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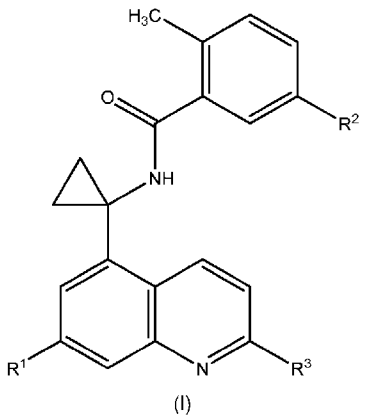
(54) Title: NOVEL 5-CYCLOPROYLQUINOLINE DERIVATIVES AS PLPRO INHIBITORS



(I)

(57) Abstract: The invention relates to compounds of Formula (I) and pharmaceutically acceptable salts thereof, wherein R^1 to R^3 are as defined in the description; to their use in medicine; to compositions containing them; to processes for their preparation; and to intermediates used in such processes. The compounds of Formula (I) may inhibit the activity and/or expression of PLpro and may be useful in the treatment, prevention, suppression, and amelioration of viral infections characterized with PLpro activity and/or expression such as coronavirus infections.

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Novel 5-Cyclopropylquinoline Derivatives As PLpro Inhibitors

PARTIES TO A JOINT RESEARCH AGREEMENT

The presently claimed invention was made by or on behalf of the below listed parties to a joint research agreement. The joint research agreement was in effect on or before the date the claimed invention was made and the claimed invention was made as a result of activities undertaken within the scope of the joint research agreement. The parties to the joint research agreement are PFIZER INC. and CLEAR CREEK BIO, INC.

BACKGROUND OF THE INVENTION

The present invention relates to novel compounds which are inhibitors of the papain-like protease (PLpro). The invention also relates to the preparation of these compounds and intermediates used in their preparation, compositions containing the compounds of the invention, and their use including their use to treat viral infections, in particular viral infections characterized with papain-like protease activity and/or expression such as coronavirus infections.

PLpro is a cysteine protease with a papain-like fold. PLpro is conserved across many coronaviruses, including SARS-CoV, MERS-CoV and SARS-CoV-2 (ACS Infect. Dis., 2020, 6, 8, 2099-2109). These viruses can cause severe acute respiratory tract infections, including the COVID-19 pandemic.

Viruses harboring PLpro, such as coronaviruses, are known in the literature to be causal agents of historic outbreaks and pandemics, for example the SARS outbreak in 2003 (N. Engl. J. Med., 2003; 349, 2431), the MERS-CoV outbreak in 2012 (Annu. Rev. Med. 2017. 68:387–99), and the COVID-19 pandemic beginning in 2020 (N. Engl. J. Med., 2020, 382, 727; Nat. Rev. Microbiol., 2022, 20, 270). They are also known in the literature to be likely to cause future pandemics (J. Infect. Dis., 2022, jiac296).

PLpro is responsible for processing cleavage sites in the viral polyproteins to produce functional units, which in turn assemble to execute RNA synthesis and other viral functions. PLpro also modulates host innate immune pathways, through deubiquitination and deISGylation activities. The enzymatic activity of PLpro is therefore essential to viral replication and evading host immune response (Nature, 2020, 587, 657-662). Numerous publications have evidenced that if PLpro can be selectively inhibited, it could prevent viral replication and be used in the treatment of viral infections (J. Med. Chem. 2022, 65, 4, 2940; Cell Chemical Biology, 2021, 28, 855–865; ACS Cent. Sci. 2021, 7, 7, 1245).

PLpro inhibitors have already been reported, for example in the aforementioned publications and in WO 2010/022355, WO 2022/192665, WO 2022/070048, WO 2022/169891 or WO 2022/189810. However, there remains a need for new compounds having an improved therapeutic profile as PLpro inhibitors, namely an improved activity. Accordingly, there remains a need for PLpro inhibitors with improved drug properties.

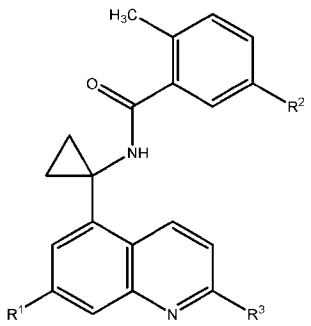
Summary of the Invention

The present invention provides, in part, compounds of Formula (I) and pharmaceutically acceptable salts thereof. Such compounds may inhibit the activity of the papain-like protease (PLpro) and may be useful in the treatment, prevention, suppression and amelioration of viral infections, in particular viral infections characterized with PLpro activity and/or expression such as coronaviruses infections, and infections caused by other nidoviruses.

Also provided are pharmaceutical compositions, comprising the compounds or salts of the invention, alone or in combination with other therapeutic agents, which may provide greater clinical benefit. Such additional therapeutic agents include, but are not limited to, viral RNA polymerase inhibitors, Mpro inhibitors, nucleoside inhibitors, host factor inhibitors, other PLpro inhibitors or metabolism boosting agents that leads to reduction in virus replication or host response that may contribute to greater clinical benefit.

The present invention also provides, in part, methods for preparing such compounds, pharmaceutically acceptable salts and compositions of the invention, and methods of using the foregoing. This summary is provided to introduce a selection of concepts in a simplified form that are further described below in the detailed description. This summary is not intended to identify key features or essential features of the claimed subject matter, nor is it intended to be used in isolation as an aid in determining the scope of the claimed subject matter.

According to an embodiment of the invention there is provided a compound of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, C_2-C_6 alkenyl, C_3-C_6 cycloalkyl, 3- to 6- membered heterocycloalkyl with one to three heteroatoms independently selected from N, O, or S, and 5- to 6-membered heteroaryl with one to three heteroatoms independently selected from N, O, or S; wherein said heterocycloalkyl or heteroaryl is optionally substituted with C_1-C_3 alkyl, C_1-C_3 fluoroalkyl, cyano, deuterium, halo (e.g., F, Cl, Br, and/or I), or C_1-C_3 alkoxy optionally substituted with 1 to 3 fluoro;

R^2 is selected from:

-NR^4R^5, wherein R^4 and R^5 taken together with the nitrogen atom (i.e., first ring nitrogen atom) to which they are attached form a 4- to 10-membered heterocycloalkyl ring containing a second ring nitrogen atom, wherein the second ring nitrogen atom is optionally substituted with (C_1-C_3)alkyl; and wherein the 4- to 10-membered heterocycloalkyl ring optionally contains a third heteroatom selected from O or S; wherein the 4- to 10-membered heterocycloalkyl ring is monocyclic, or the 4- to 10-membered heterocycloalkyl ring is bicyclic and optionally bridged, fused, or spirocyclic; or

R^2 is selected from -O-(C_1-C_6 alkyl) substituted with -NR^6R^7; wherein one of the carbon atoms of said -O-(C_1-C_6 alkyl) moiety may optionally interconnect with another carbon atom of said -O-(C_1-C_6 alkyl) moiety to form a C_3-C_4 cycloalkyl ring;

wherein R^6 is H or C_1-C_3 alkyl optionally substituted with hydroxy, 1 to 3 deuteriums, or 1 to 3 fluoro;

wherein R^7 is H or C_1-C_3 alkyl optionally substituted with hydroxy; wherein said C_1-C_3 alkyl moiety may optionally interconnect with one of the carbon atoms of said -O-(C_1-C_6 alkyl) moiety of R^2 to form a 4- or 5-membered heterocycloalkyl containing a nitrogen atom;

and wherein one to three hydrogens in R^2 may optionally be replaced by deuterium; and

R^3 is selected from the group consisting of H, D, $-CD_3$, C_1-C_6 alkyl, and C_1-C_6 fluoroalkyl.

In some embodiments, R^3 is selected from H, methyl, and fluorinated methyl (e.g., fluoromethyl, difluoromethyl, or trifluoromethyl).

Described below are embodiments of the invention, where for convenience Embodiment 1 (E1) is identical to the embodiment of Formula (I) provided above.

It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as claimed.

Detailed Description of the Invention

The present invention may be understood more readily by reference to the following detailed description of the embodiments of the invention and the Examples included herein. It is to be understood that this invention is not limited to specific synthetic methods of making that may of course vary. It is to be also understood that the terminology used herein is for the purpose of describing specific embodiments only and is not intended to be limiting.

E1 A compound of Formula (I) or a pharmaceutically acceptable salt thereof, as defined above.

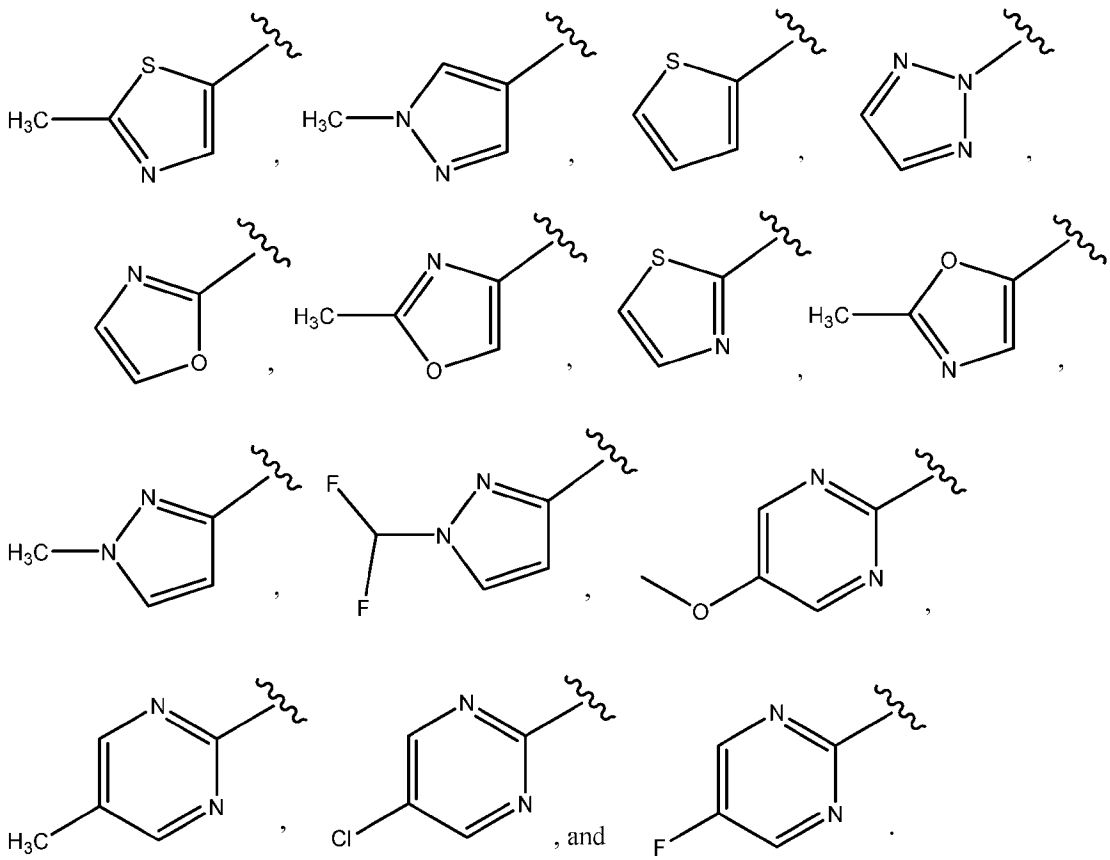
E2 A compound of embodiment E1 or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, C_2-C_6 alkenyl, 3- to 6- membered heterocycloalkyl with one to three heteroatoms independently selected from N, O, or S, and 5- to 6-membered heteroaryl with one to three heteroatoms independently selected from N, O, or S; wherein said heteroaryl is optionally substituted with C_1-C_3 alkyl, C_1-C_3 fluoroalkyl, cyano, deuterium, halo, or C_1-C_3 alkoxy optionally substituted with 1 to 3 fluoro.

E3 A compound of any one of embodiments E1 to E2 or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, C_2-C_6 alkenyl, and 5- to 6-membered heteroaryl with one to three heteroatoms independently selected from N, O, or S; wherein said heteroaryl is optionally substituted with C_1-C_3 alkyl, C_1-C_3 fluoroalkyl, halo, or C_1-C_3 alkoxy optionally substituted with 1 to 3 fluoro.

E4 A compound of any one of embodiments E1 to E3 or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, C_2-C_6 alkenyl, and 5- to 6-membered heteroaryl with one to three heteroatoms independently selected from N, O, or S; wherein said heteroaryl is optionally substituted with C_1-C_3 alkyl, C_1-C_3 fluoroalkyl, halo, or C_1-C_3 alkoxy optionally substituted with 1 to 3 fluoro.

E5 A compound of any one of embodiments E1 to E4, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from the group consisting of C_1-C_3 alkyl, C_1-C_3 fluoroalkyl, and 5- to 6-membered heteroaryl with one to three heteroatoms independently selected from N, O, or S; wherein said heterocycloalkyl is optionally substituted with C_1-C_3 alkyl, C_1-C_3 fluoroalkyl, C_1-C_3 alkoxy, fluoro or chloro.

E6 A compound of any one of embodiments E1 to E5, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from the group consisting of methyl, difluoromethyl,



E7 A compound of any one of embodiments E1 to E6, or a pharmaceutically acceptable salt thereof, wherein R^2 is selected from:

$-NR^4R^5$, wherein R^4 and R^5 taken together with the nitrogen atom (i.e., first ring nitrogen atom) to which they are attached form a 4- to 10-membered heterocycloalkyl ring containing a second ring nitrogen atom, wherein the second ring nitrogen atom is optionally substituted with $(C_1\text{-}C_3)$alkyl; and wherein the 4- to 10-membered heterocycloalkyl ring optionally contains a third heteroatom selected from O or S; wherein the 4- to 10-membered heterocycloalkyl ring is monocyclic, or the 4- to 10-membered heterocycloalkyl ring is bicyclic and optionally bridged or fused; or

R^2 is selected from -O-(C_1-C_6 alkyl) substituted with $-NR^6R^7$; wherein one of the carbon atoms of said -O-(C_1-C_6 alkyl) moiety may optionally interconnect with another carbon atom of said -O-(C_1-C_6 alkyl) moiety to form a C_3-C_4 cycloalkyl ring;

wherein R^6 is H or C_1-C_3 alkyl optionally substituted with hydroxy, or 1 to 3 deuteriums;

wherein R^7 is H or C_1-C_3 alkyl optionally substituted with hydroxy; wherein said C_1-C_3 alkyl moiety may optionally interconnect with one of the carbon atoms of said -O-(C_1-C_6 alkyl) moiety of R^2 to form a 4- or 5-membered heterocycloalkyl.

E8 A compound of any one of embodiments E1 to E7, or a pharmaceutically acceptable salt thereof, wherein R^2 is selected from the group consisting of
-NR^4R^5, wherein R^4 and R^5 taken together with the nitrogen atom (i.e., first ring nitrogen atom) to which they are attached form a 4- to 10-membered heterocycloalkyl ring containing a second ring nitrogen atom, wherein the second ring nitrogen atom is optionally substituted with (C_1-C_3)alkyl; and wherein the 4- to 10-membered heterocycloalkyl ring optionally contains a third heteroatom selected from O or S; wherein the 4- to 10-membered heterocycloalkyl ring is monocyclic or may be bicyclic and optionally bridged; or
R^2 is selected from -O-(C_1-C_6 alkyl) substituted with -NR^6R^7; wherein one of the carbon atoms of said -O-(C_1-C_6 alkyl) moiety may optionally interconnect with another carbon atom of said -O-(C_1-C_6 alkyl) moiety to form a C_3-C_4 cycloalkyl ring;
wherein R^6 is H or C_1-C_3 alkyl optionally substituted with hydroxy, or 1 to 3 deuteriums;
wherein R^7 is H or C_1-C_3 alkyl optionally substituted with hydroxy; wherein said C_1-C_3 alkyl moiety may optionally interconnect with one of the carbon atoms of said -O-(C_1-C_6 alkyl) moiety of R^2 to form a 4- or 5-membered heterocycloalkyl.

E9 A compound of any one of embodiments E1 to E8, or a pharmaceutically acceptable salt thereof, wherein R^2 is selected from the group consisting of
-NR^4R^5, wherein R^4 and R^5 taken together with the nitrogen atom (i.e., first ring nitrogen atom) to which they are attached form a 4- to 10-membered heterocycloalkyl ring containing a second ring nitrogen atom, wherein the second ring nitrogen atom is optionally substituted with (C_1-C_3)alkyl; and wherein the 4- to 10-membered heterocycloalkyl ring optionally contains a third heteroatom selected from O or S; wherein the 4- to 10-membered heterocycloalkyl ring is monocyclic or may be bicyclic and optionally bridged; or
R^2 is selected from -O-(C_1-C_6 alkyl) substituted with -NR^6R^7; wherein one of the carbon atoms of said -O-(C_1-C_6 alkyl) moiety may optionally interconnect with another carbon atom of said -O-(C_1-C_6 alkyl) moiety to form a C_3-C_4 cycloalkyl ring;
wherein R^6 is H or C_1-C_3 alkyl optionally substituted with hydroxy, or 1 to 3 deuteriums;

wherein R^7 is H or C_1-C_3 alkyl optionally substituted with hydroxy; wherein said C_1-C_3 alkyl moiety may optionally interconnect with one of the carbon atoms of said -O-(C_1-C_6 alkyl) moiety of R^2 to form a 4- or 5-membered heterocycloalkyl.

E10 A compound of any one of embodiments E1 to E9, or a pharmaceutically acceptable salt thereof, wherein R^2 is selected from the group consisting of
-NR^4R^5, wherein R^4 and R^5 taken together with the nitrogen atom (i.e., first ring nitrogen atom) to which they are attached form a 4- to 10-membered heterocycloalkyl ring containing a second ring nitrogen atom, wherein the second ring nitrogen atom is optionally substituted with (C_1-C_3)alkyl; and wherein the 4- to 10-membered heterocycloalkyl ring optionally contains a third heteroatom selected from O or S; wherein the 4- to 10-membered heterocycloalkyl ring is bicyclic and optionally bridged, fused, or spirocyclic; or
R^2 is selected from -O-(C_1-C_6 alkyl) substituted with -NR^6R^7; wherein one of the carbon atoms of said -O-(C_1-C_6 alkyl) moiety may optionally interconnect with another carbon atom of said -O-(C_1-C_6 alkyl) moiety to form a C_3-C_4 cycloalkyl ring;
wherein R^6 is H or C_1-C_3 alkyl optionally substituted with hydroxy, 1 to 3 deuteriums, or 1 to 3 fluoro;
wherein R^7 is H or C_1-C_3 alkyl optionally substituted with hydroxy; wherein said C_1-C_3 alkyl moiety may optionally interconnect with one of the carbon atoms of said -O-(C_1-C_6 alkyl) moiety of R^2 to form a 4- or 5-membered heterocycloalkyl.

E11 A compound of any one of embodiments E1 to E10, or a pharmaceutically acceptable salt thereof, wherein R^2 is selected from the group consisting of
-NR^4R^5, wherein R^4 and R^5 taken together with the nitrogen atom (i.e., first ring nitrogen atom) to which they are attached form a 6- to 9-membered heterocycloalkyl ring containing a second ring nitrogen atom, wherein the second ring nitrogen atom is optionally substituted with (C_1-C_3)alkyl; and wherein the 6- to 9-membered heterocycloalkyl ring optionally contains a third heteroatom selected from O or S; wherein the 6- to 9-membered heterocycloalkyl ring is monocyclic or may be bicyclic and optionally bridged; or
R^2 is selected from -O-(C_1-C_6 alkyl) substituted with -NR^6R^7; wherein one of the carbon atoms of said -O-(C_1-C_6 alkyl) moiety may optionally interconnect with another carbon atom of said -O-(C_1-C_6 alkyl) moiety to form a C_3-C_4 cycloalkyl ring;

wherein R^6 is H or C_1-C_3 alkyl optionally substituted with hydroxy, 1 to 3 deuteriums, or 1 to 3 fluoro;

wherein R^7 is H or C_1-C_3 alkyl optionally substituted with hydroxy; wherein said C_1-C_3 alkyl moiety may optionally interconnect with one of the carbon atoms of said -O-(C_1-C_6 alkyl) moiety of R^2 to form a 4- or 5-membered heterocycloalkyl.

E12 A compound of any one of embodiments E1 to E11, or a pharmaceutically acceptable salt thereof, wherein R^2 is selected from the group consisting of

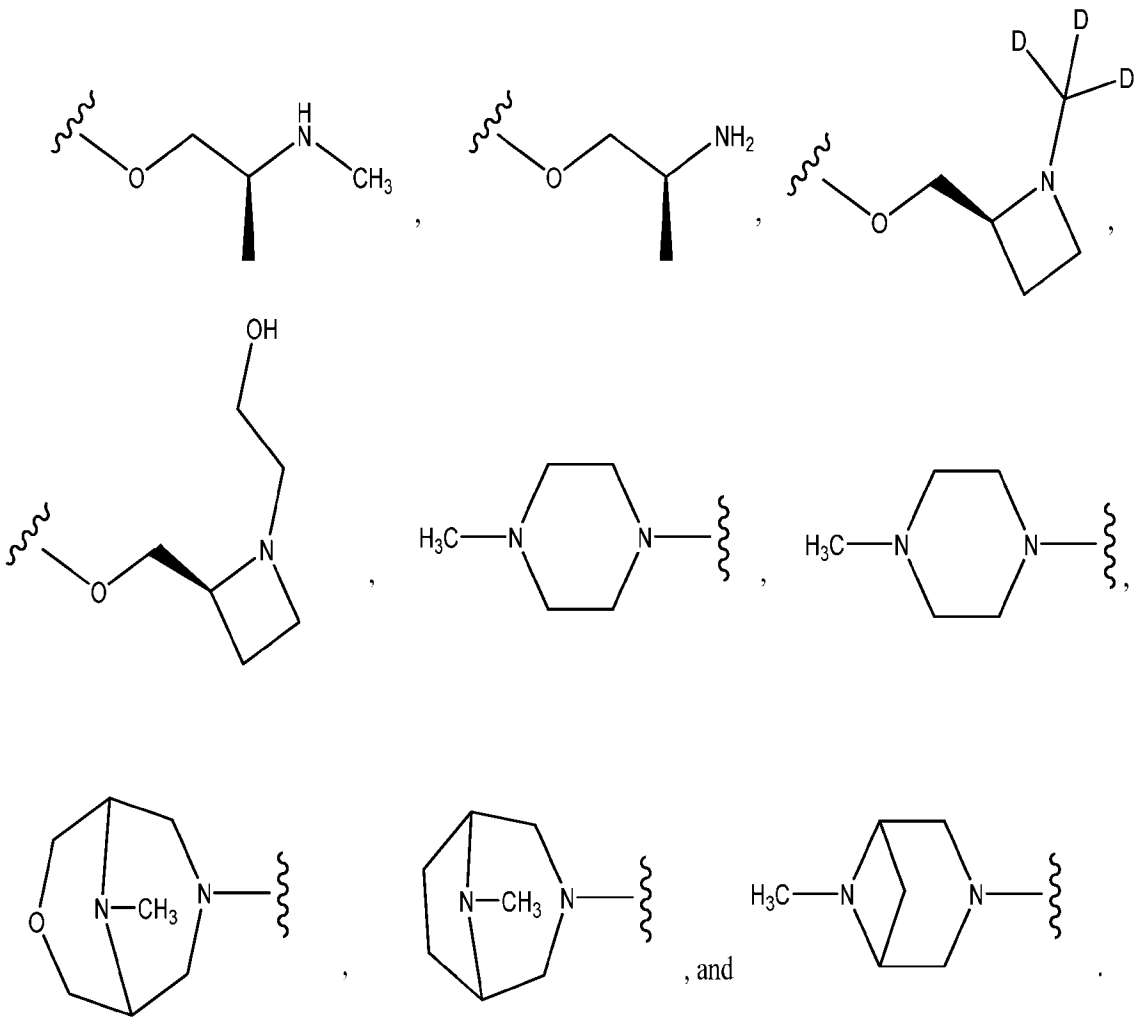
-NR^4R^5, wherein R^4 and R^5 taken together with the nitrogen atom (i.e., first ring nitrogen atom) to which they are attached form a 6- to 9-membered heterocycloalkyl ring containing a second ring nitrogen atom, wherein the second ring nitrogen atom is optionally substituted with (C_1-C_3)alkyl; and wherein the 6- to 9-membered heterocycloalkyl ring optionally contains a third heteroatom that is O; wherein the 6- to 9-membered heterocycloalkyl ring is monocyclic or may be bicyclic and optionally bridged; or

R^2 is selected from -O-(C_1-C_6 alkyl) substituted with -NR^6R^7; wherein one of the carbon atoms of said -O-(C_1-C_6 alkyl) moiety may optionally interconnect with another carbon atom of said -O-(C_1-C_6 alkyl) moiety to form a C_3-C_4 cycloalkyl ring;

wherein R^6 is H or C_1-C_3 alkyl optionally substituted with hydroxy, or 1 to 3 deuteriums;

wherein R^7 is H or C_1-C_3 alkyl optionally substituted with hydroxy; wherein said C_1-C_3 alkyl moiety may optionally interconnect with one of the carbon atoms of said -O-(C_1-C_6 alkyl) moiety of R^2 to form a 4-membered heterocycloalkyl.

E13 A compound of any one of embodiments E1 to E12, or a pharmaceutically acceptable salt thereof, wherein R^2 is selected from the group consisting of:



E14 A compound of any one of embodiments E1 to E13, or a pharmaceutically acceptable salt thereof, wherein R^3 is selected from the group consisting of H, C_1-C_6 alkyl, and C_1-C_6 fluoroalkyl.

E15 A compound of any one of embodiments E1 to E14, or a pharmaceutically acceptable salt thereof, wherein R^3 is selected from the group consisting of H, C_1-C_3 alkyl, and C_1-C_3 fluoroalkyl.

E16 A compound of any one of embodiments E1 to E15, or a pharmaceutically acceptable salt thereof, wherein R^3 is selected from the group consisting of H, methyl, and difluoromethyl.

E17 A compound of E1, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of:

(*S*)-2-methyl-5-(2-(methylamino)propoxy)-*N*-(1-(7-(2-methylthiazol-5-yl)quinolin-5-yl)cyclopropyl)benzamide;

(*S*)-2-methyl-*N*-(1-(2-methyl-7-(oxazol-2-yl)quinolin-5-yl)cyclopropyl)-5-((1-methylazetidin-2-yl)methoxy)benzamide;

(*S*)-2-methyl-5-((1-(methyl-d_3)azetidin-2-yl)methoxy)-*N*-(1-(7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)benzamide;

2-methyl-5-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)-*N*-(1-(7-(2-methyloxazol-5-yl)quinolin-5-yl)cyclopropyl)benzamide;

(*S*)-2-methyl-5-(2-(methylamino)propoxy)-*N*-(1-(7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)benzamide;

2-methyl-5-(6-methyl-3,6-diazabicyclo[3.1.1]heptan-3-yl)-*N*-(1-(7-(2-methyloxazol-5-yl)quinolin-5-yl)cyclopropyl)benzamide;

2-methyl-*N*-(1-(7-(1-methyl-1*H*-pyrazol-4-yl)quinolin-5-yl)cyclopropyl)-5-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)benzamide;

2-methyl-*N*-(1-(7-(1-methyl-1*H*-pyrazol-4-yl)quinolin-5-yl)cyclopropyl)-5-(4-methylpiperazin-1-yl)benzamide;

2-methyl-*N*-(1-(7-(2-methyloxazol-4-yl)quinolin-5-yl)cyclopropyl)-5-(4-methylpiperazin-1-yl)benzamide;

2-methyl-5-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)-*N*-(1-(7-(2-methyloxazol-4-yl)quinolin-5-yl)cyclopropyl)benzamide;

2-methyl-*N*-(1-(2-methyl-7-(2-methyloxazol-5-yl)quinolin-5-yl)cyclopropyl)-5-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)benzamide;

2-methyl-*N*-(1-(2-methyl-7-(1-methyl-1*H*-pyrazol-4-yl)quinolin-5-yl)cyclopropyl)-5-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)benzamide;

(*S*)-5-(2-aminopropoxy)-2-methyl-*N*-(1-(7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)benzamide;

(*S*)-*N*-(1-(2-(difluoromethyl)-7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)-2-methyl-5-(2-(methylamino)propoxy)benzamide;

2-methyl-*N*-(1-(2-methyl-7-(2-methyloxazol-5-yl)quinolin-5-yl)cyclopropyl)-5-(4-methylpiperazin-1-yl)benzamide;

(*S*)-2-methyl-*N*-(1-(2-methyl-7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)-5-((1-methylazetidin-2-yl)methoxy)benzamide;

(*S*)-2-methyl-*N*-(1-(2-methyl-7-(5-methylpyrimidin-2-yl)quinolin-5-yl)cyclopropyl)-5-((1-methylazetidin-2-yl)methoxy)benzamide;

(*S*)-N-(1-(7-(5-fluoropyrimidin-2-yl)-2-methylquinolin-5-yl)cyclopropyl)-2-methyl-5-((1-methylazetidin-2-yl)methoxy)benzamide;

(*S*)-N-(1-(7-(5-chloropyrimidin-2-yl)-2-methylquinolin-5-yl)cyclopropyl)-2-methyl-5-((1-methylazetidin-2-yl)methoxy)benzamide;

(*S*)-N-(1-(7-(5-methoxypyrimidin-2-yl)-2-methylquinolin-5-yl)cyclopropyl)-2-methyl-5-((1-methylazetidin-2-yl)methoxy)benzamide;

5-((1-aminocyclobutyl)methoxy)-2-methyl-*N*-(1-(7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)benzamide;

(*S*)-5-(2-aminopropoxy)-2-methyl-*N*-(1-(2-methyl-7-(thiophen-2-yl)quinolin-5-yl)cyclopropyl)benzamide;

(*S*)-5-(2-aminopropoxy)-2-methyl-*N*-(1-(2-methyl-7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)benzamide;

2-methyl-*N*-(1-(2-methyl-7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)-5-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)benzamide;

2-methyl-5-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)-*N*-(1-(7-(5-methylpyrimidin-2-yl)quinolin-5-yl)cyclopropyl)benzamide;

2-methyl-5-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)-*N*-(1-(7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)benzamide;

2-methyl-*N*-(1-(7-(1-methyl-1*H*-pyrazol-3-yl)quinolin-5-yl)cyclopropyl)-5-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)benzamide;

(*S*)-*N*-(1-(7-(2H-1,2,3-triazol-2-yl)quinolin-5-yl)cyclopropyl)-2-methyl-5-((1-methylazetidin-2-yl)methoxy)benzamide;

(*S*)-2-methyl-*N*-(1-(2-methyl-7-(2-methylthiazol-5-yl)quinolin-5-yl)cyclopropyl)-5-((1-methylazetidin-2-yl)methoxy)benzamide;

(*S*)-2-methyl-*N*-(1-(2-methyl-7-(1-methyl-1*H*-pyrazol-3-yl)quinolin-5-yl)cyclopropyl)-5-((1-methylazetidin-2-yl)methoxy)benzamide;

(*S*)-5-((1-(2-hydroxyethyl)azetidin-2-yl)methoxy)-2-methyl-*N*-(1-(7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)benzamide;

2-methyl-5-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)-*N*-(1-(7-(oxazol-2-yl)quinolin-5-yl)cyclopropyl)benzamide;

2-methyl-*N*-(1-(2-methyl-7-(2-methyloxazol-4-yl)quinolin-5-yl)cyclopropyl)-5-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)benzamide; and

(*S*)-*N*-(1-(7-(1-(difluoromethyl)-1*H*-pyrazol-3-yl)-2-methylquinolin-5-yl)cyclopropyl)-2-methyl-5-((1-methylazetidin-2-yl)methoxy)benzamide.

E18 A compound of E1, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of:

(*S*)-*N*-(1-(7-(difluoromethyl)-2-methylquinolin-5-yl)cyclopropyl)-2-methyl-5-((1-methylazetidin-2-yl)methoxy)benzamide;

(*S*)-*N*-(1-(7-(difluoromethyl)quinolin-5-yl)cyclopropyl)-2-methyl-5-((1-methylazetidin-2-yl)methoxy)benzamide;

N-(1-(7-(difluoromethyl)-2-methylquinolin-5-yl)cyclopropyl)-2-methyl-5-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)benzamide;

N-(1-(7-(difluoromethyl)quinolin-5-yl)cyclopropyl)-2-methyl-5-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)benzamide;

N-(1-(2,7-dimethylquinolin-5-yl)cyclopropyl)-2-methyl-5-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)benzamide;

2-methyl-N-(1-(2-methyl-7-(1-methyl-1*H*-pyrazol-3-yl)quinolin-5-yl)cyclopropyl)-5-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)benzamide;

2-methyl-5-(9-methyl-3-oxa-7,9-diazabicyclo[3.3.1]nonan-7-yl)-*N*-(1-(7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)benzamide;

2-methyl-5-(9-methyl-3-oxa-7,9-diazabicyclo[3.3.1]nonan-7-yl)-*N*-(1-(7-methylquinolin-5-yl)cyclopropyl)benzamide;

2-methyl-*N*-(1-(2-methyl-7-(oxazol-2-yl)quinolin-5-yl)cyclopropyl)-5-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)benzamide;

N-(1-(7-(2H-1,2,3-triazol-2-yl)quinolin-5-yl)cyclopropyl)-2-methyl-5-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)benzamide;

(*S*)-2-methyl-N-(1-(2-methyl-7-(2H-1,2,3-triazol-2-yl)quinolin-5-yl)cyclopropyl)-5-((1-methylazetidin-2-yl)methoxy)benzamide;

2-methyl-*N*-(1-(2-methyl-7-(2H-1,2,3-triazol-2-yl)quinolin-5-yl)cyclopropyl)-5-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)benzamide;

2-methyl-*N*-(1-(2-methyl-7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)-5-(9-methyl-3-oxa-7,9-diazabicyclo[3.3.1]nonan-7-yl)benzamide; and

2-methyl-*N*-(1-(2-methyl-7-(5-methylpyrimidin-2-yl)quinolin-5-yl)cyclopropyl)-5-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)benzamide.

E19 Any of the compounds described in embodiments E1 to E18, or pharmaceutically acceptable salts thereof, may be claimed individually or grouped together with one or more other compounds of embodiments E1 to E18.

E20 A pharmaceutical composition comprising a compound of any one of embodiments E1 to E19, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.

E21 A method for inhibiting the activity of the papain-like protease in a virus, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any one of embodiments E1 to E20, or a pharmaceutically acceptable salt thereof.

E22 A method for treating coronavirus infections, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any one of embodiments E1 to E20, or a pharmaceutically acceptable salt thereof, as a single agent.

E23 A method for treating COVID-19, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any one of embodiments E1 to E20, or a pharmaceutically acceptable salt thereof, as a single agent.

E24 A method for treating coronavirus infections, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any one of embodiments E1 to E20, or a pharmaceutically acceptable salt thereof, and further comprising administering a therapeutically effective amount of an additional therapeutic agent.

E25 An embodiment according to E24 wherein said additional therapeutic agent is a Mpro inhibitor, a nucleoside, or a polymerase inhibitor.

E26 A compound of any one embodiments E1 to E20, for use in the treatment of coronavirus infections.

E27 Use of a compound of any one of embodiments E1 to E20 for the manufacture of a medicament for the treatment of coronavirus infections.

E28 A method for the treatment of a disorder mediated by inhibiting papain-like protease in a subject, comprising administering to the subject in need thereof a compound of any one of embodiments E1 to E20, or a pharmaceutically acceptable salt thereof, in an amount that is effective for treating the disorder.

E29 A pharmaceutical combination comprising a compound of any one of embodiments E1 to E20 or a pharmaceutically acceptable salt thereof, and at least one additional therapeutic agent or a pharmaceutically acceptable salt thereof.

E30 A pharmaceutical composition comprising the pharmaceutical combination of embodiment E20 and at least one excipient.

In some embodiments, the disclosure provides for a compound of Formula (I), or a pharmaceutically acceptable salt thereof as described in any one of the embodiments E1 to E20 above, wherein any one or more of the hydrogens of Formula (I) are replaced with deuterium.

Each of the embodiments described herein may be combined with any other embodiment(s) described herein not inconsistent with the embodiment(s) with which it is combined. In addition, any of the compounds described in the Examples, or pharmaceutically acceptable salts thereof, may be claimed individually or grouped together with one or more other compounds of the Examples, or pharmaceutically acceptable salts thereof, for any of the embodiment(s) described herein.

Furthermore, each of the embodiments described herein envisions within its scope pharmaceutically acceptable salts of the compounds described herein.

Definitions

Unless otherwise defined herein, scientific and technical terms used in connection with the present invention have the meanings that are commonly understood by those of ordinary skill in the art.

The invention described herein suitably may be practiced in the absence of any element(s) not specifically disclosed herein.

"Compounds of the invention" include compounds of Formula I and the novel intermediates used in the preparation thereof. One of ordinary skill in the art will appreciate that compounds of the invention include conformational isomers (e.g., cis and trans isomers) and all optical isomers (e.g., enantiomers and diastereomers), racemic, diastereomeric and other mixtures of such isomers, tautomers thereof, where they may exist. One of ordinary skill in the art will also appreciate that compounds of the invention include solvates, hydrates, isomorphs, polymorphs, esters, salt forms, prodrugs, and isotopically labelled versions thereof (including deuterium substitutions), where they may be formed.

As used herein, the singular form "a", "an", and "the" include plural references unless indicated otherwise. For example, "a" substituent includes one or more substituents.

As used herein, the term "about" when used to modify a numerically defined parameter (e.g., the dose of 5 mg) means that the parameter may vary by as much as 10% below or above the stated numerical value for that parameter. For example, a dose of about 5 mg means 5 % ± 10%, i.e., it may vary between 4.5 mg and 5.5 mg.

If substituents are described as being "independently selected" from a group, each substituent is selected independent of the other. Each substituent therefore may be identical to or different from the other substituent(s).

"Optional" or "optionally" means that the subsequently described event or circumstance may, but need not occur, and the description includes instances where the event or circumstance occurs and instances in which it does not.

The terms "optionally substituted" and "substituted or unsubstituted" are used interchangeably to indicate that the particular group being described may have no non-hydrogen substituents (i.e., unsubstituted), or the group may have one or more non-hydrogen substituents (i.e., substituted). If not otherwise specified, the total number of substituents that may be present is equal to the number of H atoms present on the unsubstituted form of the group being described. Where an optional substituent is attached via a double bond, such as an oxo (=O) substituent, the group occupies two available valences, so the total number of other substituents that are included is reduced by two. In the case where optional substituents are selected independently from a list of alternatives, the selected groups may be the same or different. Throughout the disclosure, it will be understood that the number and nature of optional substituent groups will be limited to the extent that such substitutions make chemical sense to one of ordinary skill in the art.

"Halogen" or "halo" refers to fluoro, chloro, bromo and/or iodo atoms (F, Cl, Br, I).

"Cyano" refers to a substituent having a carbon atom joined to a nitrogen atom by a triple bond, i.e., -C≡N.

"Hydroxy" refers to an -OH group.

"Oxo" refers to a double bonded oxygen (=O).

"Alkyl" refers to a saturated hydrocarbon group that has a specified number of carbon atoms, including straight chain (linear) or branched chain groups. Alkyl groups may contain, but are not limited to, 1 to 12 carbon atoms ("C_1-C_{12} alkyl"), 1 to 8 carbon atoms ("C_1-C_8 alkyl"), 1 to 6 carbon atoms ("C_1-C_6 alkyl"), 1 to 5 carbon atoms ("C_1-C_5 alkyl"), 1 to 4 carbon atoms ("C_1-C_4 alkyl"), 1 to 3 carbon atoms ("C_1-C_3 alkyl"), or 1 to 2 carbon atoms ("C_1-C_2 alkyl"). Examples include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, n-heptyl, n-octyl, and the like. Alkyl groups may be optionally substituted, unsubstituted or substituted, as further defined herein.

"Fluoroalkyl" refers to an alkyl group, as defined herein, wherein from one to all of the hydrogen atoms of the alkyl group are replaced by fluoro atoms. Examples of partially substituted fluoroalkyl groups include, but are not limited to, fluoromethyl, difluoromethyl, fluoroethyl, trifluoroethyl, and tetrafluoroethyl. Examples of fully substituted fluoroalkyl groups (also referred to as perfluoroalkyl groups) include trifluoromethyl ($-CF_3$) and pentafluoroethyl ($-C_2F_5$).

"Alkoxy" refers to a linear or branched alkyl group, as defined herein, that is single bonded to an oxygen atom. The attachment point of an alkoxy radical to a molecule is through the oxygen atom. An alkoxy radical may be depicted as alkyl-O-. Alkoxy groups may contain, but are not limited to, 1 to 8 carbon atoms ("C_1-C_8 alkoxy"), 1 to 6 carbon atoms ("C_1-C_6 alkoxy"), 1 to 4 carbon atoms ("C_1-C_4 alkoxy"), or 1 to 3 carbon atoms ("C_1-C_3 alkoxy"). Alkoxy groups include, but are not limited to, methoxy, ethoxy, n-propoxy, isobutoxy, and the like.

"Alkoxyalkyl" refers to an alkyl group, as defined herein, that is substituted by an alkoxy group, as defined herein. An alkoxyalkyl group may be depicted as alkyl-O-alkyl-. Examples include, but are not limited to, CH_3OCH_2- and $CH_3CH_2OCH_2$-.

"Alkenyl" refers to an unsaturated linear or branched hydrocarbon group containing at least two carbon atoms and at least one carbon-carbon double bond. For example, as used herein, the term "C_2-C_6 alkenyl" refers to linear or branched unsaturated hydrocarbon groups containing 2 to 6 carbon atoms. Examples include, but are not limited to, vinyl (ethenyl), 1-propenyl, 2-propenyl, 1-, 2-, or 3-butenyl, and the like.

"Alkynyl" refers to an unsaturated linear or branched hydrocarbon group containing at least two carbon atoms and at least one carbon-carbon triple bond. Examples include, but are not limited to, ethynyl, 1-propynyl, 2-propynyl (propargyl), 1-, 2-, or 3-butynyl, and the like.

"Cycloalkyl" refers to a fully saturated hydrocarbon ring system that has the specified number of carbon atoms, which may be a monocyclic, bridged or fused bicyclic or polycyclic ring system that is connected to the base molecule through a carbon atom of the cycloalkyl ring. Cycloalkyl groups may contain, but are not limited to, 3 to 12 carbon atoms ("C_3-C_{12} cycloalkyl"), 3 to 8 carbon atoms ("C_3-C_8 cycloalkyl"), 3 to 6 carbon atoms ("C_3-C_6 cycloalkyl"), 3 to 5 carbon atoms ("C_3-C_5 cycloalkyl") or 3 to 4 carbon atoms ("C_3-C_4 cycloalkyl"). Examples include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantanyl, and the like. Cycloalkyl groups may be optionally substituted, unsubstituted or substituted, as further defined herein. Cycloalkyl groups may be monocyclic, bicyclic, or tricyclic, and may be bridged or fused.

