1.48 (d, <i>J</i> = 6.4 Hz, 3H)	467.0	Method M
313		2,2,2-Trifluoro-1-methoxyethyl 5-fluoro-2-((imidazo[1,2- <i>b</i>]pyridazine-3-carboxamido)methyl)benzofuran-7-carboxylate (Isomer-1)	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.23 (br t, <i>J</i> = 5.5 Hz, 1H), 8.77 (br d, <i>J</i> = 3.4 Hz, 1H), 8.44 - 8.23 (m, 2H), 7.84 (dd, <i>J</i> = 8.1, 2.6 Hz, 1H), 7.60 (br dd, <i>J</i> = 9.5, 2.4 Hz, 1H), 7.49 (dd, <i>J</i> = 9.2, 4.6 Hz, 1H), 6.96 (s, 1H), 6.55	467.1	Method F

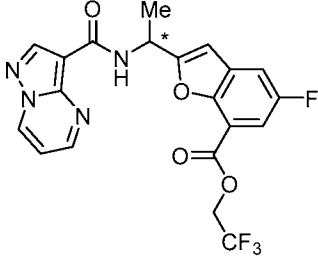
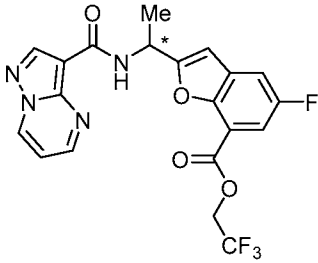
Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺	Method
			(br d, <i>J</i> = 3.7 Hz, 1H), 4.85 (br d, <i>J</i> = 5.8 Hz, 2H), 3.74 - 3.44 (m, 3H)		
314	 <p>(Isomer-2)</p>	2,2,2-Trifluoro-1-methoxyethyl 5-fluoro-2-((imidazo[1,2- <i>b</i>]pyridazine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.23 (br t, <i>J</i> = 5.5 Hz, 1H), 8.77 (br d, <i>J</i> = 3.4 Hz, 1H), 8.44 - 8.23 (m, 2H), 7.84 (dd, <i>J</i> = 8.1, 2.6 Hz, 1H), 7.60 (br dd, <i>J</i> = 9.5, 2.4 Hz, 1H), 7.49 (dd, <i>J</i> = 9.2, 4.6 Hz, 1H), 6.96 (s, 1H), 6.55 (br d, <i>J</i> = 3.7 Hz, 1H), 4.85 (br d, <i>J</i> = 5.8 Hz, 2H), 3.74 - 3.44 (m, 3H)	467.1	Method F
315	 <p>(Isomer-1)</p>	1,1,1-Trifluoropropan-2-yl 5-fluoro-2-((imidazo[1,2- <i>b</i>]pyridazine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.12 (br t, <i>J</i> = 5.3 Hz, 1H), 8.76 (br d, <i>J</i> = 4.2 Hz, 1H), 8.43 - 8.29 (m, 2H), 7.79 (dd, <i>J</i> = 8.2, 2.4 Hz, 1H), 7.57 (dd, <i>J</i> = 9.4, 2.4 Hz, 1H), 7.48 (dd, <i>J</i> = 9.2, 4.5 Hz, 1H), 6.95 (s, 1H), 5.72 (dt, <i>J</i> = 13.2, 6.6 Hz, 1H), 4.87 (br d, <i>J</i> = 5.8 Hz, 2H), 1.49 (d, <i>J</i> = 6.6 Hz, 3H)	451.3	Method D
316		1,1,1-Trifluoropropan-2-yl 5-fluoro-2-((imidazo[1,2- <i>b</i>]pyridazine-3-carboxamido)methyl)	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.12 (br t, <i>J</i> = 5.3 Hz, 1H), 8.76 (br d, <i>J</i> = 4.2 Hz, 1H), 8.43 - 8.29 (m, 2H), 7.79 (dd, <i>J</i> = 8.2, 2.4	451.3	Method D

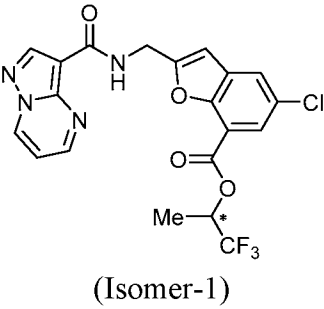
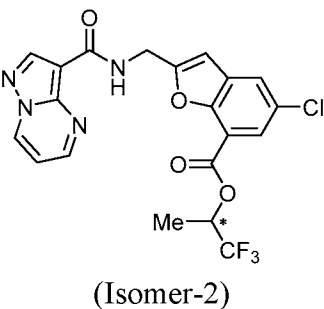
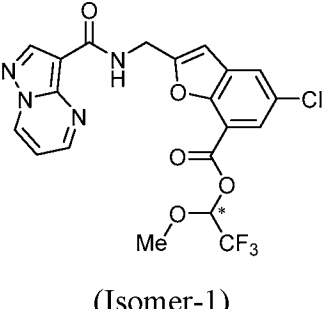
Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺	Method
	 <p>(Isomer-2)</p>	benzofuran-7-carboxylate	Hz, 1H), 7.57 (dd, <i>J</i> = 9.4, 2.4 Hz, 1H), 7.48 (dd, <i>J</i> = 9.2, 4.5 Hz, 1H), 6.95 (s, 1H), 5.72 (dt, <i>J</i> = 13.2, 6.6 Hz, 1H), 4.87 (br d, <i>J</i> = 5.8 Hz, 2H), 1.49 (d, <i>J</i> = 6.6 Hz, 3H)		
317	 <p>(Isomer-1)</p>	1,1,1-Trifluoropropan-2-yl 5-fluoro-2-((pyrazolo[1,5- <i>α</i>]pyrimidine-3-carboxamido)methyl) benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.34 (br d, <i>J</i> = 7.0 Hz, 1H), 8.84 (br d, <i>J</i> = 2.7 Hz, 1H), 8.65 (s, 1H), 8.55 (br t, <i>J</i> = 5.6 Hz, 1H), 7.83 (dd, <i>J</i> = 8.2, 2.4 Hz, 1H), 7.60 (dd, <i>J</i> = 9.3, 2.6 Hz, 1H), 7.31 (dd, <i>J</i> = 6.9, 4.1 Hz, 1H), 6.93 (s, 1H), 5.83 - 5.68 (m, 1H), 4.84 (br d, <i>J</i> = 5.8 Hz, 2H), 1.51 (d, <i>J</i> = 6.4 Hz, 3H)	451.3	Method D
318	 <p>(Isomer-2)</p>	1,1,1-Trifluoropropan-2-yl 5-fluoro-2-((pyrazolo[1,5- <i>α</i>]pyrimidine-3-carboxamido)methyl) benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.34 (br d, <i>J</i> = 7.0 Hz, 1H), 8.84 (br d, <i>J</i> = 2.7 Hz, 1H), 8.65 (s, 1H), 8.55 (br t, <i>J</i> = 5.6 Hz, 1H), 7.83 (dd, <i>J</i> = 8.2, 2.4 Hz, 1H), 7.60 (dd, <i>J</i> = 9.3, 2.6 Hz, 1H), 7.31 (dd, <i>J</i> = 6.9, 4.1 Hz, 1H), 6.93 (s, 1H), 5.83 - 5.68 (m, 1H), 4.84 (br d, <i>J</i> = 5.8 Hz, 2H), 1.51 (d, <i>J</i> = 6.4 Hz, 3H)	451.3	Method D

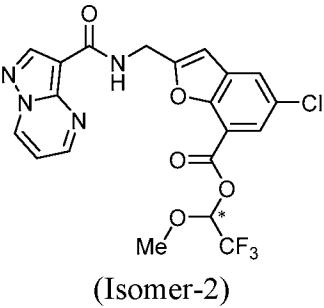
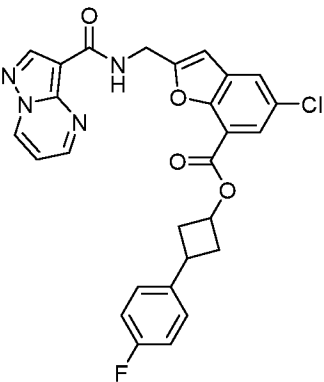
Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺	Method
319	 <p>(Isomer-1)</p>	2,2,2-Trifluoro-1-methoxyethyl 5-fluoro-2-((pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.34 (br d, <i>J</i> = 6.7 Hz, 1H), 8.83 (br d, <i>J</i> = 3.1 Hz, 1H), 8.64 (s, 1H), 8.54 (br t, <i>J</i> = 5.6 Hz, 1H), 7.85 (dd, <i>J</i> = 8.2, 2.4 Hz, 1H), 7.61 (dd, <i>J</i> = 9.2, 2.4 Hz, 1H), 7.31 (dd, <i>J</i> = 7.0, 4.3 Hz, 1H), 6.93 (s, 1H), 6.59 (br d, <i>J</i> = 3.7 Hz, 1H), 4.82 (br d, <i>J</i> = 5.8 Hz, 2H), 3.67 (s, 3H)	467.3	Method F
320	 <p>(Isomer-2)</p>	2,2,2-Trifluoro-1-methoxyethyl 5-fluoro-2-((pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.34 (br d, <i>J</i> = 6.7 Hz, 1H), 8.83 (br d, <i>J</i> = 3.1 Hz, 1H), 8.64 (s, 1H), 8.54 (br t, <i>J</i> = 5.6 Hz, 1H), 7.85 (dd, <i>J</i> = 8.2, 2.4 Hz, 1H), 7.61 (dd, <i>J</i> = 9.2, 2.4 Hz, 1H), 7.31 (dd, <i>J</i> = 7.0, 4.3 Hz, 1H), 6.93 (s, 1H), 6.59 (br d, <i>J</i> = 3.7 Hz, 1H), 4.82 (br d, <i>J</i> = 5.8 Hz, 2H), 3.67 (s, 3H)	467.3	Method F
321	 <p>(Isomer-1)</p>	2,2,3,3-Tetrafluorocyclobutyl 5-fluoro-2-((pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.24 (br d, <i>J</i> = 6.9 Hz, 1H), 8.80 (br d, <i>J</i> = 3.9 Hz, 1H), 8.60 (s, 1H), 8.50 (br t, <i>J</i> = 5.6 Hz, 1H), 7.78 (dd, <i>J</i> = 8.2, 2.1 Hz, 1H), 7.63 (dd, <i>J</i> = 9.4, 2.1 Hz, 1H), 7.26 (dd, <i>J</i> = 6.8, 4.3 Hz, 1H), 6.92	481.1	Method D

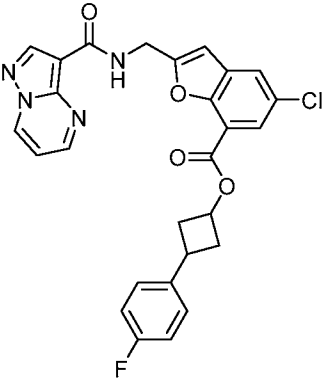
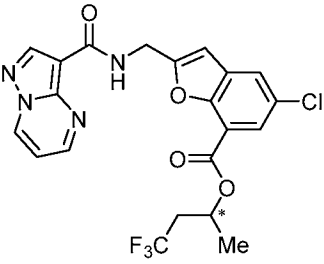
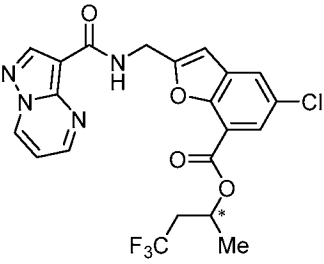
Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺	Method
			(s, 1H), 5.62 (br d, <i>J</i> = 7.2 Hz, 1H), 4.82 (br dd, <i>J</i> = 8.4, 6.5 Hz, 2H), 3.39 - 3.14 (m, 1H), 3.12 - 2.93 (m, 1H)		
322	 <p>(Isomer-2)</p>	2,2,3,3-Tetrafluorocyclobutyl 5-fluoro-2-((pyrazolo[1,5- <i>α</i>]pyrimidine-3-carboxamido)methyl) benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.24 (br d, <i>J</i> = 6.9 Hz, 1H), 8.80 (br d, <i>J</i> = 3.9 Hz, 1H), 8.60 (s, 1H), 8.50 (br t, <i>J</i> = 5.6 Hz, 1H), 7.78 (dd, <i>J</i> = 8.2, 2.1 Hz, 1H), 7.63 (dd, <i>J</i> = 9.4, 2.1 Hz, 1H), 7.26 (dd, <i>J</i> = 6.8, 4.3 Hz, 1H), 6.92 (s, 1H), 5.62 (br d, <i>J</i> = 7.2 Hz, 1H), 4.82 (br dd, <i>J</i> = 8.4, 6.5 Hz, 2H), 3.39 - 3.14 (m, 1H), 3.12 - 2.93 (m, 1H)	481.1	Method D
323	 <p>(Isomer-1)</p>	1-Ethoxy-2,2-difluoroethyl 5-fluoro-2-((pyrazolo[1,5- <i>α</i>]pyrimidine-3-carboxamido)methyl) benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.32 (dd, <i>J</i> = 7.0, 1.2 Hz, 1H), 8.83 (d, <i>J</i> = 2.7 Hz, 1H), 8.63 (s, 1H), 8.54 (br t, <i>J</i> = 5.8 Hz, 1H), 7.81 (dd, <i>J</i> = 8.2, 2.7 Hz, 1H), 7.60 (dd, <i>J</i> = 9.5, 2.4 Hz, 1H), 7.29 (dd, <i>J</i> = 6.9, 4.1 Hz, 1H), 6.91 (s, 1H), 6.42 - 6.07 (m, 2H), 4.82 (d, <i>J</i> = 6.1 Hz, 2H), 4.05 - 3.69 (m, 2H), 1.16 (t, <i>J</i> = 7.2 Hz, 3H)	463.3	Method D

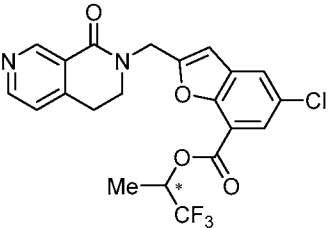
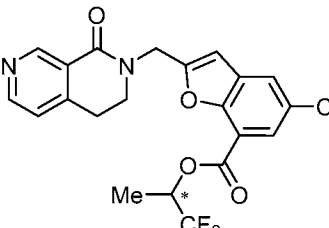
Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺	Method
324	 <p>(Isomer-2)</p>	1-Ethoxy-2,2-difluoroethyl 5-fluoro-2-((pyrazolo[1,5- α]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- d_6) δ 9.32 (dd, J = 7.0, 1.2 Hz, 1H), 8.83 (d, J = 2.7 Hz, 1H), 8.63 (s, 1H), 8.54 (br t, J = 5.8 Hz, 1H), 7.81 (dd, J = 8.2, 2.7 Hz, 1H), 7.60 (dd, J = 9.5, 2.4 Hz, 1H), 7.29 (dd, J = 6.9, 4.1 Hz, 1H), 6.91 (s, 1H), 6.42 - 6.07 (m, 2H), 4.82 (d, J = 6.1 Hz, 2H), 4.05 - 3.69 (m, 2H), 1.16 (t, J = 7.2 Hz, 3H)	463.3	Method D
325		<i>(R)</i> -1,1,1-Trifluoropropan-2-yl 5-fluoro-2-(1-(pyrazolo[1,5- α]pyrimidine-3-carboxamido)ethyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- d_6) δ 9.25 (br d, J = 6.9 Hz, 1H), 8.79 (br s, 1H), 8.60 (s, 1H), 8.35 (br d, J = 8.1 Hz, 1H), 7.78 (br d, J = 8.2 Hz, 1H), 7.57 (br d, J = 9.3 Hz, 1H), 7.34 - 7.08 (m, 1H), 6.94 (s, 1H), 5.81 - 5.65 (m, 1H), 5.50 (br t, J = 7.3 Hz, 1H), 1.66 (br d, J = 7.0 Hz, 3H), 1.49 (br d, J = 6.3 Hz, 3H)	465.3	Method H
326		<i>(R)</i> -1,1,1-Trifluoropropan-2-yl 5-fluoro-2-(1-(pyrazolo[1,5- α]pyrimidine-3-carboxamido)ethyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- d_6) δ 9.25 (br d, J = 6.9 Hz, 1H), 8.79 (br s, 1H), 8.60 (s, 1H), 8.35 (br d, J = 8.1 Hz, 1H), 7.78 (br d, J = 8.2 Hz, 1H), 7.57 (br d, J = 9.3 Hz, 1H), 7.34 - 7.08 (m, 1H), 6.94 (s, 1H),	465.2	Method H

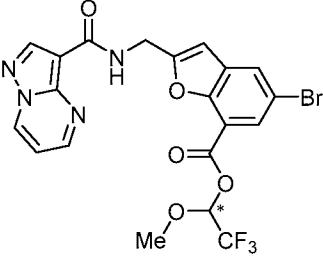
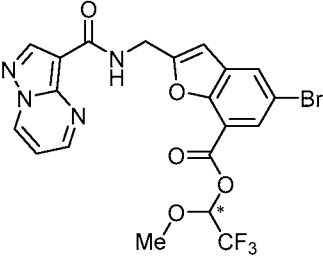
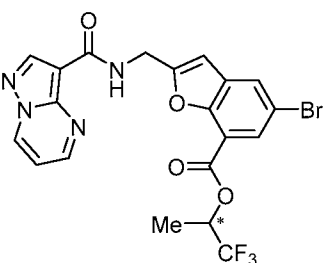
Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺	Method
			5.81 - 5.65 (m, 1H), 5.50 (br t, <i>J</i> = 7.3 Hz, 1H), 1.66 (br d, <i>J</i> = 7.0 Hz, 3H), 1.49 (br d, <i>J</i> = 6.3 Hz, 3H)		
327	 <p>(Isomer-1)</p>	2,2,2-Trifluoroethyl 5-fluoro-2-(1- (pyrazolo[1,5- <i>a</i>]pyrimidine-3- carboxamido)ethyl)be nzofuran-7- carboxylate	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.27 (d, <i>J</i> = 7.0 Hz, 1H), 8.80 (br d, <i>J</i> = 3.1 Hz, 1H), 8.61 (s, 1H), 8.41 (br d, <i>J</i> = 8.2 Hz, 1H), 7.80 (dd, <i>J</i> = 8.1, 2.3 Hz, 1H), 7.59 (dd, <i>J</i> = 9.5, 2.4 Hz, 1H), 7.27 (dd, <i>J</i> = 7.0, 4.3 Hz, 1H), 6.94 (s, 1H), 5.48 (br t, <i>J</i> = 7.3 Hz, 1H), 5.01 (q, <i>J</i> = 8.9 Hz, 2H), 1.65 (d, <i>J</i> = 6.7 Hz, 3H)	451.3	Method J
328	 <p>(Isomer-2)</p>	2,2,2-Trifluoroethyl 5-fluoro-2-(1- (pyrazolo[1,5- <i>a</i>]pyrimidine-3- carboxamido)ethyl)be nzofuran-7- carboxylate	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.27 (d, <i>J</i> = 7.0 Hz, 1H), 8.80 (br d, <i>J</i> = 3.1 Hz, 1H), 8.61 (s, 1H), 8.41 (br d, <i>J</i> = 8.2 Hz, 1H), 7.80 (dd, <i>J</i> = 8.1, 2.3 Hz, 1H), 7.59 (dd, <i>J</i> = 9.5, 2.4 Hz, 1H), 7.27 (dd, <i>J</i> = 7.0, 4.3 Hz, 1H), 6.94 (s, 1H), 5.48 (br t, <i>J</i> = 7.3 Hz, 1H), 5.01 (q, <i>J</i> = 8.9 Hz, 2H), 1.65 (d, <i>J</i> = 6.7 Hz, 3H)	451.3	Method J

Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺	Method
329	 <p>(Isomer-1)</p>	1,1,1-Trifluoropropan-2-yl 5-chloro-2-((pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl) benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.34 (br d, <i>J</i> = 6.7 Hz, 1H), 8.85 (br d, <i>J</i> = 2.7 Hz, 1H), 8.65 (s, 1H), 8.56 (br t, <i>J</i> = 5.8 Hz, 1H), 8.05 (d, <i>J</i> = 1.8 Hz, 1H), 7.77 (d, <i>J</i> = 1.8 Hz, 1H), 7.32 (dd, <i>J</i> = 7.0, 4.3 Hz, 1H), 6.92 (s, 1H), 5.86 - 5.67 (m, 1H), 4.84 (br d, <i>J</i> = 5.8 Hz, 2H), 1.51 (br d, <i>J</i> = 6.4 Hz, 3H)	467.2	Method D
330	 <p>(Isomer-2)</p>	1,1,1-Trifluoropropan-2-yl 5-chloro-2-((pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl) benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.34 (br d, <i>J</i> = 6.7 Hz, 1H), 8.85 (br d, <i>J</i> = 2.7 Hz, 1H), 8.65 (s, 1H), 8.56 (br t, <i>J</i> = 5.8 Hz, 1H), 8.05 (d, <i>J</i> = 1.8 Hz, 1H), 7.77 (d, <i>J</i> = 1.8 Hz, 1H), 7.32 (dd, <i>J</i> = 7.0, 4.3 Hz, 1H), 6.92 (s, 1H), 5.86 - 5.67 (m, 1H), 4.84 (br d, <i>J</i> = 5.8 Hz, 2H), 1.51 (br d, <i>J</i> = 6.4 Hz, 3H)	467.2	Method D
331	 <p>(Isomer-1)</p>	2,2,2-Trifluoro-1-methoxyethyl 5-chloro-2-((pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl) benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.35 (br d, <i>J</i> = 7.0 Hz, 1H), 8.84 (br d, <i>J</i> = 3.1 Hz, 1H), 8.64 (s, 1H), 8.54 (br t, <i>J</i> = 5.5 Hz, 1H), 8.08 (d, <i>J</i> = 1.8 Hz, 1H), 7.78 (d, <i>J</i> = 1.8 Hz, 1H), 7.31 (dd, <i>J</i> = 6.9, 4.1 Hz, 1H), 6.92 (s,	482.9	Method F

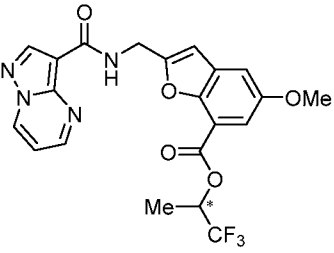
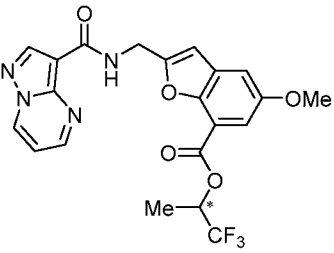
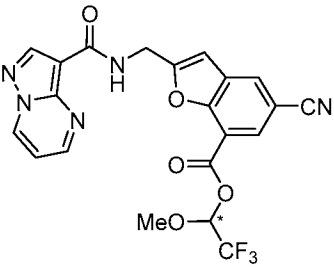
Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺	Method
			1H), 6.60 (br d, <i>J</i> = 3.7 Hz, 1H), 4.83 (br d, <i>J</i> = 5.8 Hz, 2H), 3.67 (s, 3H)		
332	 <p>(Isomer-2)</p>	2,2,2-Trifluoro-1-methoxyethyl 5-chloro-2-((pyrazolo[1,5- α]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.35 (br d, <i>J</i> = 7.0 Hz, 1H), 8.84 (br d, <i>J</i> = 3.1 Hz, 1H), 8.64 (s, 1H), 8.54 (br t, <i>J</i> = 5.5 Hz, 1H), 8.08 (d, <i>J</i> = 1.8 Hz, 1H), 7.78 (d, <i>J</i> = 1.8 Hz, 1H), 7.31 (dd, <i>J</i> = 6.9, 4.1 Hz, 1H), 6.92 (s, 1H), 6.60 (br d, <i>J</i> = 3.7 Hz, 1H), 4.83 (br d, <i>J</i> = 5.8 Hz, 2H), 3.67 (s, 3H)	482.9	Method F
333	 <p>(Isomer-1) (<i>cis</i>-/<i>trans</i>- not determined)</p>	3-(4-Fluorophenyl)cyclobutyl 5-chloro-2-((pyrazolo[1,5- α]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.24 (br d, <i>J</i> = 5.8 Hz, 1H), 8.74 (br d, <i>J</i> = 2.7 Hz, 1H), 8.58 - 8.45 (m, 2H), 7.96 (d, <i>J</i> = 1.8 Hz, 1H), 7.76 (d, <i>J</i> = 1.8 Hz, 1H), 7.37 - 7.16 (m, 3H), 7.08 (br t, <i>J</i> = 8.9 Hz, 2H), 6.88 (s, 1H), 5.17 (br t, <i>J</i> = 7.3 Hz, 1H), 4.82 (br d, <i>J</i> = 5.8 Hz, 2H), 3.28 - 3.06 (m, 1H), 2.88 - 2.73 (m, 2H), 2.19 (br d, <i>J</i> = 9.2 Hz, 2H)	519.4	Method G

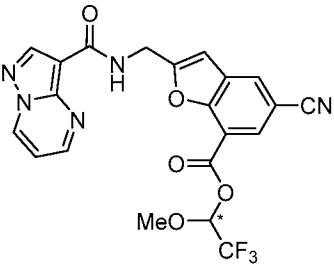
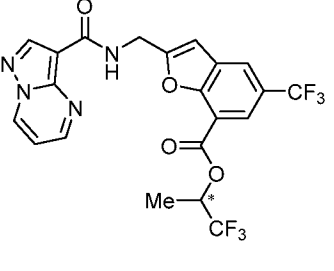
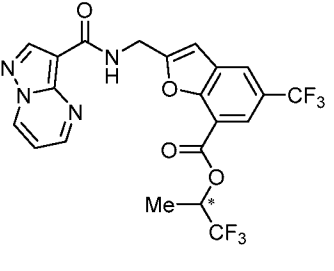
Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺	Method
334	 <p>(Isomer-2) (<i>cis-/trans-</i> not determined)</p>	3-(4-Fluorophenyl)cyclobutyl 5-chloro-2-((pyrazolo[1,5- α]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.24 (br d, <i>J</i> = 5.8 Hz, 1H), 8.74 (br d, <i>J</i> = 2.7 Hz, 1H), 8.58 - 8.45 (m, 2H), 7.96 (d, <i>J</i> = 1.8 Hz, 1H), 7.76 (d, <i>J</i> = 1.8 Hz, 1H), 7.37 - 7.16 (m, 3H), 7.08 (br t, <i>J</i> = 8.9 Hz, 2H), 6.88 (s, 1H), 5.17 (br t, <i>J</i> = 7.3 Hz, 1H), 4.82 (br d, <i>J</i> = 5.8 Hz, 2H), 3.28 - 3.06 (m, 1H), 2.88 - 2.73 (m, 2H), 2.19 (br d, <i>J</i> = 9.2 Hz, 2H)	519.4	Method G
335	 <p>(Isomer-1) (Method D)</p>	4,4,4-Trifluorobutan-2-yl 5-chloro-2-((pyrazolo[1,5- α]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.33 (dd, <i>J</i> = 7.0, 1.5 Hz, 1H), 8.83 (dd, <i>J</i> = 4.1, 1.4 Hz, 1H), 8.63 (s, 1H), 8.52 (br t, <i>J</i> = 6.0 Hz, 1H), 7.98 (d, <i>J</i> = 2.1 Hz, 1H), 7.74 (d, <i>J</i> = 2.1 Hz, 1H), 7.30 (dd, <i>J</i> = 7.0, 4.3 Hz, 1H), 6.88 (s, 1H), 5.50 - 5.34 (m, 1H), 4.82 (br t, <i>J</i> = 5.5 Hz, 2H), 2.90 - 2.66 (m, 2H), 1.38 (d, <i>J</i> = 6.4 Hz, 3H)	481.3	Method D
336		4,4,4-Trifluorobutan-2-yl 5-chloro-2-((pyrazolo[1,5- α]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.33 (dd, <i>J</i> = 7.0, 1.5 Hz, 1H), 8.83 (dd, <i>J</i> = 4.1, 1.4 Hz, 1H), 8.63 (s, 1H), 8.52 (br t, <i>J</i> = 6.0 Hz, 1H), 7.98 (d, <i>J</i> = 2.1	481.3	Method D

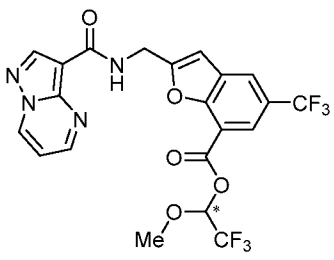
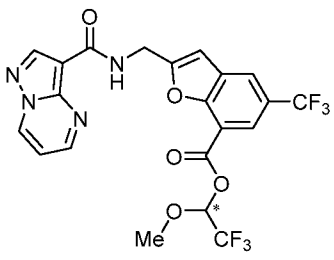
Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺	Method
	(Isomer-2)		Hz, 1H), 7.74 (d, <i>J</i> = 2.1 Hz, 1H), 7.30 (dd, <i>J</i> = 7.0, 4.3 Hz, 1H), 6.88 (s, 1H), 5.50 - 5.34 (m, 1H), 4.82 (br t, <i>J</i> = 5.5 Hz, 2H), 2.90 - 2.66 (m, 2H), 1.38 (d, <i>J</i> = 6.4 Hz, 3H)		
337		1,1,1-Trifluoropropan-2-yl 5-chloro-2-((1-oxo-3,4-dihydro-2,7-naphthyridin-2(1H)-yl)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO-d ₆) δ 8.98 (s, 1H), 8.64 (br d, <i>J</i> = 4.9 Hz, 1H), 8.08 (d, <i>J</i> = 1.5 Hz, 1H), 7.80 (d, <i>J</i> = 1.8 Hz, 1H), 7.40 (br d, <i>J</i> = 4.9 Hz, 1H), 7.04 (s, 1H), 5.84 - 5.70 (m, 1H), 5.11 - 4.87 (m, 2H), 3.75 (br t, <i>J</i> = 6.6 Hz, 2H), 3.08 (br t, <i>J</i> = 6.6 Hz, 2H), 1.49 (br d, <i>J</i> = 6.7 Hz, 3H)	453.3	Method F
338		1,1,1-Trifluoropropan-2-yl 5-chloro-2-((1-oxo-3,4-dihydro-2,7-naphthyridin-2(1H)-yl)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO-d ₆) δ 8.98 (s, 1H), 8.64 (br d, <i>J</i> = 4.9 Hz, 1H), 8.08 (d, <i>J</i> = 1.5 Hz, 1H), 7.80 (d, <i>J</i> = 1.8 Hz, 1H), 7.40 (br d, <i>J</i> = 4.9 Hz, 1H), 7.04 (s, 1H), 5.84 - 5.70 (m, 1H), 5.11 - 4.87 (m, 2H), 3.75 (br t, <i>J</i> = 6.6 Hz, 2H), 3.08 (br t, <i>J</i> = 6.6 Hz, 2H), 1.49 (br d, <i>J</i> = 6.7 Hz, 3H)	453.3	Method F

Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺	Method
339	 <p>(Isomer-1)</p>	2,2,2-Trifluoro-1-methoxyethyl 5-bromo-2-((pyrazolo[1,5- <i>α</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.25 (br d, <i>J</i> = 6.0 Hz, 1H), 8.80 (br d, <i>J</i> = 3.2 Hz, 1H), 8.60 (s, 1H), 8.54 - 8.42 (m, 1H), 8.17 (s, 1H), 7.88 (s, 1H), 7.27 (dd, <i>J</i> = 6.8, 4.3 Hz, 1H), 6.91 (s, 1H), 6.51 (br s, 1H), 4.82 (br d, <i>J</i> = 5.7 Hz, 2H), 3.65 (s, 3H)	529.2	Method F
340	 <p>(Isomer-2)</p>	2,2,2-Trifluoro-1-methoxyethyl 5-bromo-2-((pyrazolo[1,5- <i>α</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.25 (br d, <i>J</i> = 6.0 Hz, 1H), 8.80 (br d, <i>J</i> = 3.2 Hz, 1H), 8.60 (s, 1H), 8.54 - 8.42 (m, 1H), 8.17 (s, 1H), 7.88 (s, 1H), 7.27 (dd, <i>J</i> = 6.8, 4.3 Hz, 1H), 6.91 (s, 1H), 6.51 (br s, 1H), 4.82 (br d, <i>J</i> = 5.7 Hz, 2H), 3.65 (s, 3H)	529.2	Method F
341	 <p>(Isomer-1)</p>	1,1,1-Trifluoropropan-2-yl 5-bromo-2-((pyrazolo[1,5- <i>α</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.24 (d, <i>J</i> = 7.0 Hz, 1H), 8.80 (br d, <i>J</i> = 3.1 Hz, 1H), 8.64 - 8.51 (m, 2H), 8.13 (d, <i>J</i> = 1.5 Hz, 1H), 7.84 (d, <i>J</i> = 1.5 Hz, 1H), 7.27 (dd, <i>J</i> = 6.7, 4.3 Hz, 1H), 6.89 (s, 1H), 5.78 - 5.54 (m, 1H), 4.80 (br d, <i>J</i> = 4.3 Hz, 2H), 1.46 (d, <i>J</i> = 6.7 Hz, 3H)	513.2	

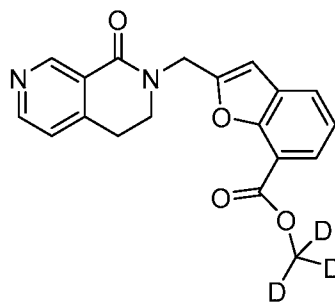
Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺	Method
342	<p>(Isomer-2)</p>	1,1,1-Trifluoropropan-2-yl 5-bromo-2-((pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.24 (d, <i>J</i> = 7.0 Hz, 1H), 8.80 (br d, <i>J</i> = 3.1 Hz, 1H), 8.64 - 8.51 (m, 2H), 8.13 (d, <i>J</i> = 1.5 Hz, 1H), 7.84 (d, <i>J</i> = 1.5 Hz, 1H), 7.27 (dd, <i>J</i> = 6.7, 4.3 Hz, 1H), 6.89 (s, 1H), 5.78 - 5.54 (m, 1H), 4.80 (br d, <i>J</i> = 4.3 Hz, 2H), 1.46 (d, <i>J</i> = 6.7 Hz, 3H)	513.2	Method D
343	<p>(Isomer-1)</p>	2,2,2-Trifluoro-1-methoxyethyl 5-methyl-2-((pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.24 (br d, <i>J</i> = 6.9 Hz, 1H), 8.78 (br d, <i>J</i> = 3.8 Hz, 1H), 8.59 (s, 1H), 8.45 (br t, <i>J</i> = 5.6 Hz, 1H), 7.74 (s, 1H), 7.65 (s, 1H), 7.25 (dd, <i>J</i> = 6.8, 4.3 Hz, 1H), 6.82 (s, 1H), 6.48 (br d, <i>J</i> = 3.4 Hz, 1H), 4.78 (d, <i>J</i> = 5.8 Hz, 2H), 3.63 (s, 3H), 2.43 (s, 3H)	463.1	Method F
344	<p>(Isomer-2)</p>	2,2,2-Trifluoro-1-methoxyethyl 5-methyl-2-((pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.28 (br d, <i>J</i> = 6.6 Hz, 1H), 8.79 (br d, <i>J</i> = 3.1 Hz, 1H), 8.60 (s, 1H), 8.44 (br t, <i>J</i> = 5.6 Hz, 1H), 7.75 (s, 1H), 7.66 (s, 1H), 7.27 (dd, <i>J</i> = 6.7, 4.4 Hz, 1H), 6.83 (s, 1H), 6.51 (br d, <i>J</i> = 3.7 Hz, 1H), 4.79 (br d, <i>J</i> = 5.8	463.1	Method F

Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺	Method
			Hz, 2H), 3.65 (s, 3H), 2.43 (s, 3H)		
345	 <p>(Isomer-1)</p>	1,1,1- Trifluoropropan-2-yl 5-methoxy-2- ((pyrazolo[1,5- α]pyrimidine-3- carboxamido)methyl) benzofuran-7- carboxylate	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.24 (br d, <i>J</i> = 6.8 Hz, 1H), 8.79 (br d, <i>J</i> = 3.3 Hz, 1H), 8.60 (s, 1H), 8.46 (br t, <i>J</i> = 5.4 Hz, 1H), 7.49 (d, <i>J</i> = 2.1 Hz, 1H), 7.32 (d, <i>J</i> = 2.1 Hz, 1H), 7.26 (dd, <i>J</i> = 6.7, 4.4 Hz, 1H), 6.83 (s, 1H), 5.83 - 5.52 (m, 1H), 4.78 (br d, <i>J</i> = 5.8 Hz, 2H), 3.82 (s, 3H), 1.48 (d, <i>J</i> = 6.6 Hz, 3H)	463.3	Method G
346	 <p>(Isomer-2)</p>	1,1,1- Trifluoropropan-2-yl 5-methoxy-2- ((pyrazolo[1,5- α]pyrimidine-3- carboxamido)methyl) benzofuran-7- carboxylate	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.24 (br d, <i>J</i> = 6.8 Hz, 1H), 8.79 (br d, <i>J</i> = 3.3 Hz, 1H), 8.60 (s, 1H), 8.46 (br t, <i>J</i> = 5.4 Hz, 1H), 7.49 (d, <i>J</i> = 2.1 Hz, 1H), 7.32 (d, <i>J</i> = 2.1 Hz, 1H), 7.26 (dd, <i>J</i> = 6.7, 4.4 Hz, 1H), 6.83 (s, 1H), 5.83 - 5.52 (m, 1H), 4.78 (br d, <i>J</i> = 5.8 Hz, 2H), 3.82 (s, 3H), 1.48 (d, <i>J</i> = 6.6 Hz, 3H)	463.3	Method G
347		2,2,2-Trifluoro-1- methoxyethyl 5- cyano-2- ((pyrazolo[1,5- α]pyrimidine-3- carboxamido)methyl)	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.27 (br d, <i>J</i> = 6.7 Hz, 1H), 8.81 (br d, <i>J</i> = 3.9 Hz, 1H), 8.69 - 8.58 (m, 1H), 8.52 (br t, <i>J</i> = 5.8 Hz, 1H), 8.46 (s, 1H), 8.18 (s, 1H), 7.28 (dd, <i>J</i> =	474.3	Method F

Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺	Method
	(Isomer-1)	benzofuran-7-carboxylate	6.7, 4.3 Hz, 1H), 7.03 (s, 1H), 6.55 (br s, 1H), 4.85 (br d, <i>J</i> = 5.8 Hz, 2H), 3.67 (s, 3H)		
348	 <p>(Isomer-2)</p>	2,2,2-Trifluoro-1-methoxyethyl 5-cyano-2-((pyrazolo[1,5- <i>α</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.27 (br d, <i>J</i> = 6.7 Hz, 1H), 8.81 (br d, <i>J</i> = 3.9 Hz, 1H), 8.69 - 8.58 (m, 1H), 8.52 (br t, <i>J</i> = 5.8 Hz, 1H), 8.46 (s, 1H), 8.18 (s, 1H), 7.28 (dd, <i>J</i> = 6.7, 4.3 Hz, 1H), 7.03 (s, 1H), 6.55 (br s, 1H), 4.85 (br d, <i>J</i> = 5.8 Hz, 2H), 3.67 (s, 3H)	474.3	Method F
349	 <p>(Isomer-1)</p>	1,1,1-Trifluoropropan-2-yl 2-((pyrazolo[1,5- <i>α</i>]pyrimidine-3-carboxamido)methyl)-5-(trifluoromethyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.28 (br d, <i>J</i> = 6.3 Hz, 1H), 8.80 (br d, <i>J</i> = 2.9 Hz, 1H), 8.60 (s, 1H), 8.50 (br t, <i>J</i> = 5.4 Hz, 1H), 8.35 (s, 1H), 8.03 (s, 1H), 7.27 (dd, <i>J</i> = 6.8, 4.3 Hz, 1H), 7.04 (s, 1H), 5.74 (dt, <i>J</i> = 13.1, 6.6 Hz, 1H), 4.86 (br d, <i>J</i> = 5.8 Hz, 2H), 1.51 (br d, <i>J</i> = 6.5 Hz, 3H)	501.1	Method D
350	 <p>(Isomer 2)</p>	1,1,1-Trifluoropropan-2-yl 2-((pyrazolo[1,5- <i>α</i>]pyrimidine-3-carboxamido)methyl)-5-(trifluoromethyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.28 (dd, <i>J</i> = 7.0, 1.2 Hz, 1H), 8.80 (dd, <i>J</i> = 4.1, 1.4 Hz, 1H), 8.61 (s, 1H), 8.56 (br t, <i>J</i> = 5.8 Hz, 1H), 8.36 (s, 1H), 8.01 (s, 1H), 7.27 (dd, <i>J</i> = 6.7, 4.3 Hz, 1H), 7.03	501.3	Method D

Ex. No.	Structure	Name	¹ H NMR	LC/MS (M+H) ⁺	Method
			(s, 1H), 5.74 (quin, <i>J</i> = 6.6 Hz, 1H), 4.84 (br d, <i>J</i> = 5.8 Hz, 2H), 1.48 (d, <i>J</i> = 6.4 Hz, 3H)		
351	 <p>(Isomer 1)</p>	2,2,2-Trifluoro-1-methoxyethyl 2-((pyrazolo[1,5- α]pyrimidine-3-carboxamido)methyl)-5-(trifluoromethyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.23 (br d, <i>J</i> = 6.7 Hz, 1H), 8.79 (br d, <i>J</i> = 2.7 Hz, 1H), 8.59 (s, 2H), 8.37 (s, 1H), 8.02 (s, 1H), 7.26 (br dd, <i>J</i> = 6.6, 4.1 Hz, 1H), 7.04 (s, 1H), 6.54 (br d, <i>J</i> = 3.4 Hz, 1H), 4.82 (br d, <i>J</i> = 5.5 Hz, 2H), 3.67 (s, 3H)	517.2	Method E
352	 <p>(Isomer 2)</p>	2,2,2-Trifluoro-1-methoxyethyl 2-((pyrazolo[1,5- α]pyrimidine-3-carboxamido)methyl)-5-(trifluoromethyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.26 (br d, <i>J</i> = 6.6 Hz, 1H), 8.80 (br d, <i>J</i> = 3.2 Hz, 1H), 8.60 (s, 1H), 8.51 (br t, <i>J</i> = 5.6 Hz, 1H), 8.38 (s, 1H), 8.05 (s, 1H), 7.27 (dd, <i>J</i> = 6.6, 4.4 Hz, 1H), 7.05 (s, 1H), 6.55 (br d, <i>J</i> = 2.9 Hz, 1H), 4.85 (br d, <i>J</i> = 5.8 Hz, 2H), 3.67 (s, 3H)	517.2	Method E

EXAMPLE 353

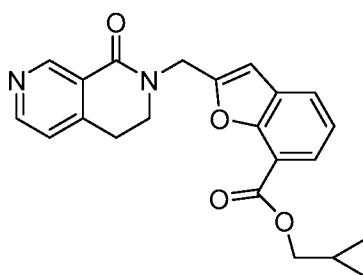


331

Methyl-D3 2-((1-oxo-3,4-dihydro-2,7-naphthyridin-2(1H)-yl)methyl)benzofuran-7-carboxylate

A mixture of 2-((1-oxo-3,4-dihydro-2,7-naphthyridin-2(1H)-yl)methyl)benzofuran-7-carboxylic acid (15 mg, 0.047 mmol, Example 129), Methanol-D3 (16.3 mg, 0.465 mmol), HATU (35.4 mg, 0.093 mmol) and Hunig's base (24.4 μ l, 0.140 mmol) in DMF (465 μ l) was stirred at room temperature for 2 hours. The reaction mixture was quenched with 1:1 DMF/AcOH and purified by preparative HPLC (Method B). The appropriate fractions were combined and dried *via* centrifugal evaporation to afford the title compound (8 mg, 50.7 % yield). ^1H NMR (500 MHz, DMSO- d_6) δ 8.97 (s, 1H), 8.63 (d, J = 5.2 Hz, 1H), 7.88 (d, J = 7.6 Hz, 1H), 7.83 (d, J = 7.6 Hz, 1H), 7.43 - 7.33 (m, 2H), 6.98 (s, 1H), 4.94 (s, 2H), 3.82 - 3.70 (m, 2H), 3.10 (t, J = 6.6 Hz, 2H); MS (ESI+) m/z = 340.0 (M+H) $^+$.

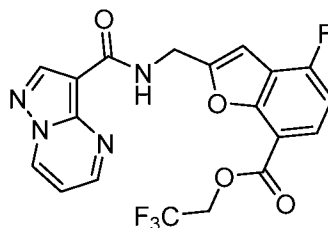
EXAMPLE 354



Cyclopropylmethyl 2-((1-oxo-3,4-dihydro-2,7-naphthyridin-2(1H)-yl)methyl)benzofuran-7-carboxylate

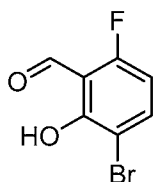
A mixture of 2-((1-oxo-3,4-dihydro-2,7-naphthyridin-2(1H)-yl)methyl)benzofuran-7-carboxylic acid (10 mg, 0.031 mmol, Example 129), Hunig's base (21.7 μ l, 0.124 mmol), PyBOP (32.3 mg, 0.062 mmol) and cyclopropanemethanol (11.2 mg, 0.155 mmol) in DMF (310 μ l) was stirred at room temperature for 72 hours. The reaction mixture was quenched with 1:1 DMF/AcOH and purified by preparative HPLC (Method B). The appropriate fractions were combined and dried *via* centrifugal evaporation to afford the title compound (6 mg, 51.4 % yield). ^1H NMR (500 MHz, DMSO- d_6) δ 8.72 (s, 1H), 8.36 (d, J = 5.0 Hz, 1H), 7.63 (d, J = 7.7 Hz, 1H), 7.61 - 7.48

(m, 1H), 7.20 - 7.04 (m, 2H), 6.72 (s, 1H), 4.69 (s, 2H), 3.90 (d, $J = 7.0$ Hz, 2H), 3.50 (t, $J = 6.6$ Hz, 2H), 2.83 (t, $J = 6.6$ Hz, 2H), 0.95 - 0.86 (m, 1H), 0.30 - 0.18 (m, 2H), 0.07 (br d, $J = 4.9$ Hz, 2H); MS (ESI+) $m/z = 377.1$ (M+H)⁺.

EXAMPLE 355

5

2,2,2-Trifluoroethyl 4-fluoro-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate

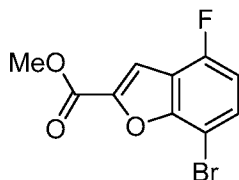


10

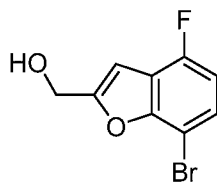
A) 3-Bromo-6-fluoro-2-hydroxybenzaldehyde

To the solution of 2-bromo-5-fluorophenol (2.70 g, 14.14 mmol) in THF (80 mL) was added triethylamine (3.94 mL, 28.3 mmol) and magnesium chloride (2.69 g, 28.3 mmol). The reaction mixture was stirred at room temperature for 15 min and then paraformaldehyde (1.27 g, 42.4 mmol) was added. The reaction mixture was stirred at 80 °C for 16 h. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in hydrochloric acid, 10% aqueous (40 mL) and stirred at room temperature for 30 minutes. Ethyl acetate (80 mL) was added and the layers were separated. The organic layer was dried over sodium sulfate and concentrated *in vacuo*. The residue was purified through a silica gel ISCO 120 g column, eluted with 0-20% EtOAc in hexane over 30 min to give the desired product as a light yellow solid (1.86 g, 60.1 % yield). ¹H NMR (400 MHz, Chloroform-*d*) δ 10.19 (s, 1H), 7.79 - 7.67 (m, 1H), 6.61 (m, 1H); MS (ESI+) $m/z = 217.9$ (M+H)⁺.

20

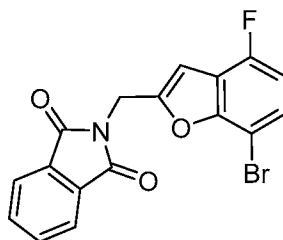
**B) Methyl 7-bromo-4-fluorobenzofuran-2-carboxylate**

To a solution of 3-bromo-6-fluoro-2-hydroxybenzaldehyde (7.0 g, 32.0 mmol) in DMF (100 mL) was added ethyl 2-bromoacetate (8.01 g, 47.9 mmol) and potassium carbonate (11 g, 80 mmol). The reaction mixture was stirred at 120 °C for 6 hours. After cooling to room temperature, 100 ml of cold water was added. The mixture was extracted with EtOAc three times. The combined organic extracts were dried over sodium sulfate, concentrated *in vacuo* and purified through a silica gel ISCO 220g column, eluting with 0-5% MeOH in DCM to give a brown solid (6.8 g, 80%). The above brown solid (6.8 g, 26.3 mmol) was dissolved in DCM (100mL) and MeOH (20 mL) and (diazomethyl)trimethylsilane, 2 M in diethyl ether (15.75 mL, 31.5 mmol) was added at room temperature dropwise. The reaction mixture was stirred at room temperature for 2 hours and concentrated *in vacuo*. The residue was purified with ISCO 220 g silica gel column, eluting with 0-30% EtOAc in DCM to give the desired product as a light yellow solid (3.01 g, 42%). ¹H NMR (400 MHz, Chloroform-d) δ 7.68 (s, 1H), 7.58 (dd, *J* = 8.6, 4.7 Hz, 1H), 6.96 (t, *J* = 8.7 Hz, 1H), 4.02 (s, 3H); MS (ESI+) *m/z* = 275.1 (M+H)⁺.

**C) (7-Bromo-4-fluorobenzofuran-2-yl)methanol**

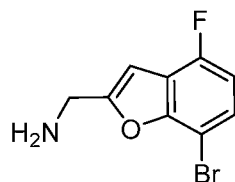
To a -20 °C stirred solution of methyl 7-bromo-4-fluorobenzofuran-2-carboxylate (3.0 g, 11 mmol) in tetrahydrofuran (80 mL) under N₂ was added lithium aluminum hydride (11.0 mL, 11.0 mmol, 1.0 M in THF) dropwise *via* syringe over 5 min. The reaction mixture was stirred at this temperature for 30 min. The reaction was quenched with Fieser Method (at -20 °C add 0.5 ml of water, add 1 ml of 15% NaOH, add 1.5 ml of

water, and stirred at rt for 30 min). Some anhydrous magnesium sulfate was added and the reaction was stirred at rt for 15 min and then filtered over celite. The filtrate was concentrated *in vacuo* and purified by ISCO silica gel 120 g column, eluting with 0-30% EtOAc in DCM, to give the product as a light yellow solid (1.82 g, 67.4 % yield). ¹H NMR (400 MHz, Chloroform-d) δ 7.39 (dd, J = 8.6, 4.7 Hz, 1H), 6.91 - 6.82 (m, 2H), 4.84 (d, J = 6.2 Hz, 2H), 2.07 (t, J = 6.4 Hz, 1H); MS (ESI+) m/z = 229.0 (M-OH)⁺.



D) 2-((7-Bromo-4-fluorobenzofuran-2-yl)methyl)isoindoline-1,3-dione

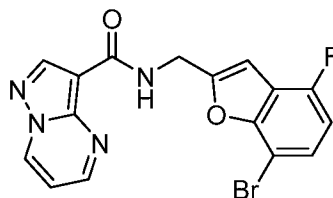
To a stirred solution of (7-bromo-4-fluorobenzofuran-2-yl)methanol (1.82 g, 7.43 mmol) and phthalimide (1.09 g, 7.43 mmol) in tetrahydrofuran (60 mL) under N₂ was added triphenylphosphine (2.338 g, 8.91 mmol) and DIAD (1.73 mL, 8.91 mmol). The reaction mixture was stirred at room temperature for 2 hours and was concentrated *in vacuo*. The residue was purified by flash chromatography to give the desired product (2.2 g, 79 % yield). ¹H NMR (400 MHz, Chloroform-d) δ 7.91 (dd, J = 5.4, 3.1 Hz, 2H), 7.76 (dd, J = 5.5, 3.1 Hz, 2H), δ 7.39 (dd, J = 8.6, 4.7 Hz, 1H), 6.91 - 6.82 (m, 2H), 5.07 (s, 2H).



E) (7-Bromo-4-fluorobenzofuran-2-yl)methanamine

To a stirred suspension of 2-((7-bromo-4-fluorobenzofuran-2-yl)methyl)isoindoline-1,3-dione (2.20 g, 5.88 mmol) in ethanol (70 mL) was added hydrazine (4.22 mL, 47.0 mmol, Aldrich). The reaction was heated at 50 °C with stirring

for 45 min. After cooling to rt, Et₂O (50 mL) was added and the mixture was stirred for 10 min. The solid was removed by filtration and washed with Et₂O. The filtrate was concentrated *in vacuo* to give an oil. To the oil was added 50 ml of ether and a solid formed. The solid was removed by filtration and washed with ether. The filtrate was concentrated again to give a white solid as the desired product solid (1.02 g, 71 % yield).
¹H NMR (400 MHz, Chloroform-d) δ 7.33 (dd, *J* = 8.6, 4.7 Hz, 1H), 6.83 (t, *J* = 8.8 Hz, 1H), 6.70 (s, 1H), 4.02 (s, 2H); MS (ESI+) *m/z* = 226.9 (M+H)⁺.



10 **F) N-((7-Bromo-4-fluorobenzofuran-2-yl)methyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide**

To a solution of (7-bromo-4-fluorobenzofuran-2-yl)methanamine (400 mg, 1.64 mmol) and pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (321 mg, 1.967 mmol) in DMF (4 mL) was added BOP (1087 mg, 2.458 mmol) and DIPEA (1.145 mL, 6.56 mmol). The reaction mixture turned into a clear solution and was stirred at room temperature for 16 h. The reaction mixture was diluted with cold water and the solid that formed was collected by filtration. The solid was purified by flash chromatography with an ISCO 80 g column eluting with 0-5% MeOH in DCM to give the desired product as a white solid (0.55 g, 87% yield). MS (ESI+) *m/z* = 391.0 (M+H)⁺.

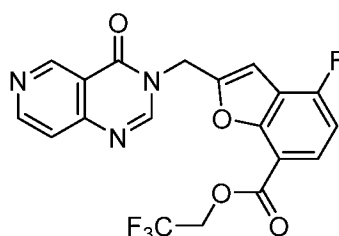
20

G) 2,2,2-Trifluoroethyl 4-fluoro-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate

To the solution of *N*-((7-bromo-4-fluorobenzofuran-2-yl)methyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (25 mg, 0.064 mmol) in DMSO (1 mL) was added 2,2,2-trifluoroethan-1-ol (129 mg, 1.285 mmol), palladium(II) acetate (1.44 mg, 6.42 μmol), DPPP (2.65 mg, 6.42 μmol) and triethylamine (0.090 mL, 0.642 mmol). The reaction mixture was degassed by bubbling argon through it and heated at 120 °C under a CO

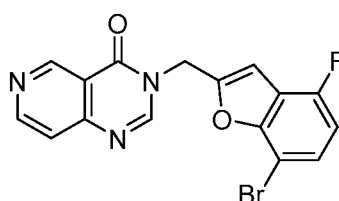
atmosphere for 18 h. The reaction mixture was cooled, dissolved in MeOH and purified by prep HPLC (Method A) to give the desired product (6.0 mg, 21%). ¹H NMR (500 MHz, DMSO-d₆) δ 9.26 (dd, *J* = 7.0, 1.2 Hz, 1H), 8.85 - 8.77 (m, 1H), 8.61 (s, 1H), 8.58 (br t, *J* = 6.0 Hz, 1H), 7.92 (dd, *J* = 8.5, 5.2 Hz, 1H), 7.32 - 7.21 (m, 2H), 6.99 (s, 1H), 5.05 - 4.92 (m, 2H), 4.81 (d, *J* = 5.8 Hz, 2H); MS (ESI+) *m/z* = 437.0 (M+H)⁺.

EXAMPLE 356



2,2,2-Trifluoroethyl 4-fluoro-2-((4-oxo-3,4-dihydropyrido[4,3-*d*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate

10



A) *N*-((7-Bromo-4-fluorobenzofuran-2-yl)methyl)-4-oxopyrido[4,3-*d*]pyrimidine-3(4*H*)-carboxamide

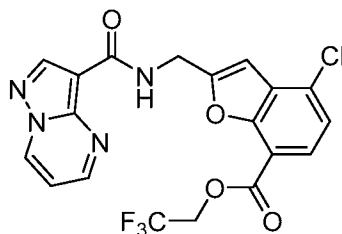
15 A mixture of 4-aminonicotinic acid (212 mg, 1.54 mmol) and *N,N*-dimethylformamide dimethylacetal (0.514 mL, 3.84 mmol) in DMF (2 mL) in a microwave vial was heated in a microwave at 100 °C for 20 min. The reaction mixture was concentrated *in vacuo*. To the residue was added acetic acid (1 mL) and (7-bromo-4-fluorobenzofuran-2-yl)methanamine (250 mg, 1.02 mmol, Step E of Example 355) and
20 the mixture was heated at 100 °C in a microwave for 20 min. The reaction mixture was concentrated *in vacuo* and purified with ISCO, 24 g column, eluted with 0-50% acetone in DCM to give the desired product (140 mg, 37%). ¹H NMR (400 MHz, Chloroform-*d*) δ 9.55 (s, 1H), 8.90 (d, *J* = 5.6 Hz, 1H), 8.50 (s, 1H), 7.59 (dd, *J* = 5.6, 0.7 Hz, 1H), 7.40

(dd, $J = 8.5, 4.6$ Hz, 1H), 7.05 (s, 1H), 6.87 (t, $J = 8.7$ Hz, 1H), 5.38 (s, 2H); MS (ESI+) $m/z = 373.9$ (M+H)⁺.

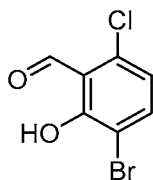
5 **B) 2,2,2-Trifluoroethyl 4-fluoro-2-((4-oxo-3,4-dihydropyrido[4,3-*d*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate**

To a solution of 3-((7-bromo-4-fluorobenzofuran-2-yl)methyl)pyrido[4,3-*d*]pyrimidin-4(3*H*)-one (14 mg, 0.0374 mmol) in DMSO (1 mL) was added 2,2,2-trifluoroethan-1-ol (74.9 mg, 0.748 mmol), palladium(II) acetate (0.840 mg, 0.0037 mmol) and triethylamine (0.52 mL, 3.74 mmol). The reaction mixture was degassed by
 10 bubbling argon through and heated at 120 °C under a CO atmosphere for 18 hours. The reaction mixture was concentrated *in vacuo* and purified by prep HPLC, Method B, to give the desired product (7.4 mg, 47%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.30 (s, 1H), 8.85 (br d, $J = 5.2$ Hz, 1H), 8.70 (s, 1H), 7.94 (br dd, $J = 8.2, 5.2$ Hz, 1H), 7.64 (br d, $J = 5.5$ Hz, 1H), 7.27 (s, 1H), 7.22 (s, 1H), 5.47 (s, 2H), 4.93 (q, $J = 8.5$ Hz, 2H); MS (ESI+)
 15 $m/z = 422.0$ (M+H)⁺.

EXAMPLE 357

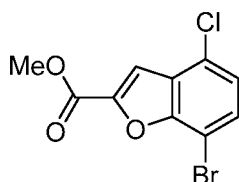


20 **2,2,2-Trifluoroethyl 4-chloro-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate**



A) 3-Bromo-6-chloro-2-hydroxybenzaldehyde

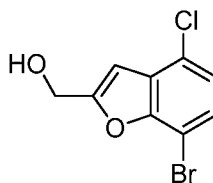
To the mixture of magnesium chloride (0.64 g, 6.75 mmol), paraformaldehyde (0.30 g, 10.1 mmol) and triethylamine (0.94 mL, 6.75 mmol) in THF (15 mL) was added 2-bromo-5-chlorophenol (0.7 g, 3.37 mmol). The reaction mixture was heated in a
5 microwave at 160 °C for 20 min. The residue was dissolved in ethyl acetate (40 mL) and washed with 1 N aqueous HCl solution and brine. The organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo* and purified through ISCO, 120 column, eluting with 0-20% EtOAc in hexane over 30 min to give the desired product as a light yellow solid. (0.29 g, 37% yield). ¹H NMR (400 MHz, CHLOROFORM-d) δ
10 12.59 (s, 1H), 10.40 (s, 1H), 7.71 (d, *J* = 8.5 Hz, 1H), 6.93 (d, *J* = 8.5 Hz, 1H).

**B) Methyl 7-bromo-4-chlorobenzofuran-2-carboxylate**

The solution of 3-bromo-6-chloro-2-hydroxybenzaldehyde (0.59 g, 2.51 mmol) in
15 DMF (10 mL) was added ethyl 2-bromoacetate (0.628 g, 3.76 mmol) and potassium carbonate (0.866 g, 6.26 mmol). The reaction mixture was stirred at 120 °C for 6 h. After cooled to rt, the reaction mixture was acidified to pH 3-4 with 1 N aqueous HCl solution, and extracted with EtOAc, 3x. The combined organic extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo* and then purified by ISCO, 80 g
20 column, eluting with 2-5% MeOH in DCM to give the product as a brown solid (530 mg, 70%). ¹H NMR (400 MHz, CHLOROFORM-d) δ 7.62 (s, 1H), 7.50 (d, *J* = 8.3 Hz, 1H), 7.17 (d, *J* = 8.3 Hz, 1H).

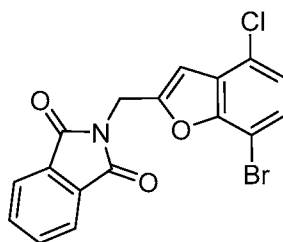
To a solution of the above acid (1.02 g, 3.70 mmol) in DCM (30mL) and MeOH (6 mL) at room temperature was added (diazomethyl)trimethylsilane, 2 M in diethyl ether
25 (3.70 mL, 7.41 mmol) dropwise. The reaction mixture was stirred for 1 h. The reaction mixture was concentrated *in vacuo* and purified with an ISCO, 80 g column, eluting with DCM to give the product as a light yellow solid (0.74 g, 69%). ¹H NMR (400 MHz,

Chloroform-d) δ 7.68 (s, 1H), 7.56 (d, $J = 8.3$ Hz, 1H), 7.22 (d, $J = 8.3$ Hz, 1H), 4.02 (s, 3H); MS (ESI+) $m/z = 290.8$ (M+H)⁺.



5 **C) (7-Bromo-4-chlorobenzofuran-2-yl)methanol**

To a stirred solution of methyl 7-bromo-4-chlorobenzofuran-2-carboxylate (0.74 g, 2.56 mmol) in THF (30 mL) at -20 °C under N₂ was added lithium aluminum hydride, 1.0 M in THF (2.56 mL, 2.56 mmol) dropwise *via* syringe over 5 min. After stirring at this temperature for 30 min, the reaction was quenched with Fieser Method (at -20 °C
10 add 0.1 ml of water, add 0.1 ml of 15% NaOH, add 0.3 ml of water, and stirred at rt for 30 min). Some anhydrous magnesium sulfate was added and the mixture was stirred at rt for 15 min and then filtered over celite. The filtrate was concentrated *in vacuo* and purified by ISCO, 80 g column, eluting with 0-30% EtOAc in DCM, to give the product as a light yellow solid (212 mg, 31.7 % yield). ¹H NMR (400 MHz, Chloroform-d) δ 7.37
15 (d, $J = 8.4$ Hz, 1H), 7.12 (d, $J = 8.3$ Hz, 1H), 6.85 (s, 1H), 4.84 (br d, $J = 3.1$ Hz, 2H), 2.32 (br s, 1H); MS (ESI+) $m/z = 244.9$ (M-OH)⁺.

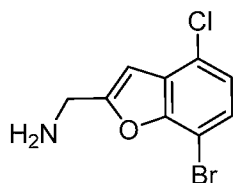


20 **D) 2-((7-Bromo-4-chlorobenzofuran-2-yl)methyl)isoindoline-1,3-dione**

To a stirred solution of (7-bromo-4-chlorobenzofuran-2-yl)methanol (0.21 g, 0.803 mmol) and phthalimide (0.118 g, 0.803 mmol) in THF (10 mL) under N₂ was added triphenylphosphine (0.253 g, 0.964 mmol) and DIAD (0.187 mL, 0.964 mmol). The reaction mixture was stirred at room temperature for 2 hours. The reaction was

concentrated and the residue was purified by flash chromatography (0% to 50% EtOAc in hexanes, 40 g column) to give the desired product (305 mg, 97 % yield). ¹H NMR (400 MHz, CHLOROFORM-d) δ 7.93 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.78 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.35 (d, *J* = 8.3 Hz, 1H), 7.10 (d, *J* = 8.4 Hz, 1H), 6.85 (s, 1H), 5.08 (d, *J* = 0.9 Hz, 2H).

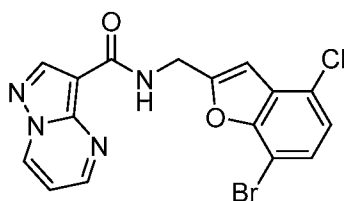
5



E) (7-Bromo-4-chlorobenzofuran-2-yl)methanamine

To a stirred suspension of 2-((7-bromo-4-chlorobenzofuran-2-yl)methyl)isoindoline-1,3-dione (0.305 g, 0.781 mmol) in ethanol (20 mL) was added hydrazine (0.560 mL, 6.25 mmol) and the reaction was heated at 50 °C with stirring for 1 hour. After the reaction mixture was cooled to rt Et₂O (50 mL) was added and the mixture was stirred for 10 min. The solid formed was removed by filtration and washed with Et₂O. The filtrate was concentrated to give an oil. To the oil was added 50 ml of ether. Some more solid formed. The solid was removed by filtration and washed with ether. The filtrate was concentrated to give the product as a white solid (175 mg, 86%). ¹H NMR (400 MHz, Chloroform-d) δ 7.33 (d, *J* = 8.4 Hz, 1H), 7.09 (d, *J* = 8.4 Hz, 1H), 6.71 (t, *J* = 0.9 Hz, 1H), 4.03 (d, *J* = 0.9 Hz, 2H), 2.43 - 2.13 (br, 2H). MS (ESI+) *m/z* = 261.0 (M+H)⁺.

20



F) N-((7-Bromo-4-chlorobenzofuran-2-yl)methyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

To a suspension of pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (98 mg, 0.599

mmol) and BOP (306 mg, 0.691 mmol) in DMF (2 mL) was added (7-bromo-4-chlorobenzofuran-2-yl)methanamine (120 mg, 0.461 mmol) and DIPEA (0.322 mL, 1.84 mmol). The reaction mixture turned into a clear solution and was stirred at room temperature for 1 hour. The reaction mixture was diluted with cold water and the solid that formed was collected by filtration, washed with water and dried under vacuum to give the desired product as an off-white solid (170 mg, 91% yield). ¹H NMR (500 MHz, DMSO-d₆) δ 9.26 (dd, *J* = 7.0, 1.2 Hz, 1H), 8.85 - 8.77 (m, 1H), 8.61 (s, 1H), 8.58 (br t, *J* = 6.0 Hz, 1H), 7.92 (dd, *J* = 8.5, 5.2 Hz, 1H), 7.32 - 7.21 (m, 2H), 6.99 (s, 1H), 4.81 (d, *J* = 5.8 Hz, 2H); MS (ESI+) *m/z* = 406. (M+H)⁺.

10

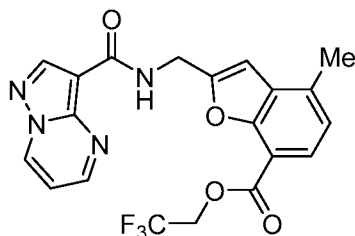
G) 2,2,2-Trifluoroethyl 4-chloro-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate

To a solution of *N*-((7-bromo-4-chlorobenzofuran-2-yl)methyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (21 mg, 0.052 mmol) in DMSO (5 mL) was added 2,2,2-trifluoroethan-1-ol (104 mg, 1.035 mmol), palladium(II) acetate (1.162 mg, 5.18 μmol), 1,3-bis(diphenylphosphanyl)propane, dppp (2.135 mg, 5.18 μmol), and triethylamine (0.072 mL, 0.518 mmol). The reaction mixture was degassed by bubbling Ar through and heated at 80 °C under a CO atmosphere for 2 hours. The reaction mixture was concentrated *in vacuo*. The residue was diluted with 10% aqueous LiCl solution and then extracted with EtOAc, 3x. The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified with prep HPLC, Method B, to give the desired product (4.2 mg, 18%). ¹H NMR (500 MHz, DMSO-d₆) δ 9.32 (dd, *J* = 7.0, 1.2 Hz, 1H), 8.83 (dd, *J* = 4.0, 1.5 Hz, 1H), 8.63 (s, 1H), 8.56 (br t, *J* = 5.6 Hz, 1H), 7.87 (d, *J* = 8.2 Hz, 1H), 7.51 (d, *J* = 8.2 Hz, 1H), 7.30 (dd, *J* = 6.9, 4.1 Hz, 1H), 6.93 (s, 1H), 5.03 (q, *J* = 9.0 Hz, 2H), 4.84 (br d, *J* = 5.8 Hz, 2H); MS (ESI+) *m/z* = 453.0 (M+H)⁺.

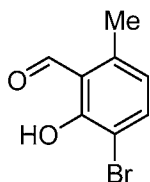
15

25

EXAMPLE 358



2,2,2-Trifluoroethyl 4-methyl-2-((pyrazolo[1,5-a]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate

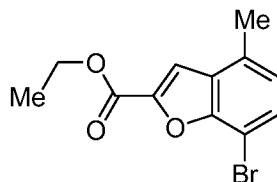


5

A) 3-Bromo-2-hydroxy-6-methylbenzaldehyde

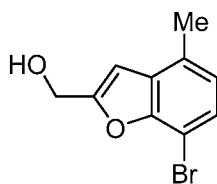
To the solution of 2-bromo-5-methylphenol (2.0 g, 10.69 mmol) in CH₃CN (40 mL) was added triethylamine (6.0 mL, 42.8 mmol) and manganese(II) chloride (2.02 g, 16.0 mmol). The reaction mixture was stirred at rt for 15 min. Then, paraformaldehyde (2.25 g, 74.9 mmol) was added. The reaction mixture was stirred at 80 °C for 16 h and then concentrated *in vacuo*. The residue was dissolved in hydrochloric acid (10% aqueous solution, 40 mL) and stirred at room temperature for 30 minutes. Ethyl acetate (40 mL) was added. The organic layer was separated, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified through flash chromatography with 120 g ISCO column, eluting with 0-20% EtOAc in hexane over 30 min to give the desired product as a light yellow solid (1.11 g, 48%). ¹H NMR (400 MHz, Chloroform-d) δ 12.56 (s, 1H), 10.29 (s, 1H), 7.66 (d, *J* = 8.1 Hz, 1H), 6.74 - 6.65 (m, 1H), 2.62 (s, 3H); MS (ESI+) *m/z* = 215.1 (M+H)⁺.

15



B) Ethyl 7-bromo-4-methylbenzofuran-2-carboxylate

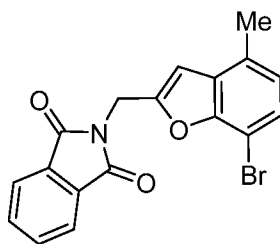
To a solution of 3-bromo-2-hydroxy-6-methylbenzaldehyde (1.1 g, 5.12 mmol) in DMF (10 mL) was added ethyl 2-bromoacetate (1.28 g, 7.67 mmol) and potassium carbonate (1.77 g, 12.8 mmol). The reaction mixture was stirred at 120 °C under a CO atmosphere for 5 h. After cooling to room temperature, cold water (30 ml) was added. The solid formed was collected by filtration and purified by flash chromatography with an 80 g ISCO column, eluting with 0-30% EtOAc in hexanes to give the product as a white solid (0.71 g, 49% yield). ¹H NMR (400 MHz, Chloroform-d) δ 7.63 (s, 1H), 7.51 (d, *J* = 7.8 Hz, 1H), 7.00 (dd, *J* = 7.9, 0.8 Hz, 1H), 4.48 (q, *J* = 7.1 Hz, 2H), 2.54 (s, 3H), 1.46 (t, *J* = 7.1 Hz, 3H); MS (ESI+) *m/z* = 284.9 (M+H)⁺.



C) (7-Bromo-4-methylbenzofuran-2-yl)methanol

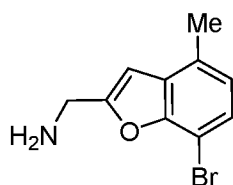
To a stirred solution of ethyl 7-bromo-4-methylbenzofuran-2-carboxylate (0.71 g, 2.49 mmol) in tetrahydrofuran (30 mL) at -20 °C under N₂ was added lithium aluminum hydride, 1.0 M in THF (2.49 mL, 2.49 mmol) dropwise *via* syringe over 5 min. After stirring at -20 °C for 30 min, the reaction was quenched with Fieser Method (at -20 °C add 0.1 ml of water, add 0.2 ml of 15% NaOH, add 0.3 ml of water, and stirred at rt for 30 min). Some anhydrous magnesium sulfate was added and stirred at rt for 15 min and filtered over celite. The filtrate was concentrated to give the desired product as a white solid (0.6 g, 100%). ¹H NMR (400 MHz, Chloroform-d) δ 7.35 (d, *J* = 7.9 Hz, 1H), 6.93 (dd, *J* = 7.9, 0.8 Hz, 1H), 6.78 (t, *J* = 0.7 Hz, 1H), 4.84 (s, 2H), 2.48 (d, *J* = 0.7 Hz, 3H);

MS (ESI+) $m/z = 224.9$ (M-OH)⁺.



D) 2-((7-Bromo-4-methylbenzofuran-2-yl)methyl)isoindoline-1,3-dione

5 To a stirred solution of (7-bromo-4-methylbenzofuran-2-yl)methanol (0.60 g, 2.489 mmol) and phthalimide (0.366 g, 2.489 mmol) in tetrahydrofuran (20 mL) under N₂ was added triphenylphosphine (0.783 g, 2.99 mmol) and DIAD (0.581 mL, 2.99 mmol). The reaction mixture was stirred at room temperature for 1 h and was concentrated *in vacuo*. The residue was purified by flash chromatography with an 80 g ISCO column,
10 eluting with 0% to 50% ethyl acetate in hexanes to give the product as a white solid (0.78 g, 84% yield). ¹H NMR (400 MHz, Chloroform-d) δ 7.97 (dd, $J = 5.4, 3.1$ Hz, 2H), 7.82 (dd, $J = 5.5, 3.1$ Hz, 2H), 7.43 - 7.27 (m, 1H), 6.93 (d, $J = 7.9$ Hz, 1H), 6.82 (s, 1H), 5.12 (s, 2H), 2.48 (s, 3H).

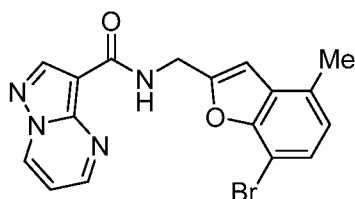


15

E) (7-Bromo-4-methylbenzofuran-2-yl)methanamine

To a stirred suspension of 2-((7-bromo-4-methylbenzofuran-2-yl)methyl)isoindoline-1,3-dione (0.77 g, 2.08 mmol) in ethanol (20 mL) was added hydrazine (1.49 mL, 16.6 mmol), and the reaction mixture was heated at 50 °C with
20 stirring for 45 min. After cooling to room temperature, Et₂O (50 mL) was added, and stirred for 10 min. The solid formed was removed by filtration. The filtrate was concentrated to give an oil. To the oil was added 50 ml of ether. Some more solid was formed. The solid was removed by filtration, and washed with ether. The filtrate was

concentrated to give the product as an oil (0.41 g, 82% yield). ^1H NMR (400 MHz, Chloroform- d) δ 7.31 (d, $J = 7.9$ Hz, 1H), 6.91 (dd, $J = 7.9, 0.7$ Hz, 1H), 6.64 (s, 1H), 4.04 (s, 2H), 2.46 (s, 3H); MS (ESI+) $m/z = 223.0$ (M-NH $_2$) $^+$.



5

F) *N*-((7-Bromo-4-methylbenzofuran-2-yl)methyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

To a suspension of pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (71.9 mg, 0.441 mmol) and BOP (225 mg, 0.508 mmol) in DMF (2 mL) was added (7-bromo-4-
10 methylbenzofuran-2-yl)methanamine (120 mg, 0.339 mmol) and DIPEA (0.237 mL, 1.36 mmol). The reaction was stirred at room temperature for 1 hour. The reaction mixture was diluted with cold water, and the solid that formed was collected by filtration, washed with water and dried under vacuum to give the product as a brown solid (0.122 g, 93%
15 yield). ^1H NMR (400 MHz, Chloroform- d) δ 8.81 (dd, $J = 7.0, 1.7$ Hz, 1H), 8.74 (s, 1H), 8.68 (dd, $J = 4.2, 1.8$ Hz, 1H), 8.46 (br s, 1H), 7.32 (d, $J = 7.8$ Hz, 1H), 7.03 (dd, $J = 7.0, 4.2$ Hz, 1H), 6.90 (dd, $J = 7.9, 0.7$ Hz, 1H), 6.81 (s, 1H), 4.91 (d, $J = 6.0$ Hz, 2H), 2.45 (s, 3H); MS (ESI+) $m/z = 387.0$ (M+H) $^+$.

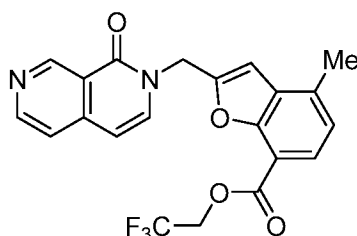
20

G) 2,2,2-Trifluoroethyl 4-methyl-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate

To the solution of *N*-((7-bromo-4-methylbenzofuran-2-yl) methyl)pyrazolo[1,5-
25 *a*]pyrimidine-3-carboxamide (120 mg, 0.312 mmol) in DMF (1 mL) was added triethylamine (0.868 mL, 6.23 mmol), 2,2,2-trifluoroethan-1-ol (623 mg, 6.23 mmol) and bis(triphenylphosphine)palladium (II) dichloride (21.9 mg, 0.031 mmol). The reaction mixture was degassed and heated at 130 $^{\circ}\text{C}$ under a CO atmosphere for 18 hours. After cooling to room temperature, the reaction mixture was filtered and purified with preparative HPLC, (Method A), to give the desired product (17.3 mg, 13% yield). ^1H

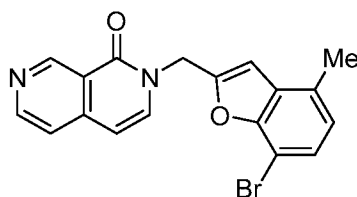
NMR (400 MHz, Chloroform-d) δ 8.81 (dd, $J = 7.0, 1.8$ Hz, 1H), 8.73 (s, 1H), 8.68 (dd, $J = 4.2, 1.7$ Hz, 1H), 8.50 (br t, $J = 5.6$ Hz, 1H), 7.87 (d, $J = 7.8$ Hz, 1H), 7.11 (dd, $J = 7.8, 0.7$ Hz, 1H), 7.03 (dd, $J = 7.0, 4.2$ Hz, 1H), 6.82 (s, 1H), 4.94 (dd, $J = 6.0, 0.6$ Hz, 2H), 4.78 (q, $J = 8.4$ Hz, 2H), 2.56 (s, 3H); MS (ESI+) $m/z = 433.0$ (M+H)⁺.

5

EXAMPLE 359

2,2,2-Trifluoroethyl 4-methyl-2-((1-oxo-1,2-dihydro-2,7-naphthyridine-2-carboxamido)methyl)benzofuran-7-carboxylate

10



A) N-((7-Bromo-4-methylbenzofuran-2-yl)methyl)-1-oxo-2,7-naphthyridine-2(1H)-carboxamide

A mixture of methyl 4-methylnicotinate (283 mg, 1.87 mmol), and DMF-DMA (1.34 mL, 10.0 mmol) in DMF (1 mL) in a microwave vial was heated in the microwave at 130 °C for 30 min. The reaction mixture was concentrated *in vacuo*. To the residue was added acetic acid (1 mL) and (7-bromo-4-methylbenzofuran-2-yl)methanamine (150 mg, 0.625 mmol, Step E of Example 358) and the mixture was heated at 130 °C in a microwave for 45 min to give the title compound (170 mg, 63% yield). ¹H NMR (400 MHz, Chloroform-d) δ 9.65 (s, 1H), 8.76 (d, $J = 5.5$ Hz, 1H), 7.57 (d, $J = 7.5$ Hz, 1H), 7.40 - 7.32 (m, 3H), 6.96 - 6.88 (m, 2H), 6.58 - 6.51 (m, 1H), 5.38 (s, 2H), 2.46 (s, 3H);

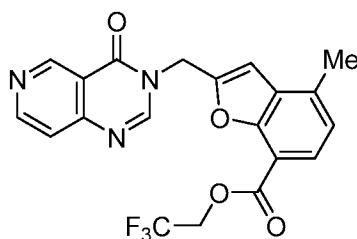
20

MS (ESI+) $m/z = 370.9 (M+H)^+$.

B) 2,2,2-Trifluoroethyl 4-methyl-2-((1-oxo-1,2-dihydro-2,7-naphthyridine-2-carboxamido)methyl)benzofuran-7-carboxylate

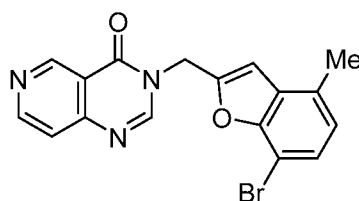
5 To a solution of 2-((7-bromo-4-methylbenzofuran-2-yl)methyl)-2,7-naphthyridin-1(2*H*)-one (170 mg, 0.46 mmol) in DMF (1 mL) was added triethylamine (1.28 mL, 9.21 mmol), 2,2,2-trifluoroethan-1-ol (921 mg, 9.21 mmol) and bis(triphenylphosphine)palladium (II) dichloride (32.3 mg, 0.046 mmol). The reaction mixture was degassed by bubbling argon through and heated at 130 °C under a CO atmosphere for 18 hours. The reaction mixture was purified by prep HPLC, Method C, to give the desired product compound (42 mg, 17% yield). ¹H NMR (400 MHz, Methanol-*d*₄) δ 9.50 (s, 1H), 8.69 (d, *J* = 6.0 Hz, 1H), 8.02 (d, *J* = 7.5 Hz, 1H), 7.87 (d, *J* = 7.8 Hz, 1H), 7.84 - 7.79 (m, 1H), 7.17 (dd, *J* = 7.8, 0.6 Hz, 1H), 7.05 (s, 1H), 6.82 (d, *J* = 7.5 Hz, 1H), 5.50 (s, 2H), 4.86 (m, 2H), 2.58 (s, 3H); MS (ESI+) $m/z = 417.0 (M+H)^+$. Prep HPLC purification also gave 4-methyl-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylic acid (30 mg, 27%) as a by-product. ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.31 - 9.21 (m, 1H), 8.82 (d, *J* = 2.7 Hz, 1H), 8.62 (s, 1H), 8.55 (br t, *J* = 5.6 Hz, 1H), 7.70 (d, *J* = 7.6 Hz, 1H), 7.27 (dd, *J* = 6.9, 4.1 Hz, 1H), 7.13 (d, *J* = 7.9 Hz, 1H), 6.88 (s, 1H), 4.79 (br d, *J* = 5.8 Hz, 2H); MS (ESI+) $m/z = 351.0 (M+H)^+$.

EXAMPLE 360



2,2,2-Trifluoroethyl 4-methyl-2-((4-oxo-3,4-dihydropyrido[4,3-*d*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate

25



A) N-((7-Bromo-4-methylbenzofuran-2-yl)methyl)-4-oxopyrido[4,3-d]pyrimidine-3(4H)-carboxamide

5 A mixture of 4-aminonicotinic acid (86 mg, 0.625 mmol) and DMF-DMA (0.21 mL, 1.56 mmol) in DMF (1 mL) in a microwave vial was heated at 100 °C in the microwave for 20 min. The reaction mixture was concentrated *in vacuo*. To the residue was added acetic acid (1 mL) and (7-bromo-4-methylbenzofuran-2-yl)methanamine (100 mg, 0.416 mmol, Step E of Example 258) and the mixture was heated at 100 °C in the
10 microwave for 20 min. The reaction mixture was concentrated and purified with ISCO, 24 g column, eluted with 0-50% acetone in DCM to give the desired product (110 mg, 71%). ¹H NMR (400 MHz, Chloroform-d) δ 9.56 (s, 1H), 8.89 (br d, *J* = 5.5 Hz, 1H), 8.50 (s, 1H), 7.58 (d, *J* = 5.5 Hz, 1H), 7.35 (d, *J* = 7.9 Hz, 1H), 6.96 (s, 1H), 6.92 (dd, *J* = 7.9, 0.7 Hz, 1H), 5.38 (s, 2H), 2.46 (s, 3H); MS (ESI+) *m/z* = 369.9 (M+H)⁺.

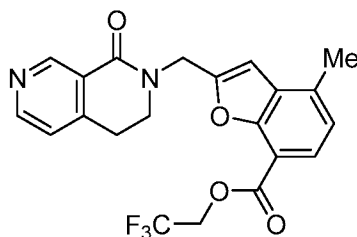
15

B) 2,2,2-Trifluoroethyl 4-methyl-2-((4-oxo-3,4-dihydropyrido[4,3-d]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate

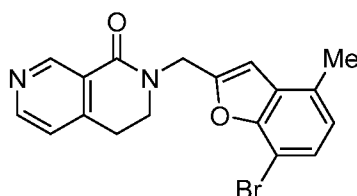
To the solution of 3-((7-bromo-4-methylbenzofuran-2-yl)methyl)pyrido[4,3-d]pyrimidin-4(3H)-one (35 mg, 0.095 mmol) in DMSO (2 mL) was added 2,2,2-
20 trifluoroethan-1-ol (189 mg, 1.89 mmol), palladium(II) acetate (2.1 mg, 9.45 μmol), 1,3-bis(diphenylphosphanyl)propane (dppp, 3.9 mg, 9.45 μmol) and triethylamine (0.132 mL, 0.945 mmol). The reaction mixture was degassed and heated at 130 °C under a CO atmosphere for 18 h. The reaction mixture was purified with prep HPLC, Method B, to give the desired product (6.3 mg, 16%). ¹H NMR (500 MHz, DMSO-d₆) δ 9.33 (s, 1H),
25 8.88 (br d, *J* = 5.5 Hz, 1H), 8.94 - 8.84 (m, 1H), 8.74 (s, 1H), 7.80 (br d, *J* = 7.9 Hz, 1H), 7.66 (br d, *J* = 5.5 Hz, 1H), 7.24 (br d, *J* = 7.9 Hz, 1H), 7.16 (s, 1H), 5.48 (s, 2H), 5.05 -

4.87 (m, 2H), 2.56 (s, 3H); MS (ESI+) $m/z = 418.0 (M+H)^+$.

EXAMPLE 361



- 5 **2,2,2-Trifluoroethyl 4-methyl-2-((1-oxo-1,2,3,4-tetrahydro-2,7-naphthyridine-2-carboxamido)methyl)benzofuran-7-carboxylate**



- 10 **A) N-((7-Bromo-4-methylbenzofuran-2-yl)methyl)-1-oxo-3,4-dihydro-2,7-naphthyridine-2(1H)-carboxamide**

The suspension of 3,4-dihydro-1H-pyrano[3,4-c]pyridin-1-one, HCl (120 mg, 0.647 mmol) (WO 2005063768) and (7-bromo-4-methylbenzofuran-2-yl)methanamine (155 mg, 0.647 mmol, Step E of Example 258) in pyridine (0.5 mL) and NMP (0.5 mL) in a 2 dram vial was stirred at 130 °C for 3 h. The reaction mixture was concentrated and purified by prep HPLC, Method C, to give the title compound (107 mg, 41%). ¹H NMR (400 MHz, Chloroform-d) δ 9.27 (s, 1H), 8.65 (d, *J* = 5.0 Hz, 1H), 7.33 (d, *J* = 7.9 Hz, 1H), 7.16 (dd, *J* = 5.0, 0.7 Hz, 1H), 6.92 (dd, *J* = 7.9, 0.8 Hz, 1H), 6.83 (s, 1H), 4.96 (s, 2H), 3.85 (t, *J* = 6.6 Hz, 2H), 3.09 (t, *J* = 6.6 Hz, 2H), 2.46 (s, 3H); MS (ESI+) $m/z = 370.9 (M+H)^+$.

20

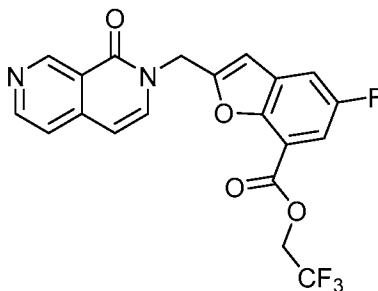
- B) 2,2,2-Trifluoroethyl 4-methyl-2-((1-oxo-1,2,3,4-tetrahydro-2,7-**

naphthyridine-2-carboxamido)methyl)benzofuran-7-carboxylate

To the solution of 2-((7-bromo-4-methylbenzofuran-2-yl)methyl)-3,4-dihydro-2,7-naphthyridin-1(2*H*)-one (40 mg, 0.108 mmol) in DMF (3 mL) was added triethylamine (0.300 mL, 2.16 mmol), 2,2,2-trifluoroethan-1-ol (216 mg, 2.16 mmol) and

5 bis(triphenylphosphine)palladium (II) dichloride (7.6 mg, 10.8 μ mol). The reaction mixture was degassed by bubbling Ar through and heated at 130 °C under a CO atmosphere for 5 h. The reaction mixture was purified with prep HPLC (Method A) to give the desired product (15.5 mg, 34%). ¹H NMR (400 MHz, Chloroform-*d*) δ 9.17 (s, 1H), 8.64 (d, *J* = 5.0 Hz, 1H), 7.31 (d, *J* = 7.9 Hz, 1H), 7.11 (dd, *J* = 5.0, 0.7 Hz, 1H),

10 6.92 (dd, *J* = 7.9, 0.8 Hz, 1H), 6.83 (s, 1H), 5.18 (s, 2H), 5.01 - 4.77 (m, 2H), 3.81 (t, *J* = 6.6 Hz, 2H), 3.12 (t, *J* = 6.6 Hz, 2H), 2.46 (s, 3H); MS (ESI+) *m/z* 419.0 = (M+H)⁺.

EXAMPLE 362

15 **2,2,2-Trifluoroethyl 5-fluoro-2-((1-oxo-2,7-naphthyridin-2(1H)-yl)methyl)benzofuran-7-carboxylate**

Methyl 4-methylnicotinate (57.1 mg, 0.378 mmol) and *N,N*-dimethylformamide dimethyl acetal (0.177 mL, 1.322 mmol) were taken up in DMF (0.5 mL) in a microwave vial. The vial was sealed and heated to 145 °C for 30 minutes in a microwave reactor.

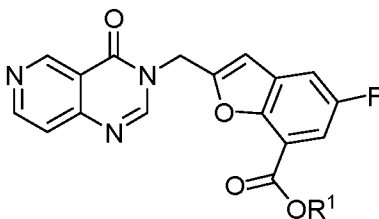
20 The reaction mixture was cooled and concentrated *in vacuo*. The residue was dissolved in DCM and concentrated *in vacuo* once again. The resulting residue was mixed with acetic acid (0.5 mL) and 2,2,2-trifluoroethyl 2-(aminomethyl)-5-fluorobenzofuran-7-carboxylate (55 mg, 0.094 mmol). The vial was sealed and heated to 110 °C for another 30 minutes in a microwave reactor. The reaction mixture was cooled and concentrated *in*

25 *vacuo*. The residue was dissolved in MeOH, filtered, and purified *via* HPLC (method B)

to give the title compound (8.8 mg, 17% yield). ¹H NMR (500 MHz, DMSO-d₆) δ 9.38 (s, 1H), 8.74 (br d, *J* = 5.3 Hz, 1H), 7.90 (d, *J* = 7.3 Hz, 1H), 7.84 (dd, *J* = 8.2, 2.5 Hz, 1H), 7.74 (d, *J* = 5.6 Hz, 1H), 7.62 (dd, *J* = 9.4, 2.5 Hz, 1H), 7.03 (s, 1H), 6.78 (d, *J* = 7.3 Hz, 1H), 5.45 (s, 2H), 5.00 (q, *J* = 8.8 Hz, 2H); MS (ESI+) *m/z* = 420.9 (M+H)⁺.

5

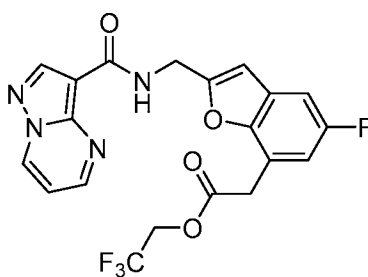
EXAMPLES 363-365



Exampel 363-365 were prepared in the same manner as exemplified by Example 362 starting from Example 39.

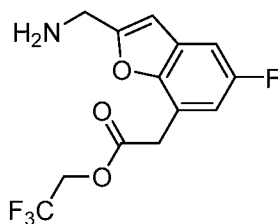
Ex. No.	R ¹	Name	¹ H NMR	LC/MS [M+H] ⁺
363		2,2,2-Trifluoroethyl 5-fluoro-2-((4-oxopyrido[4,3- <i>d</i>]pyrimidin-3(4 <i>H</i>)-yl)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.32 (s, 1H), 8.88 (d, <i>J</i> = 5.5 Hz, 1H), 8.74 (s, 1H), 7.85 (dd, <i>J</i> = 8.2, 2.4 Hz, 1H), 7.71 - 7.52 (m, 2H), 7.11 (s, 1H), 5.49 (s, 2H), 5.00 (q, <i>J</i> = 9.1 Hz, 2H)	422.2
364		1,1,1-Trifluoropropan-2-yl 5-fluoro-2-((4-oxopyrido[4,3- <i>d</i>]pyrimidin-3(4 <i>H</i>)-yl)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.30 (s, 1H), 8.86 (d, <i>J</i> = 5.5 Hz, 1H), 8.72 (s, 1H), 7.83 (dd, <i>J</i> = 8.1, 2.6 Hz, 1H), 7.64 (d, <i>J</i> = 5.5 Hz, 1H), 7.60 (dd, <i>J</i> = 9.5, 2.4 Hz, 1H), 7.11 (s, 1H), 5.79 - 5.61 (m, 1H), 5.47 (s, 2H), 1.42 (d, <i>J</i> = 6.4 Hz, 3H)	436.3
365		1,1,1-Trifluoropropan-2-yl 5-fluoro-2-((4-oxopyrido[4,3- <i>d</i>]pyrimidin-3(4 <i>H</i>)-yl)methyl)benzofuran-7-carboxylate	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.30 (s, 1H), 8.86 (d, <i>J</i> = 5.5 Hz, 1H), 8.72 (s, 1H), 7.83 (dd, <i>J</i> = 8.1, 2.6 Hz, 1H), 7.64 (d, <i>J</i> = 5.5 Hz, 1H), 7.60 (dd, <i>J</i> = 9.5, 2.4 Hz, 1H), 7.11 (s, 1H), 5.79 - 5.61 (m, 1H), 5.47 (s, 2H), 1.42 (d, <i>J</i> = 6.4 Hz, 3H)	436.3

	(Method F)	yl)methyl)benzofuran-7-carboxylate	(m, 1H), 5.47 (s, 2H), 1.42 (d, $J=6.4$ Hz, 3H)	
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EXAMPLE 366

2,2,2-Trifluoroethyl 2-(5-fluoro-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-yl)acetate

5



A) 2,2,2-Trifluoroethyl 2-(2-(aminomethyl)-5-fluorobenzofuran-7-yl)acetate

To a solution of 2-(2-(((*tert*-butoxycarbonyl)amino)methyl)-5-fluorobenzofuran-7-yl)acetic acid (100 mg, 0.309 mmol, Step C of Example 47) in DMF (1 mL) was added 2,2,2-trifluoroethan-1-ol (30.9 mg, 0.309 mmol), BOP (205 mg, 0.464 mmol) and DIPEA (0.162 mL, 0.928 mmol). The reaction mixture was stirred at room temperature for 72 hours. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic extracts were dried over sodium sulfate, filtered, concentrated and purified by ISCO, 12 g column, eluting with 0-30% EtOAc in hexanes to give the desired product.

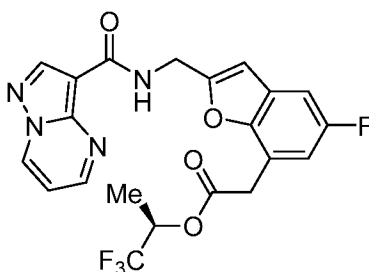
To a solution of above compound (33 mg, 0.081 mmol) in DCM (1 mL) was added TFA (0.3 mL). The reaction mixture was stirred at room temperature for 2 hours and concentrated to give the product as a light yellow solid (25 mg, 100% yield). ^1H

NMR (400 MHz, Chloroform-d) δ 7.14 (dd, J = 8.3, 2.5 Hz, 1H), 6.95 (dd, J = 9.6, 2.5 Hz, 1H), 6.60 (s, 1H), 4.54 (q, J = 8.4 Hz, 2H), 4.45 (br d, J = 5.7 Hz, 2H), 4.00 (s, 2H); MS (ESI+) m/z = 306.1 (M+H)⁺.

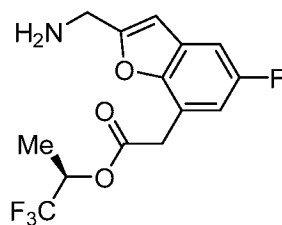
5 **B) 2,2,2-Trifluoroethyl 2-(5-fluoro-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-yl)acetate**

To a solution of 2,2,2-Trifluoroethyl 2-(2-(aminomethyl)-5-fluorobenzofuran-7-yl)acetate (25 mg, 0.081 mmol) in DMF (1 mL) were added pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (12.3 mg, 0.075 mmol), BOP (50.0 mg, 0.113 mmol) and DIPEA
 10 (0.066 mL, 0.377 mmol). The reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated and purified by preparative HPLC, Method B, to give the product (28 mg, 81% yield). ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.18 (br d, J = 6.7 Hz, 1H), 8.78 (br d, J = 3.0 Hz, 1H), 8.58 (s, 1H), 8.47 (br t, J = 5.7 Hz, 1H), 7.34 - 7.28 (m, 1H), 7.25 (dd, J = 6.9, 4.0 Hz, 1H), 7.03 (br d, J = 9.8 Hz, 1H), 6.78 (s, 1H),
 15 4.72 (br d, J = 5.7 Hz, 2H), 4.69 - 4.60 (m, 2H), 4.04 (s, 2H); MS (ESI+) m/z = 451.1 (M+H)⁺.

EXAMPLE 367



20 **(*R*)-1,1,1-Trifluoropropan-2-yl 2-(5-fluoro-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-yl)acetate**



A) (R)-1,1,1-Trifluoropropan-2-yl 2-(2-(aminomethyl)-5-fluorobenzofuran-7-yl)acetate

To a solution of 2-(2-(((*tert*-butoxycarbonyl)amino)methyl)-5-fluorobenzofuran-7-yl)acetic acid (105 mg, 0.325 mmol, Step C of Example 47) in DMF (1 mL) was added
 5 7-yl)acetic acid (105 mg, 0.325 mmol, Step C of Example 47) in DMF (1 mL) was added
 (R)-1,1,1-trifluoropropan-2-ol (185 mg, 1.62 mmol), BOP (215 mg, 0.487 mmol) and
 DIPEA (0.284 mL, 1.624 mmol). The reaction mixture was stirred at room temperature
 for 72 hours. The reaction mixture was diluted with water and extracted with EtOAc three
 times. The combined organic extracts were dried over sodium sulfate,
 10 filtered, concentrated *in vacuo*, and purified by ISCO, 12 g column, eluting with 0-30%
 EtOAc in hexanes to give the desired product.

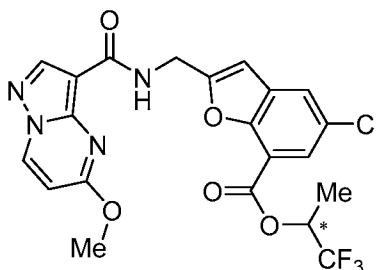
To a solution of the above compound (31 mg, 0.074 mmol) in DCM (1 mL) was
 added TFA (0.3 mL). The reaction mixture was stirred at room temperature for 2 hours
 and concentrated to give the product TFA salt as a light yellow solid (23 mg, 100%
 15 yield). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.14 (dd, *J* = 8.3, 2.5 Hz, 1H), 6.95 (dd, *J* =
 9.6, 2.4 Hz, 1H), 6.60 (s, 1H), 5.36 (dt, *J* = 13.1, 6.5 Hz, 1H), 4.45 (br d, *J* = 5.6 Hz, 2H),
 3.97 (s, 2H), 1.43 (d, *J* = 6.7 Hz, 3H); MS (ESI+) *m/z* = 306.1 (M+H)⁺.

**B) (R)-1,1,1-Trifluoropropan-2-yl 2-(5-fluoro-2-((pyrazolo[1,5-
 20 *a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-yl)acetate**

To a solution of (R)-1,1,1-trifluoropropan-2-yl 2-(2-(aminomethyl)-5-
 fluorobenzofuran-7-yl)acetate (23 mg, 0.072 mmol) in DMF (1 mL) was added
 pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (11.8 mg, 0.072 mmol), BOP (47.8 mg,
 0.108 mmol) and DIPEA (0.063 mL, 0.36 mmol). The reaction mixture was stirred at rt
 25 for 2 h. The reaction mixture was concentrated *in vacuo* and purified by prep HPLC
 (Method B) to give the desired product (25.6 mg, 76% yield). ¹H NMR (500 MHz,

DMSO- d_6) δ 9.27 - 9.17 (m, 1H), 8.83 - 8.74 (m, 1H), 8.59 (s, 1H), 8.48 - 8.41 (m, 1H), 7.31 (br d, $J = 7.6$ Hz, 1H), 7.26 (dd, $J = 5.7, 4.3$ Hz, 1H), 7.04 (br d, $J = 9.8$ Hz, 1H), 6.79 (s, 1H), 5.36 (td, $J = 6.7, 2.8$ Hz, 1H), 4.73 (br d, $J = 5.7$ Hz, 2H), 4.02 (d, $J = 1.3$ Hz, 2H), 1.28 (br d, $J = 5.2$ Hz, 3H); MS (ESI+) $m/z = 465.1$ (M+H) $^+$.

5

EXAMPLE 368

1,1,1-Trifluoropropan-2-yl 5-chloro-2-((5-methoxypyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate

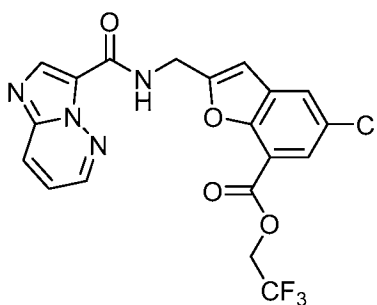
(Enantiomer 1)

10

5-Chloro-2-((5-methoxypyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylic acid (40 mg, 0.10 mmol, Example 139) was dissolved in DMF (0.4 mL) and then DIPEA (70 μ l, 0.40 mmol) and 1,1,1-trifluoropropan-2-ol (34 mg, 0.30 mmol) were added. BOP (66 mg, 0.15 mmol) was added and the reaction was stirred at room temperature overnight. The reaction was diluted with DMSO, filtered, and purified *via* HPLC (Method B) to give racemic 1,1,1-trifluoropropan-2-yl 5-chloro-2-((5-methoxypyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate. This material was further purified with chiral SFC (Method D) to give the enantiopure product as the first eluting enantiomer (7.2 mg, 0.014 mmol, 14.2 % yield) (absolute stereochemistry was not determined). ^1H NMR (500 MHz, DMSO- d_6) δ 9.02 (d, $J = 7.3$ Hz, 1H), 8.40 (s, 1H), 8.21 (br t, $J = 5.6$ Hz, 1H), 8.03 (d, $J = 2.1$ Hz, 1H), 7.74 (d, $J = 2.1$ Hz, 1H), 6.91 (s, 1H), 6.74 (d, $J = 7.6$ Hz, 1H), 5.74 (dt, $J = 13.4, 6.6$ Hz, 1H), 4.80 (br d, $J = 5.5$ Hz, 2H), 4.02 (s, 3H), 1.48 (d, $J = 6.4$ Hz, 3H); MS (ESI+) $m/z = 497.2$ (M+H) $^+$.