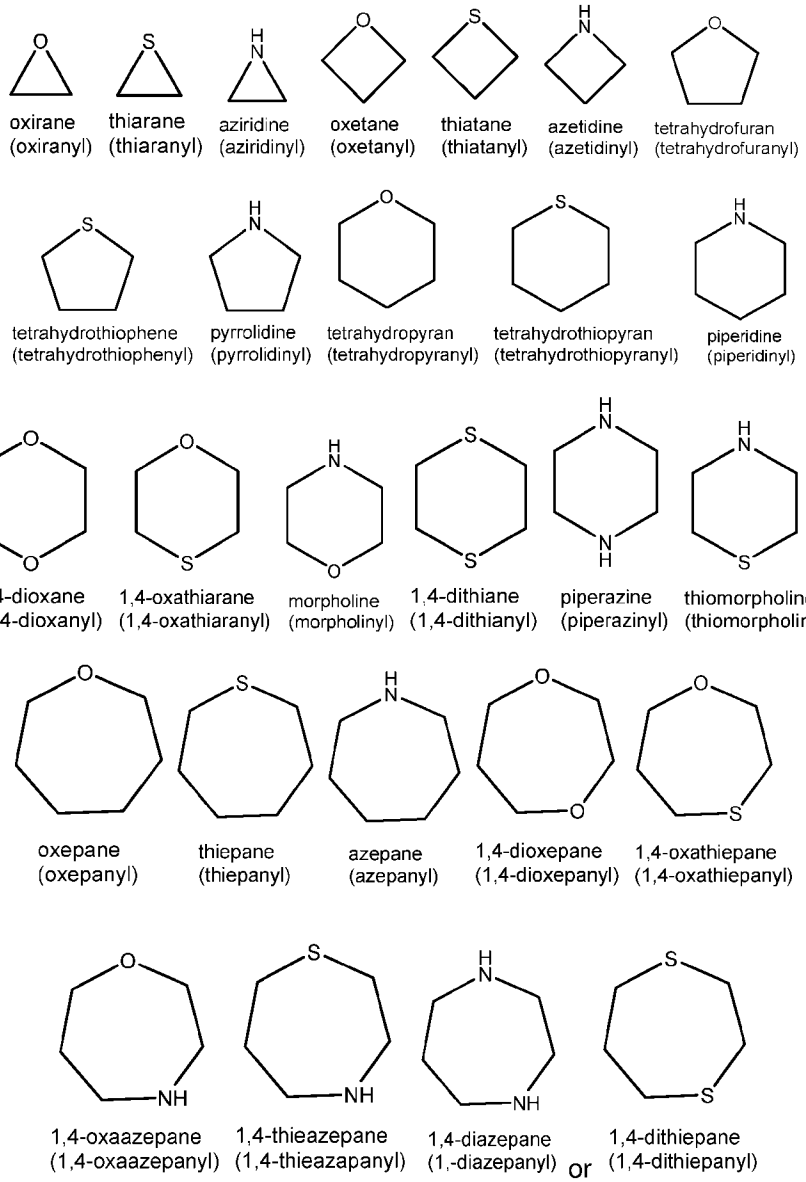
"Cycloalkoxy" refers to a cycloalkyl group, as defined herein, that is single bonded to an oxygen atom. The attachment point of a cycloalkoxy radical to a molecule is through the oxygen atom. A cycloalkoxy radical may be depicted as cycloalkyl-O-. Cycloalkoxy groups may contain, but are not limited to, 3 to 8 carbon atoms ("C_3-C_8 cycloalkoxy"), 3 to 6 carbon atoms ("C_3-C_6 cycloalkoxy"), and 3 to 4 carbon atoms ("C_3-C_4 cycloalkoxy"). Cycloalkoxy groups include, but are not limited to, cyclopropoxy, cyclobutoxy, cyclopentoxy and the like.

"Heterocycloalkyl" refers to a fully saturated ring system containing the specified number of ring atoms and containing at least one heteroatom selected from N, O and S as a ring member, where ring S atoms are optionally substituted by one or two oxo groups (i.e., $S(O)_q$, where q is 0, 1 or 2) and where the heterocycloalkyl ring is typically connected to the base molecule via a ring atom, which may be C or N. Heterocycloalkyl groups may be monocyclic, bicyclic, or tricyclic, and may be bridged or fused. Heterocycloalkyl rings include rings which are spirocyclic, bridged, or fused to one or more other heterocycloalkyl or carbocyclic rings, where such spirocyclic, bridged, or fused rings may themselves be saturated, partially unsaturated or aromatic to the extent unsaturation or aromaticity makes chemical sense, provided the point of attachment to the base molecule is an atom of the heterocycloalkyl portion of the ring system. Heterocycloalkyl rings may contain 1 to 4 heteroatoms selected from N, O, and $S(O)_q$ as ring members, or 1 to 2 ring heteroatoms, provided that such heterocycloalkyl rings do not contain two contiguous oxygen or sulfur atoms.

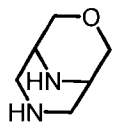
Heterocycloalkyl rings may be optionally substituted, unsubstituted or substituted, as further defined herein. Such substituents may be present on the heterocyclic ring attached to the base molecule, or on a spirocyclic, bridged or fused ring attached thereto.

Heterocycloalkyl rings may include, but are not limited to, 3-10 membered heterocyclyl groups, for example 4-7 or 4-6 membered heterocycloalkyl groups, in accordance with the definition herein.

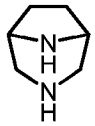
Illustrative examples of heterocycloalkyl rings include, but are not limited to a monovalent radical of:



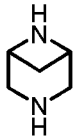
Illustrative examples of bridged and fused heterocycloalkyl groups include, but are not limited to a monovalent radical of:



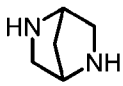
3-oxa-7,9-diazabicyclo[3.3.1]nonane
(3-oxa-7,9-diazabicyclo[3.3.1]nonanyl)



3,8-diazabicyclo[3.2.1]octane
(3,8-diazabicyclo[3.2.1]octanyl)



3,6-diazabicyclo[3.1.1]heptane
(3,6-diazabicyclo[3.1.1]heptanyl)



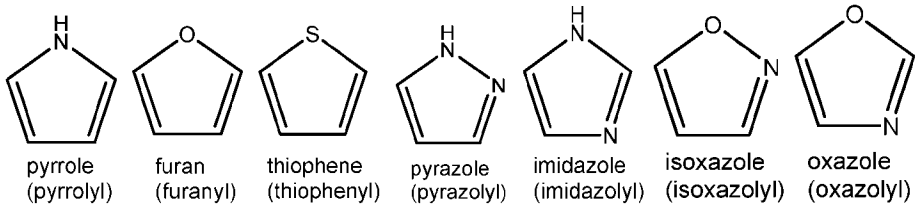
2,5-diazabicyclo[2.2.1]heptane
(2,5-diazabicyclo[2.2.1]heptanyl)

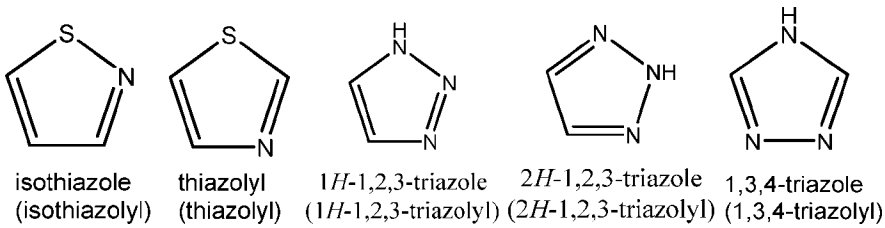
"Aryl" or "aromatic" refers to monocyclic, bicyclic (e.g., single-bonded or fused biaryl) or polycyclic ring (e.g., tricyclic or higher) systems that contain a specified number of ring atoms in which all carbon atoms in the ring are unsaturated (of sp^2 hybridization) and in which the pi electrons are in conjugation. Aryl groups may contain, but are not limited to, 6 to 20 carbon atoms ("C_6-C_{20} aryl"), 6 to 14 carbon atoms ("C_6-C_{14} aryl"), 6 to 12 carbon atoms ("C_6-C_{12} aryl"), or 6 to 10 carbon atoms ("C_6-C_{10} aryl"). Fused aryl groups may include an aryl ring (e.g., a phenyl ring) fused to another aryl ring. Examples include, but are not limited to, phenyl, biphenyl, naphthyl, anthracenyl, phenanthrenyl, indanyl, and indenyl. Aryl groups may be optionally substituted, unsubstituted or substituted, as further defined herein.

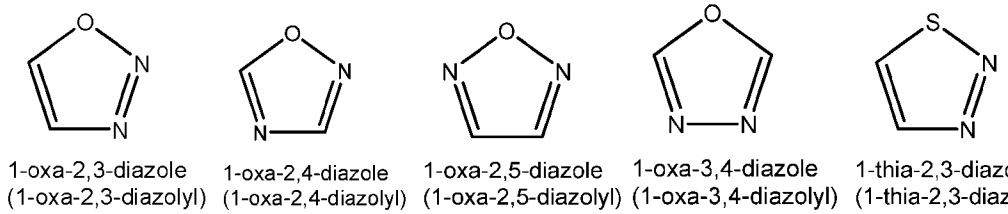
Similarly, "heteroaryl" or "heteroaromatic" refer to monocyclic, bicyclic (e.g., single-bonded or fused bi-heteroaryl or polycyclic ring systems that contain the specified number of ring atoms and include at least one heteroatom selected from N, O and S as a ring member in a ring in which all carbon atoms in the ring are of sp^2 hybridization and in which the pi electrons are in conjugation. Heteroaryl groups may contain, but are not limited to, 5 to 20 ring atoms ("5-20 membered heteroaryl"), 5 to 14 ring atoms ("5-14 membered heteroaryl"), 5 to 12 ring atoms ("5-12 membered heteroaryl"), 5 to 10 ring atoms ("5-10 membered heteroaryl"), 5 to 9 ring atoms ("5-9 membered heteroaryl"), or 5 to 6 ring atoms ("5-6 membered heteroaryl"). Heteroaryl rings are attached to the base molecule via a ring atom of the heteroaromatic ring. Thus, either 5- or 6-membered heteroaryl rings, alone or in a fused structure, may be attached to the base molecule via a ring C or N atom. Examples of heteroaryl groups include, but are not limited to, pyrrolyl, furanyl, thiophenyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isothiazolyl, thiazolyl, triazolyl, oxadiazolyl, thiadiazolyl,

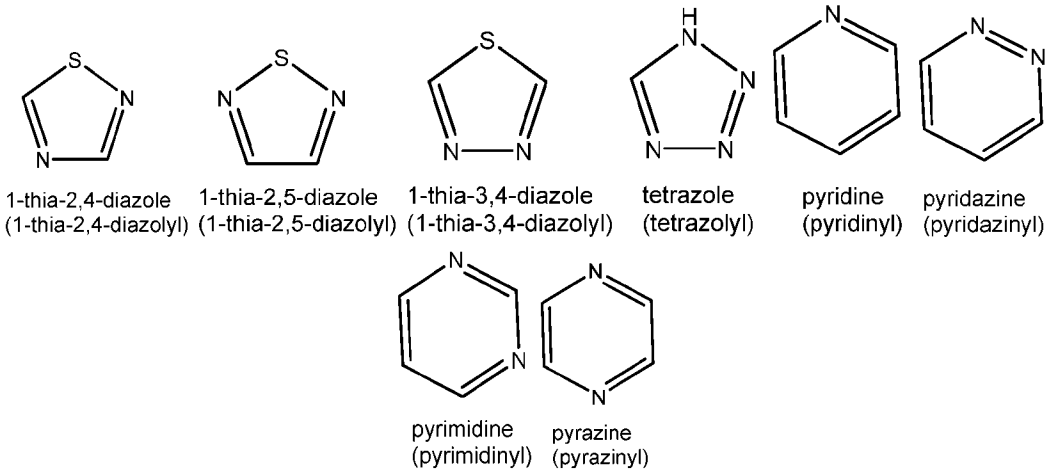
tetrazolyl, pyridinyl, pyridizinyl, pyrimidinyl, pyrazinyl, benzofuranyl, benzothiophenyl, indolyl, benzamidazolyl, indazolyl, quinolinyl, isoquinolinyl, purinyl, triazinyl, naphthyridinyl, cinnolinyl, quinazolinyl, quinoxalinyl and carbazolyl. Examples of 5- or 6-membered heteroaryl groups include, but are not limited to, pyrrolyl, furanyl, thiophenyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isothiazolyl, thiazolyl, triazolyl, pyridinyl, pyrimidinyl, pyrazinyl and pyridazinyl rings. Heteroaryl groups may be optionally substituted, unsubstituted or substituted, as further defined herein.

Illustrative examples of monocyclic heteroaryl groups include, but are not limited to a monovalent radical of:

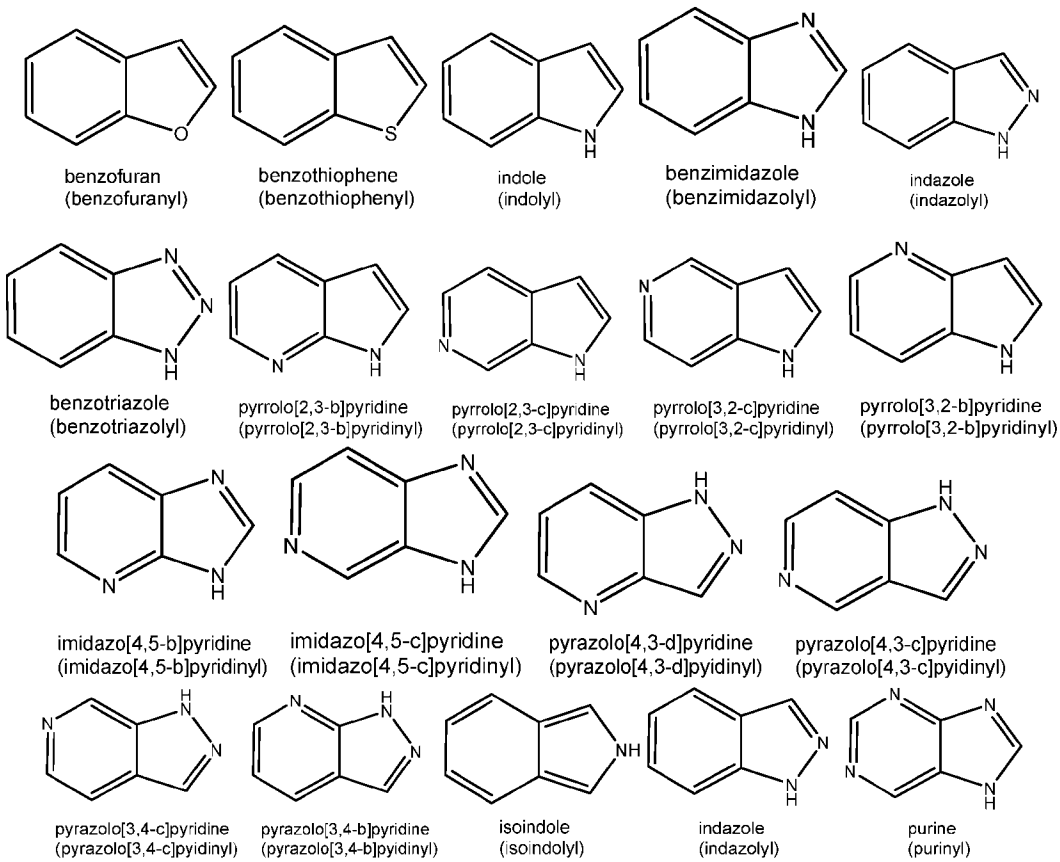


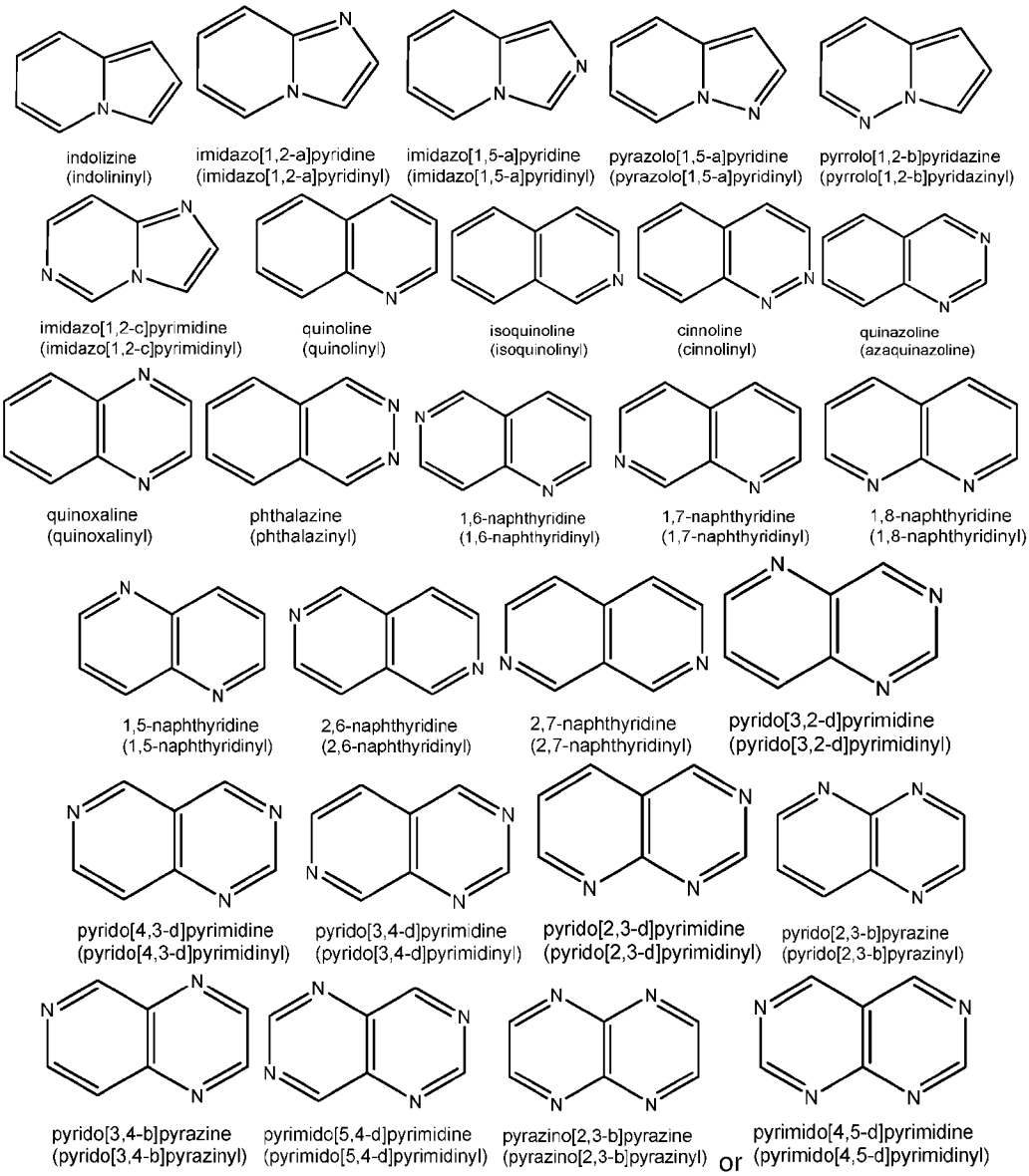






illustrative examples of fused ring heteroaryl groups include, but are not limited to:




indolizine
(indolininyl)
imidazo[1,2-a]pyridine
(imidazo[1,2-a]pyridinyl)
imidazo[1,5-a]pyridine
(imidazo[1,5-a]pyridinyl)
pyrazolo[1,5-a]pyridine
(pyrazolo[1,5-a]pyridinyl)
pyrrolo[1,2-b]pyridazine
(pyrrolo[1,2-b]pyridazinyl)
imidazo[1,2-c]pyrimidine
(imidazo[1,2-c]pyrimidinyl)
quinoline
(quinolinyl)
isoquinoline
(isoquinolinyl)
cinnoline
(cinnolinyl)
quinazoline
(azaquinazoline)
quinoxaline
(quinoxalinyl)
phthalazine
(phthalazinyl)
1,6-naphthyridine
(1,6-naphthyridinyl)
1,7-naphthyridine
(1,7-naphthyridinyl)
1,8-naphthyridine
(1,8-naphthyridinyl)
1,5-naphthyridine
(1,5-naphthyridinyl)
2,6-naphthyridine
(2,6-naphthyridinyl)
2,7-naphthyridine
(2,7-naphthyridinyl)
pyrido[3,2-d]pyrimidine
(pyrido[3,2-d]pyrimidinyl)
pyrido[4,3-d]pyrimidine
(pyrido[4,3-d]pyrimidinyl)
pyrido[3,4-d]pyrimidine
(pyrido[3,4-d]pyrimidinyl)
pyrido[2,3-d]pyrimidine
(pyrido[2,3-d]pyrimidinyl)
pyrido[2,3-b]pyrazine
(pyrido[2,3-b]pyrazinyl)
pyrido[3,4-b]pyrazine
(pyrido[3,4-b]pyrazinyl)
pyrimido[5,4-d]pyrimidine
(pyrimido[5,4-d]pyrimidinyl)
pyrazino[2,3-b]pyrazine
(pyrazino[2,3-b]pyrazinyl)
or
pyrimido[4,5-d]pyrimidine
(pyrimido[4,5-d]pyrimidinyl)

"Amino" refers to groups of the formula NRxRy, wherein Rx and Ry are independently selected from H and alkyl groups. In one embodiment, Rx and Ry are both H, in which case the amino group has the formula $-NH_2$. In other embodiments, one or both of Rx and Ry are alkyl groups, which results in an alkylamino or dialkylamino group, respectively. That is, the term "alkylamino" refers to a group -NRxRy, wherein one of Rx and Ry is an alkyl moiety and the other is H, and "dialkylamino" refers to -NRxRy wherein both of Rx and Ry are alkyl moieties, where the alkyl moieties have independently specified numbers of carbon atoms (e.g., $-NH(C_1-C_4$ alkyl) or $-N(C_1-C_4$ alkyl$)_2$).

"Aminoalkyl" refers to an alkyl group, as defined above, substituted by 1, 2, or 3 amino groups, as defined herein.

The term "pharmaceutically acceptable" means the substance (e.g., the compounds described herein) and any salt thereof, or composition containing the substance or salt of the invention is suitable for administration to a subject or patient.

Salts

Salts encompassed within the term "pharmaceutically acceptable salts" refer to the compounds of this invention which are generally prepared by reacting the free base or free acid with a suitable organic or inorganic acid, or a suitable organic or inorganic base, respectively, to provide a salt of the compound of the invention that is suitable for administration to a subject or patient.

In addition, the compounds of Formula I may also include other salts of such compounds which are not necessarily pharmaceutically acceptable salts, which may be useful as intermediates for one or more of the following: 1) preparing compounds of Formula I; 2) purifying compounds of Formula I; 3) separating enantiomers of compounds of Formula I; or 4) separating diastereomers of compounds of Formula I.

The compounds used in the methods of the invention that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. Suitable acid addition salts are formed from acids which form non-toxic salts. Examples include, but are not limited to, acetate, adipate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulfate/sulfate, borate, camsylate, citrate, cyclamate, edisylate, esylate, formate, fumarate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hibenzate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, isethionate, lactate, malate, maleate, malonate, mesylate, methylsulfate, naphthylate, 2-napsylate, nicotinate, nitrate, orotate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, pyroglutamate,

saccharate, stearate, succinate, tannate, tartrate, tosylate, trifluoroacetate, 1,5-naphathalenedisulfonic acid and xinofoate salts.

Hemisalts of acids and bases may also be formed, for example, hemisulfate and hemicalcium salts.

For a review on suitable salts, see Paulekun, G. S. et al., Trends in Active Pharmaceutical Ingredient Salt Selection Based on Analysis of the Orange Book Database, J. Med. Chem. 2007; 50(26), 6665-6672.

Pharmaceutically acceptable salts of compounds of the invention may be prepared by methods well known to one skilled in the art, including but not limited to the following procedures

(i) by reacting a compound of the invention with the desired acid;

(ii) by removing an acid-labile protecting group from a suitable precursor of a compound of the invention or by ring-opening a suitable cyclic precursor, for example, a lactone or lactam, using the desired acid; or

(iii) by converting one salt of a compound of the invention to another. This may be accomplished by reaction with an appropriate acid or by means of a suitable ion exchange procedure.

These procedures are typically carried out in solution. The resulting salt may precipitate out and be collected by filtration or may be recovered by evaporation of the solvent.

Solvates

The compounds of the invention, and pharmaceutically acceptable salts thereof, may exist in unsolvated and solvated forms. The term 'solvate' is used herein to describe a molecular complex comprising the compound of the invention, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable solvent molecules, for example, ethanol. The term 'hydrate' is employed when said solvent is water.

In addition, the compounds of Formula I may also include other solvates of such compounds which are not necessarily pharmaceutically acceptable solvates, which may be useful as intermediates for one or more of the following: 1) preparing compounds of Formula I; 2) purifying compounds of Formula I; 3) separating enantiomers of compounds of Formula I; or 4) separating diastereomers of compounds of Formula I.

A currently accepted classification system for organic hydrates is one that defines isolated site, channel, or metal-ion coordinated hydrates - see Polymorphism in Pharmaceutical Solids by K. R. Morris (Ed. H. G. Brittain, Marcel Dekker, 1995). Isolated site

hydrates are ones in which the water molecules are isolated from direct contact with each other by intervening organic molecules. In channel hydrates, the water molecules lie in lattice channels where they are next to other water molecules. In metal-ion coordinated hydrates, the water molecules are bonded to the metal ion.

When the solvent or water is tightly bound, the complex may have a well-defined stoichiometry independent of humidity. When, however, the solvent or water is weakly bound, as in channel solvates and hygroscopic compounds, the water/solvent content may be dependent on humidity and drying conditions. In such cases, non-stoichiometry will be the norm.

Complexes

Also included within the scope of the invention are multi-component complexes (other than salts and solvates) wherein the drug and at least one other component are present in stoichiometric or non-stoichiometric amounts. Complexes of this type include clathrates (drug-host inclusion complexes) and co-crystals. The latter are typically defined as crystalline complexes of neutral molecular constituents which are bound together through non-covalent interactions, for example, hydrogen bonded complex (cocrystal) may be formed with either a neutral molecule or with a salt. Co-crystals may be prepared by melt crystallization, by recrystallization from solvents, or by physically grinding the components together - see Chem Commun, 17;1889-1896, by O. Almarsson and M. J. Zaworotko (2004). For a general review of multi-component complexes, see J Pharm Sci, 64(8), 1269-1288, by Haleblian (August 1975).

Solid form

The compounds of the invention may exist in a continuum of solid states ranging from fully amorphous to fully crystalline. The term 'amorphous' refers to a state in which the material lacks long range order at the molecular level and, depending upon temperature, may exhibit the physical properties of a solid or a liquid. Typically, such materials do not give distinctive X-ray diffraction patterns and, while exhibiting the properties of a solid, are more formally described as a liquid. Upon heating, a change from solid to liquid properties occurs which is characterized by a change of state, typically second order ('glass transition'). The term 'crystalline' refers to a solid phase in which the material has a regular ordered internal structure at the molecular level and gives a distinctive X-ray diffraction pattern with defined peaks. Such

materials when heated sufficiently will also exhibit the properties of a liquid, but the change from solid to liquid is characterized by a phase change, typically first order ('melting point').

The compounds of the invention may also exist in a mesomorphic state (mesophase or liquid crystal) when subjected to suitable conditions. The mesomorphic state is intermediate between the true crystalline state and the true liquid state (either melt or solution) and consists of two dimensional order on the molecular level. Mesomorphism arising as the result of a change in temperature is described as 'thermotropic' and that resulting from the addition of a second component, such as water or another solvent, is described as 'lyotropic'. Compounds that have the potential to form lyotropic mesophases are described as 'amphiphilic' and consist of molecules which possess an ionic (such as $-COO^-Na^+$, $-COO^-K^+$, or $-SO_3^-Na^+$) or non-ionic (such as $-N^+(CH_3)_3$) polar head group. For more information, see Crystals and the Polarizing Microscope by N. H. Hartshorne and A. Stuart, 4th Edition (Edward Arnold, 1970).

Stereoisomers

Compounds of the invention may exist as two or more stereoisomers. Stereoisomers of the compounds may include *cis* and *trans* isomers (geometric isomers), optical isomers such as *R* and *S* enantiomers, diastereomers, rotational isomers, atropisomers, and conformational isomers. For example, compounds of the invention containing one or more asymmetric carbon atoms may exist as two or more stereoisomers. Where a compound of the invention contains an alkenyl or alkenylene group, geometric cis/trans (or Z/E) isomers are possible. Cis/trans isomers may also exist for saturated rings.

The pharmaceutically acceptable salts of compounds of the invention may also contain a counterion which is optically active (e.g., d-lactate or l-lysine) or racemic (e.g. dl-tartrate or dl-arginine).

Cis/trans isomers may be separated by conventional techniques well known to those skilled in the art, for example, chromatography and fractional crystallization.

Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC). Alternatively, the racemate (or a racemic precursor) may be reacted with a suitable optically active compound, for example, an alcohol, or, in the case where a compound of the invention contains a basic moiety, an acid such as tartaric acid. The resulting diastereomeric mixture may be separated by chromatography, fractional crystallization, or by using both of said techniques, and one or both of the diastereoisomers converted to the corresponding pure

enantiomer(s) by means well known to a skilled person. Chiral compounds of the invention (and chiral precursors thereof) may be obtained in enantiomerically-enriched form using chromatography, typically HPLC Concentration of the eluate affords the enriched mixture. Chiral chromatography using sub-and supercritical fluids may be employed. Methods for chiral chromatography useful in some embodiments of the present invention are known in the art (see, for example, Smith, Roger M., Loughborough University, Loughborough, UK; Chromatographic Science Series (1998), 75 (Supercritical Fluid Chromatography with Packed Columns), pp. 223-249 and references cited therein).

When any racemate crystallizes, crystals of two different types are possible. The first type is the racemic compound (true racemate) referred to above wherein one homogeneous form of crystal is produced containing both enantiomers in equimolar amounts. The second type is the racemic mixture or conglomerate wherein two crystal forms are produced in equimolar amounts each comprising a single enantiomer. While both of the crystal forms present in a racemic mixture have identical physical properties, they may have different physical properties compared to the true racemate. Racemic mixtures may be separated by conventional techniques known to those skilled in the art - see, for example, Stereochemistry of Organic Compounds by E. L. Eliel and S. H. Wilen (Wiley, 1994).

Tautomerism

Where structural isomers are interconvertible via a low energy barrier, tautomeric isomerism ('tautomerism') may occur. This may take the form of proton tautomerism in compounds of the invention containing, for example, an imino/amino, keto/enol, or oxime/nitroso group, lactam/lactim or so-called valence tautomerism in compounds which contain an aromatic moiety. It follows that a single compound may exhibit more than one type of isomerism.

It must be emphasized that while, for conciseness, the compounds of the invention have been drawn herein in a single tautomeric form, all possible tautomeric forms are included within the scope of the invention.

Isotopes

The present invention includes all pharmaceutically acceptable isotopically-labeled compounds of the invention wherein one or more atoms are replaced by atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number which predominates in nature.

Examples of isotopes suitable for inclusion in the compounds of the invention may include isotopes of hydrogen, such as ^{2}H (D, deuterium) and ^{3}H (T, tritium), carbon, such as ^{11}C, ^{13}C and ^{14}C, chlorine, such as ^{36}Cl, fluorine, such as ^{18}F, iodine, such as ^{123}I and ^{125}I, nitrogen, such as ^{13}N and ^{15}N, oxygen, such as ^{15}O, ^{17}O and ^{18}O, phosphorus, such as ^{32}P, and sulfur, such as ^{35}S.

Certain isotopically-labelled compounds of the invention, for example those incorporating a radioactive isotope, are useful in one or both of drug or substrate tissue distribution studies. The radioactive isotopes tritium, i.e., ^{3}H, and carbon-14, i.e., ^{14}C, are particularly useful for this purpose in view of their ease of incorporation and ready means of detection.

Substitution with deuterium, i.e., ^{2}H, would be expected to give a compound of the same in vitro potency, but may afford certain therapeutic advantages resulting from greater metabolic stability or altered metabolite formation. These advantages may include for example increased in vivo half-life, reduced dosage requirements, reduced CYP450 inhibition (competitive or time dependent), or an improvement in therapeutic index or tolerability.

In some embodiments, the disclosure provides deuterium-labeled (or deuterated) compounds and salts, where the formula and variables of such compounds and salts are each and independently as described herein. “Deuterated” means that at least one of the atoms in the compound is deuterium in an abundance that is greater than the natural abundance of deuterium (typically approximately 0.015%). A skilled artisan recognized that in chemical compounds with a hydrogen atom, the hydrogen atom actually represents a mixture of H and D, with about 0.015% being D. The concentration of the deuterium incorporated into the deuterium-labeled compounds and salt of the invention may be defined by the deuterium enrichment factor.

It is understood that one or more deuteriums may exchange with hydrogen under physiological conditions.

Substitution with positron emitting isotopes, such as ^{11}C, ^{18}F, ^{15}O and ^{13}N, may be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy.

Isotopically-labeled compounds of the invention may generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations using an appropriate isotopically-labeled reagent in place of the non-labeled reagent previously employed.

Pharmaceutically acceptable solvates in accordance with the invention include those wherein the solvent of crystallization may be isotopically substituted, e.g., D_2O, d_6-acetone, d_6-DMSO.

Prodrugs

A compound of the invention may be administered in the form of a prodrug. Thus, certain derivatives of a compound of the invention which may have little or no pharmacological activity themselves may, when administered into or onto the body, be converted into a compound of the invention having the desired activity, for example by hydrolytic cleavage, particularly hydrolytic cleavage promoted by an esterase or peptidase enzyme. Such derivatives are referred to as 'prodrugs'. Further information on the use of prodrugs may be found in 'The Expanding Role of Prodrugs in Contemporary Drug Design and Development, Nature Reviews Drug Discovery, 17, 559-587 (2018) (J. Rautio et al.).

Prodrugs in accordance with the invention may, for example, be produced by replacing appropriate functionalities present in compounds of the invention with certain moieties known to those skilled in the art as 'pro-moieties' as described, for example, in 'Design of Prodrugs' by H. Bundgaard (Elsevier, 1985).

Thus, a prodrug in accordance with the invention may be (a) an ester or amide derivative of a carboxylic acid when present in a compound of the invention; (b) an ester, carbonate, carbamate, phosphate or ether derivative of a hydroxyl group when present in a compound of the invention; (c) an amide, imine, carbamate or amine derivative of an amino group when present in a compound of the invention; (d) a thioester, thiocarbonate, thiocarbamate or sulfide derivatives of a thiol group when present in a compound of the invention; or (e) an oxime or imine derivative of a carbonyl group when present in a compound of the invention.

Some specific examples of prodrugs in accordance with the invention include:

(i) when a compound of the invention contains a carboxylic acid functionality (-COOH), an ester thereof, such as a compound wherein the hydrogen of the carboxylic acid functionality of the compound is replaced by C_1-C_8 alkyl (e.g., ethyl) or (C_1-C_8 alkyl)C(=O)OCH_2- (e.g., ^{t}BuC(=O)OCH_2-);

(ii) when a compound of the invention contains an alcohol functionality (-OH), an ester thereof, such as a compound wherein the hydrogen of the alcohol functionality of the compound is replaced by –CO(C_1-C_8 alkyl) (e.g., methylcarbonyl) or the alcohol is esterified with an amino acid;

(iii) when a compound of the invention contains an alcohol functionality (-OH), an ether thereof, such as a compound wherein the hydrogen of the alcohol functionality of the compound is replaced by (C_1-C_8 alkyl)C(=O)OCH_2- or $–CH_2OP(=O)(OH)_2$;

(iv) when a compound of the invention contains an alcohol functionality (-OH), a phosphate thereof, such as a compound wherein the hydrogen of the alcohol functionality of the compound is replaced by $–P(=O)(OH)_2$ or $–P(=O)(O^-Na^+)_2$ or $–P(=O)(O^-)_2Ca^{2+}$;

(v) when a compound of the invention contains a primary or secondary amino functionality (-NH_2 or -NHR where R ≠ H), an amide thereof, for example, a compound wherein, as the case may be, one or both hydrogens of the amino functionality of the compound is/are replaced by (C_1-C_{10})alkanoyl, $–COCH_2NH_2$ or the amino group is derivatized with an amino acid;

(vi) when a compound of the invention contains a primary or secondary amino functionality (-NH_2 or -NHR where R ≠ H), an amine thereof, for example, a compound wherein, as the case may be, one or both hydrogens of the amino functionality of the compound is/are replaced by $–CH_2OP(=O)(OH)_2$.

Certain compounds of the invention may themselves act as prodrugs of other compounds the invention It is also possible for two compounds of the invention to be joined together in the form of a prodrug. In certain circumstances, a prodrug of a compound of the invention may be created by internally linking two functional groups in a compound of the invention, for instance by forming a lactone.

Metabolites

Also included within the scope of the invention are active metabolites of compounds of the invention, that is, compounds formed in vivo upon administration of the drug, often by oxidation or dealkylation. Some examples of metabolites in accordance with the invention include, but are not limited to,

(i) where the compound of the invention contains an alkyl group, a hydroxyalkyl derivative thereof (-CH > -COH):

(ii) where the compound of the invention contains an alkoxy group, a hydroxy derivative thereof (-OR -> -OH);

(iii) where the compound of the invention contains a tertiary amino group, a secondary amino derivative thereof (-NRR' -> -NHR or –NHR');

(iv) where the compound of the invention contains a secondary amino group, a primary derivative thereof (-NHR -> -NH_2);

(v) where the compound of the invention contains a phenyl moiety, a phenol derivative thereof (-Ph -> -PhOH);

(vi) where the compound of the invention contains an amide group, a carboxylic acid derivative thereof ($-CONH_2$ -> COOH); and

(vii) where the compound contains a hydroxy or carboxylic acid group, the compound may be metabolized by conjugation, for example with glucuronic acid to form a glucuronide. Other routes of conjugative metabolism exist. These pathways are frequently known as Phase 2 metabolism and include, for example, sulfation or acetylation. Other functional groups, such as NH groups, may also be subject to conjugation.

Pharmaceutical Compositions

In another embodiment, the invention comprises pharmaceutical compositions. For pharmaceutical composition purposes, the compound per se or pharmaceutically acceptable salt thereof will simply be referred to as the compounds of the invention.

A "pharmaceutical composition" refers to a mixture of one or more of the compounds of the invention, or a pharmaceutically acceptable salt, solvate, hydrate or prodrug thereof as an active ingredient, and at least one pharmaceutically acceptable excipient.

The term 'excipient' is used herein to describe any ingredient other than the compound(s) of the invention. The choice of excipient will to a large extent depend on factors such as the mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form.

As used herein, "excipient" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, carriers, diluents and the like that are physiologically compatible. Examples of excipients include one or more of water, saline, phosphate buffered saline, dextrose, glycerol, ethanol and the like, as well as combinations thereof, and may include isotonic agents, for example, sugars, sodium chloride, or polyalcohols such as mannitol, or sorbitol in the composition. Examples of excipients also include various organic solvents (such as hydrates and solvates). The pharmaceutical compositions may, if desired, contain additional excipients such as flavorings, binders/binding agents, lubricating agents, disintegrants, sweetening or flavoring agents, coloring matters or dyes, and the like. For example, for oral administration, tablets containing various excipients, such as citric acid may be employed together with various disintegrants such as starch, alginic acid and certain complex silicates and with binding agents such as sucrose, gelatin and acacia. Examples, without limitation, of excipients

include calcium carbonate, calcium phosphate, various sugars and types of starch, cellulose derivatives, gelatin, vegetable oils and polyethylene glycols. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often useful for tableting purposes. Solid compositions of a similar type may also be employed in soft and hard filled gelatin capsules. Non-limiting examples of excipients, therefore, also include lactose or milk sugar and high molecular weight polyethylene glycols. When aqueous suspensions or elixirs are desired for oral administration the active compound therein may be combined with various sweetening or flavoring agents, coloring matters or dyes and, if desired, emulsifying agents or suspending agents, together with additional excipients such as water, ethanol, propylene glycol, glycerin, or combinations thereof.

Examples of excipients also include pharmaceutically acceptable substances such as wetting agents or minor amounts of auxiliary substances such as wetting or emulsifying agents, preservatives, or buffers, which enhance the shelf life or effectiveness of the compound.

The compositions of this invention may be in a variety of forms. These include, for example, liquid, semi-solid and solid dosage forms, such as liquid solutions (e.g., injectable and infusible solutions), dispersions or suspensions, tablets, capsules, pills, powders, liposomes and suppositories. The form depends on the intended mode of administration and therapeutic application.

Typical compositions are in the form of injectable or infusible solutions, such as compositions similar to those used for passive immunization of humans with antibodies in general. One mode of administration is parenteral (e.g., intravenous, subcutaneous, intraperitoneal, intramuscular). In another embodiment, the compound is administered by intravenous infusion or injection. In yet another embodiment, the compound is administered by intramuscular or subcutaneous injection.

Oral administration of a solid dosage form may be, for example, presented in discrete units, such as hard or soft capsules, pills, cachets, lozenges, or tablets, each containing a predetermined amount of at least one compound of the invention. In another embodiment, the oral administration may be in a powder or granule form. In another embodiment, the oral dosage form is sub-lingual, such as, for example, a lozenge. In such solid dosage forms, the compounds of the invention are ordinarily combined with one or more adjuvants. Such capsules or tablets may comprise a controlled release formulation. In the case of capsules, tablets, and pills, the dosage forms also may comprise buffering agents or may be prepared with enteric coatings.

In another embodiment, oral administration may be in a liquid dosage form. Liquid dosage forms for oral administration include, for example, pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art (e.g., water). Such compositions also may comprise adjuvants, such as one or more of wetting, emulsifying, suspending, flavoring (e.g., sweetening), or perfuming agents.

In another embodiment, the invention comprises a parenteral dosage form. "Parenteral administration" includes, for example, subcutaneous injections, intravenous injections, intraperitoneally, intramuscular injections, intrasternal injections, and infusion. Injectable preparations (i.e., sterile injectable aqueous or oleaginous suspensions) may be formulated according to the known art using one or more of suitable dispersing, wetting agents, or suspending agents.

In another embodiment, the invention comprises a topical dosage form. "Topical administration" includes, for example, dermal and transdermal administration, such as via transdermal patches or iontophoresis devices, intraocular administration, or intranasal or inhalation administration. Compositions for topical administration also include, for example, topical gels, sprays, ointments, and creams. A topical formulation may include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. When the compounds of this invention are administered by a transdermal device, administration will be accomplished using a patch either of the reservoir and porous membrane type or of a solid matrix variety. Typical formulations for this purpose include gels, hydrogels, lotions, solutions, creams, ointments, dusting powders, dressings, foams, films, skin patches, wafers, implants, sponges, fibers, bandages and microemulsions. Liposomes may also be used. Typical excipients include alcohol, water, mineral oil, liquid petrolatum, white petrolatum, glycerin, polyethylene glycol and propylene glycol. Penetration enhancers may be incorporated - see, for example, B. C. Finnin and T. M. Morgan, J. Pharm. Sci., vol. 88, pp. 955-958, 1999.

Formulations suitable for topical administration to the eye include, for example, eye drops wherein the compound of this invention is dissolved or suspended in a suitable excipient. A typical formulation suitable for ocular or aural administration may be in the form of drops of a micronized suspension or solution in isotonic, pH-adjusted, sterile saline. Other formulations suitable for ocular and aural administration include ointments, biodegradable (i.e., absorbable gel sponges, collagen) and non-biodegradable (i.e., silicone) implants, wafers, lenses and particulate or vesicular systems, such as niosomes or liposomes. A

polymer such as crossed linked polyacrylic acid, polyvinyl alcohol, hyaluronic acid, a cellulosic polymer, for example, hydroxypropylmethylcellulose, hydroxyethylcellulose, or methylcellulose, or a heteropolysaccharide polymer, for example, gelan gum, may be incorporated together with a preservative, such as benzalkonium chloride. Such formulations may also be delivered by iontophoresis.

For intranasal administration, the compounds of the invention are conveniently delivered in the form of a solution or suspension from a pump spray container that is squeezed or pumped by the patient or as an aerosol spray presentation from a pressurized container or a nebulizer, with the use of a suitable propellant. Formulations suitable for intranasal administration are typically administered in the form of a dry powder (either alone, as a mixture, for example, in a dry blend with lactose, or as a mixed component particle, for example, mixed with phospholipids, such as phosphatidylcholine) from a dry powder inhaler or as an aerosol spray from a pressurized container, pump, spray, atomizer (preferably an atomizer using electrohydrodynamics to produce a fine mist), or nebulizer, with or without the use of a suitable propellant, such as 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane. For intranasal use, the powder may comprise a bioadhesive agent, for example, chitosan or cyclodextrin.

In another embodiment, the invention comprises a rectal dosage form. Such rectal dosage form may be in the form of, for example, a suppository. Cocoa butter is a traditional suppository base, but various alternatives may be used as appropriate.

Other excipients and modes of administration known in the pharmaceutical art may also be used. Pharmaceutical compositions of the invention may be prepared by any of the well-known techniques of pharmacy, such as effective formulation and administration procedures. The above considerations in regard to effective formulations and administration procedures are well known in the art and are described in standard textbooks. Formulation of drugs is discussed in, for example, Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania, 1975; Liberman et al., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980; and Kibbe et al., Eds., Handbook of Pharmaceutical Excipients (3rd Ed.), American Pharmaceutical Association, Washington, 1999.