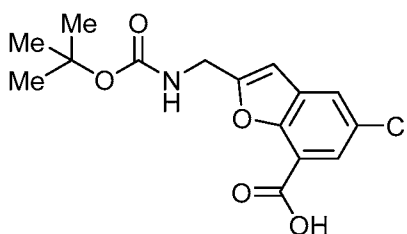
25

EXAMPLE 369



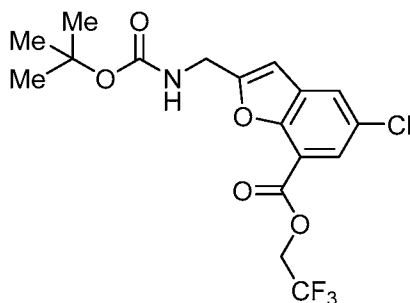
2,2,2-Trifluoroethyl 5-chloro-2-((imidazo[1,2-*b*]pyridazine-3-carboxamido)methyl)benzofuran-7-carboxylate

5



A) 2-(((*tert*-Butoxycarbonyl)amino)methyl)-5-chlorobenzofuran-7-carboxylic acid

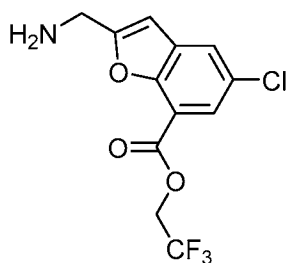
To a solution of methyl 2-(((*tert*-butoxycarbonyl)amino)methyl)-5-chlorobenzofuran-7-carboxylate (1.1 g, 3.24 mmol, Step B of Example 48) in THF (6 mL) and MeOH (6 mL) was added LiOH (2 M aqueous solution, 9.7 mL, 19.4 mmol). The reaction mixture was stirred at room temperature for 3 h. To the reaction mixture was added 1 N aqueous HCl solution to adjust the pH to about 3. The resulting mixture was extracted with ethyl acetate. The organic layer was separated, washed with brine, dried over MgSO₄, and filtered. The filtrate was concentrated *in vacuo* to give the crude title compound as a light brown solid (1.0 g, 95%) which was used in the next step without further purification. MS (ESI⁺) *m/z* = 270.1 (M-55+H)⁺.



B) 2,2,2-Trifluoroethyl 2-(((*tert*-butoxycarbonyl)amino)methyl)-5-chlorobenzofuran-7-carboxylate

To a solution of 2-(((*tert*-butoxycarbonyl)amino)methyl)-5-chlorobenzofuran-7-carboxylic acid (1.0 g, 3.07 mmol) in DMF (8 mL) was added BOP (1.49 g, 3.38 mmol), 2,2,2-trifluoroethanol (0.36 mL, 4.91 mmol) and DIPEA (0.86 mL, 4.91 mmol). The reaction mixture was stirred at room temperature for 2 hours. The reaction was diluted with ethyl acetate and saturated aqueous NaHCO₃ solution. The organic layer was separated, washed with brine, dried over MgSO₄, and filtered. The filtrate was concentrated *in vacuo*. The residue was dissolved in DCM and purified by flash chromatography (ISCO 40g column, 0-30% ethyl acetate in hexanes) to give the title compound (1.15 g, 92%) as a white solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.91 (d, *J* = 2.1 Hz, 1H), 7.75 (d, *J* = 2.1 Hz, 1H), 6.66 (s, 1H), 5.09 (br s, 1H), 4.79 (q, *J* = 8.3 Hz, 2H), 4.52 (br d, *J* = 6.0 Hz, 2H), 1.48 (s, 9H); MS (ESI+) *m/z* = 815.4 (2M+1) (M+H)⁺.

15



C) 2,2,2-Trifluoroethyl 2-(aminomethyl)-5-chlorobenzofuran-7-carboxylate

To a solution of 2,2,2-trifluoroethyl 2-(((*tert*-butoxycarbonyl)amino)methyl)-5-chlorobenzofuran-7-carboxylate (0.7 g, 1.72 mmol) in DCM (8 mL) was added TFA (1.6 mL, 20.60 mmol). The reaction mixture was stirred at room temperature for 2 hours. The

reaction was concentrated *in vacuo* to give the crude title compound (TFA salt) and as a white solid (0.7 g, 97%). ¹H NMR (400 MHz, Methanol-d₄) δ 8.03 (d, *J* = 2.2 Hz, 1H), 7.98 (d, *J* = 2.1 Hz, 1H), 7.12 (s, 1H), 4.98 (q, *J* = 8.6 Hz, 2H), 4.43 (s, 2H); MS (ESI+) *m/z* = 291.1 (M-17) (M+H)⁺.

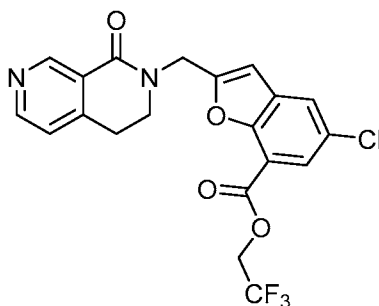
5

D) 2,2,2-Trifluoroethyl 5-chloro-2-((imidazo[1,2-*b*]pyridazine-3-carboxamido)methyl)benzofuran-7-carboxylate

To a suspension of imidazo[1,2-*b*]pyridazine-3-carboxylic acid (15.1 mg, 0.092 mmol) and BOP (44 mg, 0.10 mmol) in DMF (1 mL) was added 2,2,2-trifluoroethyl 2-(aminomethyl)-5-chlorobenzofuran-7-carboxylate, TFA (30 mg, 0.071 mmol) and DIPEA (0.05 mL, 0.285 mmol). The reaction mixture became a clear solution and was stirred at rt for 4 h. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in DMF, filtered and purified by preparative LC/MS (Method B). Fractions containing the desired product were combined and dried via centrifugal evaporation to give the title compound (32 mg, 99%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.17 (br s, 1H), 8.75 (br d, *J* = 4.4 Hz, 1H), 8.44 - 8.19 (m, 2H), 8.01 (s, 1H), 7.76 (s, 1H), 7.47 (dd, *J* = 9.3, 4.5 Hz, 1H), 6.94 (s, 1H), 4.99 (q, *J* = 8.8 Hz, 2H), 4.85 (br d, *J* = 5.7 Hz, 2H); MS (ESI+) *m/z* = 453.1 (M+H)⁺.

20

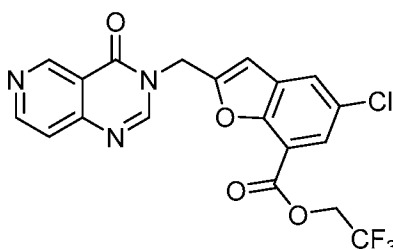
EXAMPLE 370



2,2,2-Trifluoroethyl 5-chloro-2-((1-oxo-3,4-dihydro-2,7-naphthyridin-2(1H)-yl)methyl)benzofuran-7-carboxylate

3,4-Dihydro-1*H*-pyrano[3,4-*c*]pyridin-1-one, HCl (18.40 mg, 0.099 mmol) and 2,2,2-trifluoroethyl 2-(aminomethyl)-5-chlorobenzofuran-7-carboxylate, TFA salt (38 mg, 0.090 mmol, Step C in Example 369) were taken up in Pyridine (0.8 mL) in a sealed tube. The reaction vessel was sealed and heated at 125 °C for 18 hours. The reaction mixture diluted with saturated NaHCO₃ solution and extracted with ethyl acetate. The combined organic extracts were concentrated *in vacuo*. The residue was dissolved in MeOH, filtered, and purified *via* HPLC (method B) to give the title compound (3.4 mg, 9% yield). ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.95 (br s, 1H), 8.61 (br d, *J* = 3.4 Hz, 1H), 8.05 (d, *J* = 2.1 Hz, 1H), 7.78 (d, *J* = 2.1 Hz, 1H), 7.38 (d, *J* = 4.9 Hz, 1H), 7.02 (s, 1H), 5.01 (q, *J* = 9.1 Hz, 2H), 4.93 (s, 2H), 3.74 (t, *J* = 6.6 Hz, 2H), 3.07 (t, *J* = 6.6 Hz, 2H); MS (ESI+) *m/z* = 439.1 (M+H)⁺.

EXAMPLE 371

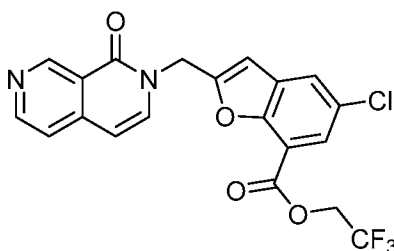


15 2,2,2-Trifluoroethyl 5-chloro-2-((4-oxopyrido[4,3-*d*]pyrimidin-3(4*H*)-yl)methyl)benzofuran-7-carboxylate

A mixture of 4-aminonicotinic acid (20.4 mg, 0.148 mmol), and 1,1-dimethoxy-*N,N*-dimethylmethanamine (0.12 mL, 0.91 mmol) in DMF (0.5 mL) in a microwave tube was heated in a microwave reactor at 100 °C for 15 min. The reaction mixture was concentrated *in vacuo*. To the residue was added 1 mL of acetic acid and 2,2,2-trifluoroethyl 2-(aminomethyl)-5-chlorobenzofuran-7-carboxylate, TFA (48 mg, 0.114 mmol, Step C in Example 369) in acetic acid (2 mL) and the mixture was again heated in a microwave at 110 °C for 15 min. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in DMF, filtered and purified by preparative HPLC (Method B). Fractions containing the desired product were combined and dried *via* centrifugal evaporation to give the title compound (13.7 mg, 27%). ¹H NMR (500 MHz, DMSO-*d*₆) δ

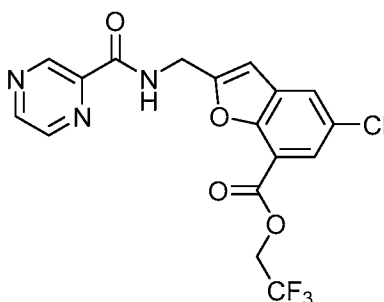
9.32 (s, 1H), 8.86 (d, $J = 5.6$ Hz, 1H), 8.69 (s, 1H), 8.05 (d, $J = 2.1$ Hz, 1H), 7.79 (d, $J = 2.1$ Hz, 1H), 7.63 (d, $J = 5.6$ Hz, 1H), 7.08 (s, 1H), 5.48 (s, 2H), 4.97 (q, $J = 8.9$ Hz, 2H); MS (ESI+) $m/z = 437.9$ (M+H)⁺.

5

EXAMPLE 372**2,2,2-Trifluoroethyl 5-chloro-2-((1-oxo-2,7-naphthyridin-2(1H)-yl)methyl)benzofuran-7-carboxylate**

A mixture of methyl 4-methylnicotinate (25.1 mg, 0.166 mmol), and 1,1-dimethoxy-N,N-dimethylmethanamine (0.18 mL, 1.33 mmol) in DMF (0.5 mL) in a
10 microwave vial was heated in a microwave reactor at 140 °C for 30 min. The reaction mixture was concentrated *in vacuo*. The residue was mixed with acetic acid (0.5 mL) and 2,2,2-trifluoroethyl 2-(aminomethyl)-5-chlorobenzofuran-7-carboxylate, TFA (35 mg, 0.083 mmol, Step C in Example 369) and heated again in a microwave reactor at 110 °C
15 for 18 min. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in DMF, filtered and purified by preparative HPLC (Method B). Fractions containing the desired product were combined and dried via centrifugal evaporation to give the title compound (7.5 mg, 20.5%). ¹H NMR (500 MHz, DMSO-d₆) δ 9.33 (br s, 1H), 8.72 (br s, 1H), 8.05 (s, 1H), 7.86 - 7.74 (m, 2H), 7.62 (br d, $J = 5.2$ Hz, 1H), 7.00 (s, 1H), 6.72 (d, $J = 7.3$ Hz, 1H), 5.43 (s, 2H), 4.97 (q, $J = 8.9$ Hz, 2H); MS (ESI+) $m/z = 437.1$ (M+H)⁺.
20

EXAMPLE 373



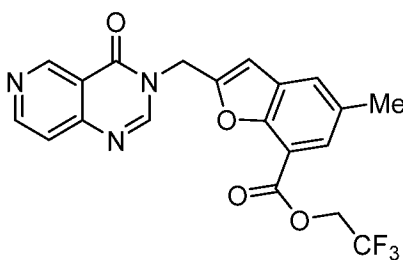
2,2,2-Trifluoroethyl 5-chloro-2-((pyrazine-2-carboxamido)methyl)benzofuran-7-carboxylate

5 To solution of pyrazine-2-carboxylic acid (10.59 mg, 0.085 mmol) and BOP (37.8 mg, 0.085 mmol) in DMF (1 mL) were added 2,2,2-trifluoroethyl 2-(aminomethyl)-5-chlorobenzofuran-7-carboxylate TFA salt (30 mg, 0.071 mmol, Step C of Example 369) and DIPEA (0.075 mL, 0.427 mmol). The reaction mixture was stirred at rt for 1 h. LC-MS showed new peak at $t_r = 0.94$ min, $[M+H]^+ = 414.2$ as the desired product peak. The

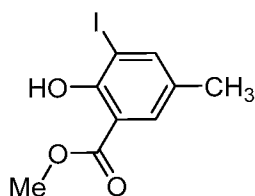
10 reaction mixture was concentrated *in vacuo* and the residue was dissolved in DMF, filtered and purified by preparative HPLC (Method B). Fractions containing the desired product were combined and dried *via* centrifugal evaporation to give the title compound (26 mg, 69%). $^1\text{H NMR}$ (500 MHz, DMSO- d_6) δ 9.58 (br t, $J = 5.8$ Hz, 1H), 9.23 (s, 1H), 8.91 (d, $J = 2.4$ Hz, 1H), 8.77 (s, 1H), 8.04 (d, $J = 1.8$ Hz, 1H), 7.77 (d, $J = 1.8$ Hz, 1H),

15 6.89 (s, 1H), 5.04 (q, $J = 8.9$ Hz, 2H), 4.74 (d, $J = 5.8$ Hz, 2H); MS (ESI+) $m/z = 414.2$ (M+H) $^+$.

EXAMPLE 374

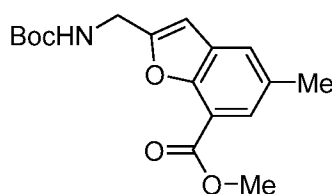


20 **2,2,2-Trifluoroethyl 5-methyl-2-((4-oxopyrido[4,3-*d*]pyrimidin-3(4*H*)-yl)methyl)benzofuran-7-carboxylate**



A) Methyl-2-hydroxy-3-iodo-5-methylbenzoate

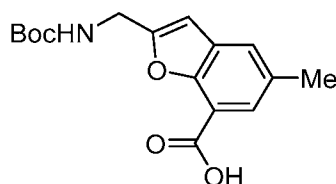
To a solution of methyl 5-methylsalicylate (5 g, 30.1 mmol) in *N,N*-
 5 dimethylformamide (40 mL) was added sodium iodide (5.41 g, 36.1 mmol) followed by
 chloramine T trihydrate (10.17 g, 36.1 mmol) slowly in portions. The reaction was stirred
 at room temperature for 3 hours. The reaction mixture was quenched with ethyl acetate
 and 1N aqueous HCl solution. The organic layer was separated, washed with saturated
 aqueous sodium chloride solution followed by 10% aqueous Na₂S₂O₃ solution, and dried
 10 with anhydrous sodium sulfate. The dried organic extracts were filtered and concentrated
in vacuo. The crude product mixture was purified by a silica gel ISCO 120 g column
 eluting with 0 - 20% ethyl acetate / hexane over a 15 minute gradient. The appropriate
 fractions were isolated and concentrated *in vacuo* to afford the product (8.2 g, 93% yield)
 as a solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 11.52 - 11.27 (m, 1H), 7.86 - 7.72 (m,
 15 1H), 7.72 - 7.52 (m, 1H), 4.09 - 3.89 (m, 3H), 2.39 - 2.08 (m, 3H); MS (ESI+) *m/z* =
 293.1 (M+H)⁺.



**B) Methyl 2-(((*tert*-butoxycarbonyl)amino)methyl)-5-methylbenzofuran-
 20 7-carboxylate**

A 100 ml flask was charged with methyl 2-hydroxy-3-iodo-5-methylbenzoate (8.2
 g, 28.1 mmol), *tert*-butyl prop-2-yn-1-ylcarbamate (5.01 g, 32.3 mmol), and copper(I)
 iodide (0.428 g, 2.25 mmol) in DMF (20 mL) and TEA (30 mL). The reaction was
 purged with nitrogen, then bis(triphenylphosphine)palladium(II) chloride (0.985 g, 1.404

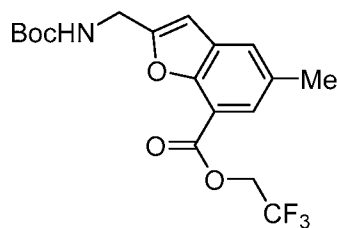
mmol) was added. The resulting mixture was heated at 80 °C for 4 hours. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate, washed with saturated aqueous sodium bicarbonate solution followed by saturated aqueous sodium chloride solution, dried with anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude product mixture was purified by a silica gel ISCO 80 g column eluting with 0-35 % ethyl acetate / hexane over a 15 minute gradient. The appropriate fractions were isolated and concentrated *in vacuo* to afford the title compound (6 g, 67 % yield) as a light brown solid. ¹H NMR (400 MHz, Chloroform-d) δ 7.86 - 7.66 (m, 1H), 7.63 - 7.38 (m, 1H), 6.75 - 6.43 (m, 1H), 4.62 - 4.43 (m, 2H), 4.20 - 3.75 (m, 3H), 2.70 - 2.16 (m, 3H), 1.55 - 1.28 (m, 9H) ; MS (ESI+) m/z = 264.1 (M-55+H)⁺.



C) 2-(((*tert*-Butoxycarbonyl)amino)methyl)-5-methylbenzofuran-7-carboxylic acid

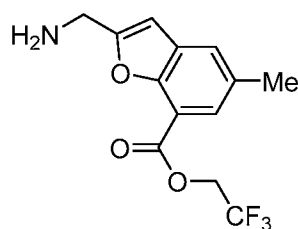
A flask was charged with methyl 2-(((*tert*-butoxycarbonyl)amino)methyl)-5-methylbenzofuran-7-carboxylate (1.0 g, 3.13 mmol), THF (6 mL) and MeOH (6 mL). To the reaction was added aqueous LiOH (2 M, 9.39 mL, 18.8 mmol). The reaction mixture was stirred at room temperature for 3 hours. The solution was concentrated *in vacuo*, acidified with 1N aqueous HCl to pH 2, and extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution, dried with anhydrous sodium sulfate, filtered and concentrated *in vacuo* to give a light brown solid (1.0 g, 100% yield). ¹H NMR (400 MHz, Methanol-d₄) δ 7.81 - 7.65 (m, 1H), 7.63 - 7.50 (m, 1H), 6.74 - 6.50 (m, 1H), 4.50 - 4.27 (m, 2H), 2.57 - 2.41 (m, 3H), 1.60 - 1.39 (m, 9H) ; MS (ESI+) m/z = 270.1 (M-55+H)⁺.

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D) 2,2,2-Trifluoroethyl 2-(((tert-butoxycarbonyl)amino)methyl)-5-methylbenzofuran-7-carboxylate

A 25 ml flask was charged with 2-(((tert-butoxycarbonyl)amino)methyl)-5-methylbenzofuran-7-carboxylic acid (0.6 g, 1.97 mmol) in DMF (8 mL). BOP (0.956 g, 2.16 mmol), 2,2,2-trifluoroethanol (0.23 mL, 3.14 mmol) and DIPEA (0.55 mL, 3.14 mmol) were added. The reaction mixture was stirred at room temperature for 16 hours, then at 60 °C for 3 hours. After cooling to RT, the reaction mixture was diluted with ethyl acetate, washed with saturated aqueous sodium bicarbonate solution followed by saturated aqueous sodium chloride solution, dried with anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude product mixture was purified by a silica gel ISCO 40 g column eluting with 0-30% ethyl acetate in hexanes over a 15 minute gradient. The appropriate fractions were isolated and concentrated *in vacuo* to afford the product (0.7 g, 92% yield) as a solid. ¹H NMR (400 MHz, Chloroform-d) δ 7.81 - 7.70 (m, 1H), 7.63 - 7.54 (m, 1H), 6.83 - 6.48 (m, 1H), 4.91 - 4.69 (m, 2H), 4.64 - 4.39 (m, 2H), 2.57 - 2.43 (m, 3H), 1.56 - 1.48 (m, 9H); MS (ESI+) m/z = 332.1 (M-55+H)⁺.



E) 2,2,2-Trifluoroethyl 2-(aminomethyl)-5-methylbenzofuran-7-carboxylate, TFA salt

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To a solution of 2,2,2-trifluoroethyl 2-(((tert-butoxycarbonyl)amino)methyl)-5-methylbenzofuran-7-carboxylate (0.7 g, 1.81 mmol) in CH₂Cl₂ (8 mL) was added TFA (1.67 mL, 21.7 mmol). The reaction mixture was stirred at RT for 2

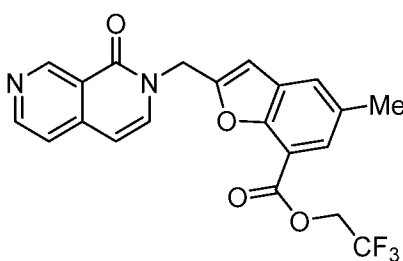
hours. The reaction mixture was concentrated *in vacuo* to afford the product 2,2,2-trifluoroethyl 2-(aminomethyl)-5-methylbenzofuran-7-carboxylate (0.677 g, 93 % yield) as a solid. ¹H NMR (400 MHz, Methanol-d₄) δ 7.87 (d, *J* = 1.7 Hz, 1H), 7.80 (dd, *J* = 1.7, 0.8 Hz, 1H), 7.04 (s, 1H), 5.01 - 4.87 (m, 2H), 4.40 (s, 2H), 2.52 (s, 3H); MS (ESI+) *m/z* = 271.0 (M-16)⁺.

F) 2,2,2-Trifluoroethyl 5-methyl-2-((4-oxopyrido[4,3-*d*]pyrimidin-3(4*H*)-yl)methyl)benzofuran-7-carboxylate

A mixture of 4-aminonicotinic acid (23.1 mg, 0.167 mmol), and N,N-dimethylformamide dimethyl acetal (0.128 mL, 0.957 mmol) in DMF (0.5 mL) in a microwave vial was heated at 100°C in the microwave for 15 min. The reaction mixture was concentrated *in vacuo*. To the residue was added 0.5 mL of acetic acid and 2,2,2-trifluoroethyl 2-(aminomethyl)-5-methylbenzofuran-7-carboxylate, TFA salt (48 mg, 0.120 mmol) and the mixture was heated at 110°C in the microwave for 15 min. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in MeOH, and white precipitate formed. The solid was filtered to yield the title compound (10 mg, 19 % yield). ¹H NMR (400 MHz, Chloroform-*d*) δ 9.55 (s, 1H), 8.88 (d, *J* = 5.6 Hz, 1H), 8.50 (s, 1H), 7.82 (d, *J* = 1.2 Hz, 1H), 7.66 - 7.54 (m, 2H), 6.91 (s, 1H), 5.38 (m, 2H), 4.78 (q, *J* = 8.4 Hz, 2H), 2.49 (s, 3H); MS (ESI+) *m/z* = 418.0 (M+H)⁺.

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EXAMPLE 375



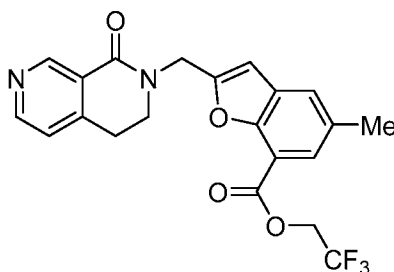
2,2,2-Trifluoroethyl 5-methyl-2-((1-oxo-2,7-naphthyridin-2(1*H*)-yl)methyl)benzofuran-7-carboxylate

A mixture of methyl 4-methylnicotinate (56.5 mg, 0.374 mmol), N,N-dimethylformamide dimethyl acetal (0.267 mL, 1.99 mmol) in DMF (0.5 mL) was heated

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in the microwave at 150°C for 60 minutes. The reaction mixture was concentrated *in vacuo*. The residue was mixed with acetic acid (0.5 mL) and 2,2,2-trifluoroethyl 2-(aminomethyl)-5-methylbenzofuran-7-carboxylate, TFA (50 mg, 0.125 mmol, Step E of Example 374) and heated in the microwave at 120°C for 30 minutes. The reaction mixture was concentrated *in vacuo*. The crude material was purified via preparative HPLC (Method C), to afford the product (24 mg, 44% yield) as a solid. ¹H NMR (400 MHz, Chloroform-d) δ 9.62 (s, 1H), 8.74 (d, J = 5.5 Hz, 1H), 7.81 (d, J = 1.2 Hz, 1H), 7.69 - 7.59 (m, 2H), 7.41 - 7.30 (m, 1H), 6.87 (s, 1H), 6.52 (d, J = 7.5 Hz, 1H), 5.37 (s, 2H), 4.79 (q, J = 8.5 Hz, 2H), 2.48 (s, 3H); MS (ESI+) m/z = 417.0 (M+H)⁺.

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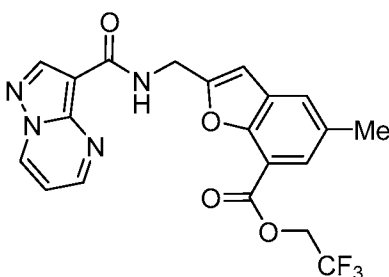
EXAMPLE 376

2,2,2-Trifluoroethyl 5-methyl-2-((1-oxo-3,4-dihydro-2,7-naphthyridin-2(1H)-yl)methyl)benzofuran-7-carboxylate

3,4-Dihydro-1H-pyrano[3,4-c]pyridin-1-one hydrochloride (24.1 mg, 0.13 mmol) (WO 2005063768) and 2,2,2-trifluoroethyl 2-(aminomethyl)-5-methylbenzofuran-7-carboxylate TFA salt (50 mg, 0.13 mmol, Step E of Example 374) were added to a pressure relief vial with pyridine (100 uL) and heated to 120 °C. After 4 hours, the reaction was cooled, concentrated *in vacuo* to remove pyridine, taken up in DMF, filtered, and purified *via* HPLC (Method B) to give 2,2,2-trifluoroethyl 5-methyl-2-((1-oxo-3,4-dihydro-2,7-naphthyridin-2(1H)-yl)methyl)benzofuran-7-carboxylate (13.1 mg, 0.031 mmol, 23.6 % yield). ¹H NMR (500 MHz, DMSO-d₆) δ 8.94 (s, 1H), 8.60 (br d, J = 4.5 Hz, 1H), 7.74 (s, 1H), 7.66 (s, 1H), 7.36 (d, J = 4.9 Hz, 1H), 6.93 (s, 1H), 4.99 (q, J = 8.7 Hz, 2H), 4.90 (s, 2H), 3.72 (br t, J = 6.2 Hz, 2H), 3.05 (br t, J = 6.3 Hz, 2H), 2.42 (s, 3H); MS (ESI+) m/z 419.2 (M+H)⁺.

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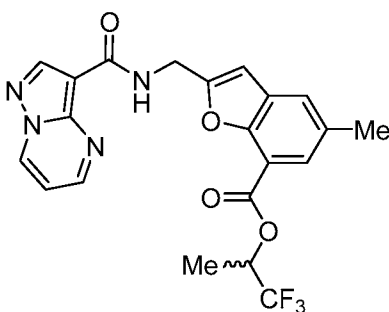
EXAMPLE 377



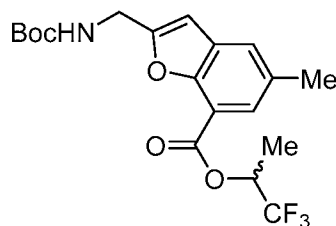
2,2,2-Trifluoroethyl 5-methyl-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate

- 5 To a suspension of pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (15 mg, 0.092 mmol) and BOP (31.3 mg, 0.071 mmol) in DMF (2 mL) was added 2,2,2-trifluoroethyl 2-(aminomethyl)-5-methylbenzofuran-7-carboxylate, TFA salt (28.4 mg, 0.071 mmol, Step E of Example 374) and DIPEA (0.049 mL, 0.283 mmol). The reaction mixture turned into a clear solution and was stirred at room temperature for 2 hours. The reaction mixture
- 10 was quenched with water, extracted with DCM, dried with anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified *via* preparative HPLC (Method C) to give the title compound as a solid (23.5 mg, 73% yield). ¹H NMR (400 MHz, Methanol-*d*₄) δ 9.10 (dd, *J* = 7.0, 1.7 Hz, 1H), 8.79 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.62 (s, 1H), 7.75 (d, *J* = 1.2 Hz, 1H), 7.67 (dd, *J* = 1.6, 0.7 Hz, 1H), 7.23 (dd, *J* = 7.0, 4.2 Hz,
- 15 1H), 6.78 (t, *J* = 0.9 Hz, 1H), 4.91 - 4.87 (m, 4H), 2.48 (s, 3H); MS (ESI+) *m/z* = 433.0 (M+H)⁺.

EXAMPLE 378



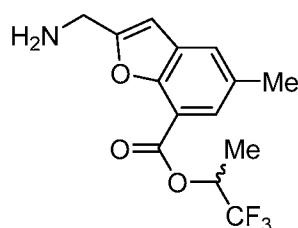
1,1,1-Trifluoropropan-2-yl 5-methyl-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate



A) 1,1,1-Trifluoropropan-2-yl 2-(((tert-butoxycarbonyl)amino)methyl)-5-methylbenzofuran-7-carboxylate

To a scintillation vial was added 2-(((tert-butoxycarbonyl)amino)methyl)-5-methylbenzofuran-7-carboxylic acid (450 mg, 1.474 mmol, Step C of Example 374), 1,1,1-trifluoropropan-2-ol (0.534 mL, 5.90 mmol), and DIPEA (1.03 mL, 5.90 mmol) in DMF (10 mL). To the solution was added BOP (978 mg, 2.21 mmol) and the reaction stirred at room temperature for 16 hours. The reaction mixture was diluted with ethyl acetate, washed with saturated aqueous sodium bicarbonate solution, water and saturated aqueous sodium chloride solution, dried with anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude product mixture was purified by a silica gel ISCO 80 g column eluting with 0-100% ethyl acetate in hexanes over a 15 minute gradient. The appropriate fractions were isolated and concentrated *in vacuo* to afford the product (0.233 g, 39% yield) as a solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.76 - 7.71 (m, 1H), 7.57 (s, 1H), 6.61 (s, 1H), 5.61 (dt, *J* = 13.2, 6.6 Hz, 1H), 4.51 (br d, *J* = 5.3 Hz, 2H), 2.49 (s, 3H), 1.59 (d, *J* = 6.6 Hz, 3H), 1.48 (s, 9H); MS (ESI+) *m/z* = 346.0 (M-55+H)⁺.

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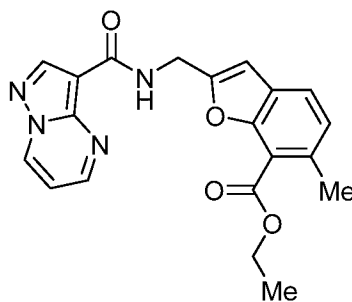
B) 1,1,1-Trifluoropropan-2-yl 2-(aminomethyl)-5-methylbenzofuran-7-carboxylate, TFA salt

To a solution of 1,1,1-trifluoropropan-2-yl 2-(((*tert*-butoxycarbonyl)amino)methyl)-5-methylbenzofuran-7-carboxylate (0.233 g, 0.58 mmol) in CH₂Cl₂ (5 mL) was added TFA (1.0 mL). The reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated *in vacuo* to afford the crude product 2,2,2-trifluoroethyl 2-(aminomethyl)-5-methylbenzofuran-7-carboxylate (0.245 g, 40 % yield) as a solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.73 (s, 1H), 7.56 (s, 1H), 6.78 (s, 1H), 5.51 (dt, *J* = 12.6, 6.3 Hz, 1H), 4.40 (br s, 2H), 2.46 (s, 3H), 1.59 - 1.48 (m, 3H); MS (ESI+) *m/z* = 302.0 (M-16)⁺.

10 **C) 1,1,1-Trifluoropropan-2-yl 5-methyl-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate**

To a solution of pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (100 mg, 0.613 mmol) and 1,1,1-trifluoropropan-2-yl 2-(aminomethyl)-5-methylbenzofuran-7-carboxylate, TFA salt (255 mg, 0.613 mmol) in DMF (2 mL) was added BOP (407 mg, 0.919 mmol) and DIPEA (0.428 mL, 2.452 mmol). The reaction mixture was stirred at room temperature for 2 hours.. The reaction was quenched with water, the precipitate that was resulted was filtered, then dissolved in 2 mL of DMF for purification. The crude material was purified *via* preparative HPLC (Method B) to afford the product (35.3 mg, 13 % yield). ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.24 (br d, *J* = 5.9 Hz, 1H), 8.79 (br d, *J* = 3.5 Hz, 1H), 8.60 (s, 1H), 8.45 (br s, 1H), 7.71 (s, 1H), 7.62 (s, 1H), 7.26 (dd, *J* = 6.7, 4.4 Hz, 1H), 6.82 (s, 1H), 5.73 - 5.65 (m, 1H), 4.79 (br d, *J* = 5.8 Hz, 2H), 2.43 (s, 3H), 1.48 (br d, *J* = 6.6 Hz, 3H); MS (ESI+) *m/z* = 447.1 (M+H)⁺.

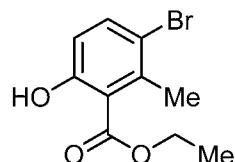
EXAMPLE 379



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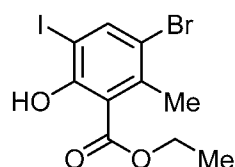
370

Ethyl 6-methyl-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate



5 **A) Ethyl 3-bromo-6-hydroxy-2-methylbenzoate**

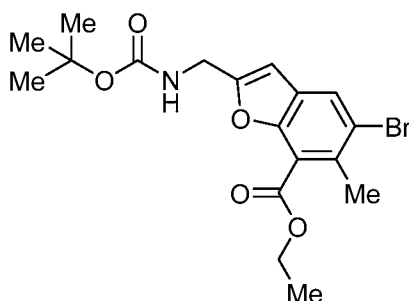
To a solution of ethyl 2-hydroxy-6-methylbenzoate (1.0 g, 5.55 mmol) in DCM (10 mL) was added CaCO₃ (0.66 g, 6.66 mmol) and bromine (0.3 mL, 5.83 mmol) in DCM (2 mL) at 0 °C very slowly over 40 min. The reaction mixture was stirred at rt for 1h. The reaction mixture was diluted with water and ethyl acetate. The organic layer was separated, washed with brine and Na₂S₂O₃ solution successively, dried over MgSO₄, and filtered. The filtrate was concentrated *in vacuo* to give the title compound as a light yellow oil (1.4 g, 97%). The crude product was dried on high vacuum for 1 hour and during this time, the product solidified. ¹H NMR (400 MHz, Chloroform-*d*) δ 10.85 (s, 1H), 7.59 (d, *J* = 8.8 Hz, 1H), 6.90 - 6.67 (m, 1H), 4.49 (q, *J* = 7.2 Hz, 2H), 2.67 (s, 3H), 1.51 - 1.41 (m, 3H); MS (ESI+) *m/z* = 261 (M+H)⁺.



20 **B) Ethyl 3-bromo-6-hydroxy-5-iodo-2-methylbenzoate**

To a solution of ethyl 3-bromo-6-hydroxy-2-methylbenzoate (1.8 g, 6.95 mmol) in *N,N*-dimethylformamide (10 mL) was added sodium iodide (1.25 g, 8.34 mmol) followed by chloramine T trihydrate (2.15 g, 7.64 mmol) slowly. The resulting mixture was stirred at rt for 2 h. The reaction mixture was diluted with ethyl acetate and 1 N aqueous HCl solution. The organic layer was separated and washed with brine followed by Na₂S₂O₃ solution, dried over MgSO₄, and filtered. The filtrate was concentrated *in vacuo* to give a light yellow solid. The solid was re-crystallized from MeOH and DCM to give the

desired product as a white solid. The filtrate was concentrated *in vacuo* and the residue was dissolved in DCM and purified by flash chromatography (ISCO column 40 g, 0 - 20% ethyl acetate in hexanes). The purified product was combined with the crystallized solid to give the title compound (2.3 g, 86%) as a white solid. ¹H NMR (400 MHz, Chloroform-d) δ 11.53 (s, 1H), 8.10 (s, 1H), 4.50 (q, $J = 7.2$ Hz, 2H), 2.64 (s, 3H), 1.46 (t, $J = 7.2$ Hz, 3H); MS (ESI+) $m/z = 386.6$ (M+H)⁺.

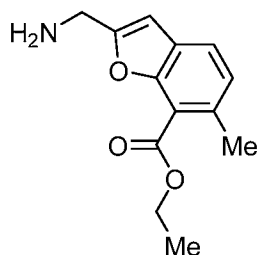


C) Ethyl 5-bromo-2-(((*tert*-butoxycarbonyl)amino)methyl)-6-methylbenzofuran-7-carboxylate

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A mixture of ethyl 3-bromo-6-hydroxy-5-iodo-2-methylbenzoate (2.2 g, 5.71 mmol), *tert*-butyl prop-2-yn-1-ylcarbamate (1.02 g, 6.57 mmol), TEA (15.93 mL, 114 mmol), and copper(I) iodide (0.11 g, 0.57 mmol) in DMF (8 mL) was purged with a nitrogen stream for 6 mins. Bis(triphenylphosphine) palladium(II) chloride (0.40 g, 0.57 mmol) was then added. The resulting mixture was heated at 80 °C for 3h. The reaction mixture was then cooled down and diluted with ethyl acetate and saturated aqueous NaHCO₃ solution. The organic layer was separated, washed with brine, dried over MgSO₄, and filtered. The filtrate was concentrated *in vacuo* and the residue was dissolved in DCM and purified by flash chromatography (ISCO column 120 g, 0 - 25% ethyl acetate in hexanes) to give the title compound (1.9 g, 81%) as a light brown oily solid. ¹H NMR (500 MHz, Chloroform-d) δ 7.82 (s, 1H), 6.55 (s, 1H), 5.15 - 4.91 (m, 1H), 4.59 - 4.47 (m, 2H), 4.47 - 4.39 (m, 2H), 2.59 (s, 3H), 1.50 - 1.41 (m, 12H); MS (ESI+) $m/z = 358.0$ (M-55+H)⁺.

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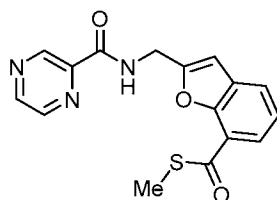
D) Ethyl 2-(aminomethyl)-6-methylbenzofuran-7-carboxylate

To a mixture of ethyl 5-bromo-2-(((*tert*-butoxycarbonyl)amino) methyl)-6-methylbenzofuran-7-carboxylate (2.0 g, 4.85 mmol) in MeOH (20 mL) and ethyl acetate (6 mL) was added palladium hydroxide on carbon (20% on carbon, 0.34 g, 0.485 mmol). The mixture was evacuated and then flushed with hydrogen three times (balloon). The reaction mixture was stirred under a hydrogen atmosphere for 6 hours. The reaction mixture was filtered through a celite pad and the filtrate was concentrated *in vacuo*. The residue was resubjected to hydrogenation. To a mixture of ethyl 5-bromo-2-(((*tert*-butoxycarbonyl)amino)methyl)-6-methylbenzofuran-7-carboxylate (2.0 g, 4.85 mmol) in MeOH (20 mL) was added palladium hydroxide on carbon (20% on carbon, 0.341 g, 0.485 mmol). The reaction mixture was evacuated and then filled with hydrogen (balloon) and stirred under a hydrogen atmosphere for another 6 hours. The reaction mixture was filtered through a celite pad and the filtrate was concentrated *in vacuo* to give the desired des-bromo intermediate. To the crude intermediate in DCM (8 mL) was added TFA (3.0 mL, 38.8 mmol). The reaction mixture was stirred at room temperature for 3 hours. The reaction mixture was concentrated *in vacuo* and the residue was mixed with ethyl acetate and saturated aqueous NaHCO₃ solution. The organic layer was separated, washed with brine, dried over MgSO₄, and filtered. The filtrate was concentrated *in vacuo* to give the crude title compound as a brown oil (0.8 g, 71%). ¹H NMR (500 MHz, Chloroform-d) δ 7.47 (d, *J* = 7.9 Hz, 1H), 7.09 (d, *J* = 7.9 Hz, 1H), 6.53 (s, 1H), 4.49 (q, *J* = 7.2 Hz, 2H), 4.05 (s, 2H), 2.65 - 2.58 (s, 3H), 1.46 (t, *J* = 7.2 Hz, 3H); MS (ESI+) *m/z* = 467.2 (2M+H)⁺.

E) Ethyl 6-methyl-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido) methyl)benzofuran-7-carboxylate

To a suspension of pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (109 mg, 0.67 mmol) and BOP (319 mg, 0.720 mmol) in DMF (3 mL) was added ethyl 2-(aminomethyl)-6-methylbenzofuran-7-carboxylate (120 mg, 0.514 mmol) and DIPEA (0.36 mL, 2.06 mmol). The reaction mixture turned into a clear solution after addition of the amine and was stirred at room temperature for 4 hours. The reaction mixture was diluted with water, ethyl acetate, and saturated aqueous NaHCO₃ solution. The organic layer was separated, washed with brine, dried over MgSO₄, and filtered. The filtrate was concentrated *in vacuo*. The residue was triturated with MeOH and filtered to give the title compound as a white solid (110 mg, 61%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.26 (br d, *J* = 6.7 Hz, 1H), 8.80 (br d, *J* = 3.5 Hz, 1H), 8.61 (s, 1H), 8.46 - 8.29 (m, 1H), 7.60 (d, *J* = 7.9 Hz, 1H), 7.27 (dd, *J* = 6.7, 4.3 Hz, 1H), 7.15 (d, *J* = 7.9 Hz, 1H), 6.78 (s, 1H), 4.77 (br d, *J* = 5.8 Hz, 2H), 4.36 (q, *J* = 7.0 Hz, 2H), 2.48 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H); MS (ESI+) *m/z* = 379.3 (M+H)⁺.

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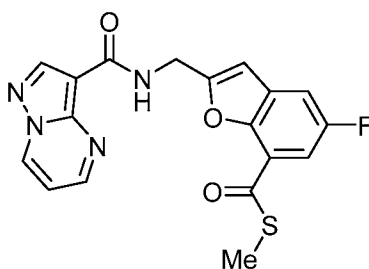
EXAMPLE 381**S-Methyl 2-((pyrazine-2-carboxamido)methyl)benzofuran-7-carbothioate**

To a suspension of 2-((pyrazine-2-carboxamido)methyl)benzofuran-7-carboxylic acid (30 mg, 0.101 mmol, Example 130) in DCE (2 mL) was added oxalyl chloride (25.6 mg, 0.202 mmol) and 2 drops of DMF. The reaction mixture was stirred at room temperature for 5 hours. The reaction mixture was concentrated *in vacuo* and dried on high vacuum for 15 minutes. To the residue was added DCE (2 mL) followed by sodium thiomethoxide (14.15 mg, 0.202 mmol), and DIPEA (0.035 mL, 0.202 mmol). The reaction mixture was stirred at room temperature overnight. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in DMF, filtered, and purified *via* HPLC (method B) to give the title compound (2.3 mg, 5%). ¹H NMR (500 MHz, DMSO-

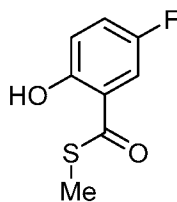
25

d₆) δ 9.43 (br t, $J = 5.4$ Hz, 1H), 9.20 (s, 1H), 8.86 (d, $J = 2.2$ Hz, 1H), 8.73 (s, 1H), 7.87 (d, $J = 7.7$ Hz, 1H), 7.78 (d, $J = 7.6$ Hz, 1H), 7.36 (t, $J = 7.7$ Hz, 1H), 6.88 (s, 1H), 4.74 (d, $J = 6.1$ Hz, 2H), 2.46 (s, 3H); MS (ESI+) $m/z = 328.3$ (M+H)⁺.

5

EXAMPLE 382

***S*-Methyl 5-fluoro-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carbothioate**



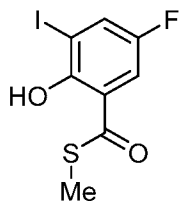
10

A) *S*-Methyl 5-fluoro-2-hydroxybenzothioate

To 5-fluoro-2-hydroxybenzoic acid (1.6 g, 10.3 mmol) was added thionyl chloride (5.24 mL, 71.7 mmol) and a few drops of DMF. The reaction mixture was stirred at room temperature for 3 hours. The reaction mixture was concentrated *in vacuo*. Toluene was added to remove excess solvents to give a white solid. To the solid was added DCE (30 mL), sodium methanethiolate (0.79 g, 11.3 mmol), and then TEA (4.29 mL, 30.7 mmol). The reaction mixture was stirred at room temperature for 26 hours. The reaction mixture was diluted with brine and DCM. The organic layer was separated, washed with brine, and dried over MgSO₄. The filtrate was concentrated *in vacuo*. The residue was dissolved in DCM and purified by flash chromatography (ISCO 40g column, 0 - 15% ethyl acetate in hexanes) to give the title compound (1.1 g, 58% yield) as a white solid. ¹H NMR (400

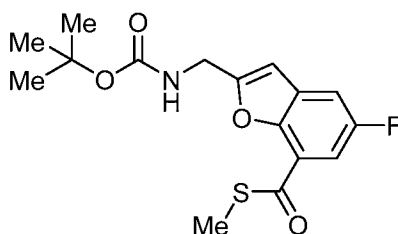
20

MHz, CHLOROFORM-*d*) δ 10.83 (s, 1H), 7.57 (dd, $J = 8.9, 3.0$ Hz, 1H), 7.22 (ddd, $J = 9.1, 7.7, 3.0$ Hz, 1H), 6.97 (dd, $J = 9.1, 4.5$ Hz, 1H), 2.52 (s, 3H).



5 **B) *S*-Methyl 5-fluoro-2-hydroxy-3-iodobenzothioate**

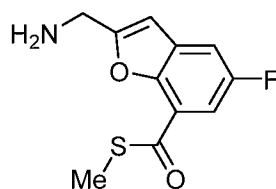
To a solution of *S*-methyl 5-fluoro-2-hydroxybenzothioate (1.1 g, 5.9 mmol) in *N,N*-dimethylformamide (15 mL) was added sodium iodide (1.06 g, 7.1 mmol), followed by chloramine T trihydrate (1.83 g, 6.5 mmol) in several batches. The resulting mixture turned brown and was stirred at room temperature for 20 hours. The reaction mixture was diluted with ethyl acetate and saturated aqueous NaHCO₃ solution. The organic layer was separated, washed with brine followed by Na₂S₂O₃ solution, and dried over MgSO₄. The filtrate was concentrated *in vacuo* to give a light yellow solid. The residue was mixed with MeOH and the resulting mixture was filtered to give the title compound as a white solid (1.1 g, 60%). ¹H NMR (400 MHz, CHLOROFORM-*d*) δ 11.72 (s, 1H), 7.74 (dd, $J = 7.2, 2.9$ Hz, 1H), 7.63 (dd, $J = 8.5, 2.9$ Hz, 1H), 2.54 (s, 3H).



20 **C) *S*-Methyl 2-(((*tert*-butoxycarbonyl)amino)methyl)-5-fluorobenzofuran-7-carbothioate**

A mixture of *S*-methyl 5-fluoro-2-hydroxy-3-iodobenzothioate (1.1 g, 3.52 mmol), *tert*-butyl prop-2-yn-1-ylcarbamate (0.63 g, 4.05 mmol), TEA (7.37 mL, 52.9 mmol), and copper(I) iodide (0.067 g, 0.352 mmol) in DMF (8 mL) was purged with a stream of nitrogen for 5 mins. Bis(triphenylphosphine)palladium(II) chloride (0.124 g, 0.176 mmol)

was then added. The resulting mixture was heated at 80 °C for 2 hours. The reaction was cooled down and stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate and saturated aqueous NaHCO₃ solution. The organic layer was separated, washed with brine, dried over MgSO₄, and filtered. The filtrate was concentrated *in vacuo*. The residue was dissolved in DCM and purified by flash chromatography (ISCO 40g column, 0 - 20% ethyl acetate in hexanes) to give the title compound (0.86 g, 72% yield) as a light brown oily solid. ¹H NMR (400 MHz, Chloroform-d) δ 7.60 (dd, *J* = 9.5, 2.6 Hz, 1H), 7.41 (dd, *J* = 7.8, 2.6 Hz, 1H), 6.68 (s, 1H), 5.21 - 4.98 (m, 1H), 4.53 (br d, *J* = 5.9 Hz, 2H), 2.56 (s, 3H), 1.49 (s, 9H); MS (ESI+) *m/z* = 284.0 (M-55+H)⁺.



D) S-Methyl 2-(aminomethyl)-5-fluorobenzofuran-7-carbothioate

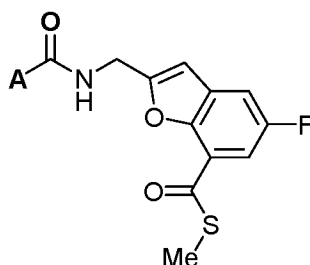
To a solution of *S*-methyl 2-(((*tert*-butoxycarbonyl)amino)methyl)-5-fluorobenzofuran-7-carbothioate (0.85 g, 2.51 mmol) in dichloromethane (6 mL) was added TFA (1.93 mL, 25.1 mmol). The reaction mixture was stirred at room temperature for 1 hour. The reaction was concentrated *in vacuo* to give the title compound (TFA salt, 0.85 g, 96%) as a light brown solid. ¹H NMR (400 MHz, Chloroform-d) δ 7.63 (dd, *J* = 9.2, 2.5 Hz, 1H), 7.45 (dd, *J* = 7.5, 2.6 Hz, 1H), 6.89 (s, 1H), 4.43 (s, 2H), 2.48 (s, 3H); MS (ESI+) *m/z* = 223.1 (M-17+H)⁺.

E) S-Methyl 5-fluoro-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carbothioate

A mixture of pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (19.8 mg, 0.121 mmol) and BOP (53.7 mg, 0.121 mmol) in DMF (1 mL) was stirred at room temperature for 10 min. A solution of *S*-methyl 2-(aminomethyl)-5-fluorobenzofuran-7-carbothioate, TFA salt (33 mg, 0.093 mmol) in THF (1 mL) and DIPEA (0.049 mL, 0.28 mmol) was added.

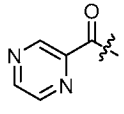
The reaction was stirred at room temperature for 1 hour. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in DMF, filtered and purified by preparative HPLC (Method B). Fractions containing the desired product were combined and dried *via* centrifugal evaporation to give the title compound (10.7 mg, 29% yield). ¹H NMR (500 MHz, DMSO-d₆) δ 9.29 (dd, *J* = 7.0, 1.2 Hz, 1H), 8.93 - 8.78 (m, 1H), 8.63 (s, 1H), 8.58 (br t, *J* = 5.8 Hz, 1H), 7.74 (dd, *J* = 8.2, 2.4 Hz, 1H), 7.53 (dd, *J* = 9.5, 2.4 Hz, 1H), 7.28 (dd, *J* = 7.0, 4.3 Hz, 1H), 6.91 (s, 1H), 4.82 (d, *J* = 5.8 Hz, 2H), 2.48 (s, 3H); MS (ESI) *m/z* = 385.1 (M+H)⁺.

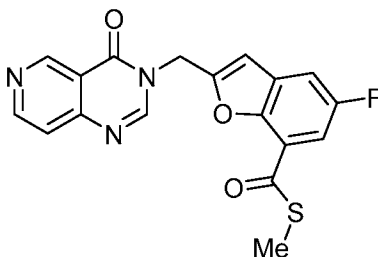
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EXAMPLES 383-384

Examples 383 and 384 were prepared in the same general way as Example 382 using the corresponding benzofuran amine (Step D in Example 382) and the required acid.

Ex. No.	A-CO-	Name	¹ H NMR	LC/MS (M+H) ⁺
383		<i>S</i> -Methyl 5-fluoro-2-((imidazo[1,2- <i>b</i>]pyridazine-3-carboxamido)methyl)benzofuran-7-carbothioate	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.25 (br t, <i>J</i> = 5.6 Hz, 1H), 8.78 (br d, <i>J</i> = 4.3 Hz, 1H), 8.46 - 8.21 (m, 2H), 7.74 (dd, <i>J</i> = 8.1, 2.3 Hz, 1H), 7.53 (dd, <i>J</i> = 9.5, 2.4 Hz, 1H), 7.48 (dd, <i>J</i> = 9.2, 4.6 Hz, 1H), 6.95 (s, 1H), 4.86 (br d, <i>J</i> = 5.8 Hz, 2H), 2.47 (s, 3H)	385.3

Ex. No.	A-CO-	Name	¹ H NMR	LC/MS (M+H) ⁺
384		<i>S</i> -Methyl 5-fluoro-2-((pyrazine-2-carboxamido)methyl)benzofuran-7-carbothioate	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.61 (br t, <i>J</i> = 6.0 Hz, 1H), 9.22 (s, 1H), 8.89 (d, <i>J</i> = 2.1 Hz, 1H), 8.76 (s, 1H), 7.74 (dd, <i>J</i> = 8.2, 2.7 Hz, 1H), 7.53 (dd, <i>J</i> = 9.5, 2.4 Hz, 1H), 6.89 (s, 1H), 4.73 (d, <i>J</i> = 5.8 Hz, 2H), 2.47 (s, 3H)	346.3

EXAMPLE 385

***S*-Methyl 5-fluoro-2-((4-oxopyrido[4,3-*d*]pyrimidin-3(4*H*)-yl)methyl)methyl)benzofuran-7-carbothioate**

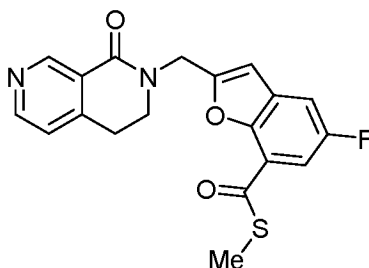
5

A mixture of 4-aminonicotinic acid (29.9 mg, 0.217 mmol) and 1,1-dimethoxy-*N,N*-dimethylmethanamine (0.171 mL, 1.27 mmol) in DMF (1 mL) in a microwave tube was heated in a microwave reactor at 120 °C for 25 min. The reaction mixture was concentrated *in vacuo*. To the residue was added 1 mL of acetic acid and *S*-methyl 2-(aminomethyl)-5-fluorobenzofuran-7-carbothioate, TFA (45 mg, 0.127 mmol, Step D of Example 382) in acetic acid (2 mL). The mixture was heated in a microwave reactor at 110 °C for 20 min. The reaction mixture was then concentrated *in vacuo*. The residue was dissolved in DMF, filtered and purified by preparative HPLC (Method B). Fractions containing the desired product were combined and dried *via* centrifugal evaporation to give the title compound (18.1 mg, 38%). ¹H NMR (500 MHz, DMSO-d₆) δ 9.32 (s, 1H), 8.86 (d, *J* = 5.5 Hz, 1H), 8.78 (s, 1H), 7.76 (dd, *J* = 8.2, 2.4 Hz, 1H), 7.65 (d, *J* = 5.5 Hz,

10

15

1H), 7.55 (dd, $J = 9.5, 2.4$ Hz, 1H), 7.08 (s, 1H), 5.48 (s, 2H), 2.44 (s, 3H); MS (ESI+) $m/z = 370.0$ (M+H)⁺.

EXAMPLE 386

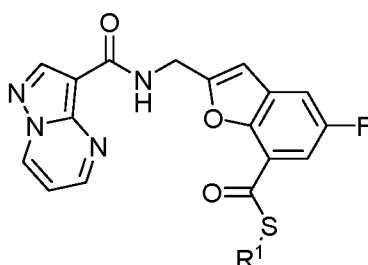
5

***S*-Methyl 5-fluoro-2-((1-oxo-3,4-dihydro-2,7-naphthyridin-2(1H)-yl)methyl)benzofuran-7-carbothioate**

A mixture of 3,4-dihydro-1*H*-pyrano[3,4-*c*]pyridin-1-one, HCl salt (23.1 mg, 0.125 mmol) (WO 2005063768) and crude *S*-methyl 2-(aminomethyl)-5-fluorobenzofuran-7-carbothioate, TFA salt (40 mg, 0.113 mmol, Step D in Example 382) in pyridine (1 mL) was heated in a vial with pressure relief septum at 125 °C for 18 hours. The reaction mixture was diluted with saturated aqueous NaHCO₃ solution and extracted with ethyl acetate. The organic layer was separated and concentrated *in vacuo*. The residue was dissolved in MeOH, filtered and purified by preparative HPLC (Method B).
Fractions containing the desired product were combined and dried *via* centrifugal evaporation to give the title compound (2 mg, 5%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.95 (s, 1H), 8.61 (br d, $J = 4.6$ Hz, 1H), 7.76 (dd, $J = 8.1, 2.3$ Hz, 1H), 7.54 (dd, $J = 9.6, 2.3$ Hz, 1H), 7.38 (br d, $J = 4.6$ Hz, 1H), 7.02 (s, 1H), 4.94 (s, 2H), 3.76 (br t, $J = 6.6$ Hz, 2H), 3.09 (br t, $J = 6.6$ Hz, 2H), 2.45 (s, 3H); MS (ESI+) $m/z = 370.9$ (M+H)⁺.

20

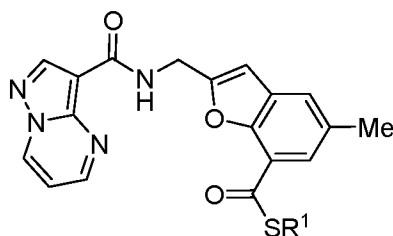
EXAMPLES 387 and 388



Examples 387 and 388 were prepared from Example 136 and the required thiol according to the procedure in Example 380.

Ex. No.	R ¹	Name	¹ H NMR	LC/MS [M+H] ⁺
387		<i>S</i> -Ethyl 5-fluoro-2-((pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carbothioate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.32 (dd, <i>J</i> = 7.0, 1.5 Hz, 1H), 8.83 (dd, <i>J</i> = 4.0, 1.5 Hz, 1H), 8.63 (s, 1H), 8.57 (br t, <i>J</i> = 5.8 Hz, 1H), 7.74 (dd, <i>J</i> = 8.2, 2.4 Hz, 1H), 7.52 (dd, <i>J</i> = 9.8, 2.4 Hz, 1H), 7.29 (dd, <i>J</i> = 6.9, 4.1 Hz, 1H), 6.90 (s, 1H), 4.83 (br d, <i>J</i> = 5.8 Hz, 2H), 3.07 (q, <i>J</i> = 7.3 Hz, 2H), 1.26 (t, <i>J</i> = 7.3 Hz, 3H)	399.3
388		<i>S</i> -(2,2,2-Trifluoroethyl) 5-fluoro-2-((pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carbothioate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.34 (br d, <i>J</i> = 6.7 Hz, 1H), 8.85 (br d, <i>J</i> = 3.1 Hz, 1H), 8.71 - 8.53 (m, 2H), 7.86 (dd, <i>J</i> = 8.1, 2.3 Hz, 1H), 7.66 (dd, <i>J</i> = 9.5, 2.1 Hz, 1H), 7.32 (dd, <i>J</i> = 6.9, 4.1 Hz, 1H), 6.97 (s, 1H), 4.87 (br d, <i>J</i> = 5.8 Hz, 2H), 4.17 (q, <i>J</i> = 10.4 Hz, 2H)	453.3

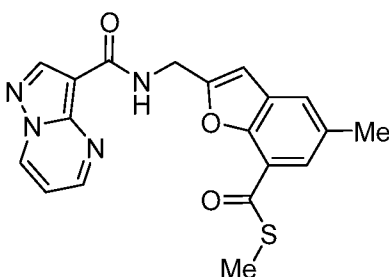
EXAMPLES 389-390



Examples 389 and 390 were prepared for corresponding acid Example 158 and the required thiol according to the procedure in Example 380.

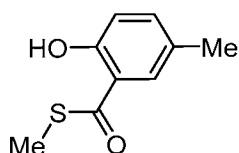
Ex. No.	R ¹	Name	¹ H NMR	LC/MS (M+H) ⁺
389		<i>S</i> -(2,2,2-Trifluoroethyl) 5-methyl-2-((pyrazolo[1,5- α]pyrimidine-3-carboxamido)methyl)-benzofuran-7-carbothioate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.27 (d, <i>J</i> = 5.8 Hz, 1H), 8.81 (br d, <i>J</i> = 2.7 Hz, 1H), 8.62 (s, 1H), 8.57 (br t, <i>J</i> = 5.8 Hz, 1H), 7.75 (s, 1H), 7.66 (s, 1H), 7.27 (dd, <i>J</i> = 6.9, 4.1 Hz, 1H), 6.86 (s, 1H), 4.81 (br d, <i>J</i> = 5.8 Hz, 2H), 4.08 (q, <i>J</i> = 10.5 Hz, 2H), 2.43 (s, 3H)	449.1
390		<i>S</i> -Ethyl 5-methyl-2-((pyrazolo[1,5- α]pyrimidine-3-carboxamido)methyl)-benzofuran-7-carbothioate	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.30 (d, <i>J</i> = 5.8 Hz, 1H), 8.82 (br d, <i>J</i> = 2.7 Hz, 1H), 8.63 (s, 1H), 8.54 (br t, <i>J</i> = 6.0 Hz, 1H), 7.67 (s, 1H), 7.58 (s, 1H), 7.28 (dd, <i>J</i> = 7.0, 4.3 Hz, 1H), 6.81 (s, 1H), 4.80 (d, <i>J</i> = 5.8 Hz, 2H), 3.04 (q, <i>J</i> = 7.4 Hz, 2H), 2.42 (s, 3H), 1.26 (t, <i>J</i> = 7.3 Hz, 3H)	395.1

EXAMPLE 391



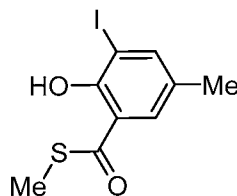
S-Methyl 5-methyl-2-((pyrazolo[1,5-a]pyrimidine-3-carboxamido)methyl)benzofuran-7-carbothioate

5



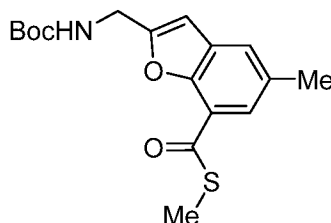
A) S-Methyl 2-hydroxy-5-methylbenzothioate

To 2-hydroxy-5-methylbenzoic acid (1.5 g, 9.86 mmol) was added thionyl chloride (5.04 mL, 69.0 mmol) and a few drops of DMF. The reaction mixture was stirred at RT for 10 minutes during which time it turned into a clear solution. The reaction mixture was concentrated *in vacuo* to give white solid. To the solid was added dichloroethane (30 mL), sodium methanethiolate (0.760 g, 10.84 mmol) and TEA (4.12 mL, 29.6 mmol). The reaction mixture was stirred at room temperature for 16 hours. The reaction mixture was diluted with saturated sodium chloride and DCM. The organic layer was separated and washed with saturated sodium chloride, dried over sodium sulfate and was concentrated *in vacuo*. The residue was purified by a silica gel ISCO 40 g column eluting with 0-15% ethyl acetate in hexanes over a 15 minute gradient. The appropriate fractions were isolated and concentrated *in vacuo* to afford the product (1.46 g, 81% yield) as a solid. ¹H NMR (400 MHz, CHLOROFORM-d) δ 10.83 (s, 1H), 7.70 - 7.65 (m, 1H), 7.31 - 7.27 (m, 1H), 6.91 (d, *J* = 8.5 Hz, 1H), 2.49 (s, 3H), 2.34 (s, 3H).



B) S-Methyl 2-hydroxy-3-iodo-5-methylbenzothioate

To a solution of S-methyl 2-hydroxy-5-methylbenzothioate (1.46 g, 8.01 mmol) in N,N-dimethylformamide (20 mL) was added sodium iodide (1.441 g, 9.61 mmol),
 5 followed by chloramine T trihydrate (2.482 g, 8.81 mmol) slowly in portions. The reaction was stirred at room temperature for 3 hours. The reaction mixture was quenched with ethyl acetate and 1N aqueous HCl solution. The organic layer was separated, washed with saturated aqueous sodium chloride solution followed by 10% Na₂S₂O₃ solution, dried with anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The
 10 crude product mixture was purified by a silica gel ISCO 80 g column eluting with 0-20% ethyl acetate in hexanes over a 15 minute gradient. The appropriate fractions were isolated and concentrated *in vacuo* to afford the product (1.6 g, 70% yield) as a solid. ¹H NMR (400 MHz, CHLOROFORM-d) δ 11.73 (s, 1H), 7.86 - 7.78 (m, 1H), 7.73 - 7.59 (m, 1H), 2.59 - 2.47 (m, 3H), 2.35 - 2.27 (m, 3H).



15

C) S-Methyl 2-(((tert-butoxycarbonyl)amino)methyl)-5-methylbenzofuran-7-carbothioate

A 100 ml flask was charged with a mixture of S-methyl 2-hydroxy-3-iodo-5-methylbenzothioate (1.6 g, 3.63 mmol), tert-butyl prop-2-yn-1-ylcarbamate (0.649 g, 4.18
 20 mmol), TEA (7.60 mL, 54.5 mmol), and copper(I) iodide (0.069 g, 0.363 mmol) in DMF (8 mL). The reaction solution was purged with a nitrogen stream for 5 mins, then bis(triphenylphosphine)palladium(II) chloride (0.128 g, 0.182 mmol) was added. The resulting mixture was heated at 85°C for 2 hours. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate, washed with saturated aqueous sodium

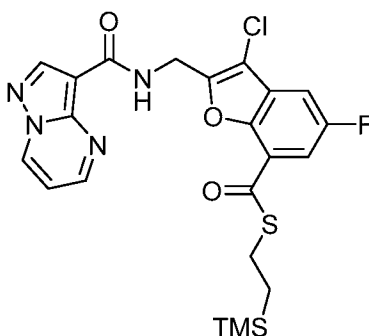
bicarbonate solution followed by saturated aqueous sodium chloride solution, dried with anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude product mixture was purified by a silica gel ISCO 80 g column eluting with 0-30 % ethyl acetate in hexanes over a 15 minute gradient. The appropriate fractions were isolated and concentrated *in vacuo* to afford the title compound (0.73 g, 60 % yield) as a light brown solid. ¹H NMR (400 MHz, Chloroform-d) δ 7.70 (d, *J* = 1.7 Hz, 1H), 7.61 - 7.44 (m, 1H), 6.61 (s, 1H), 4.51 (br d, *J* = 5.9 Hz, 2H), 2.54 (s, 3H), 2.52 - 2.44 (m, 3H), 1.51 - 1.43 (m, 9H); MS (ESI+) *m/z* = 280 (M-55+H)⁺.

10 **D) *S*-Methyl 5-methyl-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carbothioate**

The above product was dissolved in DCM (10 mL) and TFA (1 mL). The reaction solution was stirred at RT for 2 hours. The reaction was concentrated *in vacuo* and used as is subsequently. To a suspension of pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (20 mg, 0.123 mmol) and BOP (67.8 mg, 0.153 mmol) in DMF (2 mL) was added crude *S*-methyl 2-(aminomethyl)-5-methylbenzofuran-7-carbothioate, TFA salt (42.8 mg, 0.123 mmol) and DIPEA (0.086 mL, 0.490 mmol). The reaction mixture was stirred at room temperature for 16 hours. The reaction was quenched with water, and a precipitate resulted, which was filtered, then dissolved in 2 mL of DMF for purification. The crude material was purified *via* preparative HPLC (Method B) to afford the product (18.8 mg, 48.4 % yield). ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.27 (br d, *J* = 5.8 Hz, 1H), 8.82 (br d, *J* = 2.7 Hz, 1H), 8.62 (s, 1H), 8.55 (br t, *J* = 5.8 Hz, 1H), 7.67 (s, 1H), 7.58 (s, 1H), 7.27 (dd, *J* = 6.9, 4.1 Hz, 1H), 6.82 (s, 1H), 4.79 (br d, *J* = 5.8 Hz, 2H), 2.45 (s, 3H), 2.43 - 2.40 (m, 3H); MS (ESI+) *m/z* = 381.1 (M+H)⁺.