Acceptable excipients are nontoxic to subjects at the dosages and concentrations employed, and may comprise one or more of the following: 1) buffers such as phosphate, citrate, or other organic acids; 2) salts such as sodium chloride; 3) antioxidants such as ascorbic acid or methionine; 4) preservatives such as octadecyldimethylbenzyl ammonium

chloride, hexamethonium chloride, benzalkonium chloride, benzethonium chloride, phenol, butyl or benzyl alcohol; 5) alkyl parabens such as methyl or propyl paraben, catechol, resorcinol, cyclohexanol, 3-pentanol, or m-cresol; 6) low molecular weight (less than about 10 residues) polypeptides; 7) proteins such as serum albumin, gelatin, or immunoglobulins; 8) hydrophilic polymers such as polyvinylpyrrolidone; 9) amino acids such as glycine, glutamine, asparagine, histidine, arginine, or lysine; 10) monosaccharides, disaccharides, or other carbohydrates including glucose, mannose, or dextrins; 11) chelating agents such as EDTA; 12) sugars such as sucrose, mannitol, trehalose or sorbitol; 13) salt-forming counter-ions such as sodium, metal complexes (e.g., Zn-protein complexes), or 14) non-ionic surfactants such as polysorbates (e.g., polysorbate 20 or polysorbate 80), poloxamers or polyethylene glycol (PEG).

For oral administration, the compositions may be provided in the form of tablets or capsules containing 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, 50.0, 75.0, 100, 125, 150, 175, 200, 250, 300, 500, or 1000 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient. A medicament typically contains from about 0.01 mg to about 2500 mg of the active ingredient, or in another embodiment, from about 1 mg to about 500 mg of active ingredient. In another embodiment, a medicament contains from about 1 mg to about 100 mg of active ingredient. Intravenously, doses may range from about 0.01 to about 10 mg/kg/minute during a constant rate infusion.

Liposome containing compounds of the invention may be prepared by methods known in the art (See, for example, Chang, H.I.; Yeh, M.K.; Clinical development of liposome-based drugs: formulation, characterization, and therapeutic efficacy; Int J Nanomedicine 2012; 7; 49-60). Particularly useful liposomes may be generated by the reverse phase evaporation method with a lipid composition comprising phosphatidylcholine, cholesterol and PEG-derivatized phosphatidylethanolamine (PEG-PE). Liposomes are extruded through filters of defined pore size to yield liposomes with the desired diameter.

Compounds of the invention may also be entrapped in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsules and poly-(methylmethacrylate) microcapsules, respectively, in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles and nanocapsules) or in macroemulsions. Such techniques are disclosed in Remington, The Science and Practice of Pharmacy, 20th Ed., Mack Publishing (2000).

Sustained-release preparations may be used. Suitable examples of sustained-release preparations include semi-permeable matrices of solid hydrophobic polymers containing a compound of the invention, which matrices are in the form of shaped articles, e.g., films, or microcapsules. Examples of sustained-release matrices include polyesters, hydrogels (for example, poly(2-hydroxyethyl-methacrylate), or 'poly(vinylalcohol)), polylactides, copolymers of L-glutamic acid and 7 ethyl-L-glutamate, non-degradable ethylene-vinyl acetate, degradable lactic acid-glycolic acid copolymers such as those used in leuprolide acetate for depot suspension (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), sucrose acetate isobutyrate, and poly-D-(-)-3-hydroxybutyric acid.

The formulations to be used for intravenous administration must be sterile. This is readily accomplished by, for example, filtration through sterile filtration membranes. Compounds of the invention are generally placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

Suitable emulsions may be prepared using commercially available fat emulsions, such as a lipid emulsions comprising soybean oil, a fat emulsion for intravenous administration (e.g., comprising safflower oil, soybean oil, egg phosphatides and glycerin in water), emulsions containing soya bean oil and medium-chain triglycerides, and lipid emulsions of cottonseed oil. The active ingredient may be either dissolved in a pre-mixed emulsion composition or alternatively it may be dissolved in an oil (e.g., soybean oil, safflower oil, cottonseed oil, sesame oil, corn oil or almond oil) and an emulsion formed upon mixing with a phospholipid (e.g., egg phospholipids, soybean phospholipids or soybean lecithin) and water. It will be appreciated that other ingredients may be added, for example glycerol or glucose, to adjust the tonicity of the emulsion. Suitable emulsions will typically contain up to 20% oil, for example, between 5 and 20%. The fat emulsion may comprise fat droplets between 0.1 and 1.0 μm, particularly 0.1 and 0.5 μm, and have a pH in the range of 5.5 to 8.0.

For example, the emulsion compositions may be those prepared by mixing a compound of the invention with a lipid emulsions comprising soybean oil or the components thereof (soybean oil, egg phospholipids, glycerol and water).

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients

as set out above. In some embodiments, the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in preferably sterile pharmaceutically acceptable solvents may be nebulized by use of gases. Nebulized solutions may be breathed directly from the nebulizing device or the nebulizing device may be attached to a face mask, tent or intermittent positive pressure breathing machine. Solution, suspension or powder compositions may be administered, preferably orally or nasally, from devices which deliver the formulation in an appropriate manner.

A drug product intermediate (DPI) is a partly processed material that must undergo further processing steps before it becomes bulk drug product. Compounds of the invention may be formulated into drug product intermediate DPI containing the active ingredient in a higher free energy form than the crystalline form. One reason to use a DPI is to improve oral absorption characteristics due to low solubility, slow dissolution, improved mass transport through the mucus layer adjacent to the epithelial cells, and in some cases, limitations due to biological barriers such as metabolism and transporters. Other reasons may include improved solid state stability and downstream manufacturability. In one embodiment, the drug product intermediate contains a compound of the invention isolated and stabilized in the amorphous state (for example, amorphous solid dispersions (ASDs)). There are many techniques known in the art to manufacture ASD's that produce material suitable for integration into a bulk drug product, for example, spray dried dispersions (SDD's), melt extrudates (often referred to as HME's), co-precipitates, amorphous drug nanoparticles, and nano-adsorbates. In one embodiment amorphous solid dispersions comprise a compound of the invention and a polymer excipient. Other excipients as well as concentrations of said excipients and the compound of the invention are well known in the art and are described in standard textbooks. See, for example, "*Amorphous Solid Dispersions Theory and Practice*" by Navnit Shah et al.

Administration and Dosing

The term "treating", "treat" or "treatment" as used herein embraces both preventative, i.e., prophylactic, and palliative treatment, i.e., relieve, alleviate, or slow the progression of the patient's disease (or condition) or any tissue damage associated with the disease.

As used herein, the terms, "subject, "individual" or "patient," used interchangeably, refer to any animal, including mammals. Mammals according to the invention include canine, feline, bovine, caprine, equine, ovine, porcine, rodents, lagomorphs, primates, humans and

the like, and encompass mammals in utero. In an embodiment, humans are suitable subjects. Human subjects may be of any gender and at any stage of development.

As used herein, the phrase "therapeutically effective amount" refers to the amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal, individual or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which may include one or more of the following:

(1) preventing the disease; for example, preventing a disease, condition or disorder in an individual that may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease;

(2) inhibiting the disease; for example, inhibiting a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., arresting (or slowing) further development of the pathology or symptomatology or both); and

(3) ameliorating the disease; for example, ameliorating a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., reversing the pathology or symptomatology or both).

Typically, a compound of the invention is administered in an amount effective to treat a condition as described herein. The compounds of the invention may be administered as compound per se, or alternatively, as a pharmaceutically acceptable salt. For administration and dosing purposes, the compound per se or pharmaceutically acceptable salt thereof will simply be referred to as the compounds of the invention.

The compounds of the invention are administered by any suitable route in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. The compounds of the invention may be administered orally, rectally, vaginally, parenterally, topically, intranasally, or by inhalation.

The compounds of the invention may be administered orally. Oral administration may involve swallowing, so that the compound enters the gastrointestinal tract, or buccal or sublingual administration may be employed by which the compound enters the bloodstream directly from the mouth.

In another embodiment, the compounds of the invention may also be administered parenterally, for example directly into the bloodstream, into muscle, or into an internal organ. Suitable means for parenteral administration include intravenous, intraarterial,

intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular and subcutaneous. Suitable devices for parenteral administration include needle (including microneedle) injectors, needle-free injectors, and infusion techniques.

In another embodiment, the compounds of the invention may also be administered topically to the skin or mucosa, that is, dermally or transdermally. In another embodiment, the compounds of the invention may also be administered intranasally or by inhalation. In another embodiment, the compounds of the invention may be administered rectally or vaginally. In another embodiment, the compounds of the invention may also be administered directly to the eye or ear.

The dosage regimen for the compounds of the invention or compositions containing said compounds is based on a variety of factors, including the type, age, weight, sex and medical condition of the patient; the severity of the condition; the route of administration; and the activity of the particular compound employed. Thus, the dosage regimen may vary widely. In one embodiment, the total daily dose of a compound of the invention is typically from about 0.01 to about 100 mg/kg (i.e., mg compound of the invention per kg body weight) for the treatment of the indicated conditions discussed herein. In another embodiment, total daily dose of the compound of the invention is from about 0.1 to about 50 mg/kg, and in another embodiment, from about 0.5 to about 30 mg/kg. It is not uncommon that the administration of the compounds of the invention will be repeated a plurality of times in a day (typically no greater than 4 times). Multiple doses per day typically may be used to increase the total daily dose, if desired.

Therapeutic Methods and Uses

The compounds of the invention inhibit the activity of the papain-like protease and may thus be useful in the treatment, prevention, suppression, and amelioration of diseases, disorders and conditions mediated by the papain-like protease, in particular viral infections such as coronaviruses infections.

Examples of such coronavirus infections include, but are not limited to, diseases or conditions in which coronaviruses are implicated like common cold, Middle East respiratory syndrome (MERS), severe acute respiratory syndrome (SARS) or COVID-19 (Coronavirus disease 2019).

Co-administration

The compounds of the invention may be used alone, or in combination with one or more other therapeutic agents. The invention provides any of the uses, methods or compositions as defined herein wherein the compound of the invention, or pharmaceutically acceptable salt thereof, is used in combination with one or more other therapeutic agent discussed herein.

The administration of two or more compounds "in combination" means that all of the compounds are administered closely enough in time to affect treatment of the subject. The two or more compounds may be administered simultaneously or sequentially, via the same or different routes of administration, on same or different administration schedules and with or without specific time limits depending on the treatment regimen. Additionally, simultaneous administration may be carried out by mixing the compounds prior to administration or by administering the compounds at the same point in time but as separate dosage forms at the same or different site of administration. Examples of "in combination" include, but are not limited to, "concurrent administration," "co-administration," "simultaneous administration," "sequential administration" and "administered simultaneously".

A compound of the invention and the one or more other therapeutic agents may be administered as a fixed or non-fixed combination of the active ingredients. The term "fixed combination" means a compound of the invention, or a pharmaceutically acceptable salt thereof, and the one or more therapeutic agents, are both administered to a subject simultaneously in a single composition or dosage. The term "non-fixed combination" means that a compound of the invention, or a pharmaceutically acceptable salt thereof, and the one or more therapeutic agents are formulated as separate compositions or dosages such that they may be administered to a subject in need thereof simultaneously or at different times with variable intervening time limits, wherein such administration provides effective levels of the two or more compounds in the body of the subject.

In one embodiment, the compounds of this invention may be administered in combination with other therapeutic agents, which may provide greater clinical benefit. Such additional therapeutic agents include, but are not limited to, vital RNA polymerase inhibitors, Mpro inhibitors, nucleoside inhibitors, host factor inhibitors, other PLpro inhibitors and metabolism boosting agents that leads to reduction in virus replication or host response and may thus contribute to greater clinical benefit. An example of viral RNA polymerase inhibitor is remdesivir. Examples of Mpro inhibitors include, but are not limited to, nirmatrelvir (also

known as "PF-07321332"), pomotrelvir (also known as "PBI-0451"), bofutrelvir (also known as "FB2001"), EDP-235, ensitrelvir (also known as "S-217622") and ALG-097111.

Additional metabolism boosting agents such as ritonavir may also be used in combination with the compounds of the present invention or with combinations of the compounds of the present invention with other therapeutic agents as indicated above, in order to increase the therapeutic effect.

Examples of greater clinical benefits includes, but are not limited to, a larger reduction in symptoms, a faster time to alleviation of symptoms, reduced lung pathology, a larger reduction in the amount of coronavirus in the patient (viral load), and decreased disease severity or mortality.

Kits

Another aspect of the invention provides kits comprising the compound of the invention or pharmaceutical compositions comprising the compound of the invention. A kit may include, in addition to the compound of the invention or pharmaceutical composition thereof, diagnostic or therapeutic agents. A kit may also include instructions for use in a diagnostic or therapeutic method. In some embodiments, the kit includes the compound or a pharmaceutical composition thereof and a diagnostic agent or rapid test. In other embodiments, the kit includes the compound or a pharmaceutical composition thereof, one or more therapeutic agents, such as a viral RNA polymerase inhibitor – e.g., remdesivir -, a Mpro inhibitor – e.g., nirmatrelvir, PBI-0451, bofutrelvir, EDP-235, ensitrelvir and ALG-097111 - a nucleoside inhibitor, a host factor inhibitor, another PLpro inhibitor or a metabolism boosting agent, and optionally a diagnostic agent or rapid test. In yet another embodiment, the invention comprises kits that are suitable for use in performing the methods of treatment described herein. In one embodiment, the kit contains a first dosage form comprising one or more of the compounds of the invention in quantities sufficient to carry out the methods of the invention. In another embodiment, the kit comprises one or more compounds of the invention in quantities sufficient to carry out the methods of the invention and a container for the dosage.

Synthetic Methods

Compounds of the present invention may be synthesized by synthetic routes that include processes analogous to those well-known in the chemical arts, particularly in light of the description contained herein. The starting materials are generally available from

commercial sources or may be prepared using methods well known to those skilled in the art. Many of the compounds used herein, are related to, or may be derived from compounds in which one or more of the scientific interest or commercial need has occurred. Accordingly, such compounds may be one or more of 1) commercially available; 2) reported in the literature or 3) prepared from other commonly available substances by one skilled in the art using materials which have been reported in the literature.

For illustrative purposes, the reaction schemes depicted below provide potential routes for synthesizing the compounds of the present invention as well as key intermediates. For a more detailed description of the individual reaction steps, see the Examples 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 discussed below, other starting materials and reagents may be substituted to provide one or more of a variety of derivatives or reaction conditions. In addition, many of the compounds prepared by the methods described below may be further modified in light of this disclosure using conventional chemistry well known to those skilled in the art.

The skilled person will appreciate that the experimental conditions set forth in the schemes that follow are illustrative of suitable conditions for effecting the transformations shown, and that it may be necessary or desirable to vary the precise conditions employed for the preparation of compounds of the invention. It will be further appreciated that it may be necessary or desirable to carry out the transformations in a different order from that described in the schemes, or to modify one or more of the transformations, to provide the desired compound of the invention.

In the preparation of compounds of the invention it is noted that some of the preparation methods useful for the preparation of the compounds described herein may require protection of remote functionality (e.g., a primary amine, secondary amine, carboxyl, etc. in a precursor of a compound of the invention). The need for such protection will vary depending on the nature of the remote functionality and the conditions of the preparation methods. The need for such protection is readily determined by one skilled in the art. The use of such protection/deprotection methods is also within the skill in the art. For a general description of protecting groups and their use, see March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure 8th Edition.

For example, if a compound contains an amine or carboxylic acid functionality, such functionality may interfere with reactions at other sites of the molecule if left unprotected. Accordingly, such functionalities may be protected by an appropriate protecting group (PG)

which may be removed in a subsequent step. Suitable protecting groups for amine and carboxylic acid protection include those protecting groups commonly used in peptide synthesis (such as *N-tert*-butoxycarbonyl (Boc), benzyloxycarbonyl (Cbz), and 9-fluorenylmethylenoxycarbonyl (Fmoc) for amines and lower alkyl or benzyl esters for carboxylic acids) which are generally not chemically reactive under the reaction conditions described and may typically be removed without chemically altering other functionality in a compound of the invention.

General Experimental Details

In the non-limiting Examples and Preparations that illustrate the invention and that are set out in the description, and in the following Schemes, the following the abbreviations, definitions and analytical procedures may be referred to:

^{1}H NMR spectra were recorded on a 400 MHz Bruker NMR instrument with Iprobe probe. The multiplicity of a signal is designated by the following abbreviations: "s, singlet; d, doublet; t, triplet; q, quartet; p, pentet; sept, septet; dd, doublet of doublets; dt, doublet of triplets; tt, triplet of triplets; br, broad; m, multiplet". All observed coupling constants, *J*, are reported in Hertz (Hz). Exchangeable protons are not always observed.

LCMS data were obtained using Method **A**, Method **B**, or Method **C** as defined below. Samples were prepared by dissolution in methanol or chloroform to a concentration of 200 µg/500 µL.

Method **A**: Instrument: Agilent 1200 & 6120B, 5_95CD_6min-220: LC/MS (The gradient was 5% B in 0.40 min and 5-95% B at 0.40-3.40 min, hold on 95% B for 0.45 min, and then 95-5% B in 0.01 min, the flow rate was 0.8 mL/min. Mobile phase A was H_2O + 10 mM NH_4HCO_3, mobile phase B was acetonitrile. The column used for chromatography was a Xbridge C18 2.1 x 50 mm column (5 µm particles). Column temperature: 40 °C. Detection methods are diode array (DAD) detection. MS mode was positive electrospray ionization. MS range was 100-1000.

Method **B**: Instrument: Agilent 1200&6120, 5_95AB_6min-220-254: LC/MS (The gradient was 5% B in 0.40 min and 5-95% B in 2.60 min, hold on 95% B in 1.00 min, and then 95-5%B in 0.01 min, the flow rate was 1.0 mL/min. Mobile phase A was 0.04% TFA in water, mobile phase B was 0.02% TFA in acetonitrile. The column used for chromatography was a Halo C18, 3.0 x 30 mm column (5 µm particles). Column temperature: 40 °C. Detection methods are diode array (DAD) detection. MS mode was positive electrospray ionization. MS range was 100-1000.

Method **C**: Instrument: Shimadzu LC-20AD XR&MS 2020, DELIVER-5-95AB_6min-220, Description: Mobile Phase: 0.04% TFA in water (solvent A) and 0.02 % TFA in acetonitrile (solvent B), using the elution gradient 5%-95% (solvent B) over 3.0 min and holding at 95% for 1.0 min at a flow rate of 1.0 mL/min; Column: Halo C18, 3.0 x 30 mm, 5 µm; Wavelength: UV 220 nm, Column temperature: 40 °C. MS ionization: ESI. MS range was 100-1000.

Abbreviations

°2θ is degrees 2-theta;
AcCl is acetyl chloride;
AcOH is acetic acid;
ADH-101 is alcohol dehydrogenase 101;
APCI is atmospheric pressure chemical ionization;
aq is aqueous;
BH_3Me_2S is (dimethyl sulphide)trihydroboron;
BINAP is 1,1'-binaphthalene-2,2'-diyl)bis(diphenylphosphine;
Bn is benzyl;
Boc is *tert*-butoxycarbonyl;
Boc_2O is di-*tert*-butyl dicarbonate;
br is broad;
tBu is *tert*-butyl;
tBuOH is *tert*-butanol;
tBuOK is potassium *tert*-butoxide;
tBuXPhos is 2-di-*tert*-butylphosphino-2',4',6'-triisopropylbiphenyl;
tBuXPhos-Pd Gen-3 is [(2-di-*tert*-butylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)-2-(2'-amino-1,1'-biphenyl)] palladium(II) methanesulfonate;
°C is degrees celcius;
$CDCl_3$ is deutero-chloroform;
CD_3OD is methanol-d_4
CDI is 1,1'-carbonyldiimidazole;
δ is chemical shift;
d is doublet;
dd is doublet of doublets;
ddd is doublet of doublet of doublets;

dt is doublet of triplets;
DCE is 1,2-dichloroethane;
DCM is dichloromethane; methylene chloride;
DIAD is diisopropyl azodicarboxylate;
(-)-DIP-Chloride™ is (-)-B-chlorodiisopinocampheylborane;
DIPEA is N-ethyldiisopropylamine, also known as N,N-diisopropylethylamine;
DMA is N,N-dimethylacetamide;
DME is 1,2-dimethoxyethane;
DMAP is 4-dimethylaminopyridine;
DMF is N,N-dimethylformamide;
DMSO is dimethyl sulfoxide;
DMSO-d_6 is deuterodimethylsulfoxide;
DPPP is 1,3-bis(diphenylphosphino)propane;
EDC is N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide;
EDC.HCl is N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride;
ESI is electrospray ionization;
Et_2O is diethyl ether;
EtOAc is ethyl acetate;
EtOH is ethanol;
Et_3N is triethylamine;
g is gram;
HATU is 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate;
HPLC is high pressure liquid chromatography;
HOBt is 1-hydroxybenzotriazole hydrate;
hr(s) and/or h is hour(s);
IPA is isopropyl alcohol;
iPrOAc is isopropyl acetate;
Ir[dF(CF_3)ppy]$_2$(dtbpy)PF_6 is [4,4'-bis(1,1-dimethylethyl)-2,2'-bipyridine-*N*1,*N*1']bis[3,5-difluoro-2-[5-(trifluoromethyl)-2-pyridinyl-*N*]phenyl-C]iridium(III) hexafluorophosphate;
KRED101 is ketoreductase 101 enzyme;
L is liter;
LCMS is liquid chromatography mass spectrometry;
m is multiplet;

M is molar;
m-CPBA is 3-chloroperbenzoic acid;
MeCN is acetonitrile;
MeMgBr is methylmagnesium bromide;
MeNHOMe HCl is N,O-dimethylhydroxylamine hydrochloride;
MeOD_d_4 is deuterated methanol;
MeOH is methanol;
2-MeTHF is 2-methyl tetrahydrofuran;
mg is milligram;
MHz is mega Hertz;
min(s) is minute(s);
mL is milliliter;
mmol is millimole;
mol is mole;
MS (m/z) is mass spectrum peak;
MsCl is mesyl chloride;
MTBE is *tert*-butyl methyl ether;
NADP+ is nicotinamide adenine dinucleotide phosphate;
$NiCl_2$•glyme is nickel (II) chloride ethylene glycol dimethyl ether complex;
NMR is nuclear magnetic resonance;
ODS is octadecyl-silica;
ORTEP is Oak Ridge Thermal Ellipsoid Plot;
$Pd(tBu_3P)_2$ is bis(tri-*tert*-butylphosphine)palladium(0);
Pd/C is palladium on carbon;
$Pd_2(dba)_3$ is palladium tris(dibenzylideneacetone)dipalladium(0);
$Pd(dppf)Cl_2$ is [1,1'-bis(diphenylphophino)ferrocene]dichloropalladium(II);
$Pd(PPh_3)_4$ is tetrakis(triphenylphosphine)palladium(0);
Pet. ether is the petroleum fraction consisting of aliphatic hydrocarbons and boiling in the range 35–60 °C;
PMB is para-methoxybenzyl;
PMB-NH_2 is para-methoxybenzylamine;
Polycat 5 ® is bis(2-dimethylaminoethyl)(methyl)amine
PPh_3 is triphenylphosphine;
pH is power of hydrogen;

ppm is parts per million;
PSD is position sensitive detector;
psi is pounds per square inch;
PXRD is powder X-ray diffraction;
q is quartet;
rt is room temperature;
RT is retention time;
s is singlet;
SEM-Cl is 2-(trimethylsilyl)ethoxymethyl chloride;
SFC is supercritical fluid chromatography;
t is triplet;
T_3P is propylphosphonic anhydride;
TBAF is *tert*-butyl ammonium fluoride;
TBDMSCl is *tert*-butyldimethylsilyl chloride;
TFA is trifluoroacetic acid;
THF is tetrahydrofuran;
TLC is thin layer chromatography;
TMEDA is *N,N,N'N'*-tetramethylethylenediamine;
TMSCl is trimethylsilyl chloride;
TMSCN is trimethylsilyl cyanide;
$TMSCHN_2$ is (diazomethyl)trimethylsilane;
TsCl is p-toluenesulfonyl chloride;
Ts_2O is p-toluenesulfonic anhydride;
µL is microliter;
µmol is micromole; and
Xantphos is 4,5-bis(diphenylphosphno)-9,9-dimethylxanthene

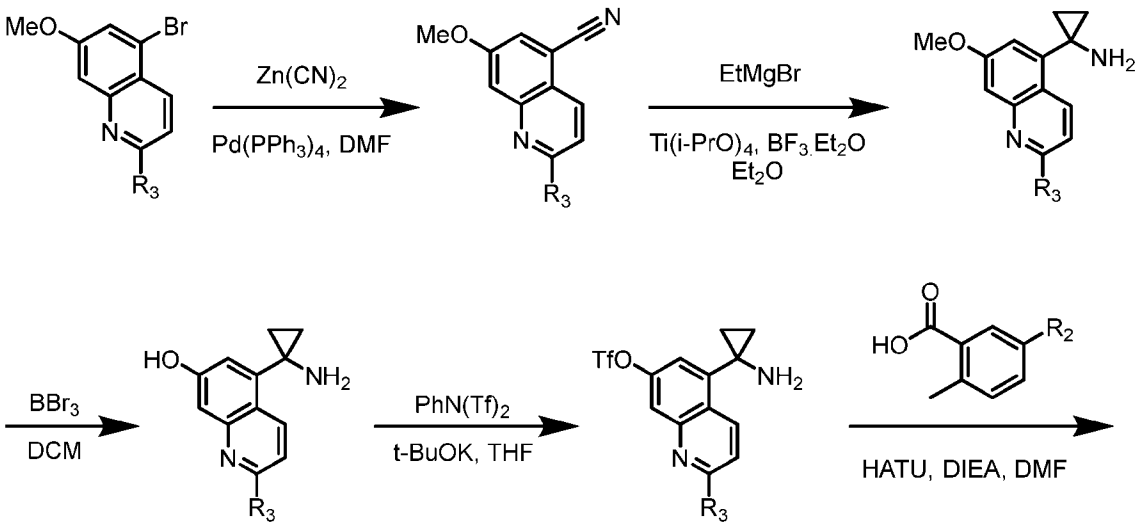
The Schemes described below are intended to provide a general description of the methodology employed in the preparation of the compounds of the present invention. Some of the compounds of the present invention contain a single chiral center. In the following Schemes, the general methods for the preparation of the compounds are shown either in racemic or enantioenriched form. It will be apparent to one skilled in the art that all of the synthetic transformations may be conducted in a precisely similar manner whether the materials are enantioenriched or racemic. Moreover, the resolution to the desired optically

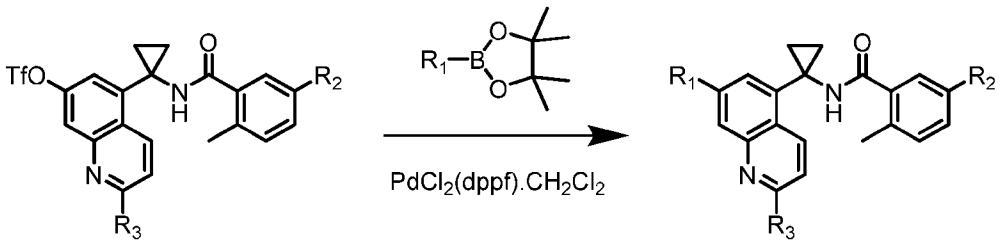
active material may take place at any desired point in the sequence using well known methods such as described herein and in the chemistry literature.

General Methods:

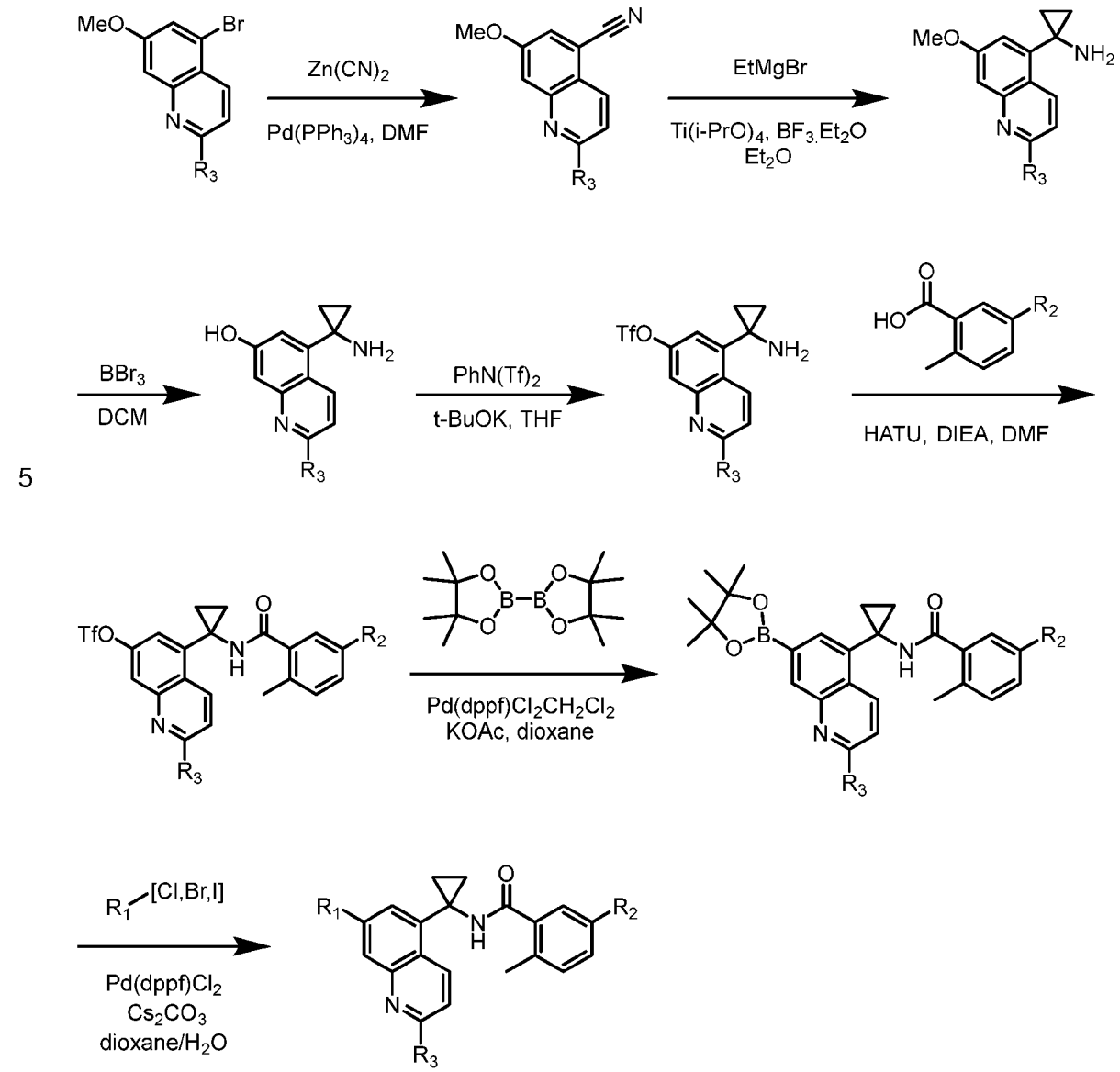
Certain compounds of Formula (I) can be prepared according to schemes **I-V** or analogous methods. Unless stated otherwise, the variables in Schemes **I-V** have the same meanings as defined herein.

Scheme **I**:

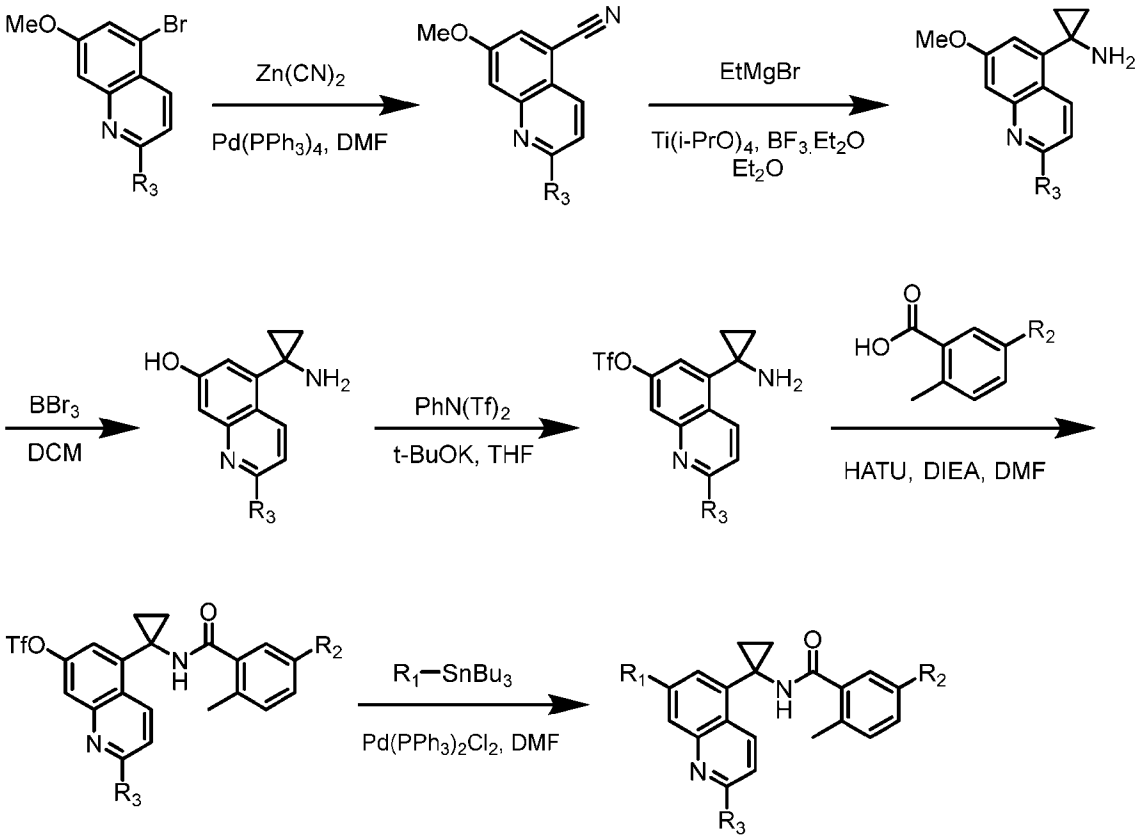




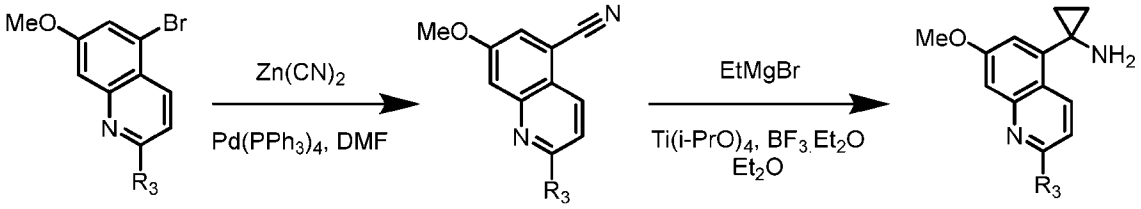
Scheme II:

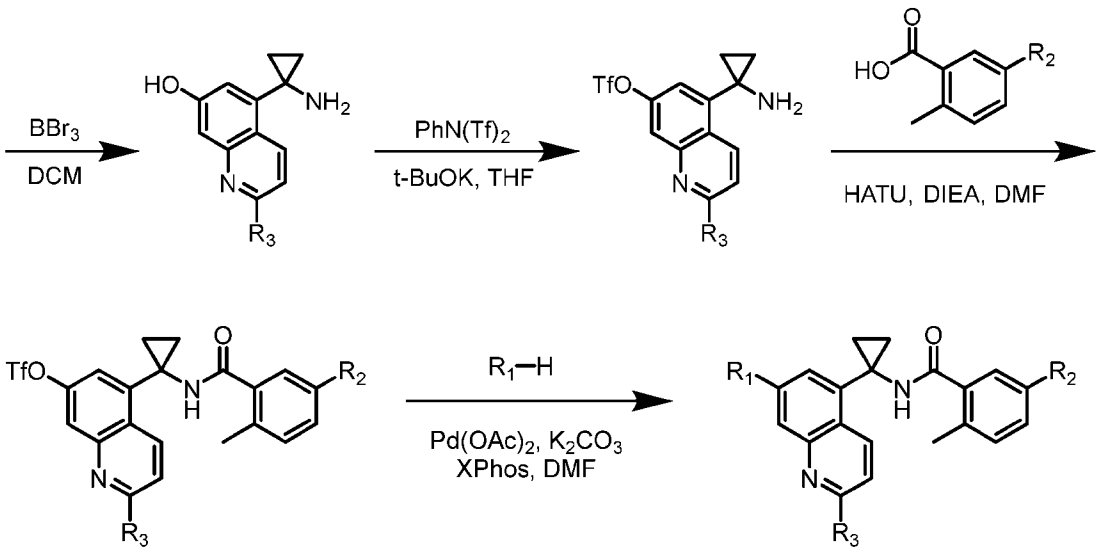

MeO
Br
N
R3
Zn(CN)2
Pd(PPh3)4, DMF
MeO
N
N
R3
EtMgBr
Ti(i-PrO)4, BF3.Et2O
Et2O
MeO
NH2
N
R3
BBr3
DCM
HO
NH2
N
R3
PhN(Tf)2
t-BuOK, THF
TfO
NH2
N
R3
HO
O
R2
HATU, DIEA, DMF
TfO
N
H
O
R2
N
R3
B
O
Pd(dppf)Cl2CH2Cl2
KOAc, dioxane
R1
[Cl,Br,I]
Pd(dppf)Cl2
Cs2CO3
dioxane/H2O

Scheme **III**:

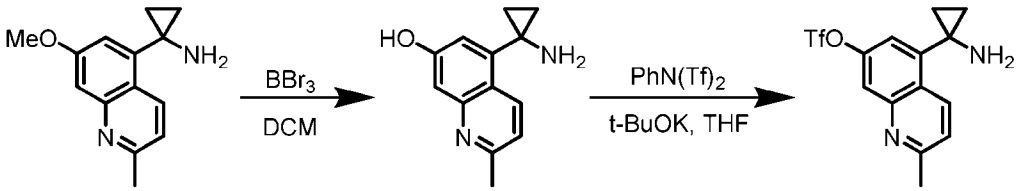


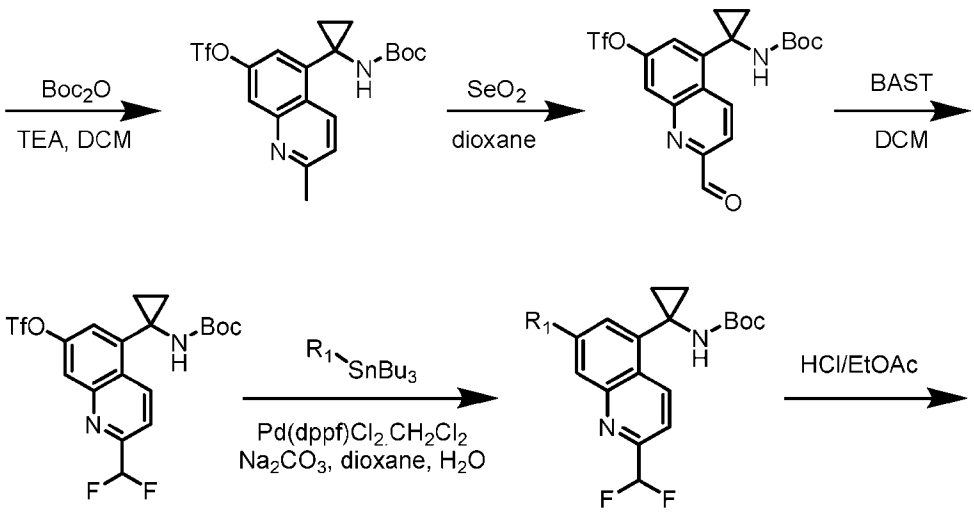
Scheme **IV**:

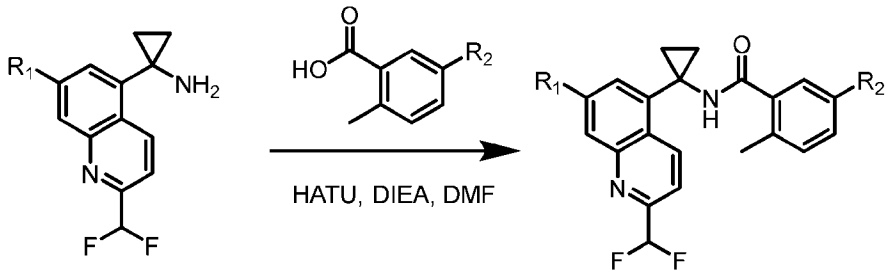



BBr3
DCM
HO
NH2
N
R3
PhN(Tf)2
t-BuOK, THF
TfO
NH2
N
R3
O
HO
R2
HATU, DIEA, DMF
TfO
N
H
O
R2
N
R3
R1—H
Pd(OAc)2, K2CO3
XPhos, DMF
R1
N
H
O
R2
N
R3

Scheme **V**:


MeO
NH2
N
BBr3
DCM
HO
NH2
N
PhN(Tf)2
t-BuOK, THF
TfO
NH2
N


Boc2O
TEA, DCM
TfO
N
H
Boc
N
SeO2
dioxane
TfO
N
H
Boc
N
O
BAST
DCM
TfO
N
H
Boc
N
F
F
R1
SnBu3
Pd(dppf)Cl2.CH2Cl2
Na2CO3, dioxane, H2O
R1
N
H
Boc
N
F
F
HCl/EtOAc



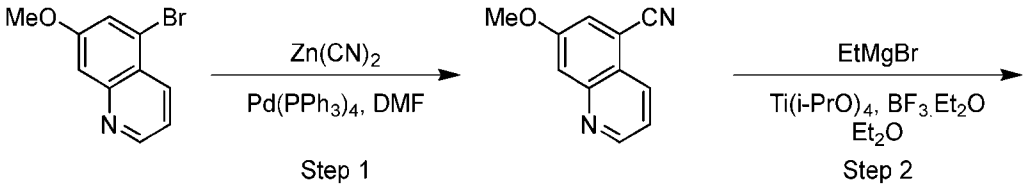
One skilled in the art will appreciate that a substituent described herein may be protected with suitable protecting groups, which may be appended or removed by additional steps in the synthetic sequence using conditions known in the art (March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure 8th Edition or *Protecting Groups*, 10 Georg Thieme Verlag, 1994). Compounds at every step may be purified by standard techniques, such as column chromatography, crystallization, or reverse phase SFC or HPLC. Variables R_1, R_2, and R_3 are as defined in the embodiments, schemes, examples, and claims herein.

EXAMPLES

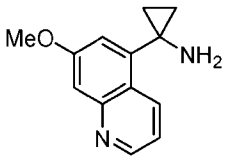
In order that this invention may be better understood, the following examples are set forth. These examples are for purposes of illustration only and are not to be construed as limiting the scope of the invention in any manner.

The compounds and intermediates described below were named using the naming convention provided with ChemDraw Professional, Version 20.1.1 (PerkinElmer Informatics, Inc., Waltham, Massachusetts). The naming convention provided with ChemDraw Professional, Version 20.1.1 is well known by those skilled in the art and it is believed that the naming convention provided with ChemDraw Professional, Version 20.1.1 generally comports with the IUPAC (International Union for Pure and Applied Chemistry) recommendations on Nomenclature of Organic Chemistry and the CAS Index rules. Unless noted otherwise, all reactants were obtained commercially without further purifications or were prepared using methods known in the literature.