25

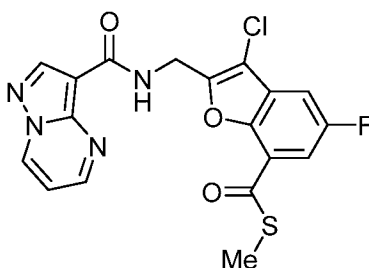
EXAMPLE 392



***S*-(2-(Trimethylsilyl)ethyl) 3-chloro-5-fluoro-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carbothioate**

5 A mixture of 3-chloro-5-fluoro-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylic acid (45 mg, 0.116 mmol, Example 172) and BOP (71.7 mg, 0.162 mmol) in DMF (2 mL) was stirred at room temperature for 10 minutes. 2-(Trimethylsilyl)ethane-1-thiol (47 mg, 0.35 mmol) and DIPEA (0.04 mL, 0.23 mmol) were then added. The reaction mixture was stirred at room temperature for 2
10 hours. The reaction mixture was diluted with ethyl acetate and saturated aqueous NaHCO₃ solution. The organic layer was separated, washed with brine, dried over MgSO₄, and filtered. The filtrate was concentrated *in vacuo*. The residue was dissolved in DMF and purified by preparative HPLC (Method B). Fractions containing the desired product were combined and dried *via* centrifugal evaporation to give the title compound
15 (40 mg, 70%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.24 (br d, *J* = 7.0 Hz, 1H), 8.78 (br d, *J* = 3.9 Hz, 1H), 8.56 (s, 1H), 8.48 (br s, 1H), 7.66 (br d, *J* = 7.5 Hz, 1H), 7.60 - 7.52 (m, 1H), 7.24 (dd, *J* = 6.8, 4.3 Hz, 1H), 4.85 (d, *J* = 5.8 Hz, 2H), 3.09 - 2.96 (m, 2H), 0.88 - 0.66 (m, 2H), 0.00 (s, 9H); MS (ESI+) *m/z* = 505.3 (M+H)⁺.

EXAMPLE 393



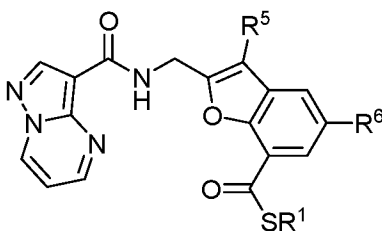
***S*-Methyl 3-chloro-5-fluoro-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carbothioate**

5 To a solution of *S*-(2-(trimethylsilyl)ethyl) 3-chloro-5-fluoro-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carbothioate (40 mg, 0.079 mmol, Example 392) in THF (2 mL) was added TBAF (1M solution in THF, 1.2 mL, 1.2 mmol) and methyl iodide (0.03 mL, 0.475 mmol). The reaction mixture was stirred at room temperature for 4 hours. The reaction mixture was concentrated *in vacuo*. The residue

10 was diluted with water and extracted with ethyl acetate. The combined organics were dried with sodium sulfate and filtered. The filtrate was concentrated *in vacuo*. The residue was dissolved in DMF and purified by preparative HPLC (Method B). Fractions containing the desired product were combined and dried *via* centrifugal evaporation to give the title compound (8.4 mg, 25%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.25 (br d, *J* = 6.4 Hz, 1H), 8.82 (br s, 1H), 8.60 (br s, 2H), 7.74 (br d, *J* = 7.6 Hz, 1H), 7.65 (br d, *J* = 7.3 Hz, 1H), 7.27 (br s, 1H), 4.85 (br d, *J* = 4.3 Hz, 2H), 2.46 - 2.40 (m, 3H); MS (ESI+) *m/z* = 419.1 (M+H)⁺.

15

EXAMPLES 394-397

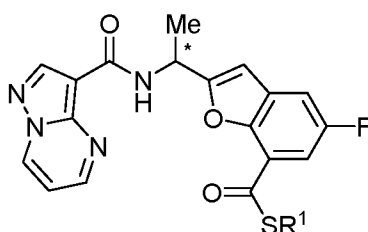


20

Examples 394 to 397 were prepared from corresponding intermediates (Examples 133, 138, 174, and 176) and the required thiol using the procedures outlined in Examples 392 and 393.

Ex. No.	R ¹ , R ⁵ , R ⁶	Name	NMR	LC/MS [M+H] ⁺
394	R ¹ = (CH ₂) ₂ -TMS R ⁵ = H R ⁶ = Cl	<i>S</i> -(2-(Trimethylsilyl)ethyl) 5-chloro-2-((pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carbothioate	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.20 (br dd, <i>J</i> = 5.2, 1.8 Hz, 1H), 8.76 (br d, <i>J</i> = 4.0 Hz, 1H), 8.55 (s, 1H), 8.47 (br s, 1H), 7.88 (s, 1H), 7.61 (s, 1H), 7.21 (dd, <i>J</i> = 6.5, 4.5 Hz, 1H), 6.84 (s, 1H), 4.77 (br d, <i>J</i> = 5.8 Hz, 2H), 3.09 - 3.01 (m, 2H), 0.83 (td, <i>J</i> = 8.6, 2.2 Hz, 2H), 0.00 (d, <i>J</i> = 1.8 Hz, 9H)	487.4
395	R ¹ = Me R ⁵ = H R ⁶ = Cl	<i>S</i> -Methyl 5-chloro-2-((pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carbothioate	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.29 (br d, <i>J</i> = 7.0 Hz, 1H), 8.82 (br d, <i>J</i> = 2.7 Hz, 1H), 8.63 (s, 1H), 8.58 (s, 1H), 7.97 (d, <i>J</i> = 1.8 Hz, 1H), 7.69 (d, <i>J</i> = 1.8 Hz, 1H), 7.28 (dd, <i>J</i> = 6.7, 4.3 Hz, 1H), 6.89 (s, 1H), 4.82 (br d, <i>J</i> = 5.8 Hz, 2H), 2.49 - 2.44 (m, 3H)	401.2
396	R ¹ = Me R ⁵ = Cl R ⁶ = Cl	<i>S</i> -Methyl 3,5-dichloro-2-((pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)methyl)benzofuran-7-carbothioate	¹ H NMR (400 MHz, CHLOROFORM-d) δ 8.81 (dd, <i>J</i> = 7.0, 1.8 Hz, 1H), 8.73 (s, 1H), 8.68 (dd, <i>J</i> = 4.1, 1.7 Hz, 1H), 8.45 (br s, 1H), 7.90 (d, <i>J</i> = 2.1 Hz, 1H), 7.74 (d, <i>J</i> = 2.1 Hz, 1H), 7.03 (dd, <i>J</i> = 7.0, 4.1 Hz, 1H), 5.00 (d, <i>J</i> = 5.9 Hz, 2H), 2.54 (s, 3H)	435.2
397	R ¹ = Me R ⁵ = Cl R ⁶ = Me	<i>S</i> -Methyl 3-chloro-5-methyl-2-((pyrazolo[1,5- <i>a</i>]pyrimidine-3-	¹ H NMR (400 MHz, CHLOROFORM-d) δ 8.80 (dd, <i>J</i> = 7.0, 1.7 Hz, 1H), 8.73 (s, 1H), 8.67 (dd, <i>J</i> = 4.1, 1.7 Hz, 1H), 8.45 (br s, 1H), 7.76	415.1

		carboxamido)methyl)benzofuran-7-carbothioate	(d, $J = 1.2$ Hz, 1H), 7.56 (d, $J = 0.9$ Hz, 1H), 7.02 (dd, $J = 7.0, 4.2$ Hz, 1H), 5.02 - 4.96 (m, 2H), 2.53 (s, 6H)	
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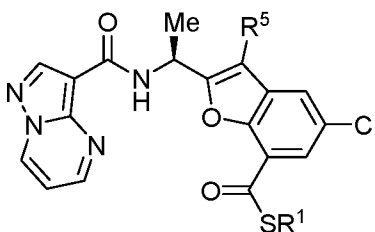
EXAMPLE 398-399

Examples 398 and 399 were prepared from corresponding intermediate Example 185 and the required thiol using the methods outlined in Examples 392 and 393.

Ex. No.	R ¹	Name	NMR	LC/MS [M+H] ⁺
398		<i>S</i> -(2-(Trimethylsilyl)ethyl) (S)-5-fluoro-2-(1-(pyrazolo[1,5- α]pyrimidine-3-carboxamido)ethyl)benzofuran-7-carbothioate	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.27 (br d, $J = 6.4$ Hz, 1H), 8.79 (br d, $J = 3.1$ Hz, 1H), 8.60 (s, 1H), 8.38 (br d, $J = 8.2$ Hz, 1H), 7.71 (dd, $J = 8.2, 2.4$ Hz, 1H), 7.48 (dd, $J = 9.5, 2.1$ Hz, 1H), 7.25 (dd, $J = 6.7, 4.3$ Hz, 1H), 6.92 (s, 1H), 5.47 (br t, $J = 7.3$ Hz, 1H), 3.08 - 2.97 (m, 2H), 1.64 (d, $J = 7.0$ Hz, 3H), 0.97 - 0.70 (m, 2H), 0.00 (s, 9H)	485.4
399		<i>S</i> -Methyl (S)-5-fluoro-2-(1-(pyrazolo[1,5- α]pyrimidine-3-carboxamido)ethyl)benzofuran-7-carbothioate	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.17 (br d, $J = 6.9$ Hz, 1H), 8.78 (br d, $J = 4.1$ Hz, 1H), 8.59 (s, 1H), 8.43 (br d, $J = 8.1$ Hz, 1H), 7.79 - 7.62 (m, 1H), 7.50 (dd, $J = 9.6, 2.3$ Hz, 1H), 7.24 (dd, $J = 6.9, 4.2$ Hz, 1H), 6.93 (s, 1H), 5.49 (br t, $J = 7.4$ Hz, 1H),	399.2

			2.44 (s, 3H), 1.66 (d, $J = 7.0$ Hz, 3H)	
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EXAMPLES 400-402

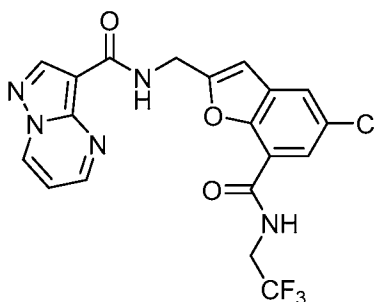


5

Examples 400 to 402 were prepared from corresponding intermediates (Examples 156 and 175) and required thiol using the methods outlined in Examples 392 and 393.

Ex. No.	R ¹ , R ⁵	Name	NMR	LC/MS [M+H] ⁺
400	R ¹ =(CH ₂) ₂ -TMS R ⁵ =H	<i>S</i> -(2-(Trimethylsilyl)ethyl) (<i>S</i>)-5-chloro-2-(1-(pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamido)ethyl)benzofuran-7-carbothioate	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.27 (br d, $J = 7.0$ Hz, 1H), 8.79 (br d, $J = 3.1$ Hz, 1H), 8.60 (s, 1H), 8.39 (br d, $J = 7.9$ Hz, 1H), 7.95 (s, 1H), 7.65 (d, $J = 1.5$ Hz, 1H), 7.25 (dd, $J = 6.9, 4.4$ Hz, 1H), 6.92 (s, 1H), 5.47 (br t, $J = 7.5$ Hz, 1H), 3.08 - 2.98 (m, 2H), 1.64 (br d, $J = 7.0$ Hz, 3H), 0.91 - 0.64 (m, 2H), 0.00 (s, 9H)	501.2
401	R ¹ =-CH ₃ R ⁵ =H	<i>S</i> -Methyl (<i>S</i>)-5-chloro-2-(1-(pyrazolo[1,5- <i>a</i>]pyrimidine-3-	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.23 (br d, $J = 6.9$ Hz, 1H), 8.80 (br d, $J = 4.0$ Hz, 1H), 8.60 (s, 1H), 8.41 (br d,	415.3

		carboxamido)ethyl)benzofuran-7-carbothioate	$J = 8.2$ Hz, 1H), 7.95 (s, 1H), 7.69 (s, 1H), 7.26 (dd, $J = 6.8, 4.2$ Hz, 1H), 6.94 (s, 1H), 5.51 (br t, $J = 7.2$ Hz, 1H), 2.48 - 2.43 (m, 3H), 1.68 (br d, $J = 6.9$ Hz, 3H)	
402	$R^1 = -CH_3$ $R^5 = Cl$	<i>S</i> -Methyl (<i>S</i>)-3,5-dichloro-2-(1-(pyrazolo[1,5- α]pyrimidine-3-carboxamido)ethyl)benzofuran-7-carbothioate	1H NMR (500 MHz, DMSO- d_6) δ 9.33 - 9.13 (m, 1H), 8.83 (br d, $J = 4.0$ Hz, 1H), 8.58 (s, 1H), 8.50 (br d, $J = 7.7$ Hz, 1H), 7.90 (s, 1H), 7.80 (s, 1H), 7.28 (dd, $J = 6.8, 4.3$ Hz, 1H), 5.60 (br t, $J = 7.2$ Hz, 1H), 3.43 (s, 3H), 1.70 (d, $J = 7.0$ Hz, 3H)	449.1

EXAMPLE 403

***N*-((5-Chloro-7-((2,2,2-trifluoroethyl)carbamoyl)benzofuran-2-yl)methyl)pyrazolo[1,5- α]pyrimidine-3-carboxamide**

5

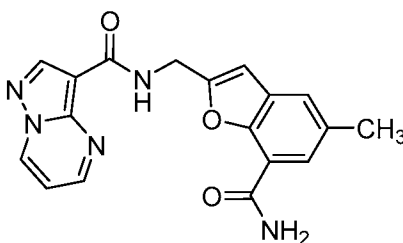
To a solution of 5-chloro-2-((pyrazolo[1,5- α]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylic acid (15 mg, 0.040 mmol) (Example 138) and BOP (26.8 mg, 0.061 mmol) in DMF (1 mL) were added 2,2,2-trifluoroethan-1-amine (20.04 mg, 0.202 mmol) and DIPEA (0.028 mL, 0.162 mmol). The reaction mixture was stirred at rt for 2 h. LC-MS showed new peak at $t_r = 0.84$ min, $[M+H]^+ = 452.2$ as the desired product peak. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in DMF, filtered and purified by preparative HPLC (Method B). Fractions containing the desired product were combined and dried *via* centrifugal

10

evaporation to give the title compound (10.8 mg, 46%). ¹H NMR (500 MHz, DMSO-d₆) δ 9.31 (br d, *J* = 7.0 Hz, 1H), 9.00 (br t, *J* = 6.1 Hz, 1H), 8.84 (br d, *J* = 2.7 Hz, 1H), 8.64 (s, 1H), 8.60 (br t, *J* = 5.8 Hz, 1H), 7.89 (d, *J* = 1.5 Hz, 1H), 7.63 (d, *J* = 1.8 Hz, 1H), 7.31 (dd, *J* = 6.7, 4.3 Hz, 1H), 6.88 (s, 1H), 4.83 (br d, *J* = 6.1 Hz, 2H), 4.28 - 4.11 (m, 2H);

5 MS (ESI+) *m/z* = 452.2 (M+H)⁺.

EXAMPLE 404



N-((7-Carbamoyl-5-methylbenzofuran-2-yl)methyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

10

To a solution of 5-methyl-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylic acid (30 mg, 0.086 mmol, Example 158) in DMF (1 mL) was added HATU (42.3 mg, 0.111 mmol). The reaction mixture was stirred at room temperature for 15 min, followed by the addition of ammonium hydroxide (0.238 mL, 1.71 mmol) and DIPEA (0.045 mL, 0.257 mmol). The reaction mixture was stirred at

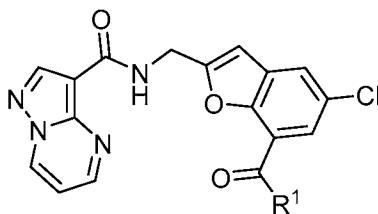
15 room temperature for 2 hours. The reaction was quenched with water, and a precipitate formed, which was filtered. The crude material was purified *via* preparative HPLC (Method B) to afford the product (12 mg, 40 % yield). ¹H NMR (500 MHz, DMSO-d₆) δ 9.22 (d, *J* = 6.7 Hz, 1H), 8.80 (br d, *J* = 3.1 Hz, 1H), 8.61 - 8.57 (m, 2H), 7.71 (br s, 1H),

20 7.69 - 7.64 (m, 1H), 7.53 (br d, *J* = 5.8 Hz, 2H), 7.26 (dd, *J* = 7.0, 4.3 Hz, 1H), 6.78 (s, 1H), 4.77 (br d, *J* = 5.8 Hz, 2H), 2.38 (s, 3H); MS (ESI+) *m/z* = 350.1 (M+H)⁺.

EXAMPLES 405-406

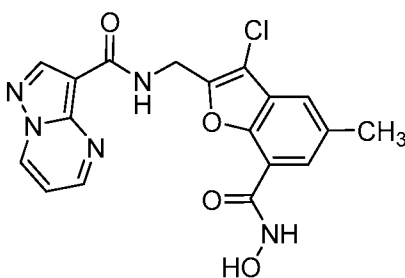
Examples 405 and 406 were prepared in the same general way as Example 403

25 starting from Example 138 and the corresponding amine.



Ex. No.	R ¹	Name	NMR	LC/MS [M+H] ⁺
405		<i>N</i> -((5-Chloro-7-(hydroxycarbonyl)benzofuran-2-yl)methyl)pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamide	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.24 (br t, <i>J</i> = 5.4 Hz, 1H), 8.88 - 8.79 (m, 1H), 8.59 (s, 1H), 8.49 (br s, 1H), 7.78 (s, 1H), 7.50 (br s, 1H), 7.26 (br dd, <i>J</i> = 6.9, 4.2 Hz, 1H), 6.83 (s, 1H), 4.79 (br d, <i>J</i> = 5.6 Hz, 2H)	386.1
406		<i>N</i> -((5-Chloro-7-(methoxycarbonyl)benzofuran-2-yl)methyl)pyrazolo[1,5- <i>a</i>]pyrimidine-3-carboxamide	¹ H NMR (500 MHz, DMSO-d ₆) δ 9.24 (br d, <i>J</i> = 6.4 Hz, 1H), 8.81 (br d, <i>J</i> = 3.1 Hz, 1H), 8.70 - 8.55 (m, 2H), 7.81 (s, 1H), 7.51 (s, 1H), 7.26 (dd, <i>J</i> = 6.9, 4.1 Hz, 1H), 6.83 (s, 1H), 4.78 (br d, <i>J</i> = 5.8 Hz, 2H), 3.64 (br s, 3H)	400.2

EXAMPLE 407

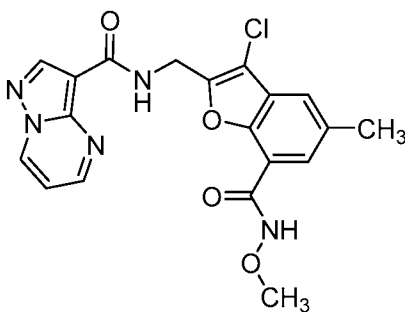


5

N-((3-chloro-7-(hydroxycarbonyl)-5-methylbenzofuran-2-yl)methyl)pyrazolo[1,5-

***a*]pyrimidine-3-carboxamide**

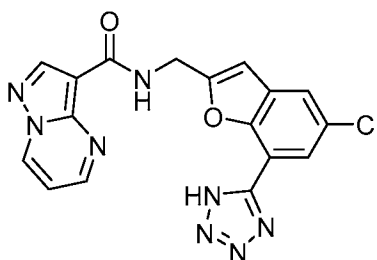
A flask was charged with 3-chloro-5-methyl-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylic acid (25 mg, 0.065 mmol, Example 176), hydroxylamine hydrochloride (6.77 mg, 0.097 mmol) and DIPEA (45.4 μ l, 0.260 mmol) in DMF (325 μ l). To the solution was added BOP (43.1 mg, 0.097 mmol) and the reaction stirred at room temperature for 1 hour. The solution was quenched with water and a precipitate formed. This precipitate was isolated *via* filtration and dissolved in 2 mL of DMF. The crude material was purified *via* preparative HPLC (Method B) to yield the title compound (8.8 mg, 33.9 % yield). ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.24 (d, *J* = 5.9 Hz, 1H), 8.84 - 8.80 (m, 1H), 8.60 - 8.58 (m, 1H), 8.47 (br t, *J* = 5.4 Hz, 1H), 7.49 (br s, 2H), 7.29 - 7.24 (m, 1H), 4.84 (d, *J* = 5.8 Hz, 2H), 2.46 - 2.44 (m, 3H); MS (ESI+) *m/z* = 400.1 (M+H)⁺.

EXAMPLE 408**N-((3-chloro-7-(methoxycarbonyl)-5-methylbenzofuran-2-yl)methyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide**

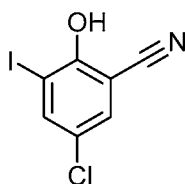
A flask was charged with 3-chloro-5-methyl-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylic acid (25 mg, 0.065 mmol, Example 176), O-methylhydroxylamine hydrochloride (8.14 mg, 0.097 mmol) and DIPEA (45.4 μ l, 0.260 mmol) in DMF (325 μ l). To the solution was added BOP (43.1 mg, 0.097 mmol) and the reaction stirred at room temperature for 1 hour. The solution was quenched with water and a precipitate formed. This precipitate was isolated *via* filtration and dissolved in 2 mL of DMF. The crude material was purified *via* preparative HPLC (Method B) to yield the title compound (20.3 mg, 72.4 % yield). ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.27

- 9.23 (m, 1H), 8.84 - 8.79 (m, 1H), 8.62 - 8.56 (m, 1H), 8.51 - 8.45 (m, 1H), 7.56 - 7.47 (m, 2H), 7.30 - 7.23 (m, 1H), 4.86 (d, $J = 5.9$ Hz, 2H), 3.72 (s, 3H), 2.48 - 2.41 (m, 3H); MS (ESI+) $m/z = 414.0$ (M+H)⁺.

5

EXAMPLE 409

***N*-((5-Chloro-7-(1*H*-tetrazol-5-yl)benzofuran-2-yl)methyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide**

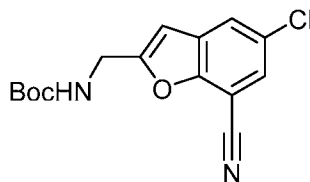


10

A) 5-Chloro-2-hydroxy-3-iodobenzonitrile

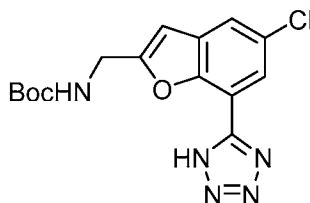
To a solution of 5-chloro-2-hydroxybenzonitrile (2.0 g, 13.02 mmol) in DMF (30 mL) were added sodium iodide (2.440 g, 16.28 mmol) and chloramine T trihydrate (4.40 g, 15.63 mmol) slowly. The reaction mixture was stirred at rt over night. The reaction mixture was diluted with ethyl acetate and brine solution. The organic layer was separated, washed with 1 N HCl solution, and Na₂S₂O₃ solution successively. The organic layer was dried over MgSO₄, filtered, and the filtrate was concentrated *in vacuo*. The residue was dissolved in DCM and purified by ISCO (80 g column, 0 - 30% ethyl acetate in DCM) to give 5-chloro-2-hydroxy-3-iodobenzonitrile as a light yellow solid (2.2 g, 60.4% yield). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.89 (d, $J = 2.4$ Hz, 1H), 7.53 (d, $J = 2.4$ Hz, 1H), 6.13 (br s, 1H); MS (ESI+) $m/z = 280.0$ (M+H)⁺.

20



B) *tert*-Butyl ((5-chloro-7-cyanobenzofuran-2-yl)methyl)carbamate

To a reaction mixture of 5-chloro-2-hydroxy-3-iodobenzonitrile (2.2 g, 7.87 mmol) and *tert*-butyl prop-2-yn-1-ylcarbamate (1.344 g, 8.66 mmol) in DMF (20 mL) were added TEA (8.78 mL, 63.0 mmol) and copper(I) iodide (0.150 g, 0.787 mmol). The reaction mixture was purged with nitrogen stream for 5 min, then bis(triphenylphosphine)palladium(II) chloride (0.553 g, 0.787 mmol) was added. The resulting mixture was heated at 80 °C under nitrogen stream for 2 hours. The reaction mixture was diluted with brine and ethyl acetate. The organic layer was separated, washed with saturated NH₄Cl solution and brine successively, dried over MgSO₄, and filtered. The filtrate was concentrated *in vacuo* to give a light yellow oil. The crude residue was dissolved in DCM and purified by silica gel column chromatography (80 g column, 0 – 40% ethyl acetate in hexanes) to give *tert*-butyl ((5-chloro-7-cyanobenzofuran-2-yl)methyl)carbamate (2.1 g, 87% yield) as a light yellow solid. ¹H NMR (400 MHz, CHLOROFORM-*d*) δ 7.75 (d, *J* = 2.0 Hz, 1H), 7.54 (d, *J* = 2.0 Hz, 1H), 6.68 (s, 1H), 5.21 - 5.01 (m, 1H), 4.51 (br d, *J* = 6.0 Hz, 2H), 1.49 (s, 9H).

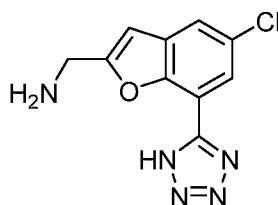


C) *tert*-Butyl ((5-chloro-7-(1H-tetrazol-5-yl)benzofuran-2-yl)methyl)carbamate

20

A reaction mixture of *tert*-butyl ((5-chloro-7-cyanobenzofuran-2-yl)methyl)carbamate (1.1 g, 3.59 mmol), sodium azide (0.280 g, 4.30 mmol) and ceric ammonium nitrate (0.197 g, 0.359 mmol) in *N,N*-dimethylformamide (12 mL) was heated at 100 °C under nitrogen atmosphere over night. The reaction mixture was cooled, and

diluted with brine and ethyl acetate. The organic layer was separated, washed with saturated NH₄Cl solution and brine successively, dried over MgSO₄, and filtered. The filtrate was concentrated *in vacuo*. The crude residue was dissolved in DCM and purified by silica gel column chromatography (40 g column, 0 – 10% MeOH in DCM) to give
 5 *tert*-butyl ((5-chloro-7-(1*H*-tetrazol-5-yl)benzofuran-2-yl)methyl)carbamate (0.8 g, 64% yield) as light yellow oil. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.26 (d, *J* = 2.0 Hz, 1H), 8.08 (s, 1H), 7.69 (d, *J* = 2.0 Hz, 1H), 6.67 (s, 1H), 5.89 - 5.73 (m, 1H), 4.52 (d, *J* = 6.2 Hz, 2H), 1.49 (s, 9H); MS (ESI+) *m/z* = 350.2 (M+H)⁺.



10

D) (5-Chloro-7-(1*H*-tetrazol-5-yl)benzofuran-2-yl)methanamine

To a solution of *tert*-butyl ((5-chloro-7-(1*H*-tetrazol-5-yl)benzofuran-2-yl)methyl)carbamate (0.8 g, 2.287 mmol) in DCM (8 mL) was added TFA (1.41 mL, 18.30 mmol). The reaction mixture was stirred at room temperature for 3 hours. The
 15 reaction mixture was concentrated *in vacuo*. To the residue was added DCM (precipitate forms) and the resulting mixture was filtered to give (5-chloro-7-(1*H*-tetrazol-5-yl)benzofuran-2-yl)methanamine, TFA salt (0.5 g, 60%) as a white solid. ¹H NMR (400 MHz, Methanol-*d*₄) δ 8.09 (d, *J* = 2.0 Hz, 1H), 7.89 (d, *J* = 2.1 Hz, 1H), 7.12 (s, 1H), 4.46 (s, 2H); MS (ESI+) *m/z* = 233.1 (M-17+H)⁺.

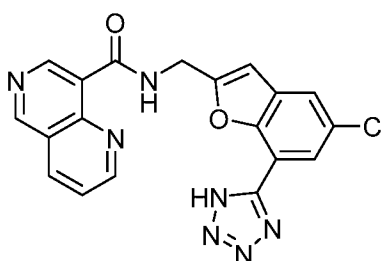
20

E) *N*-((5-chloro-7-(1*H*-tetrazol-5-yl)benzofuran-2-yl)methyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

To a suspension of pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (30 mg, 0.184 mmol) in DMF (1 mL) was added BOP (114 mg, 0.257 mmol). The reaction mixture was
 25 stirred at room temperature for 20 min, then (5-chloro-7-(1*H*-tetrazol-5-yl)benzofuran-2-yl)methanamine, TFA salt (66.9 mg, 0.184 mmol) and DIPEA (0.128 mL, 0.736 mmol)

were added. The resulting mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in DMF, filtered, and purified *via* HPLC (method B) to give *N*-((5-chloro-7-(1*H*-tetrazol-5-yl)benzofuran-2-yl)methyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (35.5 mg, 49% yield). ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.29 (d, *J* = 7.0 Hz, 1H), 8.85 - 8.75 (m, 1H), 8.62 (s, 1H), 8.54 (br t, *J* = 5.6 Hz, 1H), 7.96 - 7.81 (m, 2H), 7.28 (dd, *J* = 6.9, 4.2 Hz, 1H), 6.92 (s, 1H), 4.86 (br d, *J* = 5.9 Hz, 2H); MS (ESI+) *m/z* = 395.2 (M+H)⁺.

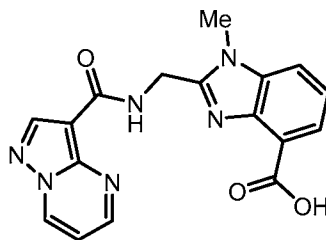
EXAMPLE 410



N-((5-Chloro-7-(1*H*-tetrazol-5-yl)benzofuran-2-yl)methyl)-1,6-naphthyridine-8-carboxamide

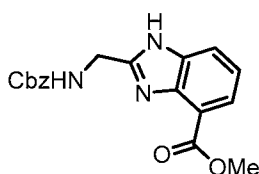
To a suspension of 1,6-naphthyridine-8-carboxylic acid HCl salt (15.06 mg, 0.071 mmol) in DMF (1 mL) was added BOP (34.1 mg, 0.077 mmol). The reaction mixture was stirred at room temperature for 20 min, then (5-chloro-7-(1*H*-tetrazol-5-yl)benzofuran-2-yl)methanamine TFA salt (58.6 mg, 0.161 mmol) (Step D of Example 409) and DIPEA (0.113 mL, 0.645 mmol) were added. The resulting mixture was stirred at rt for 1 hour. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in DMF, filtered, and purified *via* HPLC (Method B) to give *N*-((5-Chloro-7-(1*H*-tetrazol-5-yl)benzofuran-2-yl)methyl)-1,6-naphthyridine-8-carboxamid (1.2 mg, 5.4% yield). ¹H NMR (500 MHz, DMSO-*d*₆) δ 10.97 (br s, 1H), 9.58 (s, 1H), 9.34 (s, 1H), 9.30 (br d, *J* = 2.7 Hz, 1H), 8.76 (br d, *J* = 7.9 Hz, 1H), 7.89 - 7.82 (m, 2H), 7.75 (s, 1H), 6.94 (s, 1H), 4.91 (br d, *J* = 5.5 Hz, 2H); MS (ESI+) *m/z* = 405.9 (M+H)⁺.

EXAMPLE 411



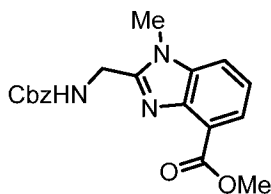
1-methyl-2-((pyrazolo[1,5-a]pyrimidine-3-carboxamido)methyl)-1H-benzo[d]imidazole-4-carboxylic acid

5



A) Methyl 2-(((benzyloxy)carbonyl)amino)methyl)-1H-benzo[d]imidazole-7-carboxylate

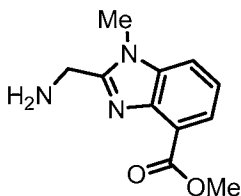
Methyl 2,3-diaminobenzoate (1.15 g, 6.92 mmol) was taken up in acetonitrile (27.7 ml). ((benzyloxy)carbonyl)glycine (1.737 g, 8.30 mmol) was added followed by DIPEA (1.813 ml, 10.38 mmol) and BOP-Cl (2.290 g, 9.00 mmol). Reaction stirred at room temperature overnight. The reaction was then diluted with sat. aq. bicarb and extracted with EtOAc. Organics were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude mixture was purified via silica gel column chromatography to give an amide intermediate (*ca.* 1.1 g). This intermediate was taken up in 30 mL of acetic acid and heated for 1 hour at 65 °C. The reaction was then concentrated in vacuo, diluted with water, and extracted with EtOAc. The organic extracts were combined, dried over sodium sulfate, filtered, and concentrated *in vacuo* to give the title compound (0.96 g, 2.83 mmol, 40.9 % yield). ¹H NMR (400 MHz, DMSO-d₆) δ 12.21 (br s, 1H), 7.88 (br d, *J*=7.9 Hz, 1H), 7.80 (d, *J*=6.9 Hz, 1H), 7.40 - 7.31 (m, 5H), 7.30 - 7.26 (m, 1H), 5.07 (s, 2H), 4.52 (d, *J*=5.9 Hz, 2H), 3.95 (s, 3H); MS (ESI+) *m/z* = 340.5 (M+H)⁺.



B) Methyl 2-(((benzyloxy)carbonyl)amino)methyl)-1-methyl-1H-benzo[d]imidazole-4-carboxylate

Methyl 2-(((benzyloxy)carbonyl)amino)methyl)-1H-benzo[d]imidazole-7-
 5 carboxylate (800 mg, 2.357 mmol) was taken up in DMF (9430 μ l) and cesium carbonate (1152 mg, 3.54 mmol) was added followed by methyl iodide (177 μ l, 2.83 mmol). The reaction was stirred at room temperature for 4 hours. The reaction was diluted with water, extracted with EtOAc, and the combined organics were back-extracted with 1/2 saturated brine to remove DMF. Organics were then dried over sodium sulfate, filtered,
 10 and concentrated *in vacuo*. The crude residue was purified via silica gel column chromatography to give the title compound (498 mg, 1.409 mmol, 59.8 % yield). ^1H NMR (500 MHz, DMSO- d_6) δ 7.82 (d, $J=7.9$ Hz, 1H), 7.76 (dd, $J=7.6, 1.0$ Hz, 1H), 7.39 - 7.28 (m, 6H), 5.08 (s, 2H), 4.57 (d, $J=5.9$ Hz, 2H), 3.88 (s, 3H), 3.83 (s, 3H); MS (ESI+) $m/z = 354.5$ (M+H) $^+$.