Intermediate A: 1-(7-Methoxyquinolin-5-yl)cyclopropanamine (Compound 333A-3)



333A-1 333A-2



333A-3

Step 1: 7-Methoxyquinoline-5-carbonitrile (333A-2)

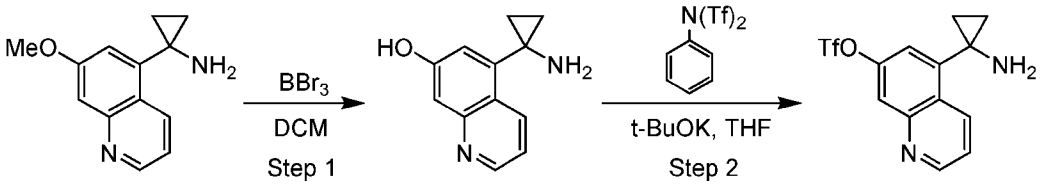
To a solution of 5-bromo-7-methoxyquinoline (10.0 g, 42.0 mmol, 1.0 eq) in DMF (250 mL) were added $Zn(CN)_2$ (9.86 g, 84.0 mmol, 2.0 eq) and $Pd(PPh_3)_4$ (4.85 g, 4.20 mmol, 0.1 eq). The mixture was degassed and purged with N_2 three times and stirred at 100 °C for 16 h under a N_2 atmosphere. LCMS indicated that the starting material was completely consumed, and the desired mass was detected. The reaction mixture was allowed to cool to room temperature and filtered. The filtrate was poured into H_2O (1.0 L) and extracted with EtOAc (500 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum to the volume to 50 mL, and a precipitate was formed. The mixture was filtered, and the filter cake was washed with EtOAc (200 mL) to give a white solid. The solid was dissolved with DCM (300 mL) and stirred at room temperature for 30 min. The mixture was filtered, and the filtrate was concentrated under vacuum to give 7-methoxyquinoline-5-carbonitrile (6.25 g, 34.0 mmol, 81% yield) as a white solid.

Step 2: 1-(7-Methoxyquinolin-5-yl)cyclopropanamine (333A-3)

A mixture of 7-methoxyquinoline-5-carbonitrile (2.00 g, 10.9 mmol, 1.0 eq) in anhydrous Et_2O (160 mL) was degassed and purged with N_2 three times. Then the white suspension was cooled to -78 °C. To this mixture was added Ti(*i*-PrO)$_4$ (4.63 g, 16.3 mmol, 4.81 mL, 1.5 eq) slowly during a period of 5 min and stirred at -78 °C for 10 min. It still was a white suspension. EtMgBr (3 M, in Et_2O, 7.96 mL, 2.2 eq) was added dropwise to maintain the temperature between -78 °C and -75 °C over 10 min under a N_2 atmosphere. The color of the mixture

turned to brown after the addition was complete. The resulting mixture was stirred at the same temperature for 10 min and then warmed to room temperature (between 15-20 °C) slowly over 1.5 h. The mixture turned to black. To the mixture was added $BF_3.Et_2O$ (3.08 g, 21.7 mmol, 2.68 mL, 2.0 eq) in portions at the same temperature with no obvious temperature change. The resulting mixture was stirred at room temperature for another 1 h. LCMS showed some SM remained and 33% desired product was detected. The reaction mixture was poured into a mixture of HCl (1 M aqueous) (100 mL) and MTBE (100 mL) and extracted with MTBE (80 mL x 2). The MTBE organic layers were discarded. The aqueous layer was basified to pH 8 by using NaOH (2 M aqueous), and a precipitate was formed. The mixture was filtered through a pad of Celite and the slurry was washed with DCM several times. The combined filtrate was extracted with DCM (100 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 7/3. 1-(7-Methoxyquinolin-5-yl)cyclopropanamine (1.00 g, 4.67 mmol, 43% yield) was obtained as a brown solid. M + H^+ = 215.0 (LCMS); ^1H NMR (400 MHz, $CDCl_3$) δ 8.79 (dd, J = 1.6, 4.3 Hz, 1H), 8.61 (dd, J = 0.9, 8.4 Hz, 1H), 7.31 – 7.27 (m, 1H), 7.21 (s, 1H), 7.18 (d, J = 2.5 Hz, 1H), 3.89 (s, 3H), 1.15 – 1.08 (m, 2H), 0.97 – 0.92 (m, 2H).

Intermediate B: 5-(1-Aminocyclopropyl)quinolin-7-yl trifluoromethanesulfonate (Compound 391A-2)



333A-3 391A-1 391A-2

Step 1: 5-(1-Aminocyclopropyl)quinolin-7-ol (391A-1)

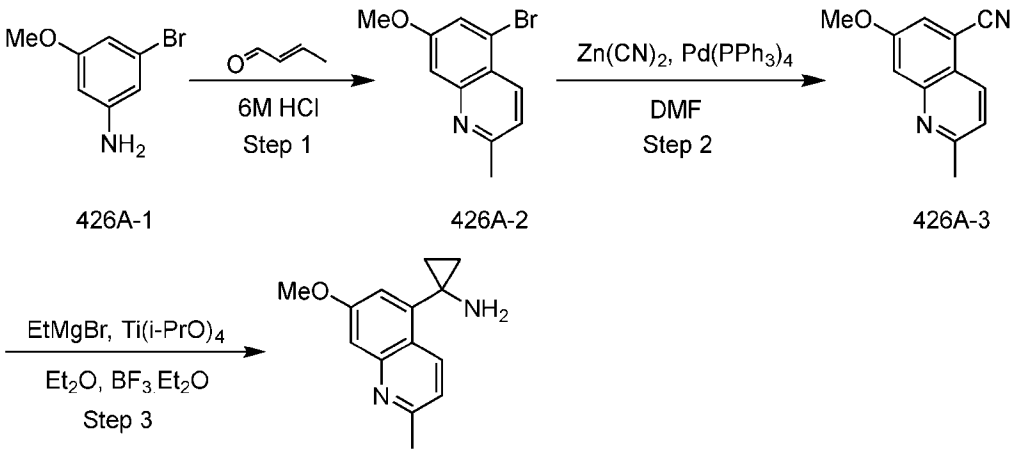
To a solution of 1-(7-methoxyquinolin-5-yl)cyclopropan-1-amine (1.50 g, 5.98 mmol, 1.0 eq) in DCM (50 mL) was added a solution of BBr_3 (22.5 g, 90.0 mmol, 8.7 mL, 15 eq) in DCM (20 mL) dropwise at -78 °C under a N_2 atmosphere. The resulting mixture was stirred at the same temperature for 2 h, then warmed to 20 °C and stirred for another 12 h. LCMS indicated that the starting material was completely consumed, and the desired mass was detected. The

reaction mixture was concentrated under vacuum to give a residue, which was diluted with MeOH (20 mL) at 0 °C and treated with $NH_3.H_2O$ to adjust the pH 8. The mixture was concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/1, followed by DCM/MeOH from 100/1 to 10/1. 5-(1-Aminocyclopropyl)quinolin-7-ol (1.73 g, 8.64 mmol, 72% yield) was obtained as a yellow solid. M + H^+ = 201.3 (LCMS); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.51 – 10.23 (m, 1H), 8.90 – 8.78 (m, 1H), 8.62 (d, J = 8.5 Hz, 1H), 7.43 (dd, J = 4.3, 8.5 Hz, 1H), 7.38 (d, J = 2.4 Hz, 1H), 7.32 (d, J = 2.3 Hz, 1H), 4.09 (q, J = 5.1 Hz, 2H), 1.55 – 1.48 (m, 2H), 1.28 – 1.15 (m, 2H).

Step 2: 5-(1-Aminocyclopropyl)quinolin-7-yl trifluoromethanesulfonate (391A-2)

To a solution of 5-(1-aminocyclopropyl)quinolin-7-ol (1.40 g, 6.99 mmol, 1.0 eq) in THF (50 mL) was added *t*-BuOK (1.57 g, 14.0 mmol, 2.0 eq) at 0 °C under a N_2 atmosphere. The mixture was stirred at 0 °C for 15 min. 1,1,1-Trifluoro-*N*-phenyl-*N*-(trifluoromethylsulfonyl)methane sulfonamide (5.00 g, 14.0 mmol, 2.0 eq) was added in portions. The resulting reaction mixture was stirred at 20 °C for 6 h. LCMS indicated that the starting material was completely consumed, and the desired mass was detected. The reaction mixture was poured into H_2O (50 mL) and extracted with EtOAc (50 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/1. 5-(1-Aminocyclopropyl)quinolin-7-yl trifluoromethanesulfonate (1.25 g, 3.76 mmol, 54% yield) was obtained as a yellow oil. M + H^+ = 333.2 (LCMS); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.05 (dd, J = 1.6, 4.1 Hz, 1H), 8.96 (d, J = 8.5 Hz, 1H), 8.05 (d, J = 2.5 Hz, 1H), 7.74 (dd, J = 4.3, 8.6 Hz, 1H), 7.67 (d, J = 2.6 Hz, 1H), 4.20 – 3.98 (m, 2H), 3.17 (s, 3H), 1.22 – 1.15 (m, 2H), 1.04 – 0.95 (m, 2H).

Intermediate C: 1-(7-Methoxy-2-methylquinolin-5-yl)cyclopropanamine (Compound 1134A-1)



426A-1 426A-2 426A-3

1134A-1

Step 1: 5-Bromo-7-methoxy-2-methylquinoline (426A-2)

A mixture of 3-bromo-5-methoxyaniline (2.50 g, 12.4 mmol, 1.0 eq) and HCl (6 M aqueous, 10 mL) was heated to 105 °C, then (*E*)-but-2-enal (1.73 g, 24.8 mmol, 2.1 mL, 2.0 eq) was added slowly. The resulting mixture was stirred at 105 °C for 1 h. LCMS indicated that the starting material was completely consumed, and the desired mass was detected. The reaction mixture was allowed to cool to room temperature, poured into ice-cold water (20 mL), treated with NH_3H_2O to adjust pH 8, and extracted with EtOAc (20 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 1/100 to 1/10. 5-Bromo-7-methoxy-2-methylquinoline (750 mg, 2.98 mmol, 24% yield) was obtained as a yellow solid. M + H^+ = 252.1 (LCMS); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.25 (d, J = 8.5 Hz, 1H), 7.57 (d, J = 2.5 Hz, 1H), 7.45 – 7.35 (m, 2H), 3.91 (s, 3H), 2.65 (s, 3H).

Step 2: 7-Methoxy-2-methylquinoline-5-carbonitrile (426A-3)

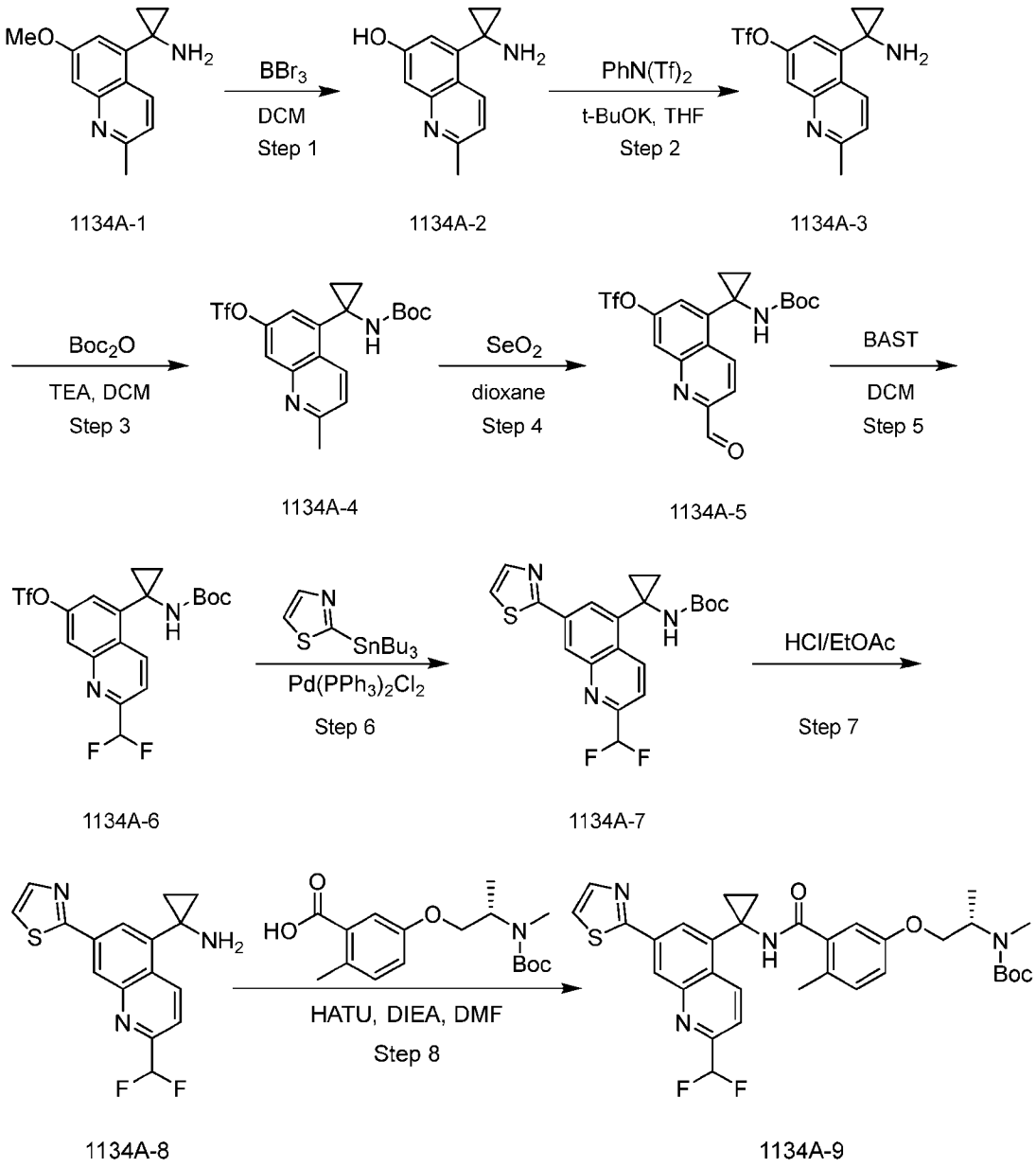
To a solution of 5-bromo-7-methoxy-2-methyl-quinoline (1.75 g, 6.94 mmol, 1.0 eq) in DMF (25 mL) were added $Zn(CN)_2$ (1.63 g, 13.9 mmol, 881 µL, 2.0 eq) and $Pd(PPh_3)_4$ (802 mg, 694 µmol, 0.1 eq). The mixture was degassed and purged with N_2 three times. The resulting

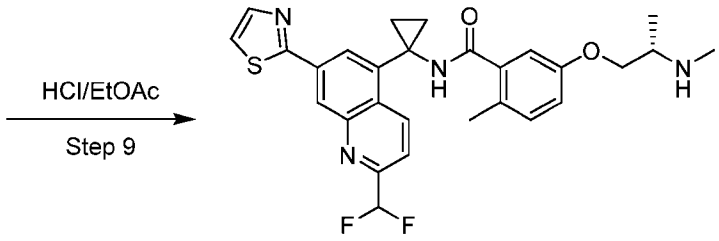
mixture was stirred at 100 °C for 12 h under a N_2 atmosphere. LCMS indicated that the starting material was completely consumed, and the desired mass was detected. The reaction mixture was allowed to cool to room temperature, poured into ice-cold water (30 mL), and extracted with EtOAc (25 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 1/100 to 3/5. 7-Methoxy-2-methylquinoline-5-carbonitrile (980 mg, 4.95 mmol, 73% yield) was obtained as a yellow solid. M + H^+ = 199.3 (LCMS); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.27 (d, J = 8.5 Hz, 1H), 7.91 (d, J = 2.5 Hz, 1H), 7.69 (d, J = 2.4 Hz, 1H), 7.51 (d, J = 8.5 Hz, 1H), 3.96 (s, 3H), 2.68 (s, 3H).

Step 3: 1-(7-Methoxy-2-methylquinolin-5-yl)cyclopropanamine (1134A-1)

A solution of 7-methoxy-2-methylquinoline-5-carbonitrile (1.30 g, 6.56 mmol, 1.0 eq) in Et_2O (160 mL) was degassed and purged with N_2 three times and cooled to -78 °C. Ti(*i*-PrO)$_4$ (2.80 g, 9.84 mmol, 2.90 mL, 1.5 eq) was added slowly and the mixture was stirred for 5 min. EtMgBr (3.0 M in Et_2O, 4.81 mL, 2.2 eq) was added dropwise at -78 °C to maintain the temperature at -78 °C under a N_2 atmosphere. The mixture was stirred at same temperature for 10 min then warmed to 20 °C over 1 h. The mixture turned to black. To the mixture was added BF_3.Et_2O (1.86 g, 13.1 mmol, 1.62 mL, 2.0 eq) in portions at the same temperature with no obvious temperature change. The resulting mixture was stirred at room temperature for another 1 h. LCMS showed some the starting material was completely consumed, and the desired mass was detected. The reaction mixture was poured into a mixture of HCl (1 M aqueous, 100 mL) and MTBE (100 mL) and extracted with MTBE (80 mL x 2). The aqueous layer was basified to pH 8 using NaOH (2 M aqueous) and a precipitate was formed. The mixture was filtered through a pad of Celite and the slurry was washed with DCM several times. The combined filtrate was extracted with DCM (50 mL x 8). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/1. 1-(7-Methoxy-2-methylquinolin-5-yl)cyclopropanamine (700 mg, 3.07 mmol, 47% yield) was obtained as a yellow oil. M + H^+ = 229.2 (LCMS); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, J = 8.4 Hz, 1H), 7.30 (d, J = 2.5 Hz, 1H), 7.24 (d, J = 8.5 Hz, 1H), 7.17 (d, J = 2.5 Hz, 1H), 3.94 (s, 3H), 2.73 (s, 3H), 1.21 – 1.13 (m, 2H), 0.99 (d, J = 2.1 Hz, 2H).

Example 1: (*S*)-*N*-(1-(2-(Difluoromethyl)-7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)-2-methyl-5-(2-(methylamino)propoxy)benzamide (Compound 1134)





Compound 1134

Step 1: 5-(1-Aminocyclopropyl)-2-methylquinolin-7-ol (1134A-2)

To a solution of 1-(7-methoxy-2-methylquinolin-5-yl)cyclopropan-1-amine (3.00 g, 13.1 mmol, 1.0 eq) in DCM (60 mL) was added BBr_3 (49.4 g, 197 mmol, 15 eq) in DCM (20 mL) slowly at -78 °C. The resulting mixture was stirred at the same temperature for 1 h, then warmed to 20 °C and stirred at 20 °C for another 12 h. LCMS indicated that the starting material was completely consumed, and the desired mass was detected. The reaction mixture was concentrated under vacuum to give a residue which was diluted with MeOH (100 mL), and the resulting mixture was adjusted to pH 8 by using $NH_3.H_2O$. The resulting mixture was concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of MeOH/DCM from 0/1 to 1/5. 5-(1-Aminocyclopropyl)-2-methylquinolin-7-ol (2.80 g, 13.1 mmol, 99% yield) was obtained as a white solid. M + H^+ = 215.0 (LCMS).

Step 2: 5-(1-Aminocyclopropyl)-2-methylquinolin-7-yl trifluoromethanesulfonate (1134A-3)

To a solution of 5-(1-aminocyclopropyl)-2-methylquinolin-7-ol (2.80 g, 13.1 mmol, 1.0 eq) in THF (90 mL) was added *t*-BuOK (2.93 g, 26.1 mmol, 2.0 eq) at 0 °C. The mixture was stirred at 0 °C for 30 min, then $PhN(Tf)_2$ (7.00 g, 19.6 mmol, 1.5 eq) was added slowly. The reaction mixture was warmed to 20 °C and stirred at the same temperature for another 5 h. LCMS indicated that the starting material was completely consumed, and the desired mass was detected. The reaction mixture was poured into water (100 mL) and extracted with DCM (50 mL x 4). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/1. 5-(1-Aminocyclopropyl)-2-methylquinolin-7-yl trifluoromethanesulfonate (3.00 g, 8.66 mmol, 66% yield) was obtained as a white solid. M + H^+ = 347.2 (LCMS); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.83 (d, *J* = 8.8 Hz, 1H), 7.90 (d, *J*

= 2.5 Hz, 1H), 7.69 – 7.43 (m, 2H), 3.82 (br d, *J* = 6.6 Hz, 2H), 2.73 – 2.66 (m, 3H), 1.16 – 1.11 (m, 2H), 1.00 – 0.92 (m, 2H).

Step 3: 5-(1-((*tert*-Butoxycarbonyl)amino)cyclopropyl)-2-methylquinolin-7-yltrifluoromethanesulfonate (1134A-4)

To a solution of 5-(1-aminocyclopropyl)-2-methylquinolin-7-yltrifluoromethanesulfonate (500 mg, 1.44 mmol, 1.0 eq) in DCM (15 mL) were added Boc_2O (315 mg, 1.44 mmol, 331 µL, 1.0 eq) and TEA (160 mg, 1.59 mmol, 221 µL, 1.1 eq). The mixture was stirred at 20 °C for 12 h. LCMS indicated that 55% of the starting material remained, and the desired mass was detected. Another batch of Boc_2O (173 mg, 794 µmol, 182 µL, 0.55 eq) and TEA (80.4 mg, 794 µmol, 110 µL, 0.55 eq) was added to the mixture. The mixture was stirred at 20 °C for 12 h. LCMS indicated that 25% of the starting material remained, and the desired mass was detected. Then, a third batch of Boc_2O (78.8 mg, 360 µmol, 82.9 µL, 0.25 eq) and TEA (36.5 mg, 360 µmol, 50.2 µL, 0.25 eq) was added to the mixture. The mixture was stirred at 20 °C for another 12 h. LCMS indicated that the starting material was completely consumed, and the desired mass was detected. The mixture was poured into water (20 mL) and extracted with DCM (20 mL x 4). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/2. 5-(1-((*tert*-Butoxycarbonyl)amino)cyclopropyl)-2-methylquinolin-7-yltrifluoromethanesulfonate (400 mg, 896 µmol, 62% yield) was obtained as a black solid. M + H^+ = 447.2 (LCMS).

Step 4: 5-(1-((*tert*-Butoxycarbonyl)amino)cyclopropyl)-2-formylquinolin-7-yltrifluoromethanesulfonate (1134A-5)

To a solution of 5-(1-((*tert*-butoxycarbonyl)amino)cyclopropyl)-2-methylquinolin-7-yl trifluoromethanesulfonate (280 mg, 627 µmol, 1.0 eq) in dioxane (10 mL) was added SeO_2 (90.5 mg, 815 µmol, 88.7 µL, 1.3 eq). The resulting mixture was stirred at 80 °C for 5 h. LCMS indicated that the starting material was completely consumed, and the desired mass was detected. The reaction mixture was allowed to cool to room temperature, poured into H_2O (10 mL) and extracted with DCM (10 mL x 5). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/5. 5-(1-((*tert*-Butoxycarbonyl)amino)cyclopropyl)-2-formylquinolin-7-yltrifluoromethanesulfonate (300 mg, crude) was obtained as colorless oil. M + H^+ = 461.2 (LCMS).

Step 5: 5-(1-((*tert*-Butoxycarbonyl)amino)cyclopropyl)-2-(difluoromethyl)quinolin-7-yl trifluoromethanesulfonate (1134A-6)

To a solution of 5-(1-((*tert*-butoxycarbonyl)amino)cyclopropyl)-2-formylquinolin-7-yltriflu oromethanesulfonate (290 mg, 630 μmol, 1.0 eq) in DCM (15 mL) was added DAST (203 mg, 1.26 mmol, 166 μL, 2.0 eq) at 0 °C. The resulting mixture was stirred at 20 °C for 1 h. LCMS indicated that the starting material was completely consumed. The mixture was poured into water (10 mL) and extracted with DCM (5.0 mL x 5). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/10. 5-(1-((*tert*-Butoxycarbonyl)amino)cyclopropyl)-2-(difluoromethyl)quinolin-7-yltrifluoro methanesulfonate (350 mg, crude) was obtained as colorless oil. M + H^+ = 483.2 (LCMS); ^1H NMR (400 MHz, $CDCl_3$) δ 9.23 – 8.94 (m, 1H), 8.02 (d, *J* = 2.4 Hz, 1H), 7.91 – 7.77 (m, 2H), 6.94 – 6.60 (m, 1H), 5.33 – 5.20 (m, 1H), 1.51 – 1.22 (m, 13H).

Step 6: *tert*-Butyl (1-(2-(difluoromethyl)-7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl) carbamate (1134A-7)

To a mixture of 5-(1-((*tert*-butoxycarbonyl)amino)cyclopropyl)-2-(difluoromethyl)quinolin-7-yltrifluoromethanesulfonate (350 mg, 726 μmol, 1.0 eq) and 2-(tributylstannyl)thiazole (407 mg, 1.09 mmol, 1.5 eq) in dioxane (15 mL) was added $Pd(PPh_3)_2Cl_2$ (50.9 mg, 72.5 μmol, 0.1 eq). The mixture was degassed and purged with N_2 three times and stirred at 100 °C for 3 h under a N_2 atmosphere. LCMS indicated that the starting material was completely consumed, and the desired mass was detected. The reaction mixture was allowed to cool to room temperature, poured into water (10 mL) and extracted with DCM (10 mL x 5). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/5. *tert*-Butyl (1-(2-(difluoromethyl)-7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)carbamate (250 mg, crude) was obtained as a white solid. M + H^+ = 418.1 (LCMS).

Step 7: 1-(2-(Difluoromethyl)-7-(thiazol-2-yl)quinolin-5-yl)cyclopropan-1-amine (1134A-8)

To a solution of *tert*-butyl (1-(2-(difluoromethyl)-7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)carbamate (200 mg, 479 μmol, 1.0 eq) in EtOAc (3.0 mL) was added HCl/EtOAc (4 M, 6.0 mL, 50 eq). The resulting mixture was stirred at 20 °C for 30 min. The mixture was

concentrated under vacuum at 30 °C to give 1-(2-(difluoromethyl)-7-(thiazol-2-yl)quinolin-5-yl)cyclopropane-1-amine (200 mg, crude, HCl salt) as a white solid. M + H^+ = 318.3 (LCMS).

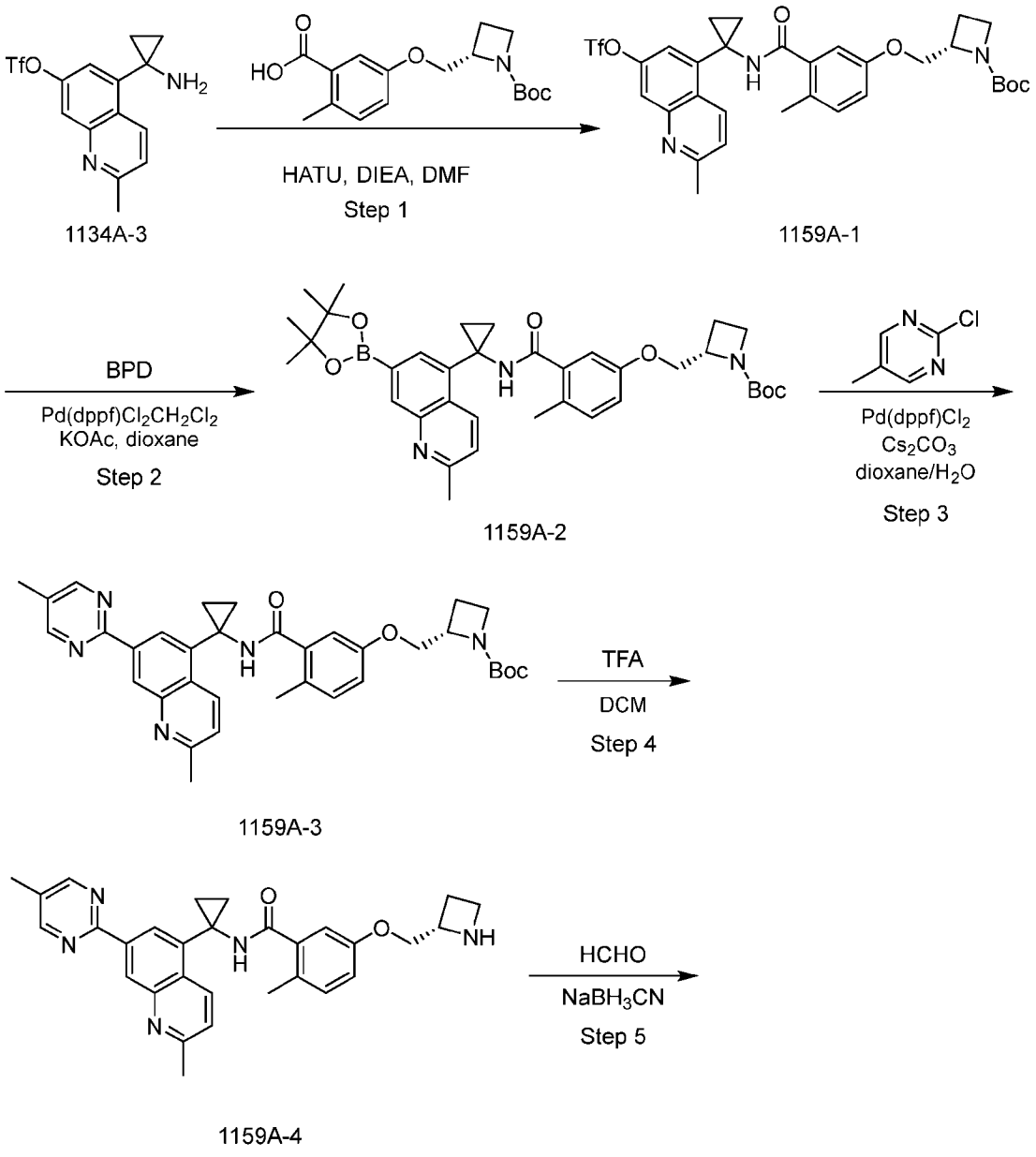
Step 8: *tert*-Butyl (*S*)-(1-(3-((1-(2-(difluoromethyl)-7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)carbamoyl)-4-methylphenoxy)propan-2-yl)(methyl)carbamate (1134A-9)

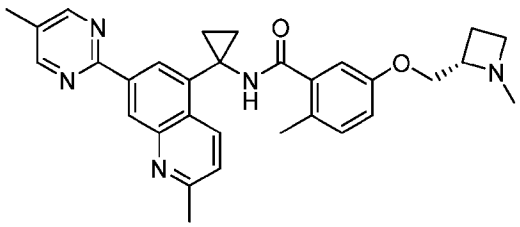
A mixture of 1-(2-(difluoromethyl)-7-(thiazol-2-yl)quinolin-5-yl)cyclopropan-1-amine (90.0 mg, 254 µmol, 1.0 eq, HCl salt), (*S*)-5-(2-((*tert*-butoxycarbonyl)(methyl)amino)propoxy)-2-methylbenzoic acid (82.3 mg, 254 µmol, 1.0 eq), HATU (193 mg, 509 µmol, 2.0 eq) and DIEA (132 mg, 1.02 mmol, 177 µL, 4.0 eq) in DMF (4.0 mL) was stirred at 20 °C for 16 h. LCMS indicated that the starting material was completely consumed, and the desired mass was detected. The reaction mixture was poured into H_2O (5.0 mL) and extracted with DCM (5.0 mL x 4). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 1/100 to 1/3. *tert*-Butyl (*S*)-(1-(3-((1-(2-(difluoromethyl)-7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)carbamoyl)-4-methylphenoxy) propan-2-yl)(methyl)carbamate (100 mg, 161 µmol, 63% yield) was obtained as a white solid. M + H^+ = 623.4 (LCMS).

Step 9: (*S*)-*N*-(1-(2-(Difluoromethyl)-7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)-2-methyl-5-(2-(methylamino)propoxy)benzamide (Compound 1134)

To a solution of *tert*-butyl (*S*)-(1-(3-((1-(2-(difluoromethyl)-7-(thiazol-2-yl)quinolin-5-yl) cyclopropyl)carbamoyl)-4-methylphenoxy)propan-2-yl)(methyl)carbamate (100 mg, 161 µmol, 1.0 eq) in EtOAc (4.0 mL) was added HCl/EtOAc (4 M, 4.0 mL, 100 eq). The mixture was stirred at 20 °C for 1 h. LCMS indicated that the starting material was completely consumed, and the desired mass was detected. The mixture was concentrated under vacuum at 20 °C to give a residue which was purified by preparative HPLC (Phenomenex Luna C18 column (80 × 30 mm, 3 µm); flow rate: 30 mL/min; gradient: 25% – 55% B over 8 min; mobile phase A: 0.04% aqueous HCl, mobile phase B: acetonitrile) to give (*S*)-*N*-(1-(2-(difluoromethyl)-7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)-2-methyl-5-(2(methylamino)pro poxy)benzamide (49.7 mg, 85.0 µmol, 53% yield, HCl salt) as a white solid. M + H^+ = 523.2 (LCMS); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.39 – 9.26 (m, 2H), 8.64 – 8.47 (m, 2H), 8.08 (d, J = 3.1 Hz, 1H), 7.99 – 7.89 (m, 2H), 7.33 – 6.85 (m, 3H), 6.72 (d, J = 2.5 Hz, 1H), 4.19 – 3.95 (m, 2H), 3.53 (br s, 1H), 2.54 (s, 3H), 1.95 (s, 3H), 1.44 (br s, 2H), 1.32 (br s, 2H), 1.26 (d, J = 6.6 Hz, 3H).

Example 2: (*S*)-2-Methyl-*N*-(1-(2-methyl-7-(5-methylpyrimidin-2-yl)quinolin-5-yl)cyclopropyl)-5-((1-methylazetidin-2-yl)methoxy)benzamide (Compound 1159)





Compound 1159

Step 1: (*S*)-*tert*-Butyl 2-((4-methyl-3-((1-(2-methyl-7-(((trifluoromethyl)sulfonyl)oxy) quinolin-5-yl)cyclopropyl)carbamoyl)phenoxy)methyl)azetidine-1-carboxylate(1159A-1)

To a solution of 5-(1-aminocyclopropyl)-2-methylquinolin-7-yl trifluoromethanesulfonate (500 mg, 1.73 mmol, 1.0 eq) and (*S*)-5-((1-(*tert*-butoxycarbonyl)azetidin-2-yl)methoxy)-2-methylbenzoic acid (557 mg, 1.73 mmol, 1.0 eq) in DMF (15 mL) were added HATU (1.65 g, 4.33 mmol, 2.5 eq) and DIEA (672 mg, 5.20 mmol, 3.0 eq). The mixture was stirred at 20 °C for 3 h. LCMS indicated that the starting material was completely consumed, and the desired mass was detected. The mixture was poured into water (10 mL) and extracted with EtOAc (20 mL x 2). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/2. (*S*)-*tert*-Butyl 2-((4-methyl-3-((1-(2-methyl-7-(((trifluoromethyl)sulfonyl)oxy) quinolin-5-yl)cyclopropyl) carbamoyl)phenoxy)methyl)azetidine-1-carboxylate (800 mg, 1.23 mmol, 72% yield) was obtained as a white solid. M + H^+ = 649.2 (LCMS).

Step 2: (*S*)-*tert*-Butyl 2-((4-methyl-3-((1-(2-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinolin-5-yl)cyclopropyl)carbamoyl)phenoxy)methyl)azetidine-1-carboxylate (1159A-2)

A solution of (*S*)-*tert*-butyl 2-((4-methyl-3-((1-(2-methyl-7-(((trifluoromethyl)sulfonyl)oxy) quinolin-5-yl)cyclopropyl) carbamoyl)phenoxy)methyl)azetidine-1-carboxylate (1.60 g, 2.46 mmol, 1.0 eq), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (1.88 g, 7.39 mmol, 3.0 eq), KOAc (604 mg, 6.16 mmol, 2.5 eq) and $Pd(dppf)Cl_2.CH_2Cl_2$ (201 mg, 246 μmol, 0.1 eq) in dioxane (20 mL) was degassed and purged with N_2 three times. The mixture was stirred at 80 °C for 4 h under a N_2 atmosphere. LCMS indicated that the starting material was completely consumed. The reaction mixture was allowed to cool to room temperature and concentrated under vacuum at 20 °C to give a residue

which purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 1/100 to 1/0. (*S*)-*tert*-Butyl 2-((4-methyl-3-((1-(2-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinolin-5-yl)cyclopropyl)carbamoyl)phenoxy) methyl)azetidine-1-carboxylate (900 mg, 1.43 mmol, 58% yield) was obtained as a pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.11 (s, 1H), 8.99 (d, *J* = 8.8 Hz, 1H), 8.15 (s, 1H), 7.99 (s, 1H), 7.51 (d, *J* = 8.8 Hz, 1H), 7.05 (d, *J* = 8.4 Hz, 1H), 6.87 (dd, *J* = 2.6, 8.4 Hz, 1H), 6.63 (d, *J* = 2.6 Hz, 1H), 4.42 – 4.34 (m, 1H), 4.13 (dd, *J* = 4.8, 10.2 Hz, 1H), 3.98 (dd, *J* = 2.8, 10.4 Hz, 1H), 3.73 (br s, 2H), 2.69 - 2.66 (m, 6H), 2.34 – 2.21 (m, 1H), 2.13 – 2.01 (m, 1H), 1.36 (s, 12H), 1.29 (br s, 9H), 1.16 (s, 4H).

Step 3: (*S*)-*tert*-Butyl 2-((4-methyl-3-((1-(2-methyl-7-(5-methylpyrimidin-2-yl)quinolin-5-yl)cyclopropyl)carbamoyl)phenoxy)methyl) azetidine-1-carboxylate (1159A-3)

To a solution of (*S*)-*tert*-butyl 2-((4-methyl-3-((1-(2-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinolin-5-yl)cyclopropyl)carbamoyl)phenoxy)methyl)azetidine-1-carboxylate (130 mg, 208 µmol, 1.0 eq) and 2-chloro-5-methyl-pyrimidine (32.0 mg, 249 µmol, 1.2 eq) in dioxane (5.0 mL) and H_2O (1.0 mL) were added Pd(dppf)Cl_2 (12.1 mg, 16.6 µmol, 1.0 eq) and Cs_2CO_3 (115 mg, 353 µmol, 1.7 eq). The mixture was degassed and purged with N_2 three times. The mixture was stirred at 100 °C for 12 h under a N_2 atmosphere. LCMS indicated that the starting material was completely consumed. The reaction mixture was allowed to cool to room temperature, poured into H_2O (5.0 mL) and extracted with EtOAc (3.0 mL x 2). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 1/100 to 1/1. (*S*)-*tert*-Butyl 2-((4-methyl-3-((1-(2-methyl-7-(5-methylpyrimidin-2-yl)quinolin-5-yl)cyclopropyl)carbamoyl)phenoxy)methyl) azetidine-1-carboxylate (120 mg, 202 µmol, 98% yield) was obtained as a white solid. M + H^+ = 594.4 (LCMS).

Step 4: (*S*)-5-(Azetidin-2-ylmethoxy)-2-methyl-*N*-(1-(2-methyl-7-(5-methylpyrimidin-2-yl)quinolin-5-yl)cyclopropyl)benzamide (1159A-4)

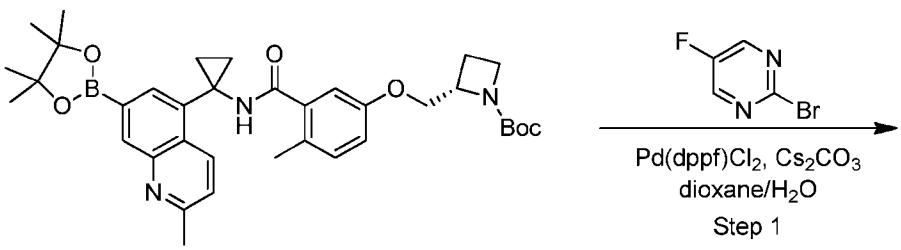
To a solution of (*S*)-*tert*-butyl 2-((4-methyl-3-((1-(2-methyl-7-(5-methylpyrimidin-2-yl)quinolin-5-yl)cyclopropyl)carbamoyl)phenoxy)methyl)azetidine-1-carboxylate (115 mg, 194 µmol, 1.0 eq) in DCM (3.0 mL) was added TFA (442 mg, 3.87 mmol, 288 µL, 20 eq). The mixture was stirredat 20 °C for 1 h. LCMS indicated that the starting material was completely consumed. The reaction mixture was concentrated under vaccum to give crude (*S*)-5-(azetidin-2-

ylmethoxy)-2-methyl-*N*-(1-(2-methyl-7-(5-methylpyrimidin-2-yl)quinolin-5-yl) cyclopropyl)benzamide (110 mg, TFA salt) as a white solid. M + H^+ = 493.2 (LCMS).

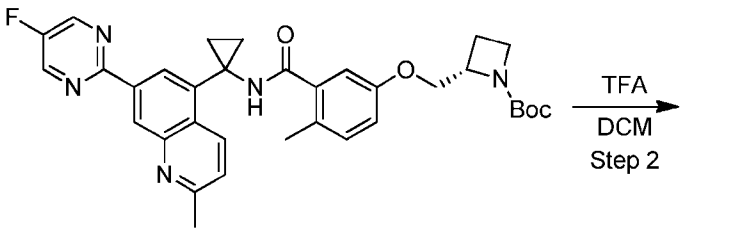
Step 5: (*S*)-2-Methyl-*N*-(1-(2-methyl-7-(5-methylpyrimidin-2-yl)quinolin-5-yl)cyclopropyl)-5-((1-methylazetidin-2-yl)methoxy)benzamide (Compound 1159)

To a solution of (*S*)-5-(azetidin-2-ylmethoxy)-2-methyl-*N*-(1-(2-methyl-7-(5-methylpyrimi din-2-yl)quinolin-5-yl)cyclopropyl)benzamide (110 mg, 181 µmol, 1.0 eq, TFA salt) in MeOH (3.0 mL) was added TEA (18.3 mg, 181 µmol, 1.0 eq), followed by formaldehyde (29.4 mg, 363 µmol, 27.0 µL, 37% wt % in water, 2.0 eq). The resulting mixture was adjusted to pH to 6 with a small amount of AcOH, then $NaBH_3CN$ (22.8 mg, 362 µmol, 2.0 eq) was added. The mixture was stirred at 20 °C for 3 h. LCMS indicated that the starting material was completely consumed. The mixture was concentrated under vacuum at 30 °C to give a residue which was purified by preparative HPLC (Phenomenex Luna C18 column (75 × 30 mm, 3 µm); flow rate: 25 mL/min; gradient: 10% – 40% B over 8 min; mobile phase A: 0.1% aqueous TFA, mobile phase B: acetonitrile). (*S*)-2-Methyl-*N*-(1-(2-methyl-7-(5-methylpyrimidin-2-yl)quinolin-5-yl)cyclopropyl)-5-((1-methylazetidin-2-yl)methoxy)benzamide (92.9 mg, 145 µmol, 81% yield, TFA salt) was obtained as a yellow solid. M + H^+ = 508.3 (LCMS); ^1H NMR (400 MHz, DMSO-d_6) δ 9.51 (d, *J* = 8.8 Hz, 1H), 9.27 (s, 1H), 8.99 (d, *J* = 2.8 Hz, 2H), 8.88 (s, 2H), 7.93 (d, *J* = 8.9 Hz, 1H), 7.09 (d, *J* = 8.5 Hz, 1H), 6.91 (dd, *J* = 2.6, 8.4 Hz, 1H), 6.71 (d, *J* = 2.6 Hz, 1H), 4.65 – 4.53 (m, 1H), 4.22 – 4.15 (m, 2H), 4.01 (dt, *J* = 4.9, 9.7 Hz, 1H), 3.89 – 3.84 (m, 1H), 2.89 (s, 3H), 2.81 (s, 3H), 2.41 – 2.28 (m, 5H), 1.93 (s, 3H), 1.47 (br s, 2H), 1.32 (br s, 2H).

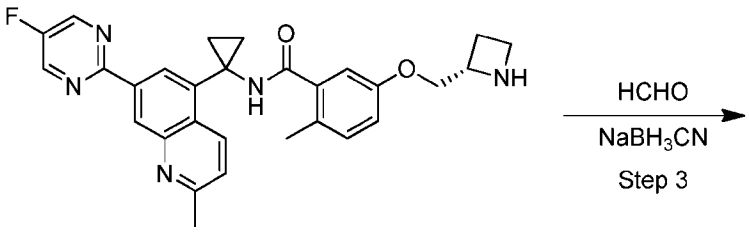
Example 5: (*S*)-*N*-(1-(7-(5-Fluoropyrimidin-2-yl)-2-methylquinolin-5-yl)cyclopropyl)-2-methyl-5-((1-methylazetidin-2-yl)methoxy)benzamide (Compound 1160)



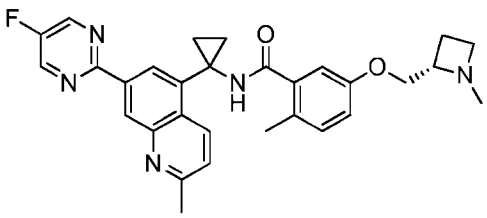
1159A-2



1160A-1



1160A-2



Compound 1160

Step 1: *tert*-Butyl (*S*)-2-((3-((1-(7-(5-fluoropyrimidin-2-yl)-2-methylquinolin-5-yl)cyclopropyl)carbamoyl)-4-methylphenoxy)methyl)azetidine-1-carboxylate (1160A-1)

To a solution of *tert*-butyl (*S*)-2-((4-methyl-3-(1-((1-(2-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinolin-5-yl)cyclopropyl)amino)vinyl)phenoxy)methyl)azetidine-1-carboxylate (130 mg, 207 μmol, 1.0 eq) and 2-bromo-5-fluoropyrimidine (44.0 mg, 249 μmol, 1.2 eq) in dioxane (3.0 mL) and H_2O (300 μL) were added $Pd(dppf)Cl_2$ (15.1 mg, 20.7 μmol, 0.1 eq) and Cs_2CO_3 (135 mg, 414 μmol, 2.0 eq). The mixture was degassed and purged with N_2 for three times, then the mixture was stirred at 100 °C for 12 h under a N_2 atmosphere. LCMS indicated that the starting material was completely consumed. The mixture was cooled to room temperature, poured into water (5.0 mL) and extracted with EtOAc (3.0 mL x 2). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/0. *tert*-Butyl (*S*)-2-((3-((1-(7-(5-fluoropyrimidin-2-yl)-2-

methylquinolin-5-yl)cyclopropyl)carbamoyl)-4-methylphenoxy)methyl)azetidine-1-carboxylate (100 mg, 167 µmol 81% yield) was obtained as a white solid. M + H^+ = 598.4 (LCMS).

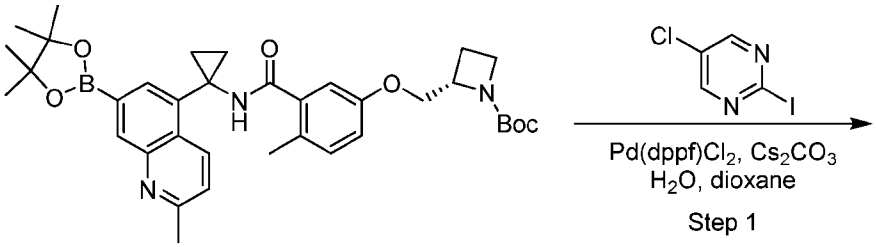
Step 2: (*S*)-5-(Azetidin-2-ylmethoxy)-*N*-(1-(7-(5-fluoropyrimidin-2-yl)-2-methylquinolin-5-yl)cyclopropyl)-2-methylbenzamide (1160A-2)

To a solution of *tert*-butyl (*S*)-2-((3-((1-(7-(5-fluoropyrimidin-2-yl)-2-methylquinolin-5-yl)cyclopropyl)car bamoyl)-4-methylphenoxy)methyl)azetidine-1-carboxylate (100 mg, 167 µmol, 1.0 eq) in DCM (3.0 mL) was added TFA (2.86 g, 25.1 mmol, 1.86 mL). The mixture was stirred at 20 °C for 1 h. The reaction mixture was concentrated under vacuum to give (*S*)-5-(azetidin-2-ylmethoxy)-*N*-(1-(7-(5-fluoropyrimidin-2-yl)-2-methylquinolin-5-yl)cyclopropyl)-2-methylbenzamide (100 mg, TFA salt) as a yellow oil. M + H^+ = 498.4 (LCMS).

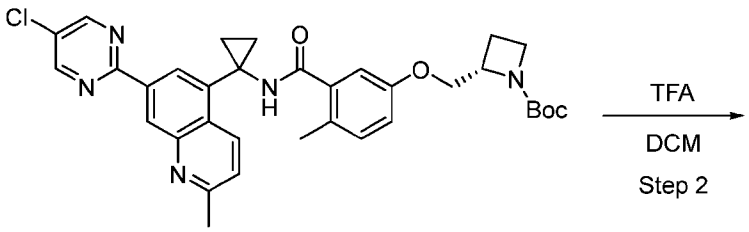
Step 3: (*S*)-*N*-(1-(7-(5-Fluoropyrimidin-2-yl)-2-methylquinolin-5-yl)cyclopropyl)-2-methyl-5-((1-methylazetidin-2-yl)methoxy)benzamide (Compound 1160)

To a solution of (*S*)-5-(azetidin-2-ylmethoxy)-*N*-(1-(7-(5-fluoropyrimidin-2-yl)-2-methylquinolin-5-yl)cyclopropyl)-2-methylbenzamide (100 mg, 164 µmol, 1.0 eq, TFA salt) in MeOH (2.0 mL) was added TEA (20.0 µL), followed by the addition of formaldehyde (23.3 mg, 287 µmol, 21.3 µL, 37% wt % in water, 2.0 eq). The resulting mixture was adjusted to pH to 6 with a small amount of AcOH. The mixture was stirred at 20 °C for 30 min, then $NaBH_3CN$ (27.0 mg, 430 µmol, 3.0 eq) was added. The resulting reaction mixture was stirred at 25 °C for another 2 h. The mixture was concentrated under vacuum at 30 °C to give a residue which was purified by preparative HPLC (Phenomenex Luna C18 column (75 × 30 mm, 3 µm); flow rate: 25 mL/min; gradient: 5% – 35% B over 8 min; mobile phase A: 0.1% aqueous TFA, mobile phase B: acetonitrile). (*S*)-*N*-(1-(7-(5-Fluoropyrimidin-2-yl)-2-methylquinolin-5-yl)cyclopropyl)-2-methyl-5-((1-methylazetidin-2-yl)methoxy)benzamide (82.5 mg, 129 µmol, 79% yield, TFA salt) was obtained as a yellow solid. M + H^+ = 512.2 (LCMS); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.36 (d, J = 8.8 Hz, 1H), 9.28 – 9.19 (m, 1H), 9.12 (s, 2H), 8.93 (d, J = 7.0 Hz, 2H), 7.85 (d, J = 8.8 Hz, 1H), 7.10 (d, J = 8.5 Hz, 1H), 6.92 (dd, J = 2.6, 8.4 Hz, 1H), 6.73 (d, J = 2.5 Hz, 1H), 4.70 – 4.53 (m, 1H), 4.22 (d, J = 5.0 Hz, 2H), 4.10 – 3.77 (m, 2H), 2.84 (d, J = 5.5 Hz, 6H), 2.44 – 2.25 (m, 2H), 1.96 (s, 3H), 1.50 – 1.25 (m, 4H).

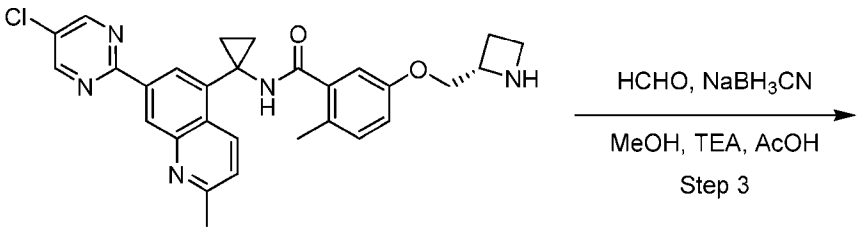
Example 3: (S)-*N*-(1-(7-(5-Chloropyrimidin-2-yl)-2-methylquinolin-5-yl)cyclopropyl)-2-methyl-5-((1-methylazetidin-2-yl)methoxy)benzamide (Compound 1164)



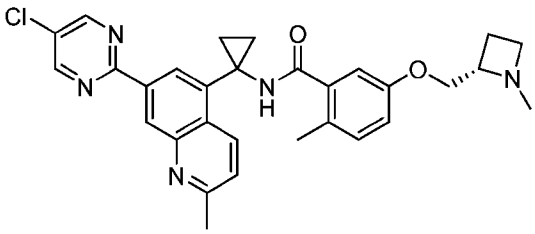
1159A-2



1164A-1



1164A-2



Compound 1164

Step 1: *tert*-Butyl (*S*)-2-((3-((1-(7-(5-chloropyrimidin-2-yl)-2-methylquinolin-5-yl) cyclopropyl)carbamoyl)-4-methylphenoxy)methyl)azetidine-1-carboxylate (1164A-1)

A mixture of *tert*-butyl (*S*)-2-((4-methyl-3-((1-(2-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinolin-5-yl)cyclopropyl)carbamoyl)phenoxy)methyl)azetidine-1-carboxylate (130 mg, 207 μmol, 1.0 eq), 5-chloro-2-iodopyrimidine (74.7 mg, 311 μmol, 1.5 eq), $Pd(dppf)Cl_2$ (15.1 mg, 20.7 μmol, 0.1 eq) and Cs_2CO_3 (135 mg, 414 μmol, 2.0 eq) in dioxane (4.0 mL) and H_2O (400 μL) was degassed and purged with N_2 three times. The resulting mixture was stirred at 80 °C for 2 h under a N_2 atmosphere. LCMS indicated that the starting material was completely consumed, and the desired mass was detected. The reaction mixture was allowed to cool to room temperature, poured into H_2O (5.0 mL) and extracted with EtOAc (3.0 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 1/100 to 1/1. *tert*-Butyl (*S*)-2-((3-((1-(7-(5-chloropyrimidin-2-yl)-2-methylquinolin-5-yl)cyclopropyl)carbamoyl)-4-methylphenoxy)methyl)azetidine-1-carboxylate (100 mg, 163 μmol, 79% yield) was obtained as a white solid. $M + H^+$ = 614.4 (LCMS); ^1H NMR (400 MHz, DMSO-d_6) δ 9.20 – 9.08 (m, 3H), 9.02 (d, *J* = 8.5 Hz, 1H), 8.83 – 8.74 (m, 2H), 7.55 (d, *J* = 8.8 Hz, 1H), 7.05 (d, *J* = 8.4 Hz, 1H), 6.88 (dd, *J* = 2.6, 8.3 Hz, 1H), 6.67 (d, *J* = 2.6 Hz, 1H), 4.38 (br d, *J* = 4.9 Hz, 1H), 4.17 – 4.10 (m, 1H), 3.98 (dd, *J* = 2.8, 10.3 Hz, 1H), 3.73 (br s, 2H), 2.70 (s, 3H), 2.32 – 2.21 (m, 1H), 2.12 – 2.02 (m, 1H), 1.95 (s, 3H), 1.41 (br s, 2H), 1.29 (br s, 9H), 1.23 (br s, 2H).

Step 2: (*S*)-5-(Azetidin-2-ylmethoxy)-*N*-(1-(7-(5-chloropyrimidin-2-yl)-2-methylquinolin-5-yl)cyclopropyl)-2-methylbenzamide (1164A-2)

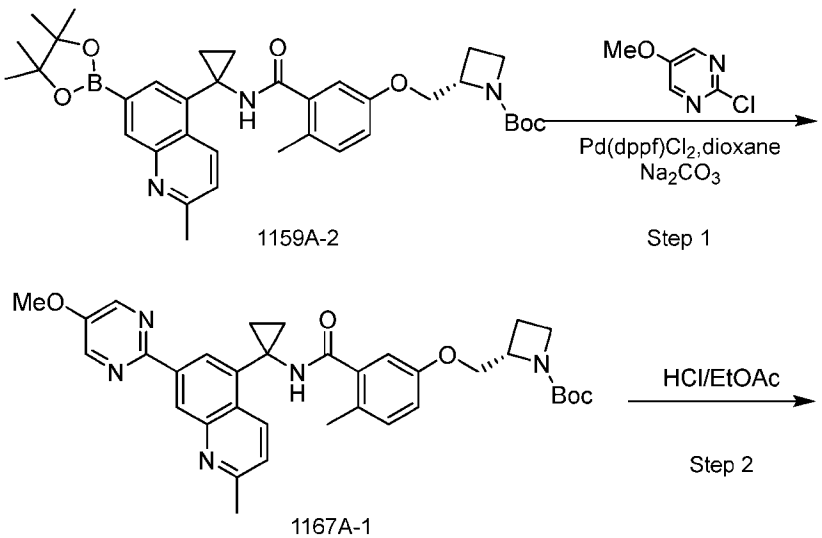
To a solution of *tert*-butyl (*S*)-2-((3-((1-(7-(5-chloropyrimidin-2-yl)-2-methylquinolin-5-yl)cyclopropyl)carbamoyl)-4-methylphenoxy)methyl)azetidine-1-carboxylate (90.0 mg, 147 μmol, 1.0 eq) in DCM (3.0 mL) was added TFA (900 μL). The mixture was stirred at 20 °C for 1 h. LCMS indicated that the starting material was completely consumed, and the desired mass was detected. The mixture was concentrated under vacuum at 20 °C to give the crude (*S*)-5-(azetidin-2-ylmethoxy)-*N*-(1-(7-(5-chloropyrimidin-2-yl)-2-methylquinolin-5-yl)cyclopro pyl)-2-methylbenzamide (90.0 mg, TFA salt) as a yellow oil. $M + H^+$ = 514.4 (LCMS).

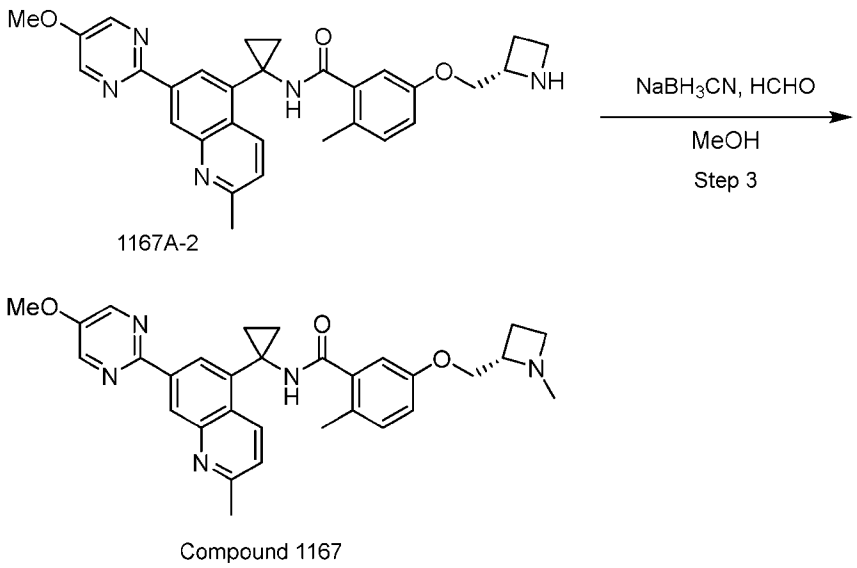
Step 3: (*S*)-*N*-(1-(7-(5-Chloropyrimidin-2-yl)-2-methylquinolin-5-yl)cyclopropyl)-2-methyl-5-((1-methylazetidin-2-yl)methoxy)benzamide (Compound 1164)

To a solution of (*S*)-5-(azetidin-2-ylmethoxy)-*N*-(1-(7-(5-chloropyrimidin-2-yl)-2-methylquinolin-5-yl)cyclopropyl)-2-methylbenzamide (90.0 mg, 143 μmol, 1.0 eq) in MeOH (2.0 mL) was added TEA (20.0 μL), followed by the addition of formaldehyde (23.3 mg, 287

μmol, 21.3 μL, 37% wt % in water, 2.0 eq). The resulting mixture was adjusted to pH to 6 with a small amount of AcOH. The mixture was stirred at 20 °C for 30 min, then $NaBH_3CN$ (27.0 mg, 430 μmol, 3.0 eq) was added. The resulting reaction mixture was stirred at 25 °C for another 2 h. LCMS indicated that the starting material was completely consumed, and the desired mass was detected. The reaction was treated with saturated $NaHCO_3$ (100 μL), then purified by preparative HPLC (Phenomenex Luna C18 column (75 × 30 mm, 3 μm); flow rate: 25 mL/min; gradient: 1% – 25% B over 8 min; mobile phase A: 0.04% aqueous HCl, mobile phase B: acetonitrile). (*S*)-*N*-(1-(7-(5-Chloropyrimidin-2-yl)-2-methylquinolin-5-yl)cyclopro pyl)-2-methyl-5-((1-methylazetidin-2-yl)methoxy)benzamide (42.3 mg, 74.1 μmol, 51% yield, HCl salt) was obtained as a yellow solid. M + H^+ = 528.3 (LCMS); ^1H NMR (400 MHz, DMSO-d_6) δ 11.00 (br s, 1H), 9.63 (br d, *J* = 7.5 Hz, 1H), 9.40 (s, 1H), 9.26 (br s, 1H), 9.21 (s, 2H), 9.01 (s, 1H), 8.04 (br d, *J* = 9.0 Hz, 1H), 7.13 – 7.06 (m, 1H), 6.92 (dd, *J* = 2.7, 8.3 Hz, 1H), 6.77 (d, *J* = 2.6 Hz, 1H), 4.68 – 4.59 (m, 1H), 4.41 (dd, *J* = 8.1, 11.3 Hz, 1H), 4.22 (dd, *J* = 3.2, 11.2 Hz, 1H), 4.00 – 3.94 (m, 1H), 3.87 – 3.83 (m, 1H), 2.99 (s, 3H), 2.80 (d, *J* = 5.0 Hz, 3H), 2.38 – 2.25 (m, 2H), 1.98 (s, 3H), 1.49 (br s, 2H), 1.32 (br s, 2H).

Example 4: (*S*)-*N*-(1-(7-(5-Methoxypyrimidin-2-yl)-2-methylquinolin-5-yl)cyclopro pyl)-2-methyl-5-((1-methylazetidin-2-yl)methoxy)benzamide (Compound 1167)





Step 1: (*S*)-*tert*-Butyl 2-((3-((1-(7-(5-methoxypyrimidin-2-yl)-2-methylquinolin-5-yl)cyclopropyl)carbamoyl)-4-methylphenoxy)methyl)azetidine-1-carboxylate (1167A-1)

To a solution of (*S*)-*tert*-butyl 2-((4-methyl-3-((1-(2-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinolin-5-yl)cyclopropyl)carbamoyl)phenoxy)methyl)azetidine-1-carboxylate (130 mg, 207 µmol, 1.0 eq) and 2-chloro-5-methoxy-pyrimidine (59.8 mg, 414 µmol, 2.0 eq) in dioxane (5.0 mL) and H_2O (500 µL) were added Na_2CO_3 (65.8 mg, 621 µmol, 3.0 eq) and Pd(dppf)Cl_2 (45.4 mg, 62.1 µmol, 0.3 eq). The mixture was degassed and purged with N_2 three times and stirred at 80 °C for 16 h under a N_2 atmosphere. LCMS indicated that the starting material was completely consumed. The reaction mixture was allowed to cool to room temperature, poured into water (40 mL) and extracted with EtOAc (20 mL x 2). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/0. (*S*)-*tert*-Butyl 2-((3-((1-(7-(5-methoxypyrimidin-2-yl)-2-methylquinolin-5-yl)cyclopropyl)carbamoyl)-4-methylphenoxy) methyl)azetidine-1-carboxylate (70.0 mg, 114 µmol, 55% yield) was obtained as a white solid. M + H^+ =610.6 (LCMS).

Step 2: (*S*)-5-(Azetidin-2-ylmethoxy)-*N*-(1-(7-(5-methoxypyrimidin-2-yl)-2-methylquinolin-5-yl)cyclopropyl)-2-methylbenzamide(1167A-2)

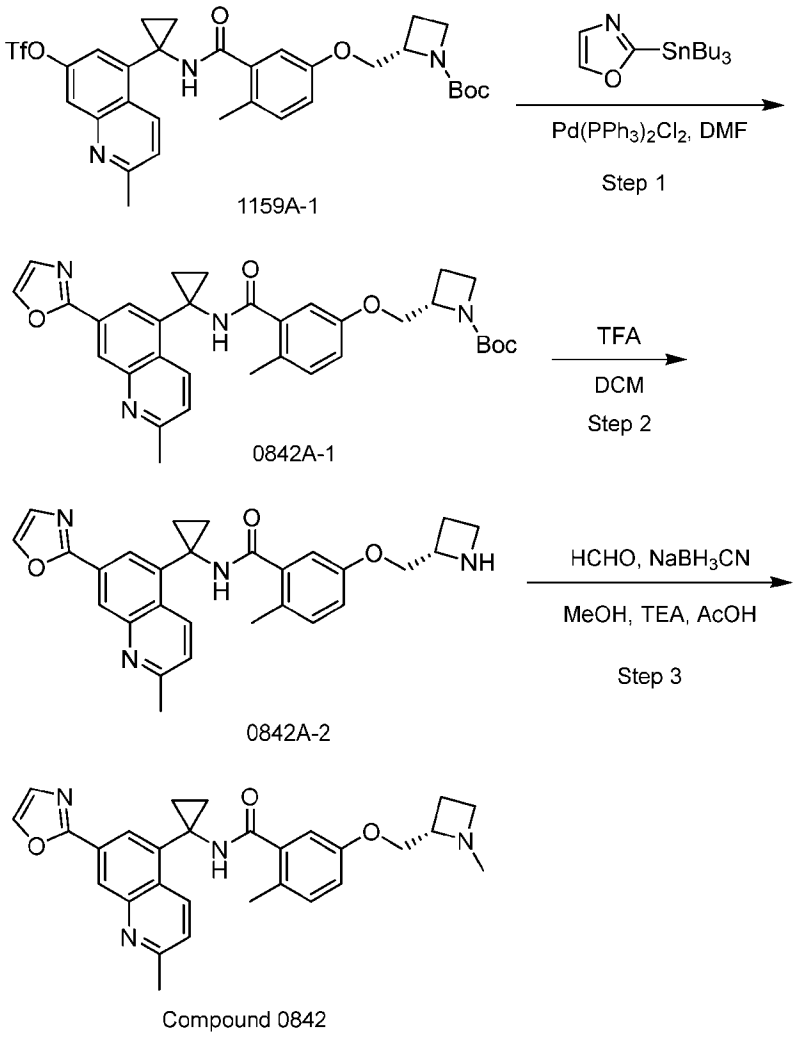
To a solution of (*S*)-*tert*-butyl 2-((3-((1-(7-(5-methoxypyrimidin-2-yl)-2-methylquinolin-5-yl)cyclopropyl)carbamoyl)-4-methylphenoxy) methyl)azetidine-1-carboxylate (70.0 mg, 42.8 µmol, 1.0 eq) in EtOAc (3.0 mL) was added HCl/EtOAc (2 M, 3.0 mL). The mixture was stirred

at 20 °C for 16 h. LCMS indicated that the starting material was completely consumed, and the desired mass was detected. The mixture was concentrated under vacuum at 20 °C to give crude (*S*)-5-(azetidin-2-ylmethoxy)-*N*-(1-(7-(5-methoxypyrimidin-2-yl)-2-methylquinolin-5-yl) cyclopropyl)-2-methylbenzamide (60.0 mg, HCl salt) as a yellow oil. M + H^+ = 510.4 (LCMS).

Step 3: (*S*)-*N*-(1-(7-(5-Methoxypyrimidin-2-yl)-2-methylquinolin-5-yl)cyclopropyl)-2-methyl-5-((1-methylazetidin-2-yl)methoxy)benzamide (Compound 1167)

To a solution of (*S*)-5-(azetidin-2-ylmethoxy)-*N*-(1-(7-(5-methoxypyrimidin-2-yl)-2-methylquinolin-5-yl) cyclopropyl)-2-methylbenzamide (60.0 mg, 110 µmol, 1.0 eq, HCl salt) in MeOH (3.0 mL) was added TEA (11.1 mg, 110 µmol, 15.3 µL, 1.0 eq), followed by the addition of formaldehyde (17.8 mg, 220 µmol, 16.4 µL, 2.0 eq). The resulting mixture was adjusted to pH to 6 with a small amount of AcOH. The mixture was stirred at 20 °C for 30 min, then $NaBH_3CN$ (13.8 mg, 220 µmol, 2.0 eq) was added. The resulting reaction mixture was stirred at 20 °C for another 16 h. LCMS indicated that the starting material was completely consumed. The reaction mixture was poured into H_2O (5.0 mL) and extracted with EtOAc (5.0 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum to give a residue which was purified by preparative HPLC (Phenomenex Luna C18 column (75 × 30 mm, 3 µm); flow rate: 60 mL/min; gradient: 1% – 30% B over 8 min; mobile phase A: 0.04% aqueous HCl, mobile phase B: acetonitrile). (*S*)-*N*-(1-(7-(5-Methoxypyrimidin-2-yl)-2-methylquinolin-5-yl)cyclopropyl)-2-methyl-5-((1-methylazetidin-2-yl)methoxy) benzamide (22.6 mg, 41.2 µmol, 37% yield, HCl salt) was obtained as a white solid. M + H^+ = 524.3 (LCMS); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.39 (d, J = 9.0 Hz, 1H), 9.25 (s, 1H), 8.91 (d, J = 3.5 Hz, 2H), 8.76 (s, 2H), 7.84 (d, J = 8.9 Hz, 1H), 7.09 (d, J = 8.6 Hz, 1H), 6.88 - 6.94 (m, 1H), 6.71 (d, J = 2.8 Hz, 1H), 4.52 - 4.63 (m, 1H), 4.19 (d, J = 5.0 Hz, 2H), 3.99 (s, 3H), 3.80 - 3.89 (m, 2H), 2.83 (d, J = 16.8 Hz, 6H), 2.27 - 2.45 (m, 2H), 1.93 (s, 3H), 1.45 (br s, 2H), 1.30 (br s, 2H).

Example 6: (*S*)-2-Methyl-*N*-(1-(2-methyl-7-(oxazol-2-yl)quinolin-5-yl)cyclopropyl)-5-((1-methylazetidin-2-yl)methoxy)benzamide (Compound 0842)



Step 1: *tert*-Butyl (*S*)-2-((4-methyl-3-((1-(2-methyl-7-(oxazol-2-yl)quinolin-5-yl)cyclopropyl)carbamoyl)phenoxy)methyl)azetidine-1-carboxylate (842A-1)

To a solution of *tert*-butyl (2*S*)-2-((4-methyl-3-((1-(2-methyl-7-(trifluoromethyl sulfonyloxy)-5-quinolyl)cyclopropyl)carbamoyl)phenoxy)methyl)azetidine-1-car boxylate (95.0 mg, 146 µmol, 1.0 eq) and tributyl(oxazol-2-yl)stannane (209 mg, 585 µmol, 4.0 eq) in DMF (2.0 mL) was added $Pd(PPh_3)_2Cl_2$ (30.8 mg, 43.9 µmol, 0.3 eq). The mixture was degassed with N_2 three times and stirred at 70 °C for 16 h under a N_2 atmosphere. LCMS indicated that the starting material was completely consumed, and the desired mass was detected. The mixture was allowed to cool to room temperature, poured into water (20 mL) and extracted with EtOAc (10

mL x 5). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum to give a residue, which was purified by preparative TLC (pure EtOAc, R_f = 0.7). *tert*-Butyl (2*S*)-2-((4-methyl-3-((1-(2-methyl-7-oxazol-2-yl-5-quinolyl)cyclopropyl) carbamoyl)phenoxy)methyl)azetidine-1-carboxylate (70.0 mg, 123 µmol, 84% yield) was obtained as a yellow oil. M + H^+ = 569.0 (LCMS).

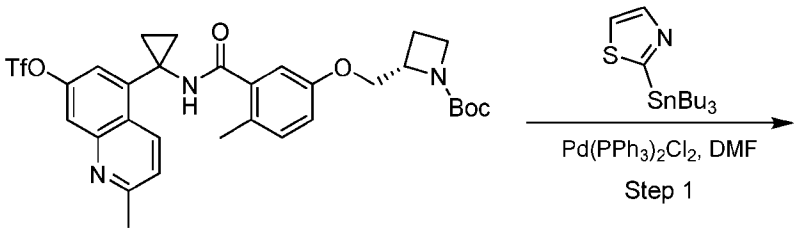
Step 2: (*S*)-5-(Azetidin-2-ylmethoxy)-2-methyl-*N*-(1-(2-methyl-7-(oxazol-2-yl)quinolin-5-yl)cyclopropyl)benzamide (842A-2)

To a mixture of *tert*-butyl (2*S*)-2-((4-methyl-3-((1-(2-methyl-7-oxazol-2-yl-5-quinolyl) cyclopropyl)carbamoyl)phenoxy)methyl)azetidine-1-carboxylate (70.0 mg, 123 µmol, 1.0 eq) in DCM (3.0 mL) was added TFA (2.15 g, 18.6 mmol, 1.40 mL). The mixture was stirred at 25 °C for 1 h. LCMS indicated that the starting material was completely consumed, and the desired mass was detected. The mixture was concentrated under vacuum at 20 °C to give the crude (*S*)-5-(azetidin-2-ylmethoxy)-2-methyl-*N*-(1-(2-methyl-7-(oxazol-2-yl)quinolin-5-yl) cyclopropyl)benzamide (82.0 mg, 81.6 µmol, 66% yield, TFA salt) as a white solid. M + H^+ = 469.2 (LCMS).

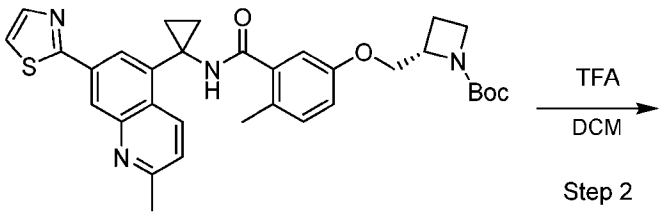
Step 3: (*S*)-2-Methyl-*N*-(1-(2-methyl-7-(oxazol-2-yl)quinolin-5-yl)cyclopropyl)-5-((1-methylazetidin-2-yl)methoxy)benzamide (Compound 842)

To a solution of (*S*)-5-(azetidin-2-ylmethoxy)-2-methyl-*N*-(1-(2-methyl-7-(oxazol-2-yl)quinolin-5-yl) cyclopropyl)benzamide (82.0 mg, 175 µmol, 1.0 eq) in MeOH (3.0 mL) was added TEA (0.1 mL), followed by the addition of formaldehyde (42.6 mg, 525 µmol, 39.1 µL, 37% wt % in water, 3.0 eq). The resulting mixture was adjusted to pH to 6 with a small amount of AcOH, then $NaBH_3CN$ (22.0 mg, 350 µmol, 2.0 eq) was added. The mixture was stirred at 20 °C for 30 min. LCMS indicated that the starting material was completely consumed, and the desired mass was detected. The mixture was poured into water (10 mL) and filtered. The filtrate was concentrated in vacuo to give a residue, which was purified by preparative HPLC (Phenomenex Luna C18 (100 × 40 mm, 5 µm); flow rate: 60 mL/min; gradient: 1% – 30% B over 8 min; mobile phase A: 0.1% aqueous TFA, mobile phase B: acetonitrile). (*S*)-2-Methyl-*N*-(1-(2-methyl-7-(oxazol-2-yl)quinolin-5-yl)cyclopropyl)-5-((1-methylazetidin-2-yl)methoxy)benzamide (23.1 mg, 47.9 µmol, 27% yield, TFA salt) was obtained as a white solid. M + H^+ = 482.9 (LCMS); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (br d, *J* = 2.1 Hz, 1H), 9.20 (s, 1H), 9.07 (d, *J* = 8.8 Hz, 1H), 8.46 - 8.40 (m, 2H), 8.36 (s, 1H), 7.63 (d, *J* = 8.8 Hz, 1H), 7.51 (s, 1H), 7.10 (d, *J* = 8.4 Hz, 1H), 6.92 (dd, *J* = 2.8, 8.4 Hz, 1H), 6.73 (d, *J* = 2.8 Hz, 1H), 4.70 - 4.53 (m, 1H), 4.26 - 4.17 (m, 2H), 4.02 (br dd, *J* = 4.6, 9.6 Hz, 2H), 2.84 (d, *J* = 4.9 Hz, 3H), 2.73 (s, 3H), 2.38 - 2.29 (m, 2H), 1.96 (s, 3H), 1.41 (br s, 2H), 1.27 (br s, 2H).

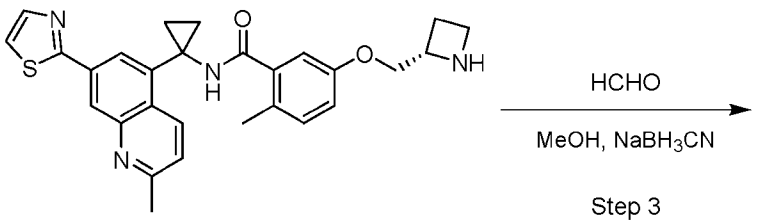
Example 7: (*S*)-2-Methyl-*N*-(1-(2-methyl-7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)-5-((1-methylazetidin-2-yl)methoxy)benzamide (Compound 1145)



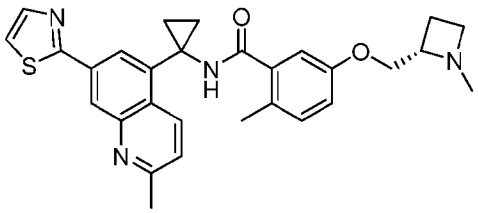
1159A-1



1145A-1



1145A-2



Compound 1145

Step 1: *tert*-Butyl (*S*)-2-((4-methyl-3-((1-(2-methyl-7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)carbamoyl)phenoxy)methyl)azetidine-1-carboxylate (1145A-1)

To a solution of *tert*-butyl (*S*)-2-((4-methyl-3-((1-(2-methyl-7-(((trifluoromethyl)sulfonyl)oxy)quinolin-5-yl)cyclopropyl)carbamoyl)phenoxy)methyl) azetidine-1-carboxylate (130 mg, 200 µmol, 1.0 eq) and tributyl(thiazol-2-yl)stannane (150 mg, 400 µmol, 2.0 eq) in DMF (5.0

mL) was added $Pd(PPh_3)_2Cl_2$ (14.1 mg, 20.0 μmol, 0.1 eq). The mixture was degassed and purged with N_2 three times and the mixture was stirred at 60 °C for 12 h under a N_2 atmosphere. LCMS indicated that the starting material was completely consumed. The reaction mixture was allowed to cool to room temperature, poured into H_2O (1.0 mL) and extracted with EtOAc (5.0 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/0. *tert*-Butyl (*S*)-2-((4-methyl-3-((1-(2-methyl-7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)carbamoyl)phenoxy)methyl)azetidine-1-carboxylate (117 mg, 200 μmol, 100% yield) was obtained as a white solid. M + H^+ = 585.2 (LCMS).

Step 2: (*S*)-5-(Azetidin-2-ylmethoxy)-2-methyl-N-(1-(2-methyl-7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)benzamide (1145A-2)

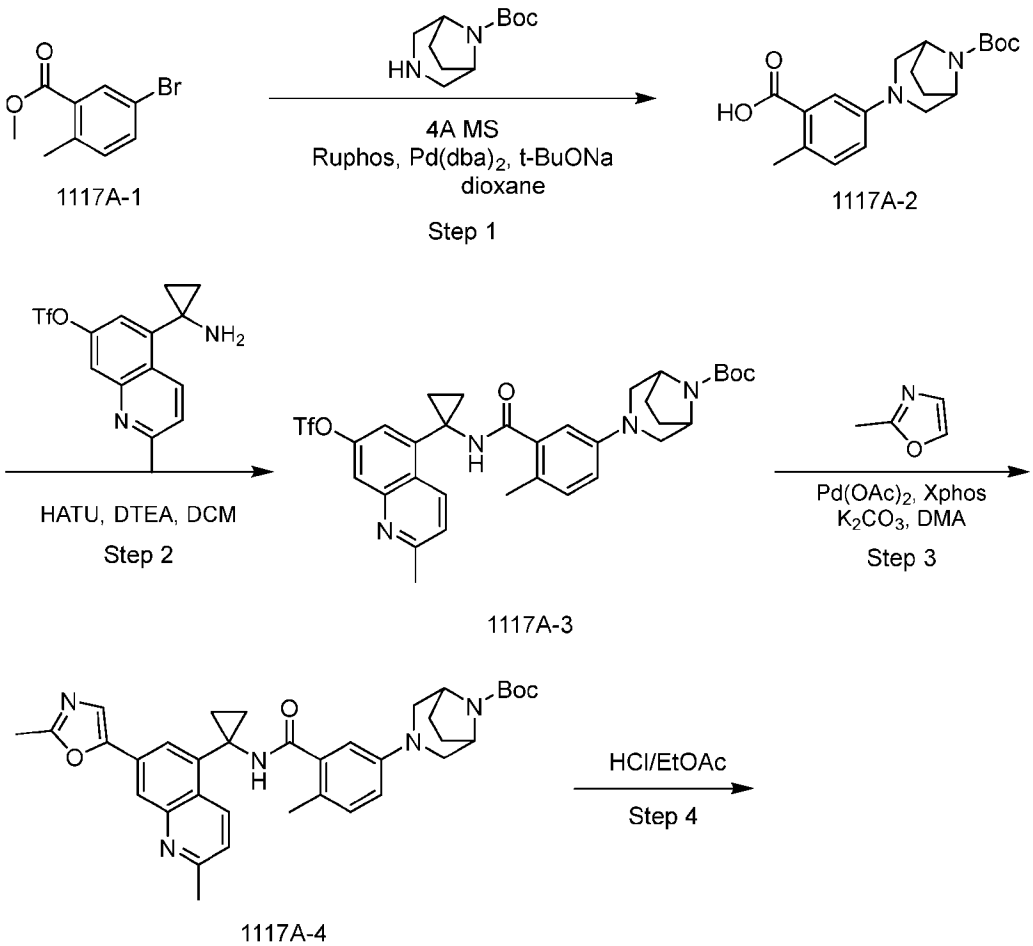
To a solution of *tert*-butyl (*S*)-2-((4-methyl-3-((1-(2-methyl-7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)carbamoyl)phenoxy)methyl)azetidine-1-carboxylate (117 mg, 201 μmol, 1.0 eq) in DCM (3.0 mL) was added TFA (457 mg, 4.00 mmol, 298 μL). The mixture was stirred at 20 °C for 1 h. LCMS indicated that the starting material was completely consumed. The reaction mixture was concentrated under vacuum to give crude (*S*)-5-(azetidin-2-ylmethoxy)-2-methyl-N-(1-(2-methyl-7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)benzamide (115 mg, 192 μmol, 96% yield, TFA salt) as a white solid. M + H^+ = 485.2 (LCMS).

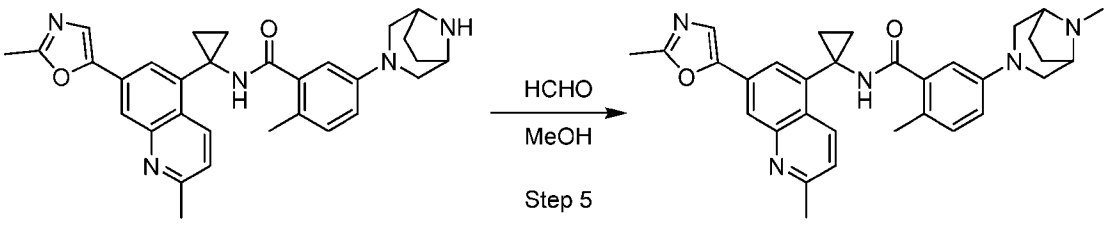
Step 3: *(S)*-2-Methyl-*N*-(1-(2-methyl-7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)-5-((1-methylazetidin-2-yl)methoxy)benzamide (Compound 1145)

To a solution of (*S*)-5-(azetidin-2-ylmethoxy)-2-methyl-*N*-(1-(2-methyl-7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)benzamide (115 mg, 192 μmol, 1.0 eq, TFA salt) in MeOH (3.0 mL) was added TEA (19.5 mg, 192 μmol, 26.8 μL, 1.0 eq), followed by the addition of formaldehyde (31.2 mg, 384 μmol, 28.7 μL, 37% wt % in water, 2.0 eq). The resulting mixture was adjusted to pH to 6 with a small amount of AcOH, then $NaBH_3CN$ (24.2 mg, 384 μmol, 2.0 eq) was added. The mixture was stirred at 20 °C for 3 h. LCMS indicated that the starting material was completely consumed, and the desired mass was detected. The mixture was concentrated under vacuum at 30 °C to give a residue which was purified by preparative HPLC (Phenomenex Luna C18 column (75 × 30 mm, 3 μm); flow rate: 25 mL/min; gradient: 10% – 40% B over 8 min; mobile phase A: 0.1% aqueous TFA, mobile phase B: acetonitrile). (*S*)-2-Methyl-*N*-(1-(2-methyl-7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)-5-((1-methylazetidin-2-yl)methoxy)benzamide (112 mg, 182 μmol, 95% yield, TFA salt) was obtained as a yellow

solid. M + H$^+$ = 499.2 (LCMS); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.36 (d, J = 8.8 Hz, 1H), 9.26 (s, 1H), 8.54 (d, J = 1.6 Hz, 1H), 8.50 (s, 1H), 8.08 (d, J = 3.1 Hz, 1H), 7.94 (d, J = 3.3 Hz, 1H), 7.84 (d, J = 8.8 Hz, 1H), 7.09 (d, J = 8.5 Hz, 1H), 6.91 (dd, J = 2.8, 8.4 Hz, 1H), 6.71 (d, J = 2.6 Hz, 1H), 4.62 – 4.53 (m, 1H), 4.22 – 4.16 (m, 2H), 4.01 (dt, J = 4.8, 9.7 Hz, 1H), 3.88 – 3.83 (m, 1H), 2.84 (s, 3H), 2.81 (s, 3H), 2.42 – 2.31 (m, 2H), 1.93 (s, 3H), 1.44 (br s, 2H), 1.32 (br s, 2H).

Example 8: 2-methyl-*N*-(1-(2-methyl-7-(2-methyloxazol-5-yl)quinolin-5-yl)cyclopropyl)-5-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)benzamide (Compound 1117)





1117A-5 Compound 1117

Step 1: 5-(8-(*tert*-Butoxycarbonyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)-2-methylbenzoic acid (1117A-2)

To a solution of methyl 5-bromo-2-methylbenzoate (1.45 g, 6.81 mmol, 1.2 eq) and *tert*-butyl 3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.30 g, 5.68 mmol, 1.0 eq) in dioxane (25 mL) were added RuPhos (265 mg, 568 μmol, 0.1 eq), $Pd(dba)_2$ (326 mg, 568 μmol, 0.1 eq), *t*-BuONa (1.64 g, 17.0 mmol, 3.0 eq) and 4A MS (300 mg). The mixture was stirred at 100 °C for 16 h under a N_2 atmosphere. LCMS indicated that the starting material was completely consumed. The reaction mixture was allowed to cool to room temperature, poured into water (30 mL) and extracted with DCM (20 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/0. 5-(8-(*tert*-Butoxycarbonyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)-2-methylben zoic acid (1.10 g, 3.18 mmol, 56% yield) was obtained as a yellow solid. $M + H^+ = 347.4$ (LCMS); ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, $J = 2.8$ Hz, 1H), 7.15 (d, $J = 8.5$ Hz, 1H), 6.94 (dd, $J = 2.8$, 8.5Hz, 1H), 4.52 – 4.25 (m, 2H), 3.47 – 3.35 (m, 2H), 3.06 – 2.94 (m, 2H), 2.55 (s, 3H), 2.02 – 1.94 (m, 2H), 1.90 – 1.84 (m, 2H), 1.49 (s, 9H).

Step 2: *tert*-Butyl 3-(4-methyl-3-((1-(2-methyl-7-(((trifluoromethyl)sulfonyl)oxy) quinolin-5-yl)cyclopropyl)carbamoyl)phenyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1117A-3)

To a solution of 5-(8-(*tert*-butoxycarbonyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)-2-methylbenzoic acid, (600 mg, 1.73 mmol, 1.0 eq) and 5-(1-aminocyclopropyl)-2-methylquinolin-7-yl trifluoromethanesulfonate (600 mg, 1.73 mmol, 1.0 eq) in DMF (15 mL) were added HATU (1.65 g, 4.33 mmol, 2.5 eq) and DIEA (672 mg, 5.20 mmol, 905 μL, 3.0 eq). The mixture was stirred at 20 °C for 3 h. LCMS indicated that the starting material was completely consumed. The reaction mixture was poured into water (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a

gradient of EtOAc/petroleum ether from 0/1 to 1/1. *tert*-Butyl 3-(4-methyl-3-((1-(2-methyl-7-(((trifluoromethyl)sulfonyl)oxy)quinolin-5-yl)cyclopropyl)carbamoyl)phenyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.00 g, 1.48 mmol, 86% yield) was obtained as a white solid. M + H^+ = 675.2 (LCMS).