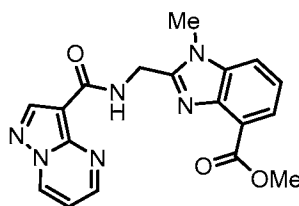
15



C) Methyl 2-(aminomethyl)-1-methyl-1H-benzo[d]imidazole-4-carboxylate

Methyl 2-(((benzyloxy)carbonyl)amino)methyl)-1-methyl-1H-
 20 benzo[d]imidazole-4-carboxylate (498 mg, 1.409 mmol) was taken up in ethanol (14 mL) and placed under a nitrogen atmosphere. Palladium on carbon (10% by wt) (150 mg, 0.141 mmol) was added and the reaction was then vacated and flushed three times with hydrogen gas (balloon). The reaction stirred overnight at room temperature under a hydrogen balloon. The reaction was filtered over celite and the filtrate was concentrated

in vacuo to the title compound (276 mg, 0.944 mmol, 67.0 % yield). ¹H NMR (400 MHz, DMSO-d₆) δ 7.10 (br d, *J*=7.3 Hz, 1H), 6.95 (br d, *J*=7.8 Hz, 1H), 6.62 - 6.52 (m, 1H), 4.04 (s, 3H), 3.17 (s, 3H), 3.07 (s, 2H); MS (ESI+) *m/z* = 220.2 (M+H)⁺.



5

D) Methyl 1-methyl-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)-1H-benzo[*d*]imidazole-4-carboxylate

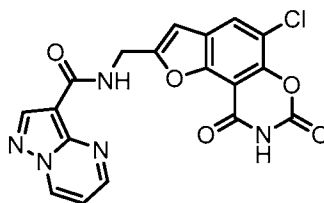
Pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (15 mg, 0.092 mmol) was dissolved in DMF (368 μl) and DIPEA (64.2 μl, 0.368 mmol) and methyl 2-(aminomethyl)-1-
 10 methyl-1H-benzo[*d*]imidazole-4-carboxylate (20.16 mg, 0.092 mmol) were added. BOP (61.0 mg, 0.138 mmol) was added and the reaction was stirred at room temperature for 2 hours. The reaction was diluted with DMF, filtered, and purified directly via preparative HPLC (method B) to give the title compound (13.4 mg, 0.035 mmol, 38.6 % yield) as a white solid. ¹H NMR (500 MHz, DMSO-d₆) δ 9.24 (dd, *J*=7.0, 1.2 Hz, 1H), 8.83 - 8.79
 15 (m, 1H), 8.71 (br t, *J*=5.2 Hz, 1H), 8.61 (s, 1H), 7.81 (d, *J*=8.2 Hz, 1H), 7.76 (d, *J*=7.3 Hz, 1H), 7.34 (t, *J*=7.9 Hz, 1H), 7.26 (dd, *J*=7.0, 4.3 Hz, 1H), 4.92 (d, *J*=5.5 Hz, 2H), 3.87 (s, 3H), 3.64 (br s, 3H); MS (ESI+) *m/z* = 365.1 (M+H)⁺.

E) 1-Methyl-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)-1H-benzo[*d*]imidazole-4-carboxylic acid

Methyl 1-methyl-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)-1H-
 20 benzo[*d*]imidazole-4-carboxylate (35 mg, 0.096 mmol) was taken up in THF (384 μl), water (384 μl), and MeOH (192 μl). LiOH (23.00 mg, 0.961 mmol) was added and reaction stirred at room temperature for 2 hours. The reaction was concentrated *in vacuo*, taken up in DMF, filtered, and purified directly by preparative HPLC (method B) to the
 25 title compound (5.7 mg, 0.016 mmol, 16.80 % yield) as a white solid. ¹H NMR (500 MHz, DMSO-d₆) δ 9.31 (br d, *J*=6.7 Hz, 1H), 8.89 (br s, 1H), 8.84 (br s, 1H), 8.64 (s, 1H), 7.88 (br d, *J*=7.6 Hz, 1H), 7.81 (br d, *J*=7.3 Hz, 1H), 7.41 (br t, *J*=7.8 Hz, 1H), 7.30

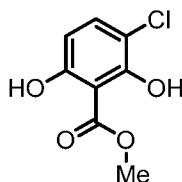
(br dd, $J=6.7, 4.3$ Hz, 1H), 4.97 (br d, $J=4.9$ Hz, 2H), 3.92 (s, 3H); MS (ESI+) $m/z = 351.3$ (M+H)⁺.

EXAMPLE 412



5

***N*-((5-chloro-7,9-dioxo-8,9-dihydro-7H-benzofuro[7,6-*e*][1,3]oxazin-2-yl)methyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide**

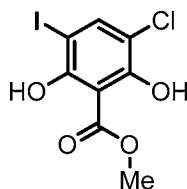


10 **A) Methyl 3-chloro-2,6-dihydroxybenzoate**

To a flask charged with methyl 2,6-dihydroxybenzoate (1.5 g, 8.92 mmol) was added sulfuryl chloride, 1 M in DCM (13.38 mL, 13.38 mmol) under N₂. The mixture was cooled to 0 °C and Et₂O (1.391 mL, 13.38 mmol) was added. The reaction mixture was warmed to room temperature and stirred for 70 min. An additional portion of

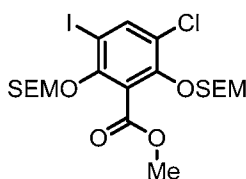
15 sulfuryl chloride, 1 M in DCM (4.5 mL, 4.5 mmol) and Et₂O (0.47 mL, 4.5 mmol) was added and the reaction mixture was stirred for 30 min. An additional portion of sulfuryl chloride, 1 M in DCM (2.3 mL, 2.3 mmol) and Et₂O (0.24 mL, 2.3 mmol) was added and the reaction mixture was stirred for 15 min. The reaction mixture was concentrated *in vacuo* to give the title compound (1.79 g, 99%). ¹H NMR (400 MHz, Chloroform-*d*) δ

20 10.31 (br s, 1H), 9.51 (br s, 1H), 7.44 (d, $J=9.0$ Hz, 1H), 6.51 (d, $J=8.9$ Hz, 1H), 4.14 (s, 3H); MS (ESI+) $m/z = 203.0$ (M+H)⁺.



B) Methyl 3-chloro-2,6-dihydroxy-5-iodobenzoate

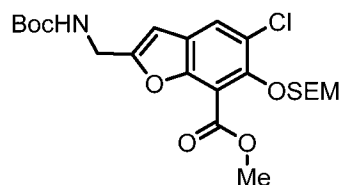
To a suspension of methyl 3-chloro-2,6-dihydroxybenzoate (1.79 g, 8.81 mmol) in AcOH (5.04 mL) was added NIS (2.97 g, 13.22 mmol). The headspace was flushed with N₂ and the vessel was sealed and heated to 65 °C for 30 min. The reaction mixture was cooled to room temperature, quenched with a saturated aqueous solutions of NaHCO₃ and Na₂S₂O₃, and extracted with EtOAc. The organic layers were combined, washed with brine, dried over MgSO₄, filtered, and concentrated *in vacuo*. The residue was dissolved in DCM and purified by silica gel flash chromatography to give the title compound (1.63 g, 56%). ¹H NMR (400 MHz, Chloroform-d) δ 10.47 (s, 1H), 10.20 (br s, 1H), 7.91 (s, 1H), 4.17 (s, 3H); MS (ESI+) m/z = not observed; product does not ionize well on MS.



C) Methyl 3-chloro-5-iodo-2,6-bis((2-(trimethylsilyl)ethoxy)methoxy)benzoate

To a solution of methyl 3-chloro-2,6-dihydroxy-5-iodobenzoate (1.74 g, 5.29 mmol) in DCM (26.4 mL) was added Hunig's Base (5.54 mL, 31.7 mmol) at 0 °C. SEMCl (2.34 mL, 13.22 mmol) was added and the reaction vessel was flushed with N₂, sealed, and warmed to room temperature and stirred for 5 hours. An additional portion of SEMCl (0.47 mL, 2.65 mmol) was added and the reaction mixture was stirred for 1.5 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layers were combined, washed with brine, dried over MgSO₄, filtered, and concentrated *in vacuo*. The residue was dissolved in DCM and purified by flash chromatography to give the title compound (3.02 g, 97%). ¹H NMR (400 MHz,

Chloroform-d) δ 7.88 (s, 1H), 5.19 (s, 2H), 5.15 (s, 2H), 3.93 (s, 3H), 3.91 - 3.81 (m, 4H), 1.05 - 0.99 (m, 4H), 0.06 (s, 9H), 0.05 (s, 9H). MS (ESI+) m/z = not observed; product does not ionize well on MS.

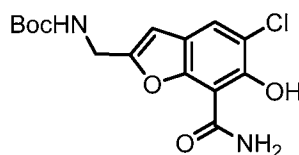


5

D) Methyl 2-(((tert-butoxycarbonyl)amino)methyl)-5-chloro-6-((2-(trimethylsilyl)ethoxy)methoxy)benzofuran-7-carboxylate

To a solution of *tert*-butyl prop-2-yn-1-ylcarbamate (916 mg, 5.90 mmol) and methyl 3-chloro-5-iodo-2,6-bis((2-(trimethylsilyl)ethoxy)methoxy)benzoate (3.02 g, 5.13 mmol) in DMF (477 μ l) was added Et₃N (638 μ l, 4.57 mmol). The mixture was sparged with N₂ for 13 min and then copper(I) iodide (98 mg, 0.513 mmol) and bis(triphenylphosphine)palladium(II) chloride (180 mg, 0.257 mmol) was added. The reaction mixture was sparged with N₂ for an additional 3 min, sealed, and heated to 80 °C for 2.5 h. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. The residue was dissolved in DCM and purified by flash chromatography to give the title compound (1.35 g, 54%). ¹H NMR (400 MHz, Chloroform-d) δ 7.66 (s, 1H), 6.57 (s, 1H), 5.22 (s, 2H), 5.00 (br d, J =2.9 Hz, 1H), 4.45 (br d, J =5.9 Hz, 2H), 4.03 (s, 3H), 3.94 - 3.87 (m, 2H), 1.48 (s, 9H), 1.02 (d, J =17.2 Hz, 2H), 0.06 (s, 9H). MS (ESI+) m/z = 524.0 (M+K)⁺.

15



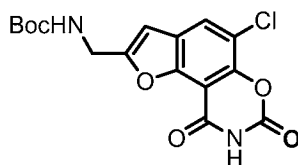
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E) Tert-butyl ((7-carbamoyl-5-chloro-6-hydroxybenzofuran-2-yl)methyl)carbamate

Methyl 2-(((tert-butoxycarbonyl)amino)methyl)-5-chloro-6-((2-(trimethylsilyl)ethoxy)methoxy)benzofuran-7-carboxylate (139.7 mg, 0.287 mmol) and ammonia, 7 M in MeOH (411 μ l, 2.87 mmol) were added to a 2 dram pressure relief vial.

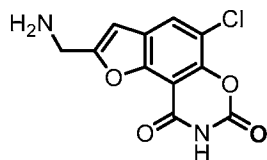
25

The suspension was sonicated to give a homogenous tan solution. The reaction was sealed with a red safety pressure relief cap, placed behind a blast shield, and stirred at room temperature under ambient atmosphere. After 1.5 hours, reaction was heated to 65 °C. After 1 hour, a second portion of ammonia, 7 M in MeOH (411 μ l, 2.87 mmol), was added. The reaction was flushed with nitrogen gas, sealed with a red safety pressure relief cap, and heated to 65 °C. After 5 hours, another 0.82 mL of ammonia, 7 M in MeOH was added and the reaction stirred at 65 °C overnight. After 20 hours, another 0.82 mL of ammonia, 7 M in MeOH was added and the reaction stirred at 65 °C overnight. The reaction was then cooled and concentrated under reduced pressure to give the title compound (105 mg, *ca.* quant) as a tan solid. ¹H NMR (400 MHz, Chloroform-d) δ 13.49 (br s, 1H), 7.68 (s, 1H), 6.55 (s, 1H), 6.02 (br s, 1H), 4.76 (br s, 1H), 4.45 (br d, J=6.1 Hz, 2H), 1.49 (s, 9H); MS (ESI+) m/z = 284.9 (M-*t*Bu+H)⁺.



15 **F) *Tert*-butyl ((5-chloro-7,9-dioxo-8,9-dihydro-7H-benzofuro[7,6-e][1,3]oxazin-2-yl)methyl)carbamate**

Tert-butyl ((7-carbamoyl-5-chloro-6-hydroxybenzofuran-2-yl)methyl)carbamate (49.7 mg, 0.146 mmol) was suspended in MeCN (729 μ l) in a 2 dram pressure relief vial and flushed with nitrogen gas. Pyridine (73.1 μ l, 0.904 mmol) was added and the reaction was cooled to 0 °C. A solution of ethyl chloroformate (15.41 μ l, 0.160 mmol) in MeCN (729 μ l) was added dropwise. The reaction was then sealed with a red safety pressure relief cap, placed behind a blast shield and heated to 100 °C for 24 hours. After 24 hours, the reaction was cooled and an additional portion of ethyl chloroformate (15.41 μ l, 0.160 mmol) in MeCN (729 μ l) was added. The reaction was again heated to 100 °C for an additional 15 hours. The reaction was purified directly via silica gel column chromatography to give the title compound (21.1 mg, 33% yield) as a colorless film. ¹H NMR (400 MHz, Chloroform-d) δ 9.05 - 8.64 (m, 1H), 7.92 (s, 1H), 6.71 (s, 1H), 5.24 (br s, 1H), 4.55 (br d, J=6.0 Hz, 2H), 1.49 (s, 9H); MS (ESI+) m/z = 310.9 (M-*t*Bu+H)⁺.



G) 2-(Aminomethyl)-5-chloro-7H-benzofuro[7,6-e][1,3]oxazine-7,9(8H)-dione

5 *Tert*-butyl ((5-chloro-7,9-dioxo-8,9-dihydro-7*H*-benzofuro[7,6-*e*][1,3]oxazin-2-yl)methyl)carbamate (21.2 mg, 0.058 mmol) was taken up in DCM (434 μ l). TFA (145 μ l) was added and the reaction mixture turned from golden tan to red. The reaction was sealed with a septa and stirred at room temperature under ambient atmosphere for 1.5 hours. The reaction was then concentrated *in vacuo* and azetroped with toluene before
 10 placing on high vacuum to give the title compound (25.4 mg, 96% yield) as a colorless film. ^1H NMR (400 MHz, MeOH- d_4) δ 8.18 (s, 1H), 7.12 (s, 1H), 5.19 (s, 1H), 4.45 (s, 2H); MS (ESI+) m/z = 267.0 (M + H) $^+$.

H) *N*-((5-chloro-7,9-dioxo-8,9-dihydro-7*H*-benzofuro[7,6-*e*][1,3]oxazin-2-yl)methyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

15 2-(Aminomethyl)-5-chloro-7*H*-benzofuro[7,6-*e*][1,3]oxazine-7,9(8*H*)-dione, TFA (25.4 mg, 0.067 mmol) was suspended in (667 μ l) in a 25 mL round bottom flask. Pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (14.15 mg, 0.087 mmol) and ((1*H*-benzo[*d*][1,2,3]triazol-1-yl)oxy)tris(dimethylamino)phosphonium
 20 hexafluorophosphate(V) (38.4 mg, 0.087 mmol) were added followed by, followed by *N*-ethyl-*N*-isopropylpropan-2-amine (41.8 μ l, 0.240 mmol). The reaction was sealed with a septa, sonicated, and stirred the suspension at room temperature under ambient atmosphere for 1 hour. The reaction was then diluted with 1.33 mL DMF, filtered and purified directly via preparative HPLC (method B) to give compound 19 (9.2 mg, 34%
 25 yield) as an off-white solid. ^1H NMR (500 MHz, DMSO- d_6) δ 12.26 (br s, 1H), 9.33 (dd, $J=7.0, 1.7$ Hz, 1H), 8.83 (dd, $J=4.2, 1.7$ Hz, 1H), 8.63 (s, 1H), 8.52 (t, $J=5.9$ Hz, 1H),

8.16 (s, 1H), 7.29 (dd, $J=7.0, 4.2$ Hz, 1H), 6.86 (s, 1H), 4.82 (d, $J=5.7$ Hz, 2H); MS (ESI+) $m/z = 412.0$ (M +H)⁺.

EVALUATION OF BIOLOGICAL ACTIVITY

5 Exemplified compounds were evaluated for direct binding to STING as well as STING agonist functional activity on both the IRF and NF- κ B pathways in a cellular reporter assay (protocols described subsequently). It was generally observed that some exemplified compounds containing carboxylic acids bound to STING but did not possess agonist activity in the cellular reporter assay. Conversely, it was generally observed that
10 some exemplified compounds containing esters did not bind to STING but did possess agonist activity in the cellular reporter assay. One possible hypothesis consistent with these observations is that acids are the active species that bind to STING, but they are not cell membrane permeable (PAMPA data supports this statement), and therefore do not show agonist activity in the reporter assay. Furthermore, esters could be acting as
15 prodrugs of the above acids that do not, themselves, bind to STING, but can pass through a cellular membrane (also supported by PAMPA data) where they are subsequently cleaved to unmask the analogous acid, which could then act as a STING agonist. Further evidence for this hypothesis includes: 1) co-crystals with either human or murine STING could only be obtained for acids and acid isosteres and not for esters, 2) cell-permeable
20 acids and acid isosteres generally showed measurable agonist activity in the cellular reporter assay, and 3) metabolism studies showed that esters displaying agonist activity were readily cleaved to acids in cellular settings.

STING Reporter Assay Protocol

25 THP1-Dual™ cells were derived from the human THP-1 monocyte cell line by stable integration of two inducible reporter constructs. To this end, THP1-Dual™ cells allow the simultaneous study of the NF- κ B pathway, by monitoring the activity of SEAP, and the IRF pathway by assessing the activity of a secreted luciferase (Lucia). Both reporter proteins are readily measurable in the cell culture supernatant when using
30 QUANTI-Blue™, a SEAP detection reagent, and QUANTI-Luc™, a luciferase detection reagent.

THP1-Dual™ cells induce the activation of NF-κB in response to STING agonists. They also trigger the IRF pathway upon stimulation with STING agonists, such as cGAMP. Here, the THP-1-Dual cells were used to assess STING specific binders for function on the cellular level.

5 Serial dilutions of compounds in DMSO were added to low volume 384 well plates at 100nl/well using an ECHO acoustic dispenser (Labcyte, model 550) to achieve final starting concentration of 100 μM in cell suspension. THP-1 Dual™ STING reporter cells (Invivogen, Dual cells cat #THPD-nfis) were added to the plates with compounds at 15,000 cells in 10 μL per well in RPMI media (Gibco, cat #11875) containing 10%
 10 human plasma in a low volume 384-well black wall clear bottom tissue culture plate (Corning, cat #3542) for SEAP assay and low volume solid white plate (Corning, cat #3826) for luciferase assay. One column of the plate was reserved for treatment with cGAMP at 100 μM for 100 % activation calculation and one column for no treatment (DMSO only) for baseline activation. Plates were then incubated in 37 °C incubator at 5%
 15 CO₂ for 20 hours.

In the SEAP assay, 5 μl of 2x QuantiBlue (Invivogen, cat # Rep-qb2) is added to 384 well black plates seeded with THP1 cells and incubated at 37 °C for 2 hours. Plates were read on the Envision (Perkin Elmer) at 620 nm wavelength (OD620). In the
 20 luciferase assay, 5 μl of Quantiluc (Invivogen, Rep-qlc2) is added to white 384 well plates seeded with THP1 cells and read at 5 minutes on the Envision (Perkin Elmer) using a luminescence protocol (RLU). 100% activation was determined by value (RLU) of THP-1 Dual STING cells stimulated with 100 μM cGAMP (Invivogen, cat # TLRL-NACGA23-5).

25

EXAMPLE #	IRF (EC₅₀ μM)	NFκB (EC₅₀ μM)
EXAMPLE 1	96	98
EXAMPLE 2	12	13
EXAMPLE 3	51	92
EXAMPLE 4	13	14
EXAMPLE 5	5.7	6.3

EXAMPLE #	IRF (EC₅₀ μM)	NFκB (EC₅₀ μM)
EXAMPLE 6	5.1	3.1
EXAMPLE 7	4.3	4.1
EXAMPLE 8	21	18
EXAMPLE 9	2.1	1.8
EXAMPLE 10	7.5	7.6
EXAMPLE 11	6.1	6.7
EXAMPLE 12	33	39
EXAMPLE 13	8.7	11
EXAMPLE 14	3.8	6.0
EXAMPLE 15	44	39
EXAMPLE 16	6.8	9.3
EXAMPLE 17	48	73
EXAMPLE 18	79	97
EXAMPLE 19	47	95
EXAMPLE 20	48	49
EXAMPLE 21	2.9	3.1
EXAMPLE 22	0.60	0.67
EXAMPLE 23	2.0	1.8
EXAMPLE 25	10	15
EXAMPLE 26	0.63	0.67
EXAMPLE 28	3.1	3.6
EXAMPLE 29	3.0	2.9
EXAMPLE 30	27	31
EXAMPLE 31	1.1	1.6
EXAMPLE 32	3.5	3.4
EXAMPLE 33	11	16
EXAMPLE 34	79	>100
EXAMPLE 35	0.53	0.77
EXAMPLE 36	3.6	4.1
EXAMPLE 37	11	12
EXAMPLE 38	2.3	2.5
EXAMPLE 39	4.0	3.6
EXAMPLE 40	2.1	3.2
EXAMPLE 41	>33	1.3
EXAMPLE 42	4.1	3.6
EXAMPLE 43	19	24
EXAMPLE 44	12	13
EXAMPLE 45	0.98	0.99

EXAMPLE #	IRF (EC₅₀ μM)	NFκB (EC₅₀ μM)
EXAMPLE 46	1.5	1.5
EXAMPLE 47	6.7	8.5
EXAMPLE 48	0.64	0.68
EXAMPLE 49	71	93
EXAMPLE 50	0.93	1.1
EXAMPLE 51	4.0	3.1
EXAMPLE 52	8.0	9.8
EXAMPLE 53	22	27
EXAMPLE 54	2.6	2.6
EXAMPLE 55	1.1	1.1
EXAMPLE 56	30	>33
EXAMPLE 57	9.5	8.1
EXAMPLE 58	2.7	2.9
EXAMPLE 59	2.4	2.6
EXAMPLE 60	7.7	8.9
EXAMPLE 61	21	21
EXAMPLE 62	42	46
EXAMPLE 63	10	16
EXAMPLE 64	68	>100
EXAMPLE 65	3.0	3.1
EXAMPLE 66	28	33
EXAMPLE 67	20	32
EXAMPLE 68	1.7	2.1
EXAMPLE 69	1.3	2.3
EXAMPLE 70	24	>100
EXAMPLE 71	24	33
EXAMPLE 72	1.2	17
EXAMPLE 73	2.1	2.6
EXAMPLE 74	3.3	3.5
EXAMPLE 75	22	37
EXAMPLE 76	3.0	4.1
EXAMPLE 77	5.5	6.3
EXAMPLE 78	3.4	3.7
EXAMPLE 79	1.5	1.7
EXAMPLE 80	0.80	1.1
EXAMPLE 81	16	22
EXAMPLE 82	27	20
EXAMPLE 83	37	48

EXAMPLE #	IRF (EC₅₀ μM)	NFκB (EC₅₀ μM)
EXAMPLE 84	30	27
EXAMPLE 85	3.5	3.6
EXAMPLE 86	1.7	1.8
EXAMPLE 87	5.5	5.8
EXAMPLE 88	21	20
EXAMPLE 89	0.21	0.19
EXAMPLE 90	2.2	3.0
EXAMPLE 91	1.2	1.5
EXAMPLE 92	0.80	0.81
EXAMPLE 93	3.7	6.0
EXAMPLE 94	1.8	2.1
EXAMPLE 95	13	16
EXAMPLE 96	1.7	2.0
EXAMPLE 97	2.1	1.5
EXAMPLE 98	11	10
EXAMPLE 99	17	12
EXAMPLE 100	2.5	2.2
EXAMPLE 101	12	10
EXAMPLE 102	2.5	3.0
EXAMPLE 103	25	23
EXAMPLE 104	63	37
EXAMPLE 105	4.7	3.4
EXAMPLE 106	0.75	1.1
EXAMPLE 107	1.4	2.0
EXAMPLE 108	21	31
EXAMPLE 109	0.90	1.1
EXAMPLE 110	0.22	0.27
EXAMPLE 111	1.2	1.4
EXAMPLE 112	0.20	0.26
EXAMPLE 113	0.32	0.51
EXAMPLE 114	0.97	0.89
EXAMPLE 115	0.60	0.82
EXAMPLE 116	2.9	3.1
EXAMPLE 117	0.20	0.28
EXAMPLE 118	0.30	0.37
EXAMPLE 119	2.6	2.6
EXAMPLE 120	2.7	3.2
EXAMPLE 121	0.40	0.28

EXAMPLE #	IRF (EC₅₀ μM)	NFκB (EC₅₀ μM)
EXAMPLE 122	0.53	0.54
EXAMPLE 123	4.3	5.9
EXAMPLE 124	5.7	6.7
EXAMPLE 125	3.9	4.4
EXAMPLE 126	1.4	1.6
EXAMPLE 127	4.7	5.6
EXAMPLE 139	90	>100
EXAMPLE 141	97	93
EXAMPLE 158	63	52
EXAMPLE 161	108	138
EXAMPLE 172	62	74
EXAMPLE 174	83	91
EXAMPLE 176	51	56
EXAMPLE 177	87	>100
EXAMPLE 178	42	50
EXAMPLE 184	73	78
EXAMPLE 186	84	>100
EXAMPLE 192	79	94
EXAMPLE 203	44	65
EXAMPLE 204	32	41
EXAMPLE 205	9.8	9.9
EXAMPLE 206	13	12
EXAMPLE 207	9.2	17
EXAMPLE 208	33	31
EXAMPLE 209	18	19
EXAMPLE 210	30	25
EXAMPLE 211	23	31
EXAMPLE 212	52	58
EXAMPLE 213	79	86
EXAMPLE 214	8.2	9.3
EXAMPLE 215	12	14
EXAMPLE 216	12	17
EXAMPLE 217	1.3	1.6
EXAMPLE 218	5.5	4.4
EXAMPLE 219	7.7	10
EXAMPLE 220	3.8	4.8
EXAMPLE 221	42	83
EXAMPLE 222	26	33

EXAMPLE #	IRF (EC₅₀ μM)	NFκB (EC₅₀ μM)
EXAMPLE 223	0.67	0.62
EXAMPLE 224	5.9	4.0
EXAMPLE 225	7.5	7.5
EXAMPLE 226	1.4	1.3
EXAMPLE 227	3.8	4.2
EXAMPLE 228	6.1	6.5
EXAMPLE 229	4.2	4.2
EXAMPLE 230	0.93	0.95
EXAMPLE 231	0.50	0.65
EXAMPLE 232	1.0	0.92
EXAMPLE 233	1.7	2.0
EXAMPLE 234	1.1	1.1
EXAMPLE 235	0.69	0.68
EXAMPLE 236	1.3	1.8
EXAMPLE 237	1.2	1.2
EXAMPLE 238	1.6	1.7
EXAMPLE 239	0.53	0.39
EXAMPLE 240	0.78	0.61
EXAMPLE 241	2.3	2.3
EXAMPLE 242	2.4	2.1
EXAMPLE 243	1.6	1.9
EXAMPLE 244	2.0	1.9
EXAMPLE 245	1.8	1.0
EXAMPLE 246	1.1	1.0
EXAMPLE 247	9.0	13
EXAMPLE 248	73	98
EXAMPLE 249	2.4	2.5
EXAMPLE 250	1.2	0.62
EXAMPLE 251	0.93	1.0
EXAMPLE 252	6.4	5.4
EXAMPLE 253	0.96	0.93
EXAMPLE 254	0.87	0.88
EXAMPLE 255	13	19
EXAMPLE 256	6.7	4.8
EXAMPLE 257	28	11
EXAMPLE 258	3.0	3.5
EXAMPLE 259	2.3	2.2
EXAMPLE 260	1.0	0.82

EXAMPLE #	IRF (EC₅₀ μM)	NFκB (EC₅₀ μM)
EXAMPLE 261	0.95	0.82
EXAMPLE 262	14	18
EXAMPLE 263	4.8	5.2
EXAMPLE 264	1.7	1.7
EXAMPLE 265	0.84	0.82
EXAMPLE 266	3.1	2.6
EXAMPLE 267	5.8	6.6
EXAMPLE 268	6.1	5.6
EXAMPLE 269	1.1	1.1
EXAMPLE 270	30	36
EXAMPLE 271	0.80	0.91
EXAMPLE 272	2.2	2.2
EXAMPLE 273	0.70	0.75
EXAMPLE 274	0.80	0.83
EXAMPLE 275	0.94	0.72
EXAMPLE 276	3.0	3.4
EXAMPLE 277	13	16
EXAMPLE 278	6.6	5.5
EXAMPLE 279	35	25
EXAMPLE 280	2.5	2.4
EXAMPLE 281	11	14
EXAMPLE 282	12	12
EXAMPLE 283	0.40	0.52
EXAMPLE 284	9.6	6.3
EXAMPLE 285	1.4	1.9
EXAMPLE 286	2.7	2.5
EXAMPLE 287	12	18
EXAMPLE 288	0.36	0.36
EXAMPLE 289	0.62	0.71
EXAMPLE 290	0.25	0.35
EXAMPLE 291	0.34	0.31
EXAMPLE 292	1.7	1.1
EXAMPLE 293	4.4	3.8
EXAMPLE 294	0.80	0.93
EXAMPLE 295	1.1	0.56
EXAMPLE 296	5.7	4.6
EXAMPLE 297	3.1	3.2
EXAMPLE 298	3.6	3.3

EXAMPLE #	IRF (EC₅₀ μM)	NFκB (EC₅₀ μM)
EXAMPLE 299	0.28	0.33
EXAMPLE 300	0.76	0.71
EXAMPLE 301	2.1	2.7
EXAMPLE 302	0.43	0.52
EXAMPLE 303	0.53	0.58
EXAMPLE 304	7.6	8.3
EXAMPLE 305	5.0	3.9
EXAMPLE 306	1.3	1.3
EXAMPLE 307	7.7	8.9
EXAMPLE 308	25	30
EXAMPLE 309	6.1	7.2
EXAMPLE 310	37	56
EXAMPLE 311	2.0	2.3
EXAMPLE 312	21	56
EXAMPLE 313	3.1	3.0
EXAMPLE 314	1.9	1.9
EXAMPLE 315	2.1	1.9
EXAMPLE 316	4.8	5.9
EXAMPLE 317	1.4	1.3
EXAMPLE 318	4.3	4.5
EXAMPLE 319	2.4	2.5
EXAMPLE 320	1.4	1.4
EXAMPLE 321	0.30	0.38
EXAMPLE 322	2.2	3.3
EXAMPLE 323	0.75	0.70
EXAMPLE 324	1.5	1.7
EXAMPLE 325	1.7	1.4
EXAMPLE 326	74	>100
EXAMPLE 327	73	79
EXAMPLE 328	1.3	1.5
EXAMPLE 329	0.88	0.89
EXAMPLE 330	4.7	5.5
EXAMPLE 331	1.7	1.8
EXAMPLE 332	1.1	1.1
EXAMPLE 333	11	12
EXAMPLE 334	16	23
EXAMPLE 335	3.5	3.5
EXAMPLE 336	3.2	2.5

EXAMPLE #	IRF (EC₅₀ μM)	NFκB (EC₅₀ μM)
EXAMPLE 337	9.8	13
EXAMPLE 338	46	48
EXAMPLE 339	1.8	1.4
EXAMPLE 340	0.91	0.92
EXAMPLE 341	1.6	2.5
EXAMPLE 342	7.2	6.0
EXAMPLE 343	0.73	0.76
EXAMPLE 344	0.63	0.76
EXAMPLE 345	5.7	3.6
EXAMPLE 346	3.2	2.3
EXAMPLE 347	3.3	2.3
EXAMPLE 348	5.6	3.9
EXAMPLE 349	3.8	3.5
EXAMPLE 350	17	54
EXAMPLE 351	1.9	2.4
EXAMPLE 352	1.9	3.4
EXAMPLE 353	10	18
EXAMPLE 354	46	70
EXAMPLE 355	0.96	1.3
EXAMPLE 356	13	18
EXAMPLE 357	0.90	1.0
EXAMPLE 358	2.9	2.0
EXAMPLE 359	3.8	4.0
EXAMPLE 360	2.8	3.4
EXAMPLE 361	5.5	7.2
EXAMPLE 362	5.7	4.6
EXAMPLE 363	3.5	3.2
EXAMPLE 364	35	21
EXAMPLE 365	7.5	4.4
EXAMPLE 366	4.0	4.0
EXAMPLE 367	7.5	9.5
EXAMPLE 368	11	11
EXAMPLE 369	0.91	1.1
EXAMPLE 370	13	16
EXAMPLE 371	2.5	2.8
EXAMPLE 372	3.7	4.6
EXAMPLE 373	3.9	3.9
EXAMPLE 374	4.3	3.5

EXAMPLE #	IRF (EC₅₀ μM)	NFκB (EC₅₀ μM)
EXAMPLE 375	2.6	2.3
EXAMPLE 376	19	16
EXAMPLE 377	0.40	0.30
EXAMPLE 378	1.3	1.2
EXAMPLE 379	13	19
EXAMPLE 381	13	12
EXAMPLE 382	1.3	1.1
EXAMPLE 383	0.92	1.1
EXAMPLE 384	3.2	3.0
EXAMPLE 385	2.1	2.5
EXAMPLE 386	3.4	3.7
EXAMPLE 387	1.9	2.1
EXAMPLE 388	1.5	1.4
EXAMPLE 389	0.58	0.56
EXAMPLE 390	0.53	0.29
EXAMPLE 391	0.75	0.61
EXAMPLE 392	3.4	2.7
EXAMPLE 393	0.39	0.30
EXAMPLE 394	>100	11
EXAMPLE 395	2.1	1.9
EXAMPLE 396	0.36	0.37
EXAMPLE 397	0.46	0.47
EXAMPLE 398	9.4	5.7
EXAMPLE 399	1.3	1.5
EXAMPLE 400	25	22
EXAMPLE 401	1.9	1.9
EXAMPLE 402	2.4	2.4
EXAMPLE 403	>100	97
EXAMPLE 404	>100	83
EXAMPLE 405	30	61
EXAMPLE 406	9.4	7.1
EXAMPLE 407	30	37
EXAMPLE 408	0.91	1.2
EXAMPLE 409	107	191
EXAMPLE 410	79	>100
EXAMPLE 412	48	37

STING Displacement and Dimerization Protocols

Dimerization Protocol: A time resolved FRET-based assay was used to assess test article-induced dimerization of the cytoplasmic domain (amino acids 155-341) of WT (232R) STING, AQ (G230A-R293Q) STING, and mouse (M) STING. His-tagged

5 STING and enzymatically biotinylated STING at a concentration of 10 nM each were incubated with 2.5 nM Tb-labeled anti-His antibody, 5 nM d2-labeled Streptavidin (Cisbio cat. no. 610SADLF), and test compound for one hour in PBS containing 0.005% Tween-20 and 0.1% BSA. Fluorescence at 660 nm and 610 nm was measured using an EnVision microplate reader to quantify FRET between Tb-labeled anti-His antibody and

10 d2-labeled Streptavidin. Background was defined as the signal obtained in the absence of STING protein, and background subtracted FRET ratios were normalized to the maximum signal obtained with complete dimerization in the presence of 150 nM 2'3'-cGAMP (InvivoGen cat. no. tlr1-nacga23-02). These values were converted to percent dimerization. Percent dimerization was determined for test compounds at 11

15 concentrations. The EC₅₀, defined as the concentration of test compound needed to induce 50% dimerization, was calculated using the 4 parameter logistic equation to fit the data.