Step 3: *tert*-Butyl 3-(4-methyl-3-((1-(2-methyl-7-(2-methyloxazol-5-yl)quinolin-5-yl)cyclopropyl)carbamoyl)phenyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1117A-4)

To a solution of *tert*-butyl 3-(4-methyl-3-((1-(2-methyl-7-(((trifluoromethyl)sulfonyl)oxy)quinolin-5-yl)cyclopropyl)carbamoyl)phenyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (100 mg, 148 μmol, 1.0 eq) and 2-methyloxazole (12.3 mg, 148 μmol, 1.0 eq) in DMA (5.0 mL) were added K_2CO_3 (61.5 mg, 445 μmol, 3.0 eq), $Pd(OAc)_2$ (6.65 mg, 29.7 μmol, 0.2 eq) and XPhos (28.3 mg, 59.3 μmol, 0.4 eq). The mixture was degassed and purged with N_2 for three times and the mixture was stirred at 100 °C for 4 h under a N_2 atmosphere. LCMS indicated that the starting material was completely consumed. The reaction mixture was allowed to cool to room temperature, poured into water (6.0 mL) and extracted with EtOAc (8.0 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/0. *tert*-Butyl 3-(4-methyl-3-((1-(2-methyl-7-(2-methyloxazol-5-yl)quinolin-5-yl)cyclopropyl)carbamoyl)phenyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (150 mg, 247 μmol, 84% yield) was obtained as a white solid. M + H^+ = 608.3 (LCMS).

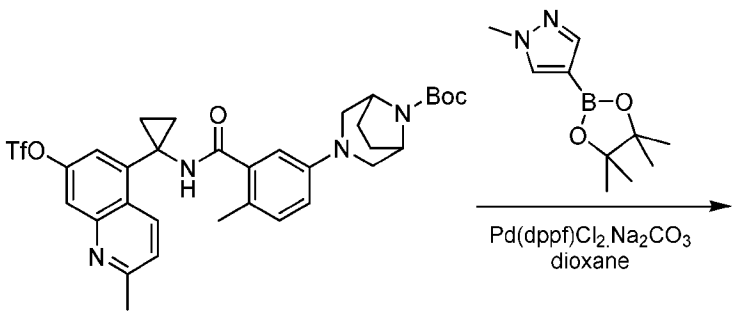
Step 4: 5-(3,8-Diazabicyclo[3.2.1]octan-3-yl)-2-methyl-*N*-(1-(2-methyl-7-(2-methyloxazol-5-yl)quinolin-5-yl)cyclopropyl)benzamide (1117A-5)

To a solution of *tert*-butyl 3-(4-methyl-3-((1-(2-methyl-7-(2-methyloxazol-5-yl)quinolin-5-yl)cyclopropyl)carbamoyl)phenyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (110 mg, 181 μmol, 1.0 eq) in EtOAc (2.0 mL) was added HCl/EtOAc (4 M, 905 μL). The mixture was stirred at 20 °C for 1 h. LCMS indicated that the starting material was completely consumed. The reaction mixture was concentrated under vacuum to give 5-(3,8-diaza bicyclo[3.2.1]octan-3-yl)-2-methyl-*N*-(1-(2-methyl-7-(2-methyloxazol-5-yl)quinolin-5-yl)cyclopropyl)benzamide(90.0 mg, crude, HCl salt). M + H^+ = 508.5 (LCMS).

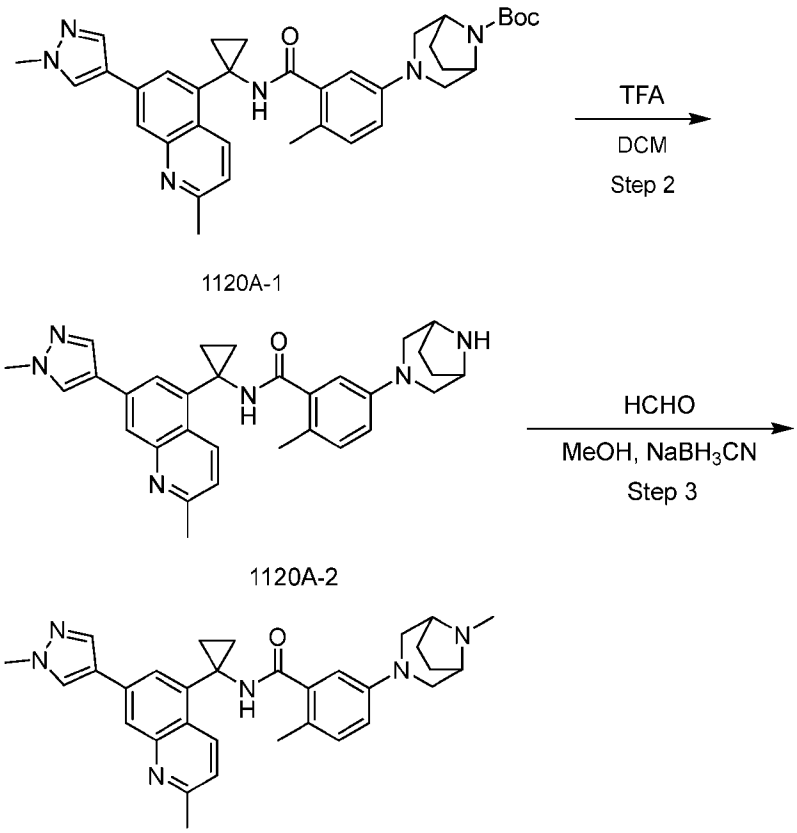
Step 5: 2-Methyl-*N*-(1-(2-methyl-7-(2-methyloxazol-5-yl)quinolin-5-yl)cyclopropyl)-5-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)benzamide (Compound 1117)

To a solution of 5-(3,8-diazabicyclo[3.2.1]octan-3-yl)-2-methyl-*N*-(1-(2-methyl-7-(2-methyloxazol-5-yl)quinolin-5-yl)cyclopropyl)benzamide (90.0 mg, 165 μmol, 1.0 eq, HCl salt) in MeOH (3.0 mL) was added TEA (16.8 mg, 165 μmol, 23.1 μL, 1.0 eq), followed by the addition of formaldehyde (26.9 mg, 331 μmol, 24.7 μL, 37% wt % in water, 2.0 eq). The resulting mixture was adjusted to pH to 6 with a small amount of AcOH, then $NaBH_3CN$ (20.8 mg, 331 μmol, 2.0 eq) was added. The mixture was stirred at 20 °C for 3 h. LCMS indicated that the starting material was completely consumed, and the desired mass was detected. The mixture was concentrated under vacuum at 30 °C to give a residue which was purified by preparative HPLC (Phenomenex Luna C18 column (75 × 30 mm, 3 μm); flow rate: 25 mL/min; gradient: 10% – 40% B over 8 min; mobile phase A: 0.04% aqueous HCl, mobile phase B: acetonitrile). 2-Methyl-*N*-(1-(2-methyl-7-(2-methyloxazol-5-yl)quinolin-5-yl)cyclo propyl)-5-(8-methyl-3,8-diazabicyclo[3.2.1] octan -3-yl)benzamide (34.6 mg, 56.8 μmol, 35% yield, 92% purity, HCl salt) was obtained as a yellow solid. M + H^+ = 522.3 (LCMS); ^1H NMR (400 MHz, DMSO-d_6) δ 9.56 (d, *J* = 8.9 Hz, 1H), 9.31 – 9.24 (m, 1H), 8.34 – 8.29 (m, 2H), 8.01 (s, 1H), 7.97 (d, *J* = 8.8 Hz, 1H), 7.00 (d, *J* = 8.6 Hz, 1H), 6.82 (dd, *J* = 2.5, 8.4 Hz, 1H), 6.61 (d, *J* = 2.4 Hz, 1H), 3.99 (br s, 2H), 3.55 – 3.41 (m, 2H), 3.17 (s, 1H), 3.14 (s, 1H), 2.94 (s, 3H), 2.72 (s, 3H), 2.58 (s, 3H), 2.19 – 2.13 (m, 2H), 1.92 – 1.88 (m, 5H), 1.44 (br s, 2H), 1.37 (br s, 2H).

Example 9: 2-Methyl-*N*-(1-(2-methyl-7-(1-methyl-1*H*-pyrazol-4-yl)quinolin-5-yl)cyclopropyl)-5-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)benzamide (Compound 1120)



1117A-3 Step 1



Step 1: *tert*-Butyl 3-(4-methyl-3-((1-(2-methyl-7-(1-methyl-1*H*-pyrazol-4-yl)quinolin-5-yl)cyclopropyl)carbamoyl)phenyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate(1120A-1)

To a solution of *tert*-butyl 3-(4-methyl-3-((1-(2-methyl-7-(((trifluoromethyl)sulfonyl)oxy) quinolin-5-yl)cyclopropyl)carbamoyl)phenyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (240 mg, 356 μmol, 1.0 eq) and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (222 mg, 1.06 mmol, 3.0 eq) in dioxane (3.0 mL) and H_2O (300 μL) were added Pd(dppf)Cl_2 (26.0 mg, 35.8 μmol, 0.1 eq) and Na_2CO_3 (113 mg, 1.06 mmol, 3.0 eq). The mixture was degassed and purged with N_2 three times and the mixture was stirred at 80 °C for 3 h under a N_2 atmosphere. LCMS indicated that the starting material was completely consumed, and the desired mass was detected. The mixture was cooled to room temperature, poured into water (20 mL) and extracted with EtOAc (20 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum to give a residue which was purified by preparative TLC (DCM/MeOH = 10/1, R_f = 0.6). *tert*-Butyl 3-(4-methyl-3-((1-(2-

methyl-7-(1-methylpyrazol-4-yl)-5-quinolyl)cyclopropyl)carbamoyl)phenyl) -3,8-diazabicyclo [3.2.1]octane-8-carboxylate (200 mg, 330 μmol, 92% yield) was obtained as a yellow solid. M + H^+ = 607.5 (LCMS).

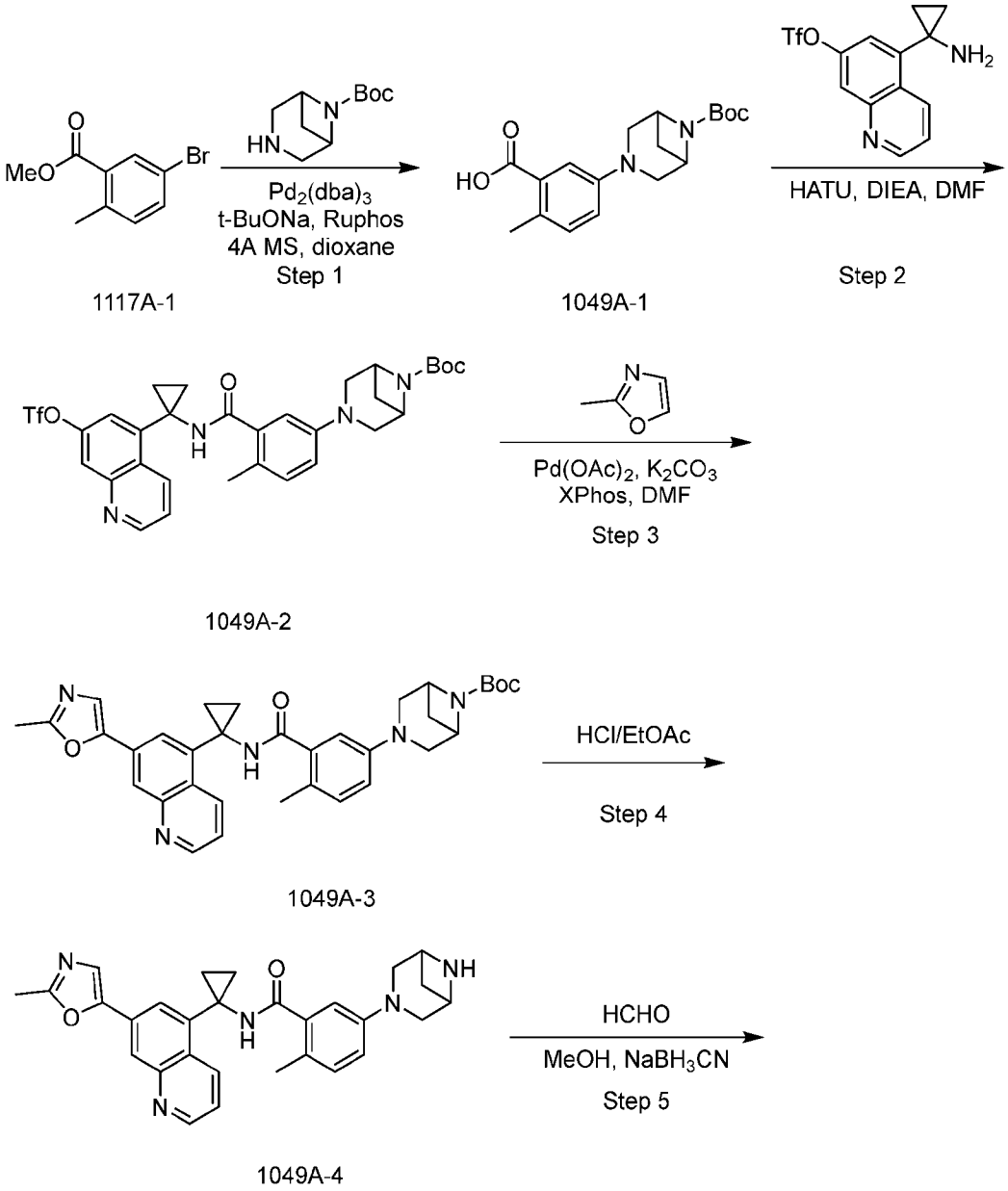
Step 2: 5-(3,8-Diazabicyclo[3.2.1]octan-3-yl)-2-methyl-*N*-(1-(2-methyl-7-(1-methyl-1*H*-pyrazol-4-yl)quinolin-5-yl)cyclopropyl)benzamide(1120A-2)

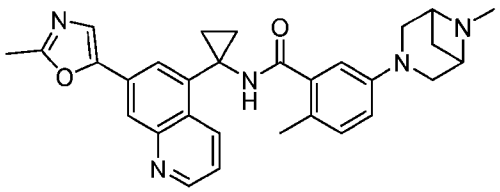
To a solution of *tert*-butyl 3-(4-methyl-3-((1-(2-methyl-7-(1-methylpyrazol-4-yl)-5-quinolyl)cyclopropyl)carbamoyl)phenyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (190 mg, 264 μmol, 1.0 eq) in DCM (1.0 mL) was added TFA (1.54 g, 13.7 mmol, 1.00 mL). The mixture was stirred at 0 °C for 1 h. LCMS indicated that the starting material was completely consumed, and the desired mass was detected. The mixture was concentrated under vacuum at 30 °C to give the crude product 5-(3,8-diazabicyclo[3.2.1]octan-3-yl)-2-methyl-*N*-(1-(2-methyl-7-(1-methyl-1H-pyrazol-4-yl)quinolin-5-yl) cyclopropyl) benzamide (100 mg, TFA salt) as a yellow oil. M + H^+ = 507.4 (LCMS).

Step 3: 2-Methyl-*N*-(1-(2-methyl-7-(1-methyl-1*H*-pyrazol-4-yl)quinolin-5-yl)cyclopropyl) -5-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)benzamide (Compond 1120)

To a solution of 5-(3,8-diazabicyclo[3.2.1]octan-3-yl)-2-methyl-*N*-(1-(2-methyl-7-(1-methyl-1*H*-pyrazol-4-yl)quinolin-5-yl)cyclopropyl)benzamide (100 mg, 161 μmol, 1.0 eq, TFA salt) in MeOH (1.0 mL) was added TEA (0.1 mL), followed by the addition of formaldehyde (39.2 mg, 483 μmol, 35.9 μL, 37% wt % in water, 3.0 eq). The resulting mixture was adjusted to pH to 6 with a small amount of AcOH. The mixture was stirred at 20 °C for 15 min, then $NaBH_3CN$ (20.3 mg, 322 μmol, 2.0 eq) was added. The resulting mixture was stirred at 20 °C for another 30 min. LCMS indicated that the starting material was completely consumed, and the desired mass was detected. The mixture was diluted with water (2 mL) and filtered, and the filtrate was concentrated in vacuo to give a residue which was purified by preparative HPLC (Phenomenex Luna C18 (100 × 40mm, 3 μm); flow rate: 60 mL/min; gradient: 1% – 30% B over 8 min; mobile phase A: 0.1% aqueous TFA, mobile phase B: acetonitrile). 2-Methyl-*N*-(1-(2-methyl-7-(1-methyl-1*H*-pyrazol-4-yl)quinolin-5-yl)cyclopropyl)-5-(8-methyl-3,8-diaza bicyclo[3.2.1]octan-3-yl)benzamide (60.1 mg, 114 μmol, 70% yield, TFA salt) was obtained as a yellow solid. M + H^+ = 521.4 (LCMS); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.98 (br d, J = 3.5 Hz, 1H), 9.30 (br d, J = 8.1 Hz, 1H), 9.12 (s, 1H), 8.48 (s, 1H), 8.18 – 8.06 (m, 3H), 7.79 – 7.67 (m, 1H), 7.00 (d, J = 8.5 Hz, 1H), 6.82 (dd, J = 2.6, 8.4 Hz, 1H), 6.60 (d, J = 2.6 Hz, 1H), 4.02 (br s, 2H), 3.95 (s, 3H), 3.60 (br d, J = 10.9 Hz, 2H), 3.00 (br d, J = 12.3 Hz, 2H), 2.83 (s, 3H), 2.75 (d, J = 4.9 Hz, 3H), 2.22 – 2.12 (m, 2H), 1.95 – 1.87 (m, 5H), 1.42 – 1.32 (m, 4H).

Example 10: 2-Methyl-5-(6-methyl-3,6-diazabicyclo[3.1.1]heptan-3-yl)-*N*-(1-(7-(2-methyloxazol-5-yl)quinolin-5-yl)cyclopropyl)benzamide (Compound 1049)





Compound 1049

Step 1: 5-(6-(*tert*-Butoxycarbonyl)-3,6-diazabicyclo[3.1.1]heptan-3-yl)-2-methylbenzoic acid (1049A-1)

A mixture of methyl 5-bromo-2-methylbenzoate (385 mg, 1.70 mmol, 1.0 eq) and *tert*-butyl 3,6-diazabicyclo[3.1.1]heptane-6-carboxylate (500 mg, 2.50 mmol, 1.5 eq) in dioxane (20 mL) was degassed and purged with N_2 three times. To the mixture were added RuPhos (78.5 mg, 168 µmol, 0.1 eq), $Pd_2(dba)_3$ (154 mg, 168 µmol, 0.1 eq), *t*-BuONa (485 mg, 5.00 mmol, 3.0 eq) and 4A MS (100 mg). The mixture was degassed and purged with N_2 three times, then stirred at 100 °C for 16 h under a N_2 atmosphere. LCMS indicated that the starting material was completely consumed, and the desired mass was detected. The reaction mixture was allowed to cool to room temperature, poured into H_2O (20 mL) and extracted with DCM (8.0 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/0. 5-(6-(*tert*-Butoxycarbonyl)-3,6-diazabicyclo[3.1.1]heptan-3-yl)-2-methylbenzoic acid (400 mg, 1.20 mmol, 72% yield) was obtained as a brown solid. M + H^+ = 333.1 (LCMS); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.72 – 12.61 (m, 1H), 7.16 – 7.06 (m, 2H), 6.82 (dd, J = 2.8, 8.4 Hz, 1H), 4.20 (br d, J = 5.9 Hz, 2H), 3.84 – 3.65 (m, 2H), 3.30 – 3.22 (m, 2H), 2.51 (br s, 2H), 2.38 (s, 3H), 1.26 (s, 9H).

Step 2: *tert*-Butyl 3-(4-methyl-3-((1-(7-(((trifluoromethyl)sulfonyl)oxy)quinolin-5-yl)cyclopropyl)carbamoyl)phenyl)-3,6-diazabicyclo[3.1.1]heptane-6-carboxylate (1049A-2)

To a solution of 5-(6-(*tert*-butoxycarbonyl)-3,6-diazabicyclo[3.1.1]heptan-3-yl)-2-methylbenzoic acid (300 mg, 903 µmol, 1.0 eq) in DMF (5.0 mL) were added 5-(1-aminocyclopropyl)quinolin-7-yl trifluoromethanesulfonate (300 mg, 903 µmol, 1.0 eq), DIEA (350 mg, 2.71 mmol, 472 µL, 3.0 eq) and HATU (858 mg, 2.26 mmol, 2.5 eq). The mixture was stirred at 20 °C for 16 h. LCMS indicated that the starting material was completely consumed, and the desired mass was detected. The reaction mixture was poured into H_2O (5.0 mL) and extracted with DCM (3.0 mL x 3). The combined organic layers were dried over

Na_2SO_4, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/3. *tert*-Butyl 3-(4-methyl-3-((1-(7-(((trifluoromethyl)sulfonyl)oxy)quinolin-5-yl)cyclopropyl) carbamoyl)phenyl)-3,6-diazabicyclo[3.1.1]heptane-6-carboxylate (400 mg, 619 µmol, 69% yield) was obtained as a yellow solid. M + H^+ = 647.2 (LCMS); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.22 – 9.12 (m, 2H), 9.07 – 8.99 (m, 1H), 8.08 (d, *J* = 2.3 Hz, 1H), 7.87 (d, *J* = 2.5 Hz, 1H), 7.73 (dd, *J* = 4.1, 8.6 Hz, 1H), 6.95 (d, *J* = 8.5 Hz, 1H), 6.62 (dd, *J* = 2.4, 8.4 Hz, 1H), 6.37 (d, *J* = 2.4 Hz, 1H), 4.17 (br d, *J* = 5.8 Hz, 2H), 3.72 – 3.52 (m, 2H), 3.16 (br d, *J* = 10.6 Hz, 2H), 2.69 (s, 3H), 2.58 – 2.52 (m, 2H), 1.41 (br s, 2H), 1.29 (br s, 2H), 1.27 – 1.22 (m, 9H).

Step 3: *tert*-Butyl 3-(4-mthyl-3-((1-(7-(2-methyloxazol-5-yl)quinolin-5-yl)cyclopropyl) carbamoyl)phenyl)-3,6-diazabicyclo[3.1.1]heptane-6-carboxylate (1049A-3)

A mixture of *tert*-butyl 3-(4-methyl-3-((1-(7-(((trifluoromethyl)sulfonyl)oxy)quinolin-5-yl)cyclopropyl)carbamoyl)phenyl)-3,6-diazabicyclo[3.1.1]heptane-6-carboxylate (400 mg, 619 µmol, 1.0 eq) and 2-methyloxazole (77.1 mg, 928 µmol, 1.5 eq) in DMA (20 mL) was degassed and purged with N_2 three times. To the mixture were added $Pd(OAc)_2$ (27.8 mg, 124 µmol, 0.2 eq), K_2CO_3 (256 mg, 1.86 mmol, 3.0 eq) and XPhos (118 mg, 247 µmol, 0.4 eq). The mixture was degassed and purged with N_2 three times, then stirred at 100 °C for 2 h under a N_2 atmosphere. LCMS indicated that the starting material was completely consumed, and the desired mass was detected. The reaction mixture was allowed to cool to room temperature, poured into H_2O (20 mL) and extracted with DCM (8.0 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/3. *tert*-Butyl 3-(4-methyl-3-((1-(7-(2-methyloxazol-5-yl)quinolin-5-yl)cyclopropyl) carbamoyl)phenyl)-3,6-diazabicyclo[3.1.1]heptane-6-carboxylate (200 mg, 345 µmol, 56% yield) was obtained as a brown solid. M + H^+ = 580.5 (LCMS).

Step 4: 5-(3,6-Diazabicyclo[3.1.1]heptan-3-yl)-2-methyl-*N*-(1-(7-(2-methyloxazol-5-yl)quinolin-5-yl)cyclopropyl)benzamide (1049A-4)

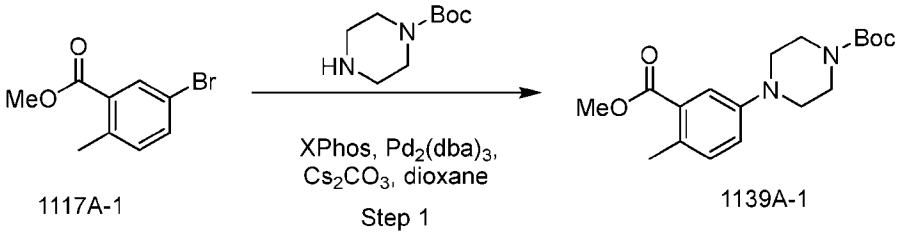
To a solution of *tert*-butyl 3-(4-methyl-3-((1-(7-(2-methyloxazol-5-yl)quinolin-5-yl)cyclopropyl)carbamoyl)phenyl)-3,6-diazabicyclo[3.1.1]heptane-6-carboxylate (90.0 mg, 155 µmol, 1.0 eq) in EtOAc (5.0 mL) was added HCl/EtOAc (4 M, 1.0 mL). The resulting mixture was stirred at 25 °C for 30 min. LCMS indicated that the starting material was completely consumed, and the desired mass was detected. The reaction mixture was concentrated under vacuum to give 5-(3,6-diazabicyclo[3.1.1]heptan-3-yl)-2-methyl-*N*-(1-(7-(2-methyloxazol-5-

yl)quinolin-5-yl)cyclopropyl)benzamide (80.0 mg, HCl salt) as a white solid, which was used in the next step without any further purification. M + H^+ = 480.4 (LCMS).

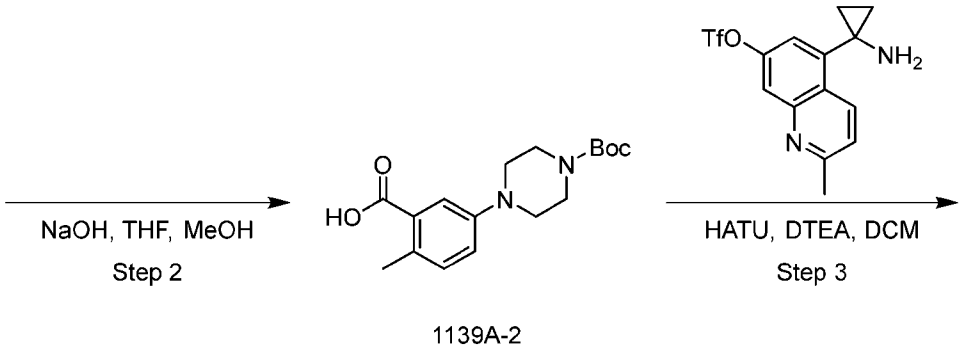
Step 5: 2-Methyl-5-(6-methyl-3,6-diazabicyclo[3.1.1]heptan-3-yl)-*N*-(1-(7-(2-methyl oxazol-5-yl)quinolin-5-yl)cyclopropyl)benzamide (Compound 1049)

To a solution of 5-(3,6-diazabicyclo[3.1.1]heptan-3-yl)-2-methyl-*N*-(1-(7-(2-methyloxazol-5-yl)quinolin-5-yl)cyclopropyl)benzamide (80.0 mg, HCl salt) in MeOH (5.0 mL) was added TEA (50.0 µL), followed by the addition of formaldehyde (22.0 mg, 271 µmol, 20.2 µL, 37% wt % in water, 2.0 eq). The resulting mixture was adjusted to pH to 6 with a small amount of AcOH. The mixture was stirred at 20 °C for 30 min, then $NaBH_3CN$ (17.5 mg, 271 µmol, 2.0 eq) was added. The resulting reaction mixture was stirred at 20 °C for another 16 h. LCMS indicated that the starting material was completely consumed, and the desired mass was detected. The mixture was treated with H_2O (5.0 mL) and extracted with DCM (1.0 mL x 5). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum to give a residue which was purified by preparative HPLC (Phenomenex Luna C18 column (75 × 30 mm, 3 µm); flow rate: 25 mL/min; gradient: 5% – 35% B over 8 min; mobile phase A: 0.04% aqueous HCl, mobile phase B: acetonitrile). 2-Methyl-5-(6-methyl-3,6-diazabicyclo[3.1.1]heptan-3-yl)-*N*-(1-(7-(2-methyloxazol-5-yl)quinolin-5-yl)cyclopropyl) benzamide (28.4 mg, 53.3 µmol, 39% yield, HCl salt) was obtained as an orange solid. M + H^+ = 494.4 (LCMS); ^1H NMR (400 MHz, DMSO-d_6) δ 9.50 – 9.41 (m, 1H), 9.06 (d, J = 4.6 Hz, 1H), 8.27 (s, 2H), 7.88 – 7.78 (m, 2H), 7.10 – 6.91 (m, 1H), 6.69 (br dd, J = 2.4, 8.3 Hz, 1H), 6.47 (dd, J = 2.3, 10.4 Hz, 1H), 4.45 (br d, J = 6.3 Hz, 1H), 4.30 (br d, J = 5.8 Hz, 1H), 3.79 – 3.64 (m, 3H), 3.62 – 3.57 (m, 1H), 3.02 (s, 1H), 2.96 – 2.80 (m, 1H), 2.56 (s, 3H), 2.42 (s, 2H), 1.94 (s, 3H), 1.88 (br d, J = 10.1 Hz, 1H), 1.51 – 1.45 (m, 2H), 1.35 (br s, 2H).

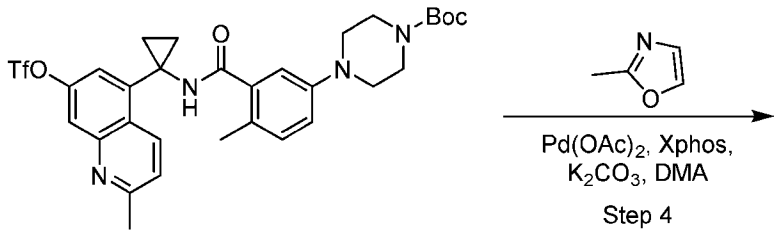
Example 11: 2-Methyl-*N*-(1-(2-methyl-7-(2-methyloxazol-5-yl)quinolin-5-yl)cyclopropyl)-5-(4-methylpiperazin-1-yl)benzamide (Compound 1139)



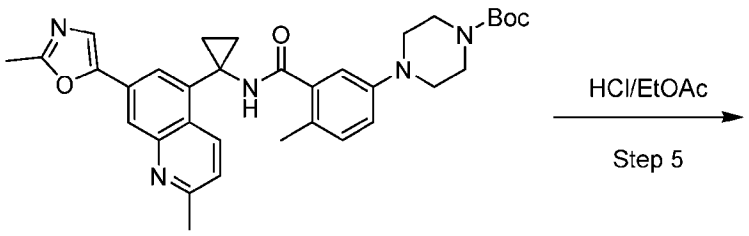
1117A-1 Step 1 1139A-1



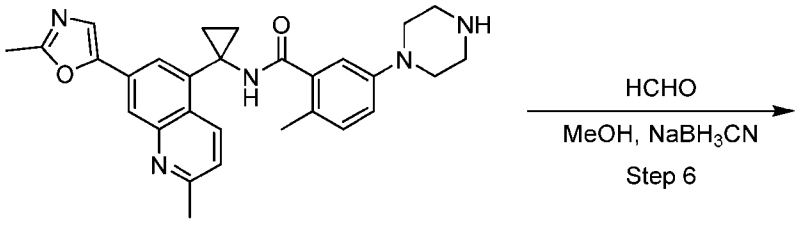
1139A-2



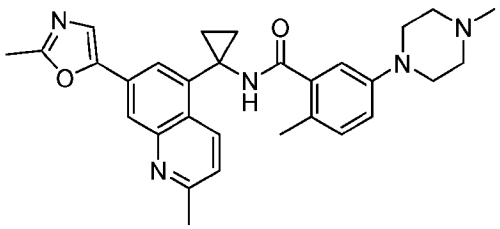
1139A-3



1139A-4



1139A-5



Compound 1139

Step 1: *tert*-Butyl 4-(3-(methoxycarbonyl)-4-methylphenyl)piperazine-1-carboxylate (1139A-1)

A mixture of methyl 5-bromo-2-methylbenzoate (1.00 g, 4.37 mmol, 1.0 eq) and *tert*-butyl piperazine-1-carboxylate (976 mg, 5.24 mmol, 1.2 eq) in dioxane (30 mL) was degassed and purged with N_2 three times. To the mixture were added XPhos (250 mg, 524 µmol, 0.1 eq), $Pd_2(dba)_3$ (120 mg, 131 µmol, 0.03 eq), and Cs_2CO_3 (2.84 g, 8.73 mmol, 2.0 eq). The mixture was degassed and purged with N_2 three times, then stirred at 110 °C for 16 h under a N_2 atmosphere. LCMS indicated that the starting material was completely consumed, and the desired mass was detected. The reaction mixture was allowed to cool to room temperature, poured into H_2O (20 mL) and extracted with DCM (10 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/2. *tert*-Butyl 4-(3-(methoxycarbonyl)-4-methylphenyl)piperazine-1-carboxylate (2.60 g, 7.77 mmol, 89% yield) was obtained as a white solid. M + H^+ = 334.3 (LCMS); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.34 (d, J = 2.6 Hz, 1H), 7.19 – 7.15 (m, 1H), 7.11 – 7.07 (m, 1H), 3.81 (s, 3H), 3.49 – 3.41 (m, 4H), 3.10 – 3.04 (m, 4H), 2.39 (s, 3H), 1.42 (s, 9H).

Step 2: 5-(4-(*tert*-Butoxycarbonyl)piperazin-1-yl)-2-methylbenzoic acid (1139A-2)

To a solution of *tert*-butyl 4-(3-(methoxycarbonyl)-4-methylphenyl)piperazine-1-carboxylate (2.60 g, 7.80 mmol, 1.0 eq) in THF (30 mL) and MeOH (10 mL) was added NaOH (2 M aqueous, 7.8 mL, 2.0 eq). The mixture was stirred at 70 °C for 16 h. LCMS indicated that the starting material was completely consumed, and the desired mass was detected. The reaction mixture was allowed to cool to room temperature, poured into H_2O (30 mL) and extracted with petroleum ether (20 mL x 2). The aqueous phase was adjusted to pH 4 by using HCl (1 M aqueous) and extracted with EtOAc (10 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum to give a crude product 5-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)-2-methylbenzoic acid (2.2 g) as a white solid, which was used

in the next step without any further purification. M + H^+ = 321.3 (LCMS); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.95 – 12.57 (m, 1H), 7.35 (d, J = 2.6 Hz, 1H), 7.19 – 7.11 (m, 1H), 7.10 – 7.02 (m, 1H), 3.49 – 3.41 (m, 4H), 3.13 – 2.98 (m, 4H), 2.40 (s, 3H), 1.42 (s, 9H).

Step 3: *tert*-Butyl 4-(4-methyl-3-((1-(2-methyl-7-(((trifluoromethyl)sulfonyl)oxy) quinolin-5-yl)cyclopropyl)carbamoyl)phenyl)piperazine-1-carboxylate (1139A-3)

To a solution of 5-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)-2-methylbenzoic acid (87.9 mg, 274 μmol, 1.0 eq) in DMF (5.0 mL) were added 5-(1-aminocyclopropyl)-2-methylquinolin-7-yl trifluoromethanesulfonate (100 mg, 289 μmol, 1.0 eq), DIEA (112 mg, 866 μmol, 151 μL, 3.0 eq) and HATU (274 mg, 722 μmol, 2.5 eq). The mixture was stirred at 20 °C for 16 h. LCMS indicated that the starting material was completely consumed, and the desired mass was detected. The reaction mixture was poured into H_2O (5.0 mL) and extracted with DCM (3.0 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/1. *tert*-Butyl 4-(4-methyl-3-((1-(2-methyl-7-(((trifluoromethyl)sulfonyl)oxy)quinolin-5-yl)cyclopropyl)carbamoyl)phenyl)piperazine-1-carboxylate (100 mg, 154.2 μmol, 53% yield) was obtained as a yellow solid. M + H^+ = 649.3 (LCMS).

Step 4: *tert*-Butyl 4-(4-methyl-3-((1-(2-methyl-7-(2-methyloxazol-5-yl)quinolin-5-yl)cyclopropyl)carbamoyl)phenyl)piperazine-1-carboxylate (1139A-4)

A mixture of *tert*-butyl 4-(4-methyl-3-((1-(2-methyl-7-(((trifluoromethyl)sulfonyl)oxy) quinolin-5-yl)cyclopropyl)carbamoyl)phenyl)piperazine-1-carboxylate (100 mg, 154 μmol, 1.0 eq) and 2-methyloxazole (19.0 mg, 231 μmol, 1.5 eq) in DMA (2.0 mL) was degassed and purged with N_2 three times. To the mixture were added $Pd(OAc)_2$ (7.00 mg, 31.0 μmol, 0.2 eq), K_2CO_3 (64.0 mg, 462 μmol, 3.0 eq) and XPhos (29.4 mg, 61.7 μmol, 0.4 eq). The mixture was degassed and purged with N_2 three times, then stirred at 100 °C for 2 h under a N_2 atmosphere. LCMS indicated that the starting material was completely consumed, and the desired mass was detected. The reaction mixture was allowed to cool to room temperature, poured into H_2O (2.0 mL) and extracted with DCM (1.0 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/1. *tert*-Butyl 4-(4-methyl-3-((1-(2-methyl-7-(2-methyloxazol-5-yl)quinolin-5-yl)cyclopropyl) carba moyl)phenyl)piperazine-1-carboxylate (80.0 mg, 138 μmol, 89% yield) was obtained as a yellow oil. M + H^+ = 582.5 (LCMS).

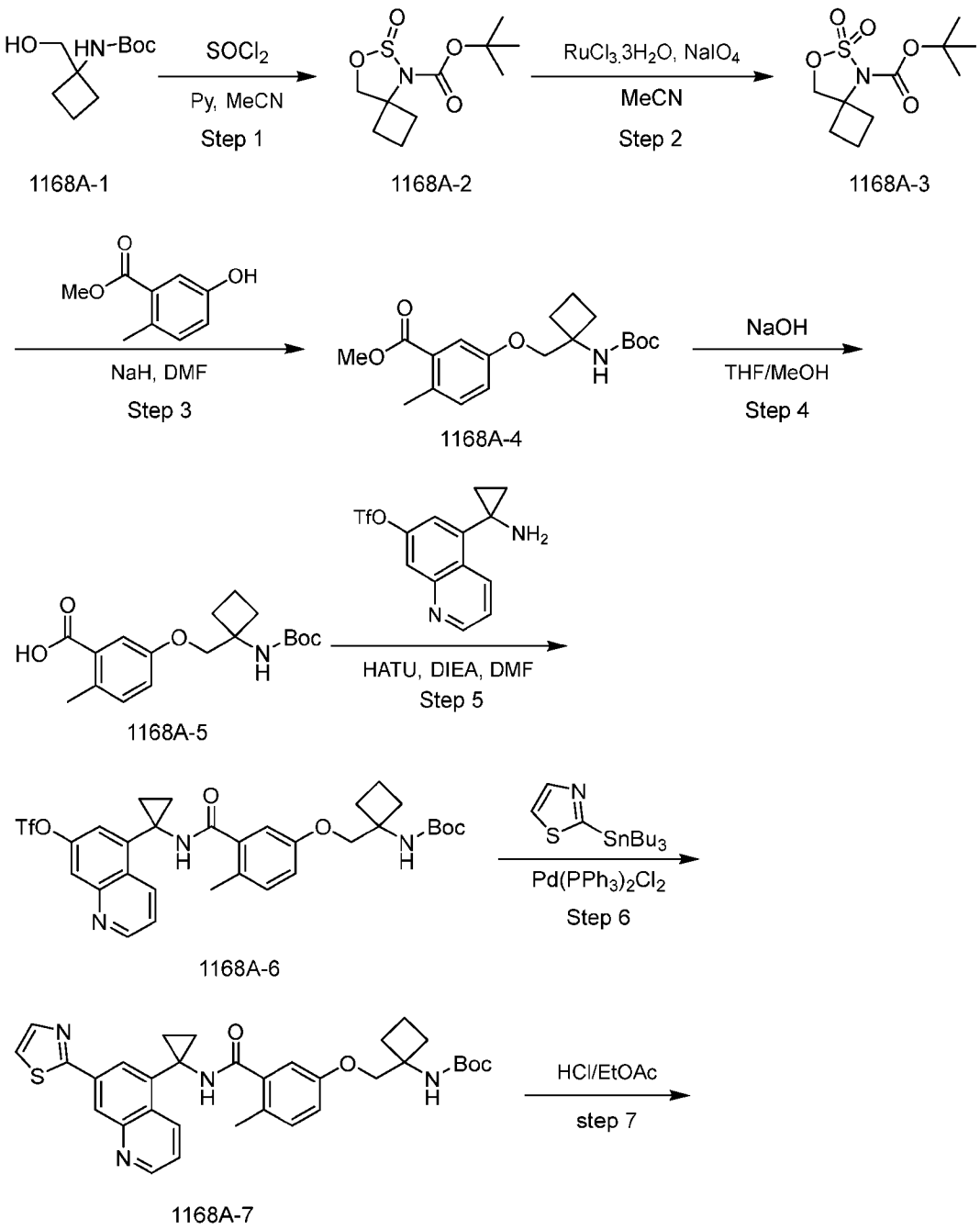
Step 5: 2-Methyl-*N*-(1-(2-methyl-7-(2-methyloxazol-5-yl)quinolin-5-yl)cyclopropyl)-5-(piperazin-1-yl)benzamide (1139A-5)

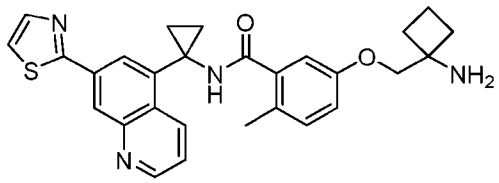
To a solution of *tert*-butyl 4-(4-methyl-3-((1-(2-methyl-7-(2-methyloxazol-5-yl)quinolin-5-yl)cyclopropyl)carbamoyl)phenyl)piperazine-1-carboxylate (80.0 mg, 138 μmol, 1.0 eq) in EtOAc (3.0 mL) was added HCl/EtOAc (4 M, 1.0 mL). The resulting mixture was stirred at 25 °C for 30 min. LCMS indicated that the starting material was completely consumed, and the desired mass was detected. The reaction mixture was concentrated under vacuum to give 2-methyl-*N*-(1-(2-methyl-7-(2-methyloxazol-5-yl)quinolin-5-yl)cyclopropyl)-5-(piperazin-1-yl)benzamide (60.0 mg, HCl salt) as a yellow solid, which was used in the next step without any further purification. M + H^+ = 482.4 (LCMS).

Step 6: 2-Methyl-*N*-(1-(2-methyl-7-(2-methyloxazol-5-yl)quinolin-5-yl)cyclopropyl)-5-(4-methylpiperazin-1-yl)benzamide (Compound 1139)

To a solution of 2-methyl-*N*-(1-(2-methyl-7-(2-methyloxazol-5-yl)quinolin-5-yl)cyclopropyl)-5-(piperazin-1-yl)benzamide (60.0 mg, HCl salt) in MeOH (2.0 mL) was added TEA (50.0 μL), followed by the addition of formaldehyde (19.0 mg, 232 μmol, 17.2 μL, 37% wt % in water, 2.0 eq). The resulting mixture was adjusted to pH to 6 with a small amount of AcOH. The mixture was stirred at 20 °C for 30 min, then $NaBH_3CN$ (14.5 mg, 232 μmol, 2.0 eq) was added. The resulting reaction mixture was stirred at 20 °C for another 16 h. LCMS indicated that the starting material was completely consumed, and the desired mass was detected. The mixture was treated with H_2O (2.0 mL) and extracted with DCM (1.0 mL x 5). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum to give a residue which was purified by preparative HPLC (Waters Xbridge BEH C18 column (100 × 30 mm, 10 μm); flow rate: 25 mL/min; gradient: 20% – 50% B over 8 min; mobile phase A: 0.05% aqueous HCl, mobile phase B: acetonitrile). 2-Methyl-*N*-(1-(2-methyl-7-(2-methyloxazol-5-yl)quinolin-5-yl)cyclopropyl)-5-(4-methylpiperazin-1-yl)benzamide (14.0 mg, 26.3 μmol, 23% yield) was obtained as a yellow solid. M + H^+ = 496.3 (LCMS); ^1H NMR (400 MHz, DMSO-d_6) δ 9.07 (s, 1H), 8.94 (d, J = 8.8 Hz, 1H), 8.14 – 8.00 (m, 2H), 7.78 (s, 1H), 7.47 (d, J = 8.8 Hz, 1H), 6.96 (d, J = 8.5 Hz, 1H), 6.83 (dd, J = 2.7, 8.4 Hz, 1H), 6.57 (d, J = 2.6 Hz, 1H), 3.03 – 2.97 (m, 4H), 2.67 (s, 3H), 2.55 (s, 3H), 2.42 – 2.37 (m, 4H), 2.19 (s, 3H), 1.91 (s, 3H), 1.36 (br s, 2H), 1.25 (br s, 2H).

Example 12: 5-((1-Aminocyclobutyl)methoxy)-2-methyl-*N*-(1-(7-(thiazol-2-yl)quinolin -5-yl)cyclopropyl)benzamide (Compound 1168)





Compound 1168

Step 1: *tert*-Butyl 7-oxa-6-thia-5-azaspiro[3.4]octane-5-carboxylate 6-oxide (1168A-2)

A solution of $SOCl_2$ (1.48 g, 12.4 mmol, 902 µL, 2.5 eq) in MeCN (15 mL) was cooled to -40 °C under a N_2 atmosphere, then *tert*-butyl (1-(hydroxymethyl)cyclobutyl)carbamate (1.00 g, 4.97 mmol, 1.0 eq) in MeCN (10 mL) was added dropwise. The resulting mixture was stirred at -40 °C for 1 h, then pyridine (1.97 g, 24.8 mmol, 2.00 mL, 5.0 eq) was added. The resulting mixture was stirred at -40 °C for 30 min. TLC indicated that the starting material was completely consumed. The mixture was allowed to warm to room temperature and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/50. *tert*-Butyl 7-oxa-6-thia-5-azaspiro[3.4]octane-5-carboxylate 6-oxide (650 mg, 2.63 mmol, 53% yield) was obtained as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.94 (d, J = 8.4 Hz, 1H), 4.79 (d, J = 9.2 Hz, 1H), 3.46 – 3.23 (m, 1H), 2.92 – 2.73 (m, 1H), 2.18 – 2.05 (m, 2H), 1.91 (tq, J = 3.2, 10.8 Hz, 1H), 1.72 – 1.64 (m, 1H), 1.56 (s, 9H).

Step 2: *tert*-Butyl 7-oxa-6-thia-5-azaspiro[3.4]octane-5-carboxylate 6,6-dioxide (1168A-3)

To a solution of tert-butyl 7-oxa-6-thia-5-azaspiro[3.4]octane-5-carboxylate 6-oxide (650 mg, 2.63 mmol, 1.0 eq) in MeCN (15 mL) and H_2O (15 mL) were added $RuCl_3.3H_2O$ (7.93 mg, 30.3 µmol, 0.01 eq) and $NaIO_4$ (618 mg, 3.34 mmol, 1.1 eq) at 0 °C. The resulting mixture was stirred at 0 °C for 30 min. TLC indicated that the starting material was completely consumed. The mixture was allowed to warm to room temperature, poured into saturated aqueous $Na_2S_2O_3$ (10 mL), and extracted with DCM (10 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum to give *tert*-butyl 7-oxa-6-thia-5-azaspiro[3.4]octane-5-carboxylate 6,6-dioxide (500 mg, 1.65 mmol, 63% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.54 (s, 2H), 3.21 – 3.09 (m, 2H), 2.21 – 2.08 (m, 2H), 1.97 (td, J = 3.4, 11.5 Hz, 1H), 1.70 (td, J = 9.2, 11.7 Hz, 1H), 1.58 (s, 9H).

Step 3: Methyl 5-((1-((*tert*-butoxycarbonyl)amino)cyclobutyl)methoxy)-2-methylbenzoate (1168A-4)

A solution of methyl 5-hydroxy-2-methyl-benzoate (300 mg, 1.81 mmol, 1.0 eq) in DMF (20 mL) was degassed and purged with N_2 for three times, then NaH (108 mg, 2.71 mmol, 60% wt % in mineral oil, 1.5 eq) was added under a N_2 atmosphere at 0 °C. The mixture was stirred at the same temperature for 30 min, then *tert*-butyl 7-oxa-6-thia-5-azaspiro [3.4]octane-5-carboxylate 6,6-dioxide (500 mg, 1.99 mmol, 1.1 eq) was added. The mixture was stirred at 70 °C for 2 h. TLC indicated that the starting material was completely consumed, and the desired mass was detected. The reaction mixture was allowed to cool to room temperature, poured into cold water (30 mL) and extracted with EtOAc (25 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 1/100 to 1/5. Methyl 5-((1-((*tert*-butoxycarbonyl)amino)cyclobutyl)methoxy)-2-methylbenzoate (350 mg, 963 µmol, 67% yield) was obtained as a colorless oil.

Step 4: 5-((1-((*tert*-Butoxycarbonyl)amino)cyclobutyl)methoxy)-2-methylbenzoic acid (1168A-5)

To a solution of methyl 5-((1-((*tert*-butoxycarbonyl)amino)cyclobutyl)methoxy)-2-methylbenzoate (350 mg, 963 µmol, 1.0 eq) in THF (4 mL) and MeOH (1.5 mL) was added NaOH (2 M aqueous, 1.50 mL, 3.0 eq), then the mixture was stirred at 70 °C for 2 h. LCMS indicated that the starting material was completely consumed, and the desired mass was detected. The reaction mixture was allowed to cool to room temperature, poured into water (5.0 mL) and extracted with TBME (5.0 mL x 2). The aqueous phase was adjusted to pH 4 by adding HCl (1 M aqueous) and extracted with DCM (5.0 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum to give the crude 5-((1-((*tert*-butoxycarbonyl)amino)cyclobutyl)methoxy)-2-methylbenzoic acid (350 mg) as a white solid. M + Na^+ = 358.2 (LCMS).

Step 5: 5-(1-(5-((1-((*tert*-Butoxycarbonyl)amino)cyclobutyl)methoxy)-2-methylbenzamido)cyclopropyl)quinolin-7-yl trifluoromethanesulfonate (1168A-6)

To a mixture of 5-((1-((*tert*-butoxycarbonyl)amino)cyclobutyl)methoxy)-2-methylbenzoic acid (200 mg, 596 µmol, 1.0 eq) and 5-(1-aminocyclopropyl)quinolin-7-yl trifluoromethan esulfonate (198 mg, 596 µmol, 1.0 eq) in DMF (10 mL) were added HATU (453 mg, 1.19 mmol, 2.0 eq) and DIEA (231 mg, 1.79 mmol, 312 µL, 3.0 eq), then the mixture was stirred at 20 °C for 1 h.

LCMS indicated that the starting material was completely consumed, and the desired mass was detected. The reaction mixture was poured into cold water (10 mL) and extracted with EtOAc (15 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 1/100 to 1/2. 5-(1-(5-((1-((*tert*-Butoxycarbonyl)amino)cyclobutyl)methoxy)-2-methylbenzamido)cyclopropyl)quino lin-7-yl trifluoromethanesulfonate (300 mg) was obtained as a white solid. M + Na^+ = 672.3 (LCMS).

Step 6: *tert*-Butyl (1-((4-methyl-3-((1-(7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)carbamoyl)phenoxy)methyl)cyclobutyl)carbamate (1168A-7)

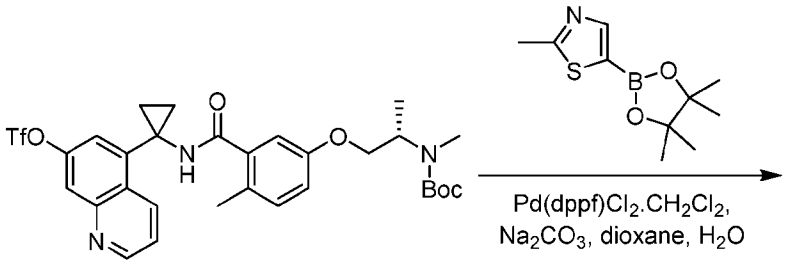
To a mixture of 5-(1-(5-((1-((tert-butoxycarbonyl)amino)cyclobutyl)methoxy)-2-methylbenzamido)cyclopropyl)quino lin-7-yl trifluoromethanesulfonate (180 mg, 277 μmol, 1.0 eq) and 2-(tributylstannyl)thiazole (207 mg, 554 μmol, 2.0 eq) in DMF (10 mL) was added $Pd(PPh_3)_2Cl_2$ (19.5 mg, 27.7 μmol, 0.1 eq). The mixture was degassed and purged with N_2 for three times, and the mixture was stirred at 60 °C for 2 h under a N_2 atmosphere. LCMS indicated that the starting material was completely consumed, and the desired mass was detected. The reaction mixture was allowed to cool to room temperature, poured into water (10 mL) and extracted with EtOAc (15 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 1/100 to 1/1. *tert*-Butyl (1-((4-methyl-3-((1-(7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)carbamoyl)phenoxy)methyl)cyclobutyl)carbamate (230 mg) was obtained as a white solid. M + H^+ = 585.4 (LCMS).

Step 7: 5-((1-Aminocyclobutyl)methoxy)-2-methyl-*N*-(1-(7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)benzamide (Compound 1168)

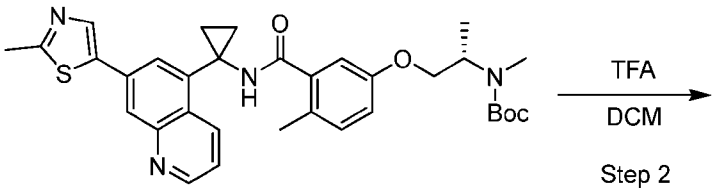
To a solution of *tert*-butyl (1-((4-methyl-3-((1-(7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)carbamoyl)phenoxy)methyl)cyclobutyl)carbamate (180 mg, 308 μmol, 1.0 eq) in EtOAc (3.0 mL), and added HCl/EtOAc (4 M, 6.0 mL), then the mixture was stirred at 20 °C for 1 h. LCMS indicated that the starting material was completely consumed, and the desired mass was detected. The reaction mixture was concentrated under vacuum to give a residue which was purified by preparative HPLC (Phenomenex Gemini C18 column (75 × 30 mm, 3 μm); flow rate: 25 mL/min; gradient: 5% – 35% B over 8 min; mobile phase A: 0.04% aqueous HCl, mobile phase B: acetonitrile). 5-((1-Aminocyclobutyl)methoxy)-2-methyl-*N*-(1-(7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)benzamide (48.3 mg, 92.4 μmol, 30% yield, HCl salt) was obtained

as a white solid. M + H$^+$ = 485.2 (LCMS); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.45 (d, J = 8.5 Hz, 1H), 9.32 (s, 1H), 9.17 (dd, J = 1.2, 4.6 Hz, 1H), 8.66 – 8.48 (m, 2H), 8.10 (d, J = 3.3 Hz, 1H), 7.99 (d, J = 3.3 Hz, 1H), 7.91 (dd, J = 4.8, 8.6 Hz, 1H), 7.09 (d, J = 8.5 Hz, 1H), 6.93 (dd, J = 2.8, 8.4 Hz, 1H), 6.75 (d, J = 2.6 Hz, 1H), 4.10 (s, 2H), 2.32 – 2.23 (m, 2H), 2.08 (br d, J = 5.4 Hz, 2H), 1.97 (s, 3H), 1.94 – 1.84 (m, 2H), 1.51 – 1.31 (m, 4H).

Example 13: (*S*)-2-Methyl-5-(2-(methylamino)propoxy)-*N*-(1-(7-(2-methylthiazol-5-yl)quinolin-5-yl)cyclopropyl)benzamide (Compound 839)



0839A-1



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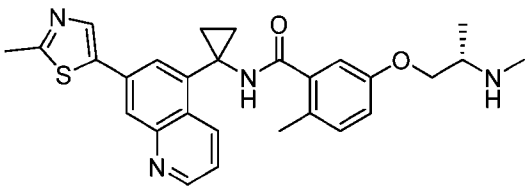


Compound 0839

Step 1: *tert*-Butyl (*S*)-methyl(1-(4-methyl-3-((1-(7-(2-methylthiazol-5-yl)quinolin-5-yl)cyclopropyl)carbamoyl)phenoxy)propan-2-yl)carbamate (839A-2)

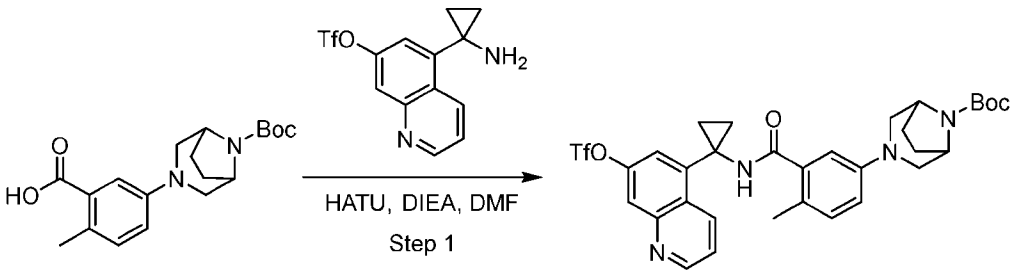
A solution of (*S*)-5-(1-(5-(2-((*tert*-butoxycarbonyl)(methyl)amino)propoxy)-2-methylbenzamido)cyclopropyl)quinolin-7-yl trifluoromethanesulfonate (100 mg, 156 μmol, 1.0 eq), 2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiazole (35.3 mg, 156 μmol, 1.0

eq), $Pd(dppf)Cl_2.CH_2Cl_2$ (11.5 mg, 15.6 μmol, 0.1 eq), and Na_2CO_3 (49.9 mg, 470 μmol, 3.0 eq) in dioxane (2.0 mL) and H_2O (200 μL) was stirred at 80 °C under a N_2 atmosphere for 12 h. LCMS indicated that the starting material was completely consumed. The reaction was allowed to cool to room temperature, poured into H_2O (30 mL), and extracted with EtOAc (20 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum to give *tert*-butyl (*S*)-methyl(1-(4-methyl-3-((1-(7-(2-methylthiazol-5-yl)quinolin-5-yl)cyclopropyl)carbamoyl)phenoxy)propan-2-yl)carbamate (150 mg) as a yellow oil. M + H^+ = 587.3 (LCMS).

Step 2: (*S*)-2-Methyl-5-(2-(methylamino)propoxy)-*N*-(1-(7-(2-methylthiazol-5-yl)quinolin-5-yl)cyclopropyl)benzamide (Compound 839)

To a solution of *tert*-butyl (*S*)-methyl(1-(4-methyl-3-((1-(7-(2-methylthiazol-5-yl)quinolin-5-yl)cyclopropyl)carbamoyl)phenoxy)propan-2-yl)carbamate (100 mg, 170 μmol, 1.0 eq) in DCM (2.0 mL) was added TFA (500 μL). The mixture was stirred at 20 °C for 1 h. LCMS indicated that the starting material was completely consumed, and the desired mass was detected. The mixture was concentrated under vacuum to give a residue which was purified by preparative HPLC (Phenomenex Luna C18 column (100 × 40 mm, 5 μm); flow rate: 25 mL/min; gradient: 1% – 35% B over 8 min; mobile phase A: 0.1% aqueous TFA, mobile phase B: acetonitrile). *(S)*-2-Methyl-5-(2-(methylamino)propoxy)-*N*-(1-(7-(2-methylthiazol-5-yl)quinolin-5-yl)cyclopropyl)benzamide (39.1 mg, 65.1 μmol, 38% yield, TFA salt) was obtained as a yellow solid. M + H^+ = 487.2 (LCMS); ^1H NMR (400 MHz, DMSO-d_6) δ 9.19 (s, 1H), 9.09 (d, *J* = 8.5 Hz, 1H), 8.97 (dd, *J* = 1.4, 4.2 Hz, 1H), 8.61 – 8.45 (m, 2H), 8.31 (s, 1H), 8.12 (s, 2H), 7.64 (dd, *J* = 4.3, 8.5 Hz, 1H), 7.09 (d, *J* = 8.5 Hz, 1H), 6.91 (dd, *J* = 2.8, 8.4 Hz, 1H), 6.68 (d, *J* = 2.6 Hz, 1H), 4.10 (dd, *J* = 3.6, 10.8 Hz, 1H), 3.95 (dd, *J* = 6.3, 10.7 Hz, 1H), 3.53 (br dd, *J* = 4.4, 10.2 Hz, 1H), 2.74 (s, 3H), 2.57 (t, *J* = 5.4 Hz, 3H), 1.97 (s, 3H), 1.39 (br s, 2H), 1.34 (br s, 2H), 1.25 (d, *J* = 6.8 Hz, 3H).

Example 14: 2-Methyl-*N*-(1-(7-(1-methyl-1H-pyrazol-4-yl)quinolin-5-yl)cyclopropyl)-5-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)benzamide (Compound 1077)



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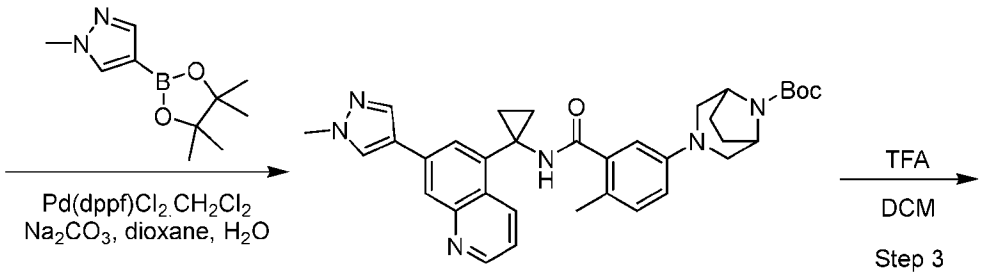

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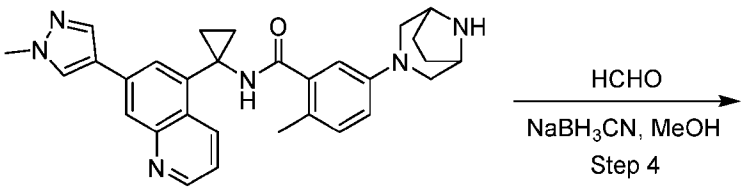
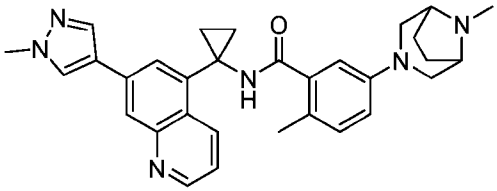


1077A-3



Compound 1077

Step 1: *tert*-Butyl 3-(4-methyl-3-((1-(7-(((trifluoromethyl)sulfonyl)oxy)quinolin-5-yl)cyclopropyl)carbamoyl)phenyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1077A-1)

To a solution of 5-(8-*tert*-butoxycarbonyl-3,8-diazabicyclo[3.2.1]octan-3-yl)-2-methyl-benzoic acid (700 mg, 2.02 mmol, 1.0 eq) and 5-(1-aminocyclopropyl)quinolin-7-yl trifluoromethanesulfonate (671 mg, 2.02 mmol, 1.0 eq) in DMF (10 mL) were added HATU (1.54 g, 4.04 mmol, 2.0 eq) and DIEA (783 mg, 6.06 mmol, 1.00 mL, 3.0 eq) at 20 °C. The mixture was stirred at 20 °C for 1 h. LCMS indicated that the starting material was completely consumed, and 28% of desired compound was detected. The reaction mixture was diluted with H_2O (30 mL) and extracted with EtOAc (30 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 1/100 to 1/3. *tert*-Butyl 3-(4-methyl-3-((1-(7-(((trifluoromethyl)sulfonyl)oxy)quinolin-5-yl)cyclopropyl)carbamoyl)phenyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (800 mg, 1.21 mmol, 59% yield) was obtained as a yellow solid. M + H^+ = 661.3 (LCMS); ^1H NMR (400 MHz, $CDCl_3$) δ 9.15 – 8.97 (m, 2H), 8.04 – 7.86 (m, 2H), 7.56 (dd, *J* = 4.3, 8.6 Hz, 1H), 6.97 (d, *J* = 8.5 Hz, 1H), 6.70 (dd, J = 2.5, 8.5 Hz, 1H), 6.61 – 6.49 (m, 2H), 4.29 (br s, 2H), 3.25 (br d, J = 10.8 Hz, 2H), 2.86 (br s, 2H), 2.05 (s, 3H), 1.89 (br d, *J* = 4.8 Hz, 2H), 1.76 (br d, *J* = 6.3 Hz, 2H), 1.67 – 1.61 (m, 2H), 1.45 (s, 9H), 1.43 – 1.38 (m, 2H).

Step 2: *tert*-Butyl 3-(4-methyl-3-((1-(7-(1-methyl-1H-pyrazol-4-yl)quinolin-5-yl)cyclopropyl)carbamoyl)phenyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1077A-2)

To a solution of *tert*-butyl 3-(4-methyl-3-((1-(7-(((trifluoromethyl)sulfonyl)oxy)quinolin-5-yl)cyclopropyl)carbamoyl)phenyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (300 mg, 454 µmol, 1.0 eq) and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (141 mg, 681 µmol, 1.5 eq) in dioxane (10 mL) and H_2O (1.0 mL) were added Na_2CO_3 (110 mg, 1.04 mmol, 2.3 eq) and $Pd(dppf)Cl_2.CH_2Cl_2$ (37.0 mg, 45.4 µmol, 0.1 eq) at 20 °C. The mixture was stirred at 80 °C for 12 h under a N_2 atmosphere. LCMS indicated that the starting material was completely consumed, and 81% of desired compound was detected. The reaction was allowed to cool to room temperature, diluted with H_2O (20 mL), and extracted with EtOAc (20 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum to give a residue. *tert*-Butyl 3-(4-methyl-3-((1-(7-(1-methyl-1H-pyrazol-4-yl)quinolin-5-yl)cyclopropyl)carbamoyl)phenyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (400 mg, crude) was obtained as a black oil. M + H^+ = 593.4 (LCMS).

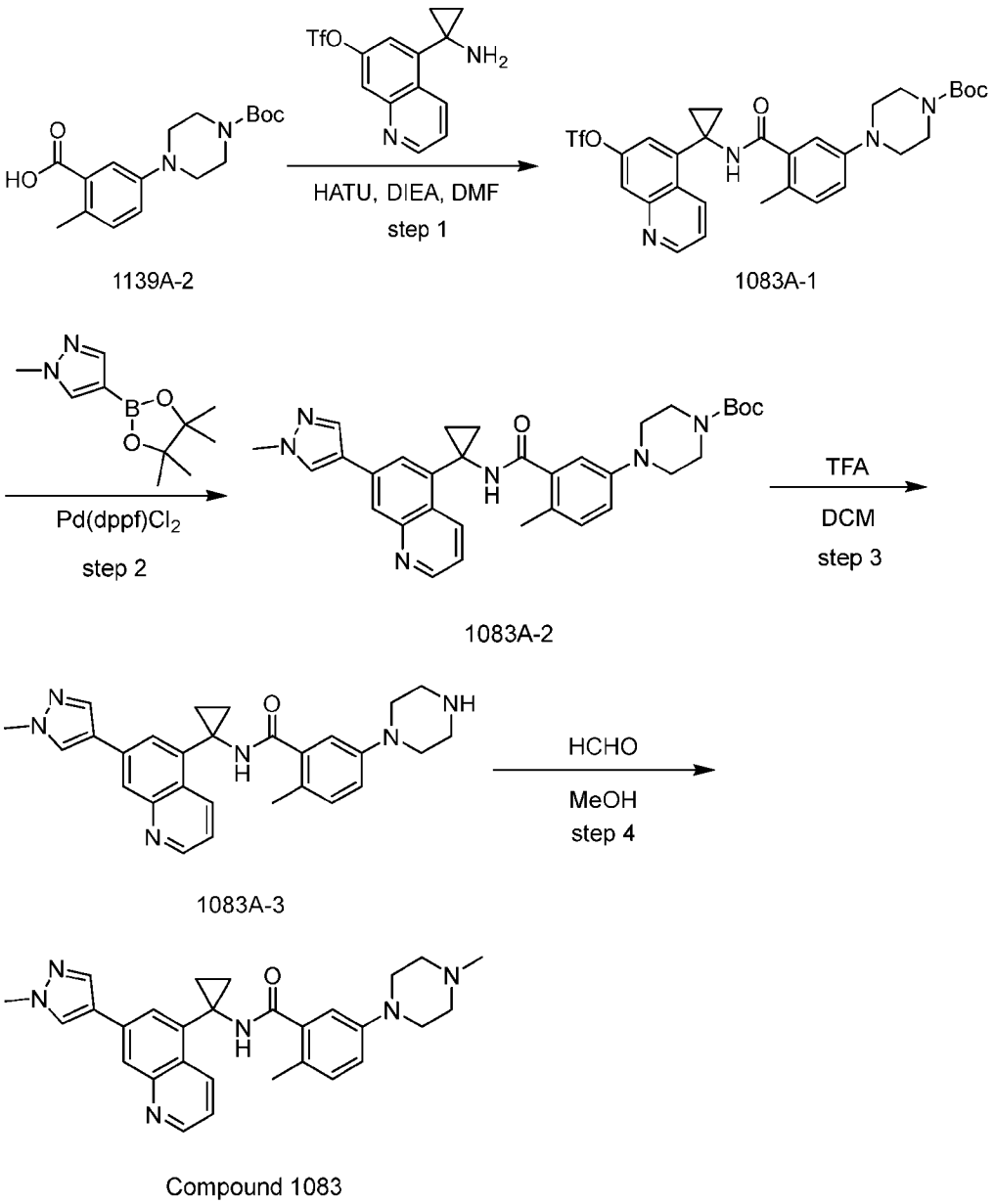
Step 3: 5-(3,8-Diazabicyclo[3.2.1]octan-3-yl)-2-methyl-*N*-(1-(7-(1-methyl-1H-pyrazol-4-yl)quinolin-5-yl)cyclopropyl)benzamide (1077A-3)

To a solution of *tert*-butyl 3-(4-methyl-3-((1-(7-(1-methyl-1H-pyrazol-4-yl)quinolin-5-yl)cyclopropyl)carbamoyl)phenyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (300 mg, 506 µmol, 1.0 eq) in DCM (5.0 mL) was added TFA (1.46 g, 12.8 mmol, 952 µL, 25 eq) at 20 °C. The mixture was stirred at 20 °C for 1 h. LCMS indicated that the starting material was completely consumed, and 67% of desired compound was detected. The reaction mixture was concentrated under vacuum to give 5-(3,8-diazabicyclo[3.2.1]octan-3-yl)-2-methyl-*N*-(1-(7-(1-methyl-1H-pyrazol-4-yl)quinolin-5-yl)cyclopropyl)benzamide (300 mg, crude, TFA salt) as a black oil. M + H^+ = 493.3 (LCMS).

Step 4: 2-Methyl-*N*-(1-(7-(1-methyl-1H-pyrazol-4-yl)quinolin-5-yl)cyclopropyl)-5-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)benzamide (Compound 1077)

To a solution of 5-(3,8-diazabicyclo[3.2.1]octan-3-yl)-2-methyl-*N*-(1-(7-(1-methyl-1H-pyrazol-4-yl)quinolin-5-yl)cyclopropyl)benzamide (300 mg, 609 µmol, 1.0 eq) in MeOH (3.0 mL) was added TEA (61.6 mg, 609 µmol, 84.0 µL, 1.0 eq), followed by formaldehyde (98.8 mg, 1.22 mmol, 90.0 µL, 37% wt % in water, 2.0 eq). The resulting mixture was adjusted to pH to 6 with a small amount of AcOH, then $NaBH_3CN$ (114 mg, 1.83 mmol, 3.0 eq) was added. The mixture was stirred at 20 °C for another 12 h. LCMS indicated that the starting material was completely consumed, and 68% of desired compound was detected. The reaction was filtered. The filtrate was purified by preparative HPLC (Phenomenex Gemini C18 column (75 × 30 mm, 3 µm); flow rate: 25 mL/min; gradient: 5% – 35% B over 8 min; mobile phase A: 0.1% aqueous TFA, mobile phase B: acetonitrile). 2-Methyl-*N*-(1-(7-(1-methyl-1H-pyrazol-4-yl)quinolin-5-yl)cyclopropyl)-5-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)benzamide (150 mg, 239 µmol, 39% yield, TFA salt) was obtained as a yellow solid. M + H^+ = 507.4 (LCMS); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.85 (br s, 1H), 9.20 (br d, J = 8.5 Hz, 1H), 9.10 (s, 1H), 8.99 (d, J = 3.8 Hz, 1H), 8.45 (s, 1H), 8.16 – 8.08 (m, 3H), 7.66 (dd, J = 4.5, 8.4 Hz, 1H), 7.00 (d, J = 8.5 Hz, 1H), 6.82 (dd, J = 2.6, 8.4 Hz, 1H), 6.58 (d, J = 2.5 Hz, 1H), 4.01 (br s, 2H), 3.93 (s, 3H), 3.59 (br d, J = 11.1 Hz, 2H), 2.97 (br d, J = 12.3 Hz, 2H), 2.75 (d, J = 4.9 Hz, 3H), 2.22 – 2.11 (m, 2H), 1.96 – 1.86 (m, 5H), 1.43 – 1.30 (m, 4H).

Example 15: 2-Methyl-*N*-(1-(7-(1-methyl-1H-pyrazol-4-yl)quinolin-5-yl)cyclopropyl)-5-(4-methylpiperazin-1-yl)benzamide (Compound 1083)



Step 1: *tert*-Butyl 4-(4-methyl-3-((1-(7-(((trifluoromethyl)sulfonyl)oxy)quinolin-5-yl)cyclopropyl)carbamoyl)phenyl)piperazine-1-carboxylate (1083A-1)

To a solution of 5-(4-*tert*-butoxycarbonylpiperazin-1-yl)-2-methylbenzoic acid (964 mg, 3.01 mmol, 1.0 eq) and 5-(1-aminocyclopropyl)quinolin-7-yl trifluoromethanesulfonate (1.00 g, 3.01

mmol, 1.0 eq) in DMF (10 mL) were added HATU (2.29 g, 6.02 mmol, 2.0 eq) and DIEA (1.17 g, 9.03 mmol, 1.57 mL, 3.0 eq). The mixture was stirred at 20 °C for 1 h. LCMS indicated that the starting material was completely consumed, and 26% of desired compound was detected. The reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (30 mL x 3), dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 1/100 to 1/3. *tert*-Butyl 4-(4-methyl-3-((1-(7-(((trifluoromethyl)sulfonyl)oxy)quinolin-5-yl)cyclopropyl) carbamoyl)phenyl)piperazine-1-carboxylate (1.26 g, 1.99 mmol, 65% yield) was obtained as a yellow oil. M + H^+ = 635.3 (LCMS).

Step 2: *tert*-Butyl 4-(4-methyl-3-((1-(7-(1-methyl-1H-pyrazol-4-yl)quinolin-5-yl)cyclopropyl)carbamoyl)phenyl)piperazine-1-carboxylate (1083A-2)

To a solution of *tert*-butyl 4-(4-methyl-3-((1-(7-(((trifluoromethyl)sulfonyl)oxy)quinolin-5-yl)cyclopropyl)carbamoyl)phenyl)piperazine-1-carboxylate (200 mg, 315 µmol, 1.0 eq), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (65.5 mg, 315 µmol, 1.0 eq) in dioxane (2.0 mL) and H_2O (200 µL) were added Cs_2CO_3 (256 mg, 787 µmol, 2.5 eq) and XPhos Pd G3 (24.0 mg, 28.3 µmol, 0.1 eq). The mixture was stirred at 90 °C for 12 h under a N_2 atmosphere. LCMS indicated that the starting material was completely consumed, and 68% of desired compound was detected. The reaction was allowed to cool to room temperature, diluted with H_2O (5.0 ml), and extracted with EtOAc (5.0 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum to give *tert*-butyl 4-(4-methyl-3-((1-(7-(1-methyl-1H-pyrazol-4-yl)quinolin-5-yl)cyclopropyl)carbamoyl) phenyl)piperazine-1-carboxylate (250 mg, crude) as a yellow solid. M + H^+ = 567.4 (LCMS).

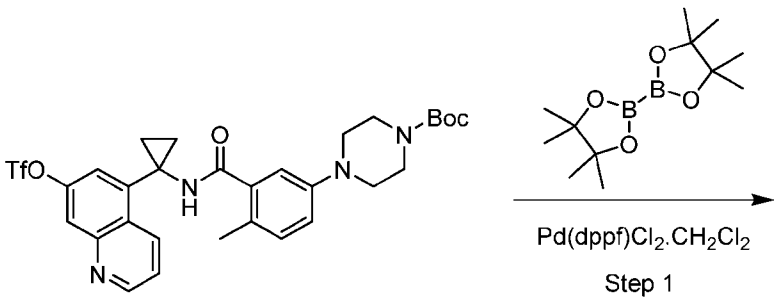
Step 3: 2-Methyl-*N*-(1-(7-(1-methyl-1H-pyrazol-4-yl)quinolin-5-yl)cyclopropyl)-5-(piperazin-1-yl)benzamide (1083A-3)

To a solution of *tert*-butyl 4-(4-methyl-3-((1-(7-(1-methyl-1H-pyrazol-4-yl)quinolin-5-yl)cyclopropyl)carbamoyl)phenyl)piperazine-1-carboxylate (250 mg, 441 µmol, 1.0 eq) in DCM (1.5 mL) was added TFA (500 µL). The mixture was stirred at 20 °C for 1 h. LCMS indicated that the starting material was completely consumed, and 50% of desired compound was detected. The reaction mixture was concentrated under vacuum to give 2-methyl-*N*-(1-(7-(1-methyl-1H-pyrazol-4-yl)quinolin-5-yl)cyclopropyl)-5-(piperazin-1-yl)benzamide (120 mg, crude, TFA salt) as a yellow solid. M + H^+ = 467.3 (LCMS).

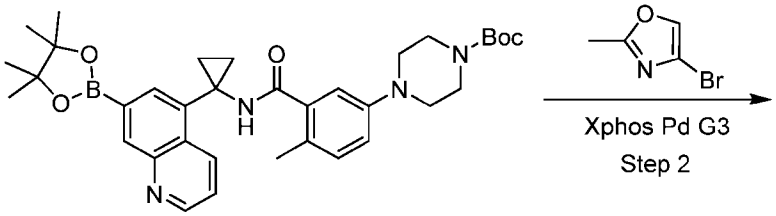
Step 4: 2-Methyl-*N*-(1-(7-(1-methyl-1H-pyrazol-4-yl)quinolin-5-yl)cyclopropyl)-5-(4-methylpiperazin-1-yl)benzamide (Compound 1083)

To a solution of 2-methyl-*N*-(1-(7-(1-methyl-1H-pyrazol-4-yl)quinolin-5-yl)cyclopropyl)-5-(piperazin-1-yl)benzamide (120 mg, 206 μmol, 1.0 eq, TFA) in MeOH (2.0 mL) was added TEA (20.9 mg, 206 μmol, 28.7 μL, 1.0 eq), followed by formaldehyde (33.5 mg, 413 μmol, 30.7 μL, 37% wt % in water, 2.0 eq). The resulting mixture was adjusted to pH to 6 with a small amount of AcOH, then $NaBH_3CN$ (38.9 mg, 620 μmol, 3.0 eq) was added. The mixture was stirred at 20 °C for another 11 h. LCMS indicated that the starting material was completely consumed, and 59% of desired compound was detected. The reaction mixture was filtered, and the filtrate was purified by preparative HPLC (Phenomenex Gemini C18 column (75 × 30 mm, 3 μm); flow rate: 25 mL/min; gradient: 1% – 30% B over 8 min; mobile phase A: 0.1% aqueous TFA, mobile phase B: acetonitrile). 2-Methyl-*N*-(1-(7-(1-methyl-1H-pyrazol-4-yl)quinolin-5-yl)cyclopropyl)-5-(4-methylpiperazin-1-yl)benzamide (20.0 mg, 33.1 μmol, 16% yield, 98% purity, TFA salt) was obtained as a white solid. $M + H^+ = 481.3$ (LCMS); ^1H NMR (400 MHz, DMSO-d_6) δ 9.05 (s, 1H), 9.01 (d, J = 8.5 Hz, 1H), 8.89 – 8.84 (m, 1H), 8.40 (s, 1H), 8.08 (s, 2H), 8.03 (d, J = 1.1 Hz, 1H), 7.49 (dd, J = 4.2, 8.4 Hz, 1H), 6.95 (d, J = 8.5 Hz, 1H), 6.83 (dd, J = 2.4, 8.4 Hz, 1H), 6.57 (d, J = 2.4 Hz, 1H), 3.92 (s, 3H), 3.04 – 2.95 (m, 4H), 2.43 – 2.35 (m, 4H), 2.19 (s, 3H), 1.92 (s, 3H), 1.36 (br s, 2H), 1.29 (br s, 2H).

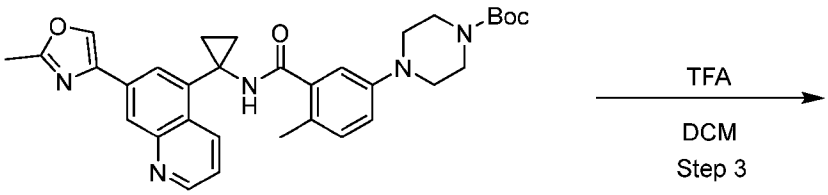
Example 16: 2-Methyl-*N*-(1-(7-(2-methyloxazol-4-yl)quinolin-5-yl)cyclopropyl)-5-(4-methylpiperazin-1-yl)benzamide (Compound 1091)



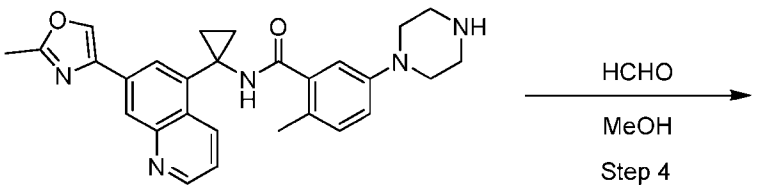
1083A-1



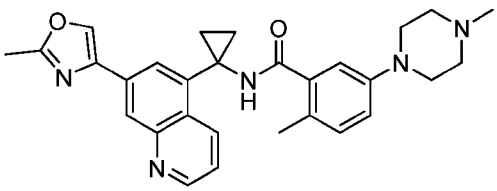
1091A-1



1091A-2



1091A-3



Compound 1091

Step 1: *tert*-Butyl 4-(4-methyl-3-((1-(7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinolin-5-yl)cyclopropyl)carbamoyl)phenyl)piperazine-1-carboxylate (1091A-1)

To a solution of *tert*-butyl 4-(4-methyl-3-((1-(7-(((trifluoromethyl)sulfonyl)oxy)quinolin-5-yl)cyclopropyl)carbamoyl)phenyl)piperazine-1-carboxylate (1.60 g, 2.52 mmol, 1.0 eq), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (640 mg, 2.52 mmol, 1.0 eq) in dioxane (10 mL) were added KOAc (618 mg, 6.30 mmol, 2.5 eq) and $Pd(dppf)Cl_2.CH_2Cl_2$ (205 mg, 252 μmol, 0.1 eq). The resulting mixture was stirred at 80 °C under a N_2 atmosphere for 12 h. LCMS and HPLC indicated that the starting material was completely consumed. The reaction was allowed to cool to room temperature. The reaction mixture was concentrated under vacuum, poured into H_2O (10 mL), and extracted with EtOAc (10 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/2. *tert*-Butyl 4-(4-methyl-3-((1-(7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinolin-5-yl)cyclopropyl) carbamoyl)phenyl)piperazine-1-carboxylate (1.10 g, 2.07 mmol, 82% yield) was obtained as a yellow solid. $M + H^+ = 531.4$ (LCMS).

Step 2: *tert*-Butyl 4-(4-methyl-3-((1-(7-(2-methyloxazol-4-yl)quinolin-5-yl)cyclopropyl)carbamoyl)phenyl)piperazine-1-carboxylate (1091A-2)

To a solution of *tert*-butyl 4-(4-methyl-3-((1-(7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinolin-5-yl)cyclopropyl)carbamoyl)phenyl)piperazine-1-carboxylate (200 mg, 377 μmol, 1.0 eq) and 4-bromo-2-methyloxazole (51.9 mg, 320 μmol, 0.9 eq) in dioxane (2.0 mL) and H_2O (200 μL) were added Cs_2CO_3 (307 mg, 942 μmol, 2.5 eq) and Xphos Pd G3 (28.7 mg, 33.9 μmol, 0.1 eq). The resulting mixture was stirred at 90 °C under a N_2 atmosphere for 12 h. LCMS indicated that the starting material was completely consumed. The reaction was allowed to cool to room temperature, concentrated under vacuum to remove solvent. The reaction mixture was then poured into H_2O (3.0 mL) and extracted with EtOAc (3.0 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 3/5. *tert*-Butyl 4-(4-methyl-3-((1-(7-(2-methyloxazol-4-yl)quinolin-5-yl)cyclopropyl)carbamoyl)phenyl)piperazine-1-carboxylate (118 mg, 207 μmol, 55% yield) was obtained as a yellow solid. $M + H^+ = 568.5$ (LCMS).

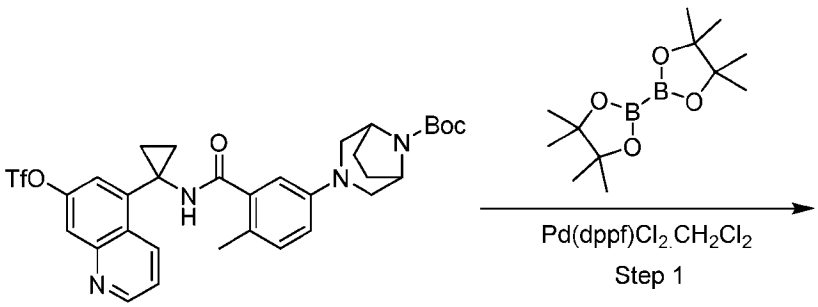
Step 3: 2-Methyl-*N*-(1-(7-(2-methyloxazol-4-yl)quinolin-5-yl)cyclopropyl)-5-(piperazin-1-yl)benzamide (1091A-3)

To a solution of *tert*-butyl 4-(4-methyl-3-((1-(7-(2-methyloxazol-4-yl)quinolin-5-yl)cyclopropyl)carbamoyl)phenyl)piperazine-1-carboxylate (118 mg, 207 µmol, 1.0 eq) in DCM (2.0 mL) was added TFA (500 µL). The resulting mixture was stirred at 20 °C for 1 h. LCMS indicated that the starting material was completely consumed. The reaction mixture was concentrated under vacuum to remove solvent. 2-Methyl-*N*-(1-(7-(2-methyloxazol-4-yl)quinolin-5-yl)cyclopropyl)-5-(piperazin-1-yl)benzamide (90.0 mg, crude, TFA salt) was obtained as a yellow oil. M + H^+ = 468.4 (LCMS).