Competition Binding (Displacement) Protocol: A time resolved FRET-based

20 competition binding assay was used to assess test article binding to the cytoplasmic domain (amino acids 155-341) of WT (232R) STING, AQ (G230A-R293Q) STING, and mouse (M) STING. His-tagged STING cytoplasmic domain at a concentration of 20 nM was incubated with 2.5 nM Tb-labeled anti-His antibody, test compound, and fluorescein-labeled cGAMP analog probe (BioLog cat. no. C195) at a concentration of 200 nM (WT

25 STING) or 40 nM (G230A-R293Q STING and mouse STING) for one hour in PBS containing 0.005% Tween-20 and 0.1% BSA. Fluorescence at 495 nm and 520 nm was measured using an EnVision microplate reader to quantify FRET between Tb-labeled anti-His antibody and fluorescein-labeled probe. Background was defined as the signal obtained in the absence of STING protein, and background subtracted FRET ratios were

30 normalized to the maximum signal obtained in the absence of test compound. These values were converted to a percent inhibition. Percent inhibition was determined for test compounds at 11 concentrations. The IC₅₀, defined as the concentration of competing

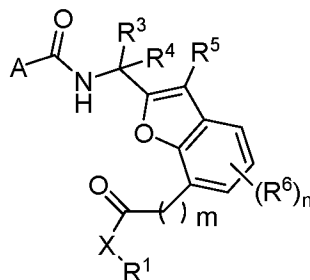
test compound needed to reduce specific binding of the probe by 50%, was calculated using the 4 parameter logistic equation to fit the data.

EXAMPLE #	Dimerization EC ₅₀ μ M			Displacement IC ₅₀ μ M		
	WT	AQ	M	WT	AQ	M
EXAMPLE 24	>100	97	31	>100	31	5.0
EXAMPLE 27	>100	45	35	90	15	7.7
EXAMPLE 130	>100	>100	>100	>100	>100	24
EXAMPLE 131	71	50	14	40	15	1.1
EXAMPLE 132	>100	88	26	44	16	3.0
EXAMPLE 133	>100	83	65	58	24	19
EXAMPLE 134	>100	71	34	>100	21	5.1
EXAMPLE 135	>100	>100	>100	>100	>100	45
EXAMPLE 136	54	19	4.1	15	2.2	0.34
EXAMPLE 137	>100	>100	>100	>100	>100	8.1
EXAMPLE 138	57	26	16	20	5.0	1.0
EXAMPLE 140	>100	>100	>100	>100	58	45
EXAMPLE 142	>100	96	34	>100	41	4.0
EXAMPLE 143	>100	>100	>100	>100	>100	98
EXAMPLE 144	40	28	18	23	8.2	2.1
EXAMPLE 147	>100	36	15	21	4.9	1.5
EXAMPLE 148	>100	>100	77	41	20	9.2
EXAMPLE 149	>100	97	50	99	39	16
EXAMPLE 150	>100	>100	>100	>100	88	40
EXAMPLE 151	>100	>100	35	>100	44	8.6
EXAMPLE 152	>100	>100	43	>100	51	8.9
EXAMPLE 153	>100	>100	51	99	35	6.7
EXAMPLE 154	>100	>100	>100	>100	>100	41
EXAMPLE 155	>100	>100	>100	>100	>100	42
EXAMPLE 156	>100	64	52	78	34	17
EXAMPLE 157	56	31	15	29	8.5	2.4
EXAMPLE 160	>100	41	24	21	7.6	2.6
EXAMPLE 162	>100	>100	>100	>100	73	20
EXAMPLE 163	>100	>100	>100	>100	>100	42
EXAMPLE 164	>100	>100	66	>100	94	25
EXAMPLE 165	>100	>100	>100	>100	98	57
EXAMPLE 166	94	35	10	90	14	2.7
EXAMPLE 167	>100	87	16	>100	32	1.8

EXAMPLE #	Dimerization EC ₅₀ □M			Displacement IC ₅₀ □M		
	WT	AQ	M	WT	AQ	M
EXAMPLE 168	>100	>100	>100	>100	57	2.9
EXAMPLE 169	67	37	17	15	4.9	0.54
EXAMPLE 170	>100	>100	>100	>100	>100	16
EXAMPLE 171	38	11	9.0	20	3.3	0.65
EXAMPLE 173	>100	69	60	80	19	16
EXAMPLE 175	>100	82	77	72	16	18
EXAMPLE 179	>100	76	39	>100	35	28
EXAMPLE 180	>100	>100	>100	>100	61	69
EXAMPLE 182	>100	>100	>100	>100	49	48
EXAMPLE 183	>100	59	35	87	13	3.3
EXAMPLE 185	>100	>100	61	28	4.5	2.6
EXAMPLE 187	>100	>100	61	>100	41	8.4
EXAMPLE 188	>100	>100	22	>100	72	2.2
EXAMPLE 189	>100	45	22	98	18	4.9
EXAMPLE 190	>100	>100	71	>100	64	40
EXAMPLE 191	>100	>100	47	94	50	5.6
EXAMPLE 194	>100	>100	20	69	30	2.1
EXAMPLE 195	>100	49	38	62	14	6.6
EXAMPLE 196	59	46	>100	85	38	37
EXAMPLE 197	>100	>100	38	>100	40	23
EXAMPLE 201	59	28	37	15	3.8	5.0
EXAMPLE 202	>100	42	65	60	8.8	19
EXAMPLE 411	12	2.5	29	3.8	23	4.8

We claim:

1. A compound of formula I



5

wherein

A is a 5-12 membered heterocyclic group substituted with 0-4 R² groups,

X is O, S or NH,

R¹ is hydrogen, CD₃, CF₃, OH, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, halo C₁₋₃ alkyl, aryl C₁₋₃ alkyl, hydroxy C₁₋₄ alkyl, halo C₁₋₃ alkoxy, NHR', 4-10 membered heterocycle or aryl, all of said alkyl, cycloalkyl, heterocyclyl or aryl groups substituted with 0-4 R^{1a}; with the proviso that R¹ is OH only when X is NH;

R^{1a} is halogen, CN, C₁₋₄ alkyl, halo C₁₋₃ alkyl, 4-10 membered heterocycle or aryl, all of said alkyl, heterocyclyl or aryl groups substituted with 0-2 R^{1b};

15 R^{1b} is halogen or C₁₋₄ alkyl,

R' is hydrogen, OH, C₁₋₃ alkoxy or C₁₋₃ alkyl;

R² is, independently at each occurrence, hydrogen, halogen, CN, OH, COOH, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, halo C₁₋₃ alkyl, hydroxy C₁₋₄ alkyl, halo C₁₋₃ alkoxy, NHR', 4-10 membered heterocycle or aryl, all of said alkyl, heterocyclyl or aryl groups substituted with 0-2 R^{2a},

20

R^{2a} is halogen,

R³ and R⁴ are independently hydrogen or C₁₋₃ alkyl,

R⁵ is hydrogen, halogen, CF₃, C₁₋₆ alkyl, C₁₋₆ alkoxy or C₁₋₆ alkenyl,;

R⁶ is hydrogen, halogen, OH, CF₃, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkenyl, CN or C₃₋₆

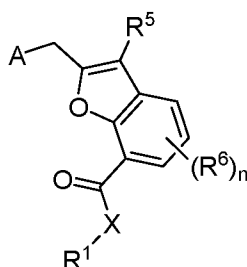
25 cycloalkyl

m is 0 or 1,

n is 0, 1, 2 or 3,
or a pharmaceutically acceptable salt thereof.

2. A compound of formula II

5



wherein

10 A is a 5-12 membered heterocyclic group substituted with 0-4 R² groups,
X is O, S or NH,

R¹ is hydrogen, CD₃, CF₃, OH, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, halo C₁₋₃ alkyl, aryl C₁₋₃ alkyl, hydroxy C₁₋₄ alkyl, halo C₁₋₃ alkoxy, NHR², 4-10 membered heterocycle or aryl, all of said alkyl, cycloalkyl, heterocyclyl or aryl groups substituted
15 with 0-4 R^{1a}, with the proviso that R¹ is OH only when X is NH;

R^{1a} is halogen, CN, C₁₋₄ alkyl, halo C₁₋₃ alkyl, 4-10 membered heterocycle or aryl, all of said alkyl, heterocyclyl or aryl groups substituted with 0-2 R^{1b};

R^{1b} is halogen or C₁₋₄ alkyl,

R² is hydrogen, OH, C₁₋₃ alkoxy or C₁₋₃ alkyl;

20 R² is, independently at each occurrence, hydrogen, halogen, CN, OH, carbonyl, COOH, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, halo C₁₋₃ alkyl, hydroxy C₁₋₄ alkyl, halo C₁₋₃ alkoxy, NHR², 4-10 membered heterocycle or aryl, all of said alkyl, heterocyclyl or aryl groups substituted with 0-2 R^{2a},

R^{2a} is halogen,

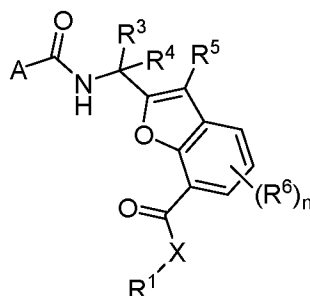
25 R⁵ is hydrogen, halogen, CF₃, C₁₋₆ alkyl, C₁₋₆ alkoxy or C₁₋₆ alkenyl,

R⁶ is hydrogen, halogen, OH, CF₃, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkenyl, CN or C₃₋₆ cycloalkyl

n is 0, 1, 2 or 3,

or a pharmaceutically acceptable salt thereof.

3. The compound according to claim 1 of the formula



5

wherein

A is a 5-12 membered heterocyclic group substituted with 0-4 R² groups,

X is O, S or NH,

10 R¹ is hydrogen, CD₃, CF₃, OH, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, halo C₁₋₃ alkyl, aryl C₁₋₃ alkyl, hydroxy C₁₋₄ alkyl, halo C₁₋₃ alkoxy, NHR', 4-10 membered heterocycle or aryl, all of said alkyl, cycloalkyl, heterocyclyl or aryl groups substituted with 0-4 R^{1a}, with the proviso that R¹ is OH only when X is NH;

15 R^{1a} is halogen, CN, C₁₋₄ alkyl, halo C₁₋₃ alkyl, 4-10 membered heterocycle or aryl, all of said alkyl, heterocyclyl or aryl groups substituted with 0-2 R^{1b};

R^{1b} is halogen or C₁₋₄ alkyl,

R' is hydrogen, OH, C₁₋₃ alkoxy or C₁₋₃ alkyl;

20 R² is, independently at each occurrence, hydrogen, halogen, CN, OH, COOH, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, halo C₁₋₃ alkyl, hydroxy C₁₋₄ alkyl, halo C₁₋₃ alkoxy, NHR', 4-10 membered heterocycle or aryl, all of said alkyl, heterocyclyl or aryl groups substituted with 0-2 R^{2a},

R^{2a} is halogen,

R³ and R⁴ are independently hydrogen or C₁₋₃ alkyl,

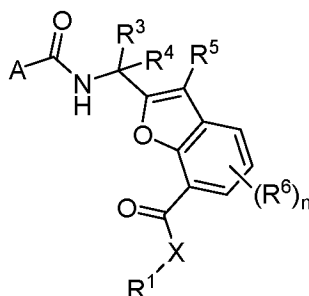
R⁵ is hydrogen, halogen, CF₃, C₁₋₆ alkyl, C₁₋₆ alkoxy or C₁₋₆ alkenyl,

25 R⁶ is hydrogen, halogen, OH, CF₃, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkenyl, CN or C₃₋₆ cycloalkyl

n is 0, 1, 2 or 3,

or a pharmaceutically acceptable salt thereof.

4. The compound according to claim 3 of the formula



5

wherein

A is a 5-12 membered heterocyclic group substituted with 0-4 R^2 groups,

X is O,

10 R^1 is hydrogen, CD_3 , CF_3 , C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, halo C_{1-3} alkyl, aryl C_{1-3} alkyl, hydroxy C_{1-4} alkyl, halo C_{1-3} alkoxy, NHR^7 , 4-10 membered heterocycle or aryl, all of said alkyl, cycloalkyl, heterocyclyl or aryl groups substituted with 0-4 R^{1a} ;

R^{1a} is halogen, CN, C_{1-4} alkyl, halo C_{1-3} alkyl, 4-10 membered heterocycle or aryl, all of said alkyl, heterocyclyl or aryl groups substituted with 0-2 R^{1b} ;

15 R^{1b} is halogen or C_{1-4} alkyl,

R^7 is hydrogen, OH, C_{1-3} alkoxy or C_{1-3} alkyl;

R^2 is, independently at each occurrence, hydrogen, halogen, CN, OH, COOH, C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, halo C_{1-3} alkyl, hydroxy C_{1-4} alkyl, halo C_{1-3} alkoxy, NHR^7 , 4-10 membered heterocycle or aryl, all of said alkyl, heterocyclyl or aryl groups

20 substituted with 0-2 R^{2a} ,

R^{2a} is halogen,

R^3 and R^4 are independently hydrogen or C_{1-3} alkyl,

R^5 is hydrogen, halogen, CF_3 , C_{1-6} alkyl, C_{1-6} alkoxy or C_{1-6} alkenyl,

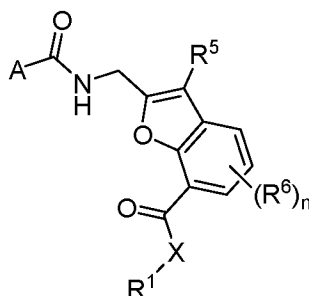
R^6 is hydrogen, halogen, OH, CF_3 , C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkenyl, CN or C_{3-6}

25 cycloalkyl

n is 0, 1, 2 or 3,

or a pharmaceutically acceptable salt thereof.

5. The compound according to claim 4 of the formula



5

wherein

A is a 5-12 membered heterocyclic group substituted with 0-4 R² groups,

X is O,

R¹ is hydrogen, CD₃, CF₃, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, halo C₁₋₃ alkyl,
 10 aryl C₁₋₃ alkyl, hydroxy C₁₋₄ alkyl, halo C₁₋₃ alkoxy, NHR', 4-10 membered heterocycle or
 aryl, all of said alkyl, cycloalkyl, heterocyclyl or aryl groups substituted with 0-4 R^{1a};

R^{1a} is halogen, CN, C₁₋₄ alkyl, halo C₁₋₃ alkyl, 4-10 membered heterocycle or aryl,
 all of said alkyl, heterocyclyl or aryl groups substituted with 0-2 R^{1b};

R^{1b} is halogen or C₁₋₄ alkyl,

15 R' is hydrogen, OH, C₁₋₃ alkoxy or C₁₋₃ alkyl;

R² is, independently at each occurrence, hydrogen, halogen, CN, OH, COOH, C₁₋₆
 alkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, halo C₁₋₃ alkyl, hydroxy C₁₋₄ alkyl, halo C₁₋₃ alkoxy,
 NHR', 4-10 membered heterocycle or aryl, all of said alkyl, heterocyclyl or aryl groups
 substituted with 0-2 R^{2a},

20 R^{2a} is halogen,

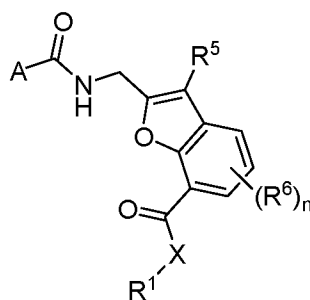
R⁵ is hydrogen, halogen, CF₃, C₁₋₆ alkyl, C₁₋₆ alkoxy or C₁₋₆ alkenyl,

R⁶ is hydrogen, halogen, OH, CF₃, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkenyl, CN or C₃₋₆
 cycloalkyl

n is 0, 1, 2 or 3,

25 or a pharmaceutically acceptable salt thereof.

6. The compound according to claim 5 of the formula



wherein

5 A is a 6-10 membered heterocyclic group substituted with 0-4 R^2 groups,
 X is O,

R^1 is hydrogen, CD_3 , CF_3 , C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, halo C_{1-3} alkyl, aryl C_{1-3} alkyl, hydroxy C_{1-4} alkyl, halo C_{1-3} alkoxy, NHR^7 , 4-10 membered heterocycle or aryl, all of said alkyl, cycloalkyl, heterocyclyl or aryl groups substituted with 0-4 R^{1a} ;

10 R^{1a} is halogen, CN, C_{1-4} alkyl, halo C_{1-3} alkyl, 4-10 membered heterocycle or aryl, all of said alkyl, heterocyclyl or aryl groups substituted with 0-2 R^{1b} ;

R^{1b} is halogen or C_{1-4} alkyl,

R^7 is hydrogen, OH, C_{1-3} alkoxy or C_{1-3} alkyl;

15 R^2 is, independently at each occurrence, hydrogen, halogen, CN, OH, COOH, C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, halo C_{1-3} alkyl, hydroxy C_{1-4} alkyl, halo C_{1-3} alkoxy, NHR^7 , 4-10 membered heterocycle or aryl, all of said alkyl, heterocyclyl or aryl groups substituted with 0-2 R^{2a} ,

R^{2a} is halogen,

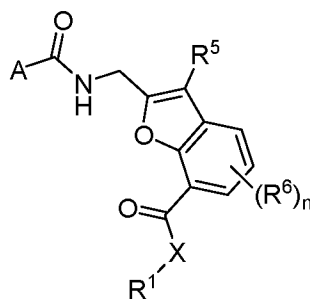
R^5 is hydrogen, halogen, CF_3 , C_{1-6} alkyl, C_{1-6} alkoxy or C_{1-6} alkenyl,

20 R^6 is hydrogen, halogen, OH, CF_3 , C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkenyl, CN or C_{3-6} cycloalkyl

 n is 0, 1, 2 or 3,

 or a pharmaceutically acceptable salt thereof.

25 7. The compound according to claim 6 of the formula



wherein

A is a pyrazinyl group, a pyrimidinyl group, a pyridinyl group, a pyrazole-pyrimidinyl group, an imidazo-pyridazinyl group, a thiazolo-pyridinyl group, imidazo-pyridinyl group or a naphthyridinyl group, each of said groups substituted with 0-4 R² groups,

X is O,

R¹ is hydrogen, CD₃, CF₃, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, halo C₁₋₃ alkyl, aryl C₁₋₃ alkyl, hydroxy C₁₋₄ alkyl, halo C₁₋₃ alkoxy, NHR', 4-10 membered heterocycle or aryl, all of said alkyl, cycloalkyl, heterocyclyl or aryl groups substituted with 0-4 R^{1a};

R^{1a} is halogen, CN, C₁₋₄ alkyl, halo C₁₋₃ alkyl, 4-10 membered heterocycle or aryl, all of said alkyl, heterocyclyl or aryl groups substituted with 0-2 R^{1b};

R^{1b} is halogen or C₁₋₄ alkyl,

R' is hydrogen, OH, C₁₋₃ alkoxy or C₁₋₃ alkyl;

R² is, independently at each occurrence, hydrogen, halogen, CN, OH, COOH, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, halo C₁₋₃ alkyl, hydroxy C₁₋₄ alkyl, halo C₁₋₃ alkoxy, NHR', 4-10 membered heterocycle or aryl, all of said alkyl, heterocyclyl or aryl groups substituted with 0-2 R^{2a},

R^{2a} is halogen,

R⁵ is hydrogen, halogen, CF₃, C₁₋₆ alkyl, C₁₋₆ alkoxy or C₁₋₆ alkenyl,

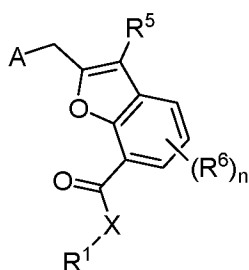
R⁶ is hydrogen, halogen, OH, CF₃, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkenyl, CN or C₃₋₆ cycloalkyl

n is 0, 1, 2 or 3,

or a pharmaceutically acceptable salt thereof.

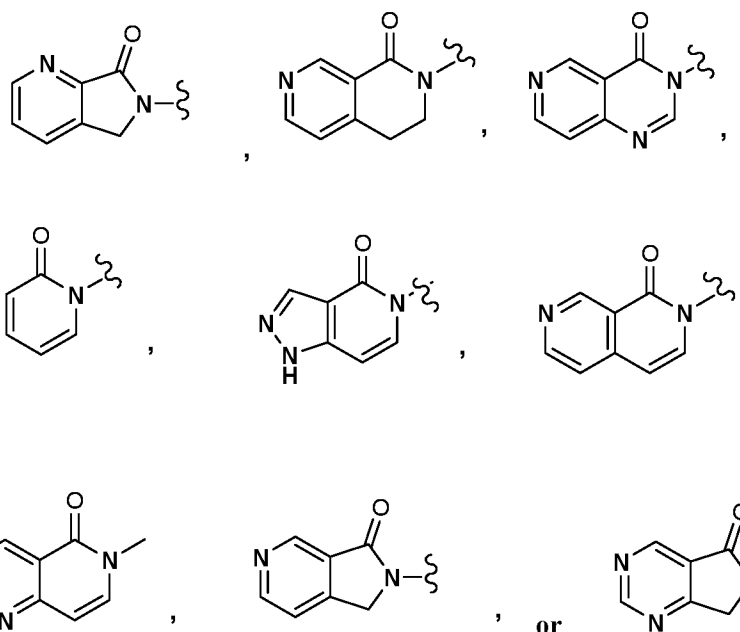
25

8. The compound according to claim 2 of the formula



wherein A is

5



substituted with 0-4 R^2 groups,

X is O, S or NH,

10

R^1 is hydrogen, CD_3 , CF_3 , OH, C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, halo C_{1-3} alkyl, aryl C_{1-3} alkyl, hydroxy C_{1-4} alkyl, halo C_{1-3} alkoxy, NHR' , 4-10 membered heterocycle or aryl, all of said alkyl, cycloalkyl, heterocyclyl or aryl groups substituted with 0-4 R^{1a} , with the proviso that R^1 is OH only when X is NH;

R^{1a} is halogen, CN, C_{1-4} alkyl, halo C_{1-3} alkyl, 4-10 membered heterocycle or aryl,

15

all of said alkyl, heterocyclyl or aryl groups substituted with 0-2 R^{1b} ;

R^{1b} is halogen or C_{1-4} alkyl,

R¹ is hydrogen, OH, C₁₋₃ alkoxy or C₁₋₃ alkyl;

R² is, independently at each occurrence, hydrogen, halogen, CN, OH, COOH, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, halo C₁₋₃ alkyl, hydroxy C₁₋₄ alkyl, halo C₁₋₃ alkoxy, NHR³, 4-10 membered heterocycle or aryl, all of said alkyl, heterocyclyl or aryl groups

5 substituted with 0-2 R^{2a},

R^{2a} is halogen or R^{1a} is halogen,

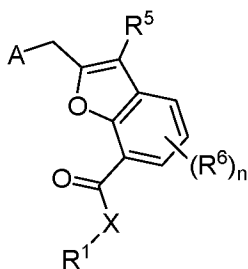
R⁵ is hydrogen, halogen, CF₃, C₁₋₆ alkyl, C₁₋₆ alkoxy or C₁₋₆ alkenyl,

R⁶ is hydrogen, halogen, OH, CF₃, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkenyl, CN or C₃₋₆ cycloalkyl

10 n is 0, 1, 2 or 3,

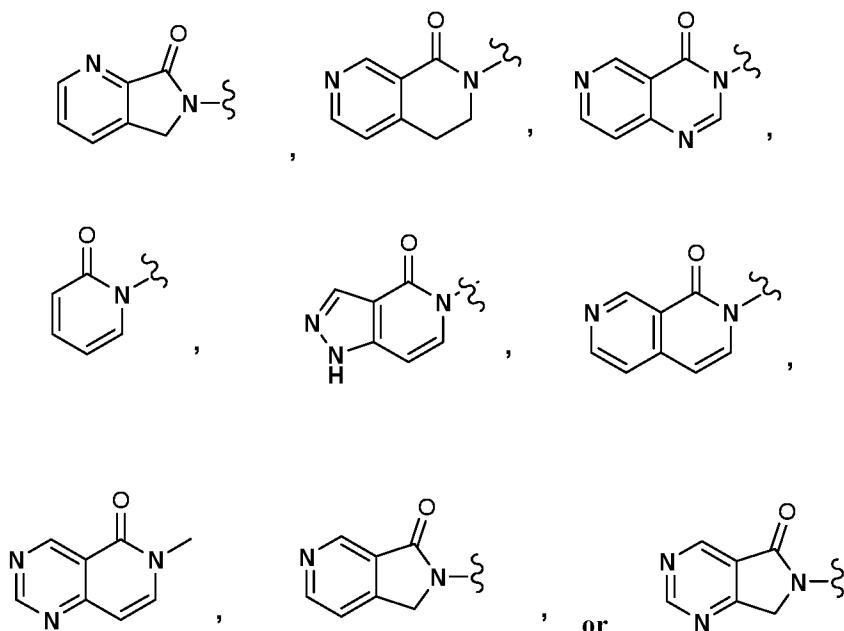
or a pharmaceutically acceptable salt thereof.

9. The compound according to claim 8 of the formula



15

wherein A is



substituted with 0-4 R² groups,

X is O,

5 R¹ is hydrogen, CD₃, CF₃, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl or halo C₁₋₃ alkyl, all of said alkyl groups substituted with 0-4 R^{1a};

R^{1a} is halogen;

R² is, independently at each occurrence, hydrogen, halogen, CN, OH, COOH, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, halo C₁₋₃ alkyl, hydroxy C₁₋₄ alkyl, halo C₁₋₃ alkoxy,

10 NHR', 4-10 membered heterocycle or aryl, all of said alkyl, heterocyclyl or aryl groups substituted with 0-2 R^{2a},

R^{2a} is halogen or R^{1a} is halogen,

R⁵ is hydrogen, halogen, CF₃, C₁₋₆ alkyl, C₁₋₆ alkoxy or C₁₋₆ alkenyl;

R⁶ is hydrogen, halogen, OH, CF₃, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkenyl, CN or C₃₋₆

15 cycloalkyl

n is 0, 1, 2 or 3,

or a pharmaceutically acceptable salt thereof.

10. A compound selected from

20 *Tert*-butyl 3-((5-chloro-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carbonyl)oxy)azetidine-1-carboxylate,(247)

Acetoxymethyl 5-chloro-2-((4,5-pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate, (259)

((Ethoxycarbonyloxy)methyl 5-chloro-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate, (260),

5 1-((Ethoxycarbonyloxy)ethyl 5-chloro-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate, (261)

1-Ethoxy-2,2-difluoroethyl 5-fluoro-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carboxylate, (323,324)

10 *S*-(2-(Trimethylsilyl)ethyl) 3-chloro-5-fluoro-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)benzofuran-7-carbothioate, (392)

S-(2-(Trimethylsilyl)ethyl) (*S*)-5-fluoro-2-(1-(pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)ethyl)benzofuran-7-carbothioate (398)

S-(2-(Trimethylsilyl)ethyl) (*S*)-5-chloro-2-(1-(pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)ethyl)benzofuran-7-carbothioate (400)

15 *N*-((5-Chloro-7-(1*H*-tetrazol-5-yl)benzofuran-2-yl)methyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (409),

N-((5-Chloro-7-(1*H*-tetrazol-5-yl)benzofuran-2-yl)methyl)-1,6-naphthyridine-8-carboxamide (410), or

a pharmaceutically acceptable salt thereof.

20

11. A pharmaceutical composition comprising a compound according to claim 1 or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable carriers, diluents or excipients.

25 12. A pharmaceutical composition comprising a compound according to claim 2 or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable carriers, diluents or excipients.

30 13. A method of treating diseases and conditions in which the modulation of STING is indicated in a subject in need thereof which comprises administering a therapeutically effective amount of compound according to claim 1 or a pharmaceutically acceptable salt thereof.

14. A method of treating cancer comprising administering a therapeutically effective amount of one or more compounds according to claim 1 or a pharmaceutically acceptable salt thereof.

5 15. The method of claim 14 wherein the cancer is small cell lung cancer, non-small cell lung cancer, colorectal cancer, melanoma, renal cell carcinoma, head and neck cancer, Hodgkin's lymphoma, bladder cancer, esophageal carcinoma, gastric carcinoma, ovarian carcinoma, cervical carcinoma, pancreatic carcinoma, prostate carcinoma, breast cancers, urinary carcinoma, brain tumors such as glioblastoma, non-Hodgkin's
10 lymphoma, acute lymphatic leukemia (ALL), chronic lymphatic leukemia (CLL), acute myeloid leukemia (AML), chronic myeloid leukemia (CML), hepatocellular carcinoma, multiple myeloma, gastrointestinal stromal tumors, mesothelioma, and other solid tumors or other hematological cancers.

15 16. The method of claim 15 wherein the cancer is small cell lung cancer, non-small cell lung cancer, colorectal cancer, melanoma, renal cell carcinoma, head and neck cancer, Hodgkin's lymphoma or bladder cancer.

17. A method for treating cancer in a subject in need thereof, comprising
20 administering an effective amount of a compound, according to claim 1, or a pharmaceutically acceptable salt thereof,

in combination with the administration of a therapeutically effective amount of one or more immuno-oncology agents.

25 18. A compound selected from
N-((5-chloro-7,9-dioxo-8,9-dihydro-7H-benzofuro[7,6-*e*][1,3]oxazin-2-yl)methyl)pyrazolo[1,5-*α*]pyrimidine-3-carboxamide,

N-((5-Chloro-7-(1*H*-tetrazol-5-yl)benzofuran-2-yl)methyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide,

N-((5-Chloro-7-(1*H*-tetrazol-5-yl)benzofuran-2-yl)methyl)-1,6-naphthyridine-8-carboxamide,

5 1-methyl-2-((pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)methyl)-1*H*-benzo[*d*]imidazole-4-carboxylic acid,

or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2022/015010

A. CLASSIFICATION OF SUBJECT MATTER		
INV. C07D405/06	C07D405/12	C07D413/14
C07D519/00	A61P35/00	A61K31/343
ADD.		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols) C07D A61P		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EPO-Internal, CHEM ABS Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>LEE SUN-KYUNG ET AL: "Studies on Benzofuran-7-carboxamides as Poly(ADP-ribose) Polymerase-1 (PARP-1) Inhibitors", BULLETIN OF THE KOREAN CHEMICAL SOCIETY, vol. 33, no. 4, 20 April 2012 (2012-04-20), pages 1147-1153, XP055905923, KR</p> <p>ISSN: 0253-2964, DOI: 10.5012/bkcs.2012.33.4.1147</p> <p>Retrieved from the Internet: URL:http://koreascience.or.kr/article/JAKO201213151420610.pdf> abstract</p> <p>* scheme 1 *;</p> <p>page 1148</p> <p>page 1149; table 1</p> <p align="center">-----</p> <p align="right">-/--</p>	2, 12, 14
<input checked="" type="checkbox"/>	Further documents are listed in the continuation of Box C.	<input checked="" type="checkbox"/> See patent family annex.
* Special categories of cited documents :		
"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention	
"E" earlier application or patent but published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone	
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art	
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family	
"P" document published prior to the international filing date but later than the priority date claimed		
Date of the actual completion of the international search	Date of mailing of the international search report	
4 April 2022	19/04/2022	
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Dunet, Guillaume	

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2022/015010

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95/09159 A1 (OTSUKA PHARMA CO LTD [JP]; KOMATSU MAKOTO [JP] ET AL.) 6 April 1995 (1995-04-06) abstract page 319; example 71 examples 1-487 claims 1-33	1, 3-6, 11
X	----- DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 28 August 2017 (2017-08-28), XP002806121, retrieved from STN Database accession no. 2121519-00-2 * RN 2121519-00-2, 2121518-82-7, 2121518-69-0 *	2
X	----- DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 25 August 2017 (2017-08-25), XP002806122, retrieved from STN Database accession no. 2120032-19-9 * RN 2120032-19-9, 2119999-30-1 *	2
X	----- DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 19 April 2016 (2016-04-19), XP002806123, retrieved from STN Database accession no. 1893159-27-7 * RN 1893159-27-7, 1893007-10-7 *	2
Y	----- WO 2018/234808 A1 (CURADEV PHARMA LTD [GB]) 27 December 2018 (2018-12-27) abstract examples 16, 22-24, 27, 32, 47, 48, 50, 52, 58 examples 1-300 claims 1-42	1-18
Y	----- WO 2018/234805 A1 (CURADEV PHARMA LTD [GB]) 27 December 2018 (2018-12-27) abstract examples 40, 69, 70, 208, 210, 235, 241 examples 1-285 examples 1-46	1-18
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INTERNATIONAL SEARCH REPORT

International application No PCT/US2022/015010
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>GB 2 572 526 A (CURADEV PHARMA LTD [GB]) 9 October 2019 (2019-10-09) abstract examples 34, 36, 101, 102, 106 examples 1-112 claims 1-42</p> <p align="center">-----</p>	1-18
Y	<p>GB 2 574 862 A (CURADEV PHARMA LTD [GB]) 25 December 2019 (2019-12-25) abstract examples 6, 27 examples 1-36 claims 1-36</p> <p align="center">-----</p>	1-18

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No PCT/US2022/015010
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date	
WO 9509159	A1	06-04-1995	AU 674613 B2	02-01-1997
			CA 2150345 A1	06-04-1995
			CN 1114834 A	10-01-1996
			EP 0670831 A1	13-09-1995
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			TW 284760 B	01-09-1996
			WO 9509159 A1	06-04-1995

WO 2018234808	A1	27-12-2018	AR 114975 A1	11-11-2020
			AU 2018288018 A1	16-01-2020
			BR 112019027127 A2	07-07-2020
			CA 3067257 A1	27-12-2018
			CL 2019003793 A1	07-08-2020
			CN 111132972 A	08-05-2020
			CO 2020000562 A2	31-01-2020
			EC SP20004580 A	29-05-2020
			EP 3642198 A1	29-04-2020
			JP 2020524719 A	20-08-2020
			KR 20200031616 A	24-03-2020
			PE 20200696 A1	16-06-2020
			PH 12019502870 A1	28-09-2020
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