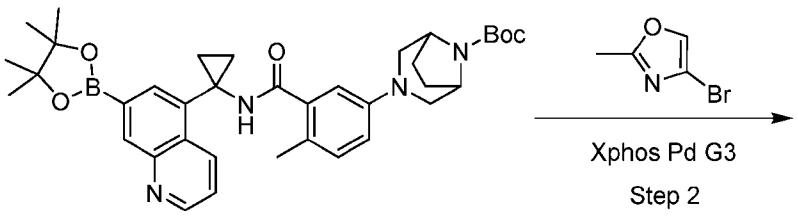
Step 4: 2-Methyl-*N*-(1-(7-(2-methyloxazol-4-yl)quinolin-5-yl)cyclopropyl)-5-(4-methylpiperazin-1-yl)benzamide (Compound 1091)

To a solution of 2-methyl-*N*-(1-(7-(2-methyloxazol-4-yl)quinolin-5-yl)cyclopropyl)-5-(piperazin-1-yl)benzamide (90.0 mg, 154 µmol, 1.0 eq, TFA) in MeOH (2.0 mL) was added TEA (15.6 mg, 154 µmol, 21.5 µL, 1.0 eq), followed by formaldehyde (25.1 mg, 309 µmol, 23.0 µL, 37% wt % in water, 2.0 eq). The resulting mixture was adjusted to pH to 6 with a small amount of AcOH, then $NaBH_3CN$ (29.1 mg, 464 µmol, 3.0 eq) was added. The resulting mixture was stirred at 20 °C for 1 h. LCMS indicated that the starting material was completely consumed, and the desired mass was detected. The mixture was concentrated under vacuum to give a residue which was purified by preparative HPLC (Phenomenex Gemini C18 column (75 × 30 mm, 3 µm); flow rate: 25 mL/min; gradient: 1% – 30% B over 8 min; mobile phase A: 0.1% aqueous TFA, mobile phase B: acetonitrile). 2-Methyl-*N*-(1-(7-(2-methyloxazol-4-yl)quinolin-5-yl)cyclopropyl)-5-(4-methylpiperazin-1-yl)benzamide (56.5 mg, 94.6 µmol, 61% yield, TFA salt) was obtained as a pale yellow solid.. M + H^+ = 482.2 (LCMS); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.75 – 9.60 (m, 1H), 9.19 – 9.08 (m, 2H), 8.98 (d, *J* = 3.1 Hz, 1H), 8.83 – 8.77 (m, 1H), 8.35 – 8.23 (m, 2H), 7.67 – 7.61 (m, 1H), 7.03 (d, *J* = 8.6 Hz, 1H), 6.96 – 6.86 (m, 1H), 6.66 (d, *J* = 2.5 Hz, 1H), 3.71 (br d, *J* = 13.1 Hz, 2H), 3.48 (br d, *J* = 11.8 Hz, 2H), 3.09 (br d, *J* = 10.5 Hz, 2H), 2.87 – 2.79 (m, 5H), 2.56 – 2.52 (m, 3H), 1.96 – 1.90 (m, 3H), 1.42 – 1.27 (m, 4H).

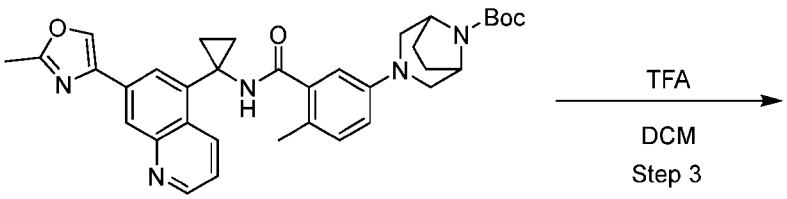
Example 17: 2-Methyl-5-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)-*N*-(1-(7-(2-methyloxazol-4-yl)quinolin-5-yl)cyclopropyl)benzamide (Compound 1096)



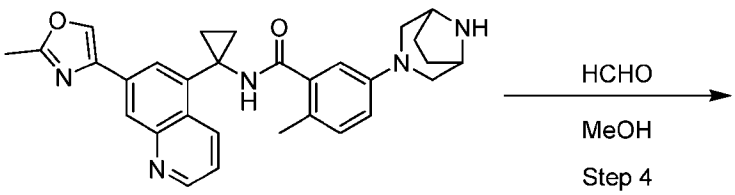
1077A-1



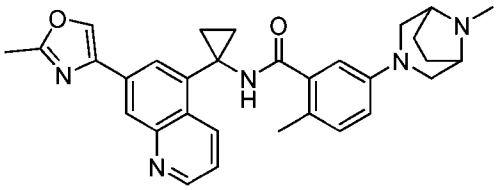
1096A-1



1096A-2



1096A-3



Compound 1096

Step 1: *tert*-Butyl 3-(4-methyl-3-((1-(7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinolin-5-yl)cyclopropyl)carbamoyl)phenyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1096A-1)

To a solution of *tert*-butyl 3-(4-methyl-3-((1-(7-(((trifluoromethyl)sulfonyl)oxy)quinolin-5-yl)cyclopropyl)carbamoyl)phenyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (2.20 g, 3.33 mmol, 1.0 eq) in dioxane (50 mL) were added 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.69 g, 6.66 mmol, 2.0 eq), KOAc (816 mg, 8.32 mmol, 2.5 eq), and $Pd(dppf)Cl_2.CH_2Cl_2$ (271 mg, 332 μmol, 0.1 eq) at 20 °C. The mixture was stirred at 80 °C for 12 h under a N_2 atmosphere. LCMS indicated that the starting material was completely consumed, and 89% of desired compound was detected. The reaction was allowed to cool to room temperature, diluted with H_2O (50 mL), and extracted with EtOAc (50 mL x 4). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 1/100 to 1/1. *tert*-Butyl 3-(4-methyl-3-((1-(7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinolin-5-yl)cyclopropyl)carbamoyl)phenyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.40 g, 2.52 mmol, 75% yield) was obtained as a yellow solid. $M + H^+ = 557.4$ (LCMS).

Step 2: *tert*-Butyl 3-(4-methyl-3-((1-(7-(2-methyloxazol-4-yl)quinolin-5-yl)cyclopropyl)carbamoyl)phenyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1096A-2)

To a solution of *tert*-butyl 3-(4-methyl-3-((1-(7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinolin-5-yl)cyclopropyl)carbamoyl)phenyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (300 mg, 539 μmol, 1.0 eq) and 4-bromo-2-methyloxazole (74.2 mg, 458 μmol, 0.8 eq) in dioxane (5.0 mL) and H_2O (500 μL) were added Cs_2CO_3 (439 mg, 1.35 mmol, 2.5 eq) and XPhos Pd G3 (41.0 mg, 48.5 μmol, 0.1 eq) at 20 °C. The mixture was stirred at 90 °C for 12 h under a N_2 atmosphere. LCMS indicated that the starting material was completely consumed, and 77% of desired compound was detected. The reaction was allowed to cool to room

temperature, diluted with H_2O (20 mL), and extracted with EtOAc (20 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum to give *tert*-butyl 3-(4-methyl-3-((1-(7-(2-methyloxazol-4-yl)quinolin-5-yl)cyclopropyl)carbamoyl) phenyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (400 mg, crude) as a black oil. M + H^+ = 594.4 (LCMS).

Step 3: 5-(3,8-Diazabicyclo[3.2.1]octan-3-yl)-2-methyl-*N*-(1-(7-(2-methyloxazol-4-yl)quinolin-5-yl)cyclopropyl)benzamide (1096A-3)

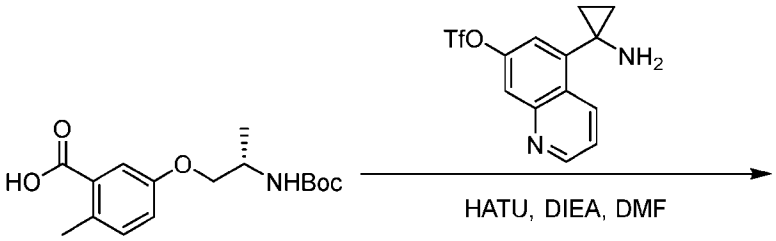
To a solution of *tert*-butyl 3-(4-methyl-3-((1-(7-(2-methyloxazol-4-yl)quinolin-5-yl)cyclopropyl)carbamoyl)phenyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (300 mg, 505 µmol, 1.0 eq) in DCM (5.0 mL) was added TFA (1.46 g, 12.8 mmol, 951 µL, 25 eq) at 20 °C. The mixture was stirred at 20 °C for 1 h. LCMS indicated that the starting material was completely consumed, and 75% of desired compound was detected. The reaction mixture was concentrated under vacuum to give 5-(3,8-diazabicyclo[3.2.1]octan-3-yl)-2-methyl-*N*-(1-(7-(2-methyloxazol-4-yl)quinolin-5-yl)cyclopropyl)benzamide (300 mg, crude, TFA salt) as a black oil. M + H^+ = 494.4 (LCMS).

Step 4: 2-Methyl-5-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)-N-(1-(7-(2-methyloxazol-4-yl)quinolin-5-yl)cyclopropyl)benzamide (Compound 1096)

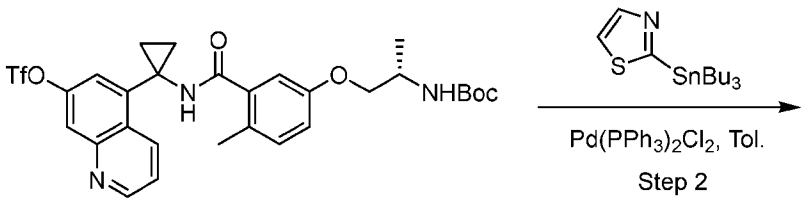
To a solution of 5-(3,8-diazabicyclo[3.2.1]octan-3-yl)-2-methyl-*N*-(1-(7-(2-methyloxazol-4-yl)quinolin-5-yl)cyclopropyl)benzamide (300 mg, 607 µmol, 1.0 eq) in MeOH (5.0 mL) was added TEA (61.5 mg, 607 µmol, 84.0 µL, 1.0 eq), followed by formaldehyde (98.6 mg, 1.22 mmol, 90.0 µL, 37% wt % in water, 2.0 eq). The resulting mixture was adjusted to pH to 6 with a small amount of AcOH, then $NaBH_3CN$ (114 mg, 1.82 mmol, 3.0 eq) was added. The mixture was stirred at 20 °C for another 12 h. LCMS indicated that the starting material was completely consumed, and the desired compound was detected. The reaction was filtered, and the filtrate was purified by preparative HPLC (Phenomenex Gemini C18 column (100 × 40 mm, 3 µm); flow rate: 25 mL/min; gradient: 1% – 30% B over 8 min; mobile phase A: 0.1% aqueous TFA, mobile phase B: acetonitrile). 2-Methyl-5-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)-*N*-(1-(7-(2-methyloxazol-4-yl)quinolin-5-yl)cyclopropyl) benzamide (107 mg, 172 µmol, 28% yield, TFA salt) was obtained as a yellow solid. M + H^+ = 508.3 (LCMS); ^1H NMR (400 MHz, DMSO-d_6) δ 9.93 – 9.80 (m, 1H), 9.21 – 9.08 (m, 2H), 8.99 (d, *J* = 4.3 Hz, 1H), 8.81 (s, 1H), 8.35 – 8.24 (m, 2H), 7.62 (s, 1H), 7.00 (d, *J* = 8.5 Hz, 1H), 6.82 (dd, *J* = 2.4, 8.3 Hz, 1H), 6.58 (d, *J* = 2.4 Hz, 1H), 4.02 (br s, 2H), 3.59 (br d, *J* = 11.5 Hz, 2H), 2.98 (br d, *J* = 12.5 Hz, 2H), 2.75 (d, *J* =

4.9 Hz, 3H), 2.54 (s, 3H), 2.23 – 2.11 (m, 2H), 1.97 – 1.86 (m, 5H), 1.40 (br s, 2H), 1.30 (br s, 2H).

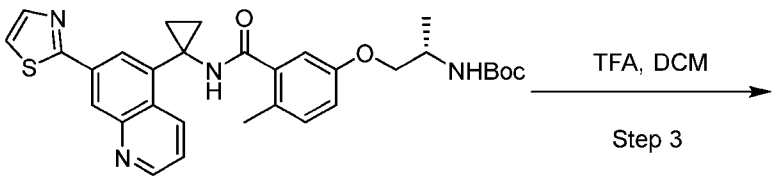
Example 18: (*S*)-5-(2-Aminopropoxy)-2-methyl-*N*-(1-(7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)benzamide (Compound 1128)



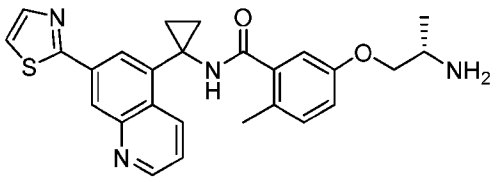
1128A-1



1128A-2



1128A-3



Compound 1128

Step 1: (*S*)-5-(1-(5-(2-((*tert*-Butoxycarbonyl)amino)propoxy)-2-methylbenzamido)cyclopropyl)quinolin-7-yl trifluoromethanesulfonate (1128A-2)

To a solution of 5-(1-aminocyclopropyl)quinolin-7-yl trifluoromethanesulfonate (1.00 g, 3.01 mmol, 1.2 eq) and (*S*)-5-(2-((*tert*-butoxycarbonyl)amino)propoxy)-2-methylbenzoic acid (776 mg, 2.51 mmol, 1.0 eq) in DMF (20 mL) were added DIEA (972 mg, 7.52 mmol, 3.0 eq) and HATU (1.91 g, 5.02 mmol, 2.0 eq). The mixture was stirred at 20 °C for 12 h. LCMS indicated that the starting material was completely consumed. The reaction mixture was poured into H_2O (30 mL) and extracted with EtOAc (20 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/5. (*S*)-5-(1-(5-(2-((*tert*-Butoxycarbonyl)amino)propoxy)-2-methylbenzamido) cyclopropyl)quinolin-7-yl trifluoromethanesulfonate (1.20 g, 1.56 mmol, 62% yield) was obtained as a white solid. M + H^+ = 624.2 (LCMS).

Step 2: *tert*-Butyl (*S*)-(1-(4-methyl-3-((1-(7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl) carbamoyl)phenoxy)propan-2-yl)carbamate (1128A-3)

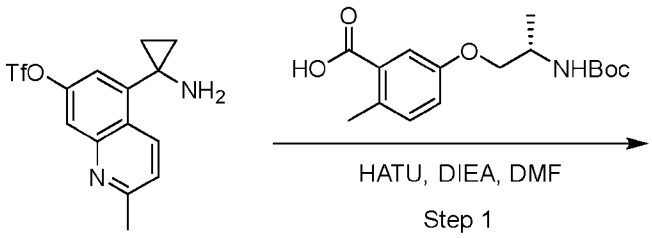
A mixture of (*S*)-5-(1-(5-(2-((*tert*-butoxycarbonyl)amino)propoxy)-2-methylbenzamido) cyclopropyl)quinolin-7-yl trifluoromethanesulfonate (200 mg, 320 μmol, 1.0 eq), 2-(tributylstannyl)thiazole (180 mg, 481 μmol, 1.5 eq), and $Pd(PPh_3)_2Cl_2$ (45.0 mg, 64.1 μmol, 0.2 eq) in toluene (2.0 mL) was stirred at 120 °C under a N_2 atmosphere for 12 h. LCMS indicated that the starting material was completely consumed. The reaction was allowed to cool to room temperature, poured into H_2O (30 mL), and extracted with EtOAc (20 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum to give *tert*-butyl *(S)*-(1-(4-methyl-3-((1-(7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)carbamoyl) phenoxy)propan-2-yl)carbamate (100 mg, crude) as a white solid. M + H^+ = 559.2 (LCMS).

Step 3: (*S*)-5-(2-Aminopropoxy)-2-methyl-*N*-(1-(7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl) benzamide (Compound 1128)

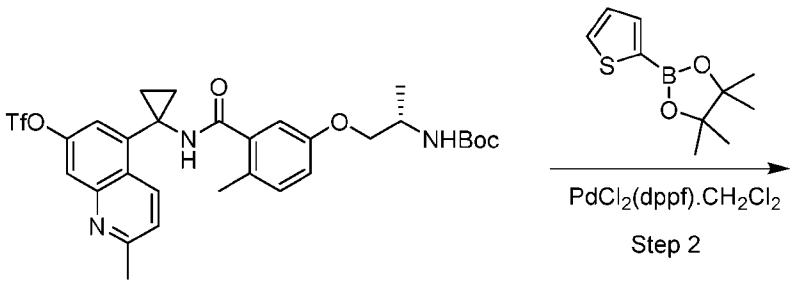
To a solution of *tert*-butyl (S)-(1-(4-methyl-3-((1-(7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl) carbamoyl)phenoxy)propan-2-yl)carbamate (100 mg, 179 μmol, 1.0 eq) in DCM (2.0 mL) was added TFA (204 mg, 1.79 mmol, 10 eq). The mixture was stirred at 20 °C for 30 min. LCMS indicated that the starting material was completely consumed, and the desired mass was detected. The mixture was concentrated under vacuum to give a residue which was purified

by preparative HPLC (Phenomenex Luna C18 column (100 × 40 mm, 3 μm); flow rate: 25 mL/min; gradient: 1% – 35% B over 8 min; mobile phase A: 0.1% aqueous TFA, mobile phase B: acetonitrile). (S)-5-(2-Aminopropoxy)-2-methyl-N-(1-(7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)benzamide (50.1 mg, 87.1 μmol, 48% yield, TFA salt) was obtained as a yellow solid. M + H+ = 459.2 (LCMS); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.23 (s, 1H), 9.14 (d, *J* = 8.5 Hz, 1H), 9.02 (dd, *J* = 1.5, 4.3 Hz, 1H), 8.55 – 8.42 (m, 2H), 8.06 (d, *J* = 3.1 Hz, 1H), 7.94 (d, *J* = 3.3 Hz, 3H), 7.69 (dd, *J* = 4.3, 8.6 Hz, 1H), 7.09 (d, *J* = 8.5 Hz, 1H), 6.90 (dd, *J* = 2.6, 8.4 Hz, 1H), 6.69 (d, *J* = 2.8 Hz, 1H), 4.03 (dd, *J* = 3.9, 10.3 Hz, 1H), 3.85 (dd, *J* = 7.1, 10.3 Hz, 1H), 3.61 – 3.48 (m, 1H), 1.97 (s, 3H), 1.42 (br s, 2H), 1.30 (br s, 2H), 1.22 (d, *J* = 6.6 Hz, 3H).

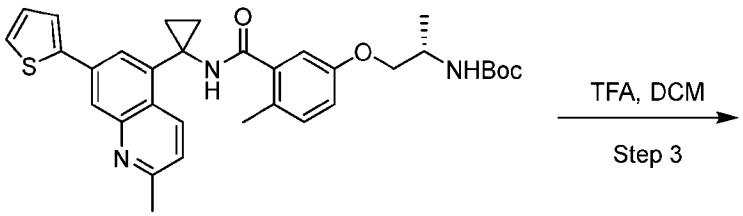
Example 19: (S)-5-(2-Aminopropoxy)-2-methyl-*N*-(1-(2-methyl-7-(thiophen-2-yl)quinolin-5-yl)cyclopropyl)benzamide (Compound 1170)



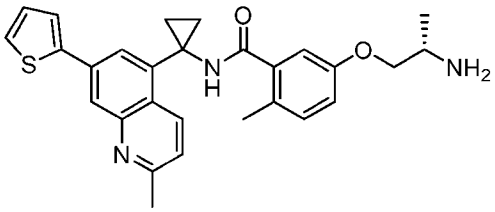
1134A-3



1170A-1



1170A-2



Compound 1170

Step 1: (*S*)-5-(1-(5-(2-((*tert*-Butoxycarbonyl)amino)propoxy)-2-methylbenzamido) cyclopropyl)-2-methylquinolin-7-yl trifluoromethanesulfonate (1170A-1)

To a solution of (*S*)-5-(2-((*tert*-butoxycarbonyl)amino)propoxy)-2-methylbenzoic acid (700 mg, 2.26 mmol, 1.0 eq) in DMF (7.0 mL) were added DIEA (877 mg, 6.79 mmol, 1.20 mL, 3.0 eq) and HATU (1.72 g, 4.53 mmol, 2.0 eq) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min, then 5-(1-aminocyclopropyl)-2-methylquinolin-7-yl trifluoromethanesulfonate (940 mg, 2.72 mmol, 1.2 eq) was added. The mixture was stirred at 20 °C for 12 h. LCMS indicated that the starting material was completely consumed, and 25% of desired compound was detected. The reaction mixture was diluted with H_2O (10 mL), then extracted with EtOAc (10 mL x 4). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/5. (*S*)-5-(1-(5-(2-((*tert*-Butoxycarbonyl)amino)propoxy)-2-methylbenzamido)cyclopropyl)-2-methylquinolin-7-yl trifluoromethanesulfonate (800 mg, 1.25 mmol, 55% yield) was obtained as a yellow solid. M + H^+ = 638.3 (LCMS).

Step 2: *tert*-Butyl (*S*)-(1-(4-methyl-3-((1-(2-methyl-7-(thiophen-2-yl)quinolin-5-yl)cyclopropyl)carbamoyl)phenoxy)propan-2-yl)carbamate (1170A-2)

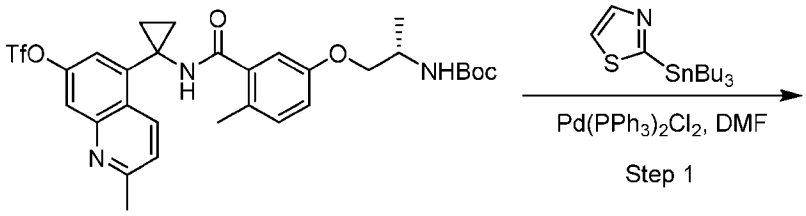
To a solution of (*S*)-5-(1-(5-(2-((*tert*-butoxycarbonyl)amino)propoxy)-2-methylbenzamido)cyclopropyl)-2-methylquinolin-7-yl trifluoromethanesulfonate (200 mg, 313 µmol, 1.0 eq) and 4,4,5,5-tetramethyl-2-(thiophen-2-yl)-1,3,2-dioxaborolane (79.0 mg, 376

μmol, 1.2 eq) in dioxane (5.0 mL) and H_2O (500 μL) were added $PdCl_2(dppf).CH_2Cl_2$ (22.9 mg, 31.3 μmol, 0.1 eq) and Na_2CO_3 (99.7 mg, 940 μmol, 3.0 eq) at 20 °C. The mixture was stirred at 80 °C for 12 h under a N_2 atmosphere. LCMS indicated that the starting material was completely consumed, and 73% of desired compound was detected. The reaction was allowed to cool to room temperature, diluted with H_2O (15 mL), and extracted with EtOAc (15 mL x 4). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum to give *tert*-butyl (*S*)-(1-(4-methyl-3-((1-(2-methyl-7-(thiophen-2-yl)quinolin-5-yl)cyclopropyl)carbamoyl)phenoxy)propan-2-yl)carbamate (170 mg, crude) as a black solid. M + H^+ = 572.4 (LCMS).

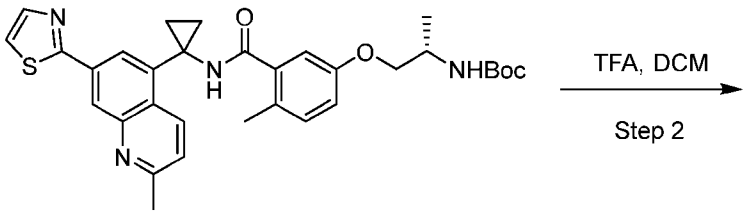
Step 3: (*S*)-5-(2-Aminopropoxy)-2-methyl-*N*-(1-(2-methyl-7-(thiophen-2-yl)quinolin-5-yl)cyclopropyl)benzamide (Compound 1170)

To a solution of *tert*-butyl (*S*)-(1-(4-methyl-3-((1-(2-methyl-7-(thiophen-2-yl)quinolin-5-yl)cyclopropyl)carbamoyl)phenoxy)propan-2-yl)carbamate (170 mg, 297 μmol, 1.0 eq) in DCM (5.0 mL) was added TFA (859 mg, 7.53 mmol, 559 μL, 25 eq) at 20 °C. The mixture was stirred at 20 °C for 1 h. LCMS indicated that the starting material was completely consumed, and 77% of desired compound was detected. The reaction was filtered and the filtrate was purified by preparative HPLC (Phenomenex Gemini C18 column (75 × 30 mm, 3 μm); flow rate: 25 mL/min; gradient: 10% – 40% B over 8 min; mobile phase A: 0.1% aqueous TFA, mobile phase B: acetonitrile). (*S*)-5-(2-Aminopropoxy)-2-methyl-*N*-(1-(2-methyl-7-(thiophen-2-yl)quinolin-5-yl)cyclopropyl)benzamide (164 mg, 278 μmol, 93% yield, TFA salt) was obtained as a yellow solid. M + H^+ = 472.4 (LCMS); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.24 – 9.09 (m, 2H), 8.21 – 8.12 (m, 2H), 7.94 (br d, *J* = 2.4 Hz, 3H), 7.81 (dd, *J* = 0.8, 3.6 Hz, 1H), 7.73 (dd, *J* = 0.8, 5.1 Hz, 1H), 7.65 (br d, *J* = 8.8 Hz, 1H), 7.26 (dd, *J* = 3.6, 5.0 Hz, 1H), 7.09 (d, *J* = 8.5 Hz, 1H), 6.90 (dd, *J* = 2.8, 8.4 Hz, 1H), 6.69 (d, *J* = 2.8 Hz, 1H), 4.03 (dd, *J* = 3.9, 10.3 Hz, 1H), 3.86 (dd, *J* = 7.1, 10.3 Hz, 1H), 3.60 – 3.50 (m, 1H), 2.76 (s, 3H), 1.98 (s, 3H), 1.43 – 1.30 (m, 4H), 1.22 (d, *J* = 6.8 Hz, 3H).

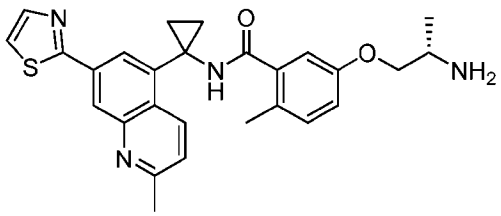
Example 20: (*S*)-5-(2-Aminopropoxy)-2-methyl-*N*-(1-(2-methyl-7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)benzamide (Compound 1172)



1170A-1



1172A-1



Compound 1172

Step 1: *tert*-Butyl (*S*)-(1-(4-methyl-3-((1-(2-methyl-7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)carbamoyl)phenoxy)propan-2-yl)carbamate (1172A-1)

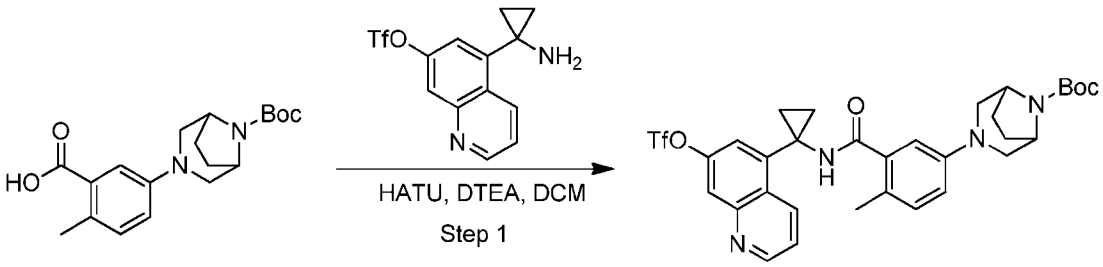
To a solution of (*S*)-5-(1-(5-(2-((*tert*-butoxycarbonyl)amino)propoxy)-2-methylbenzamido)cyclopropyl)-2-methylquinolin-7-yl trifluoromethanesulfonate (160 mg, 250 µmol, 1.0 eq) and 2-(tributylstannyl)thiazole (187 mg, 501 µmol, 157 µL, 2.0 eq) in DMF (5.0 mL) was added $Pd(PPh_3)_2Cl_2$ (17.6 mg, 25.0 µmol, 0.1 eq) at 20 °C. The mixture was stirred at 60 °C for 12 h under a N_2 atmosphere. LCMS indicated that the starting material was completely consumed, and 16% of desired compound was detected. The reaction was allowed to cool to room temperature, diluted with H_2O (20 mL), and extracted with EtOAc (20 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum to give *tert*-butyl (*S*)-(1-(4-methyl-3-((1-(2-methyl-7-(thiazol-2-yl)quinolin-5-

yl)cyclopropyl)carbamoyl)phenoxy)propan-2-yl)carbamate (140 mg, crude) as a black oil. M + H^+ = 573.3 (LCMS).

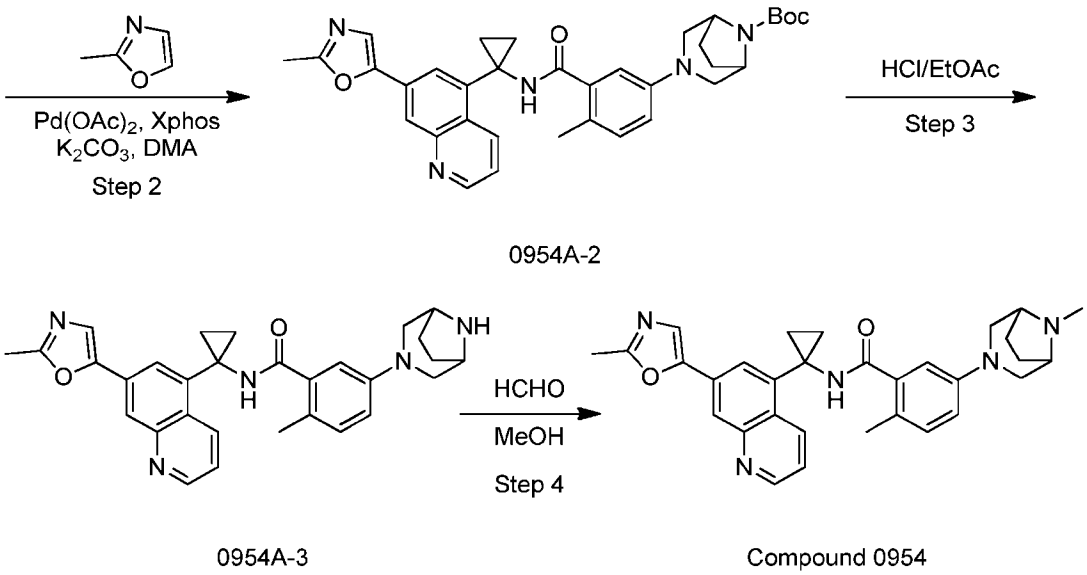
Step 2: (*S*)-5-(2-Aminopropoxy)-2-methyl-*N*-(1-(2-methyl-7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)benzamide (Compound 1172)

To a solution of *tert*-butyl (*S*)-(1-(4-methyl-3-((1-(2-methyl-7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)carbamoyl)phenoxy)propan-2-yl)carbamate (170 mg, 296 µmol, 1.0 eq) in DCM (4.0 mL) was added TFA (857 mg, 7.52 mmol, 558 µL, 25 eq) at 20 °C. The mixture was stirred at 20 °C for 1 h. LCMS indicated that the starting material was completely consumed, and 67% of desired compound was detected. The reaction was filtered and the filtrate was purified by preparative HPLC (Phenomenex Gemini C18 column (75 × 30 mm, 3 µm); flow rate: 25 mL/min; gradient: 10% – 40% B over 8 min; mobile phase A: 0.1% aqueous TFA, mobile phase B: acetonitrile). (*S*)-5-(2-Aminopropoxy)-2-methyl-*N*-(1-(2-methyl-7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)benzamide (164 mg, 278 µmol, 93% yield TFA salt) was obtained as a yellow solid. M + H^+ = 473.4 (LCMS); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.28 – 9.15 (m, 2H), 8.51 – 8.41 (m, 2H), 8.11 – 7.93 (m, 5H), 7.72 (d, *J* = 8.8 Hz, 1H), 7.09 (d, *J* = 8.6 Hz, 1H), 6.90 (dd, *J* = 2.8, 8.4 Hz, 1H), 6.71 (d, *J* = 2.8 Hz, 1H), 4.03 (dd, *J* = 3.9, 10.3 Hz, 1H), 3.87 (dd, *J* = 7.1, 10.3 Hz, 1H), 3.60 – 3.49 (m, 1H), 2.78 (s, 3H), 1.97 (s, 3H), 1.42 (br s, 2H), 1.30 (br s, 2H), 1.23 (d, *J* = 6.8 Hz, 3H).

Example 21: 2-Methyl-5-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)-*N*-(1-(7-(2-methyloxazol-5-yl)quinolin-5-yl)cyclopropyl)benzamide (Compound 0954)



1117A-2 0954A-1



Step 1: *tert*-Butyl 3-(4-methyl-3-((1-(7-(((trifluoromethyl)sulfonyl)oxy)quinolin-5-yl)cyclopropyl)carbamoyl)phenyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (0954A-1)

To a solution of 5-(8-(*tert*-butoxycarbonyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)-2-methylbenzoic acid (280 mg, 808 µmol, 1.0 eq) and 5-(1-aminocyclopropyl)quinolin-7-yl trifluoromethanesulfonate (282 mg, 849 µmol, 1.1 eq) in DMF (14 mL) were added HATU (615 mg, 1.62 mmol, 2.0 eq) and DIEA (313 mg, 2.42 mmol, 422 µL, 3.0 eq). The mixture was stirred at 20 °C for 16 h. LCMS indicated that the starting material was completely consumed. The reaction mixture was poured into water (20 mL) and extracted with EtOAc (20 mL x 5). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/2. *tert*-Butyl 3-(4-methyl-3-((1-(7-(((trifluoromethyl)sulfonyl)oxy)quinolin-5-yl)cyclopropyl)carbamoyl)phenyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (420 mg, 636 µmol, 79% yield) was obtained as a yellow solid. M + H^+ = 661.4 (LCMS); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.11 (d, *J* = 8.3 Hz, 1H), 9.02 (dd, *J* = 1.5, 4.0 Hz, 1H), 8.04 – 7.99 (m, 1H), 7.88 (d, *J* = 2.6 Hz, 1H), 7.58 (dd, *J* = 4.3, 8.7 Hz, 1H), 6.99 (d, *J* = 8.4 Hz, 1H), 6.73 (dd, *J* = 2.6, 8.4 Hz, 1H), 6.59 (d, *J* = 2.5 Hz, 1H), 6.34 (s, 1H), 4.47 - 4.21 (m, 2H), 3.27 (br d, *J* = 11.3 Hz, 2H), 2.06 (s, 3H), 1.96 – 1.89 (m, 2H), 1.82 – 1.75 (m, 2H), 1.67 – 1.63 (m, 2H), 1.57 (br s, 2H), 1.46 (s, 9H), 1.42 (s, 2H).

Step 2: *tert*-Butyl 3-(4-methyl-3-((1-(7-(2-methyloxazol-5-yl)quinolin-5-yl) cyclopropyl)carbamoyl)phenyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (0954A-2)

To a solution of *tert*-butyl 3-(4-methyl-3-((1-(7-(((trifluoromethyl)sulfonyl)oxy)quinolin-5-yl)cyclopropyl)carbamoyl)phenyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (200 mg, 303 µmol, 1.0 eq) and 2-methyloxazole (32.7 mg, 394 µmol, 1.3 eq) in DMA (10 mL) were added K_2CO_3 (126 mg, 908 µmol, 3.0 eq), $Pd(OAc)_2$ (13.6 mg, 60.5 µmol, 0.2 eq) and XPhos (57.7 mg, 121 µmol, 0.4 eq). The mixture was degassed and purged with N_2 three times, then stirred at 100 °C for 16 h under a N_2 atmosphere. LCMS indicated that the starting material was completely consumed. The reaction mixture was allowed to cool to room temperature, poured into water (20 mL) and extracted with EtOAc (20 mL x 5). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/1. *tert*-Butyl 3-(4-methyl-3-((1-(7-(2-methyloxazol-5-yl)quinolin-5-yl)cyclopropyl)carbamoyl)phenyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (180 mg, 303 µmol, 50% yield) was obtained as a yellow solid. M + H^+ = 594.4 (LCMS); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 – 8.91 (m, 2H), 8.29 (s, 1H), 8.17 (d, *J* = 1.6 Hz, 1H), 7.51 – 7.46 (m, 2H), 6.98 (d, *J* = 8.5 Hz, 1H), 6.71 (dd, *J* = 2.8, 8.4 Hz, 1H), 6.58 (d, *J* = 2.6 Hz, 1H), 6.36 (s, 1H), 4.38 – 4.20 (m, 2H), 3.26 (br d, *J* = 8.7 Hz, 2H), 2.60 (s, 3H), 2.18 (s, 3H), 1.94 – 1.87 (m, 2H), 1.77 (br d, *J* = 7.3 Hz, 2H), 1.67 – 1.63 (m, 2H), 1.49 – 1.41 (m, 13H).

Step 3: 5-(3,8-Diazabicyclo[3.2.1]octan-3-yl)-2-methyl-*N*-(1-(7-(2-methyloxazol-5-yl)quinolin-5-yl)cyclopropyl)benzamide (0954A-3)

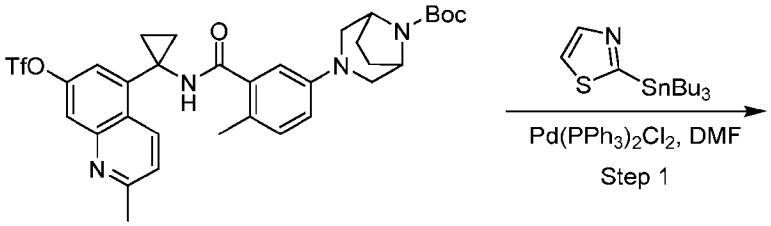
To a solution of *tert*-butyl 3-(4-methyl-3-((1-(7-(2-methyloxazol-5-yl)quinolin-5-yl)cyclopropyl)carbamoyl)phenyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (180 mg, 303 µmol, 1.0 eq) in EtOAc (2.0 mL) was added HCl/EtOAc (4 M, 1.0 mL). The mixture was stirred at 20 °C for 1 h. LCMS indicated that the starting material was completely consumed. The reaction mixture was concentrated under vacuum to give 5-(3,8-diazabicyclo[3.2.1]octan-3-yl)-2-methyl-*N*-(1-(7-(2-methyloxazol-5-yl)quinolin-5-yl) cyclopropyl)benzamide (90.0 mg, crude, HCl salt) as a white solid. M + H^+ = 494.0 (LCMS).

Step 4: 2-Methyl-5-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)-*N*-(1-(7-(2-methyloxazol-5-yl)quinolin-5-yl)cyclopropyl)benzamide (Compound 0954)

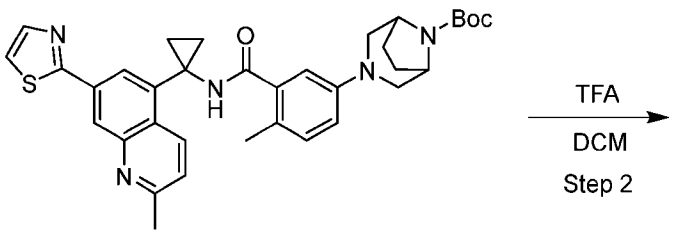
To a solution of 5-(3,8-diazabicyclo[3.2.1]octan-3-yl)-2-methyl-*N*-(1-(7-(2-methyloxazol-5-yl)quinolin-5-yl) cyclopropyl)benzamide (90.0 mg, 170 µmol, 1.0 eq, HCl salt) in MeOH (2.0

mL) was added TEA (17.1 mg, 170 µmol, 23.1 µL, 1.0 eq), followed by the addition of formaldehyde (10.2 mg, 340 µmol, 9.36 µL, 37% wt% in water, 2.0 eq). The resulting mixture was adjusted to pH 6 with a small amount of AcOH, then $NaBH_3CN$ (20.8 mg, 331 µmol, 2.0 eq) was added. The mixture was stirred at 20 °C for 30 min. LCMS indicated that the starting material was completely consumed, and the desired mass was detected. The mixture was concentrated under vacuum at 30 °C to give a residue which was purified by preparative HPLC (Phenomenex Luna C18 column (75 × 30 mm, 3 µm); flow rate: 25 mL/min; gradient: 5% – 35% B over 8 min; mobile phase A: 0.04% aqueous HCl, mobile phase B: acetonitrile). 2-Methyl-5-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)-*N*-(1-(7-(2-methyloxazol-5-yl)quinolin-5-yl) cyclopropyl)benzamide (21.8 mg, 38.5 µmol, 23% yield, HCl salt) was obtained as a yellow solid. M + H^+ = 508.0 (LCMS); ^1H NMR (400 MHz, DMSO-d_6) δ 9.27 (br d, *J* = 8.6 Hz, 1H), 9.17 (s, 1H), 9.06 (d, *J* = 4.0 Hz, 1H), 8.22 (s, 2H), 7.90 (s, 1H), 7.77 (dd, *J* = 4.3, 8.7 Hz, 1H), 7.00 (d, *J* = 8.5 Hz, 1H), 6.82 (dd, *J* = 2.6, 8.5 Hz, 1H), 6.58 (d, *J* = 2.3 Hz, 1H), 3.99 (br s, 2H), 3.59 (br s, 1H), 3.56 (br s, 1H), 3.04 (s, 1H), 3.01 (s, 1H), 2.73 (s, 3H), 2.56 (s, 3H), 2.22 – 2.11 (m, 2H), 1.93 – 1.85 (m, 5H), 1.41 (br s, 2H), 1.33 (br s, 2H).

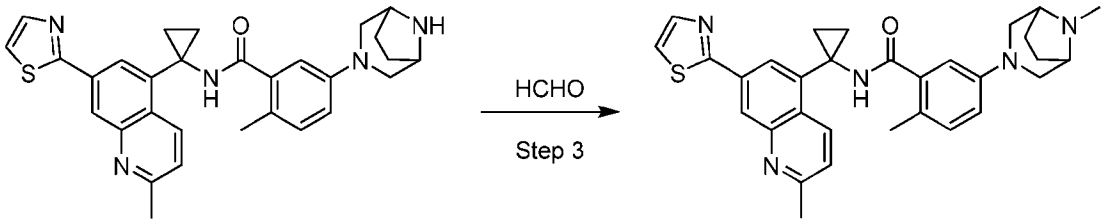
Example 22: 2-Methyl-*N*-(1-(2-methyl-7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)-5-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)benzamide (Compound 1185)



1117A-3



1185A-1



1185A-2 Compound 1185

Step 1: *tert*-Butyl 3-(4-methyl-3-((1-(2-methyl-7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl) carbamoyl)phenyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1185A-1)

To a solution of *tert*-butyl 3-(4-methyl-3-((1-(2-methyl-7-(((trifluoromethyl)sulfonyl)oxy) quinolin-5-yl)cyclopropyl)carbamoyl)phenyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (130 mg, 193 µmol, 1.0 eq) and 2-(tributylstannyl)thiazole (145 mg, 385 µmol, 2.0 eq) in DMF (10 mL) was added $Pd(PPh_3)_2Cl_2$ (13.5 mg, 19.3 µmol, 0.1 eq). The mixture was degassed and purged with N_2 three times, then stirred at 60 °C for 12 h under a N_2 atmosphere. LCMS indicated that the starting material was completely consumed. The reaction mixture was allowed to cool to room temperature, poured into water (5.0 mL), and extracted with EtOAc (5.0 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/0. *tert*-Butyl 3-(4-methyl-3-((1-(2-methyl-7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)carbamoyl)phenyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (110 mg, 181 µmol, 94% yield) was obtained as a yellow solid. M + Na^+ = 632.4 (LCMS).

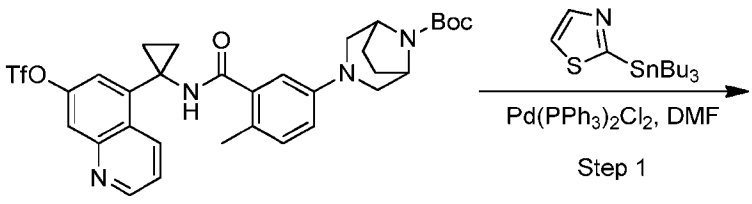
Step 2: 5-(3,8-Diazabicyclo[3.2.1]octan-3-yl)-2-methyl-*N*-(1-(2-methyl-7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)benzamide (1185A-2)

To a solution of *tert*-butyl 3-(4-methyl-3-((1-(2-methyl-7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)carbamoyl)phenyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (105 mg, 173 µmol, 1.0 eq) in DCM (3.0 mL) was added TFA (256 µL). The mixture was stirred at 20 °C for 1 h. LCMS indicated that the starting material was completely consumed. The reaction mixture was concentrated under vacuum to give crude 5-(3,8-diazabicyclo[3.2.1]octan-3-yl)-2-methyl-*N*-(1-(2-methyl-7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)benzamide (107 mg, TFA salt) as a yellow solid. M + H= 510.4 (LCMS).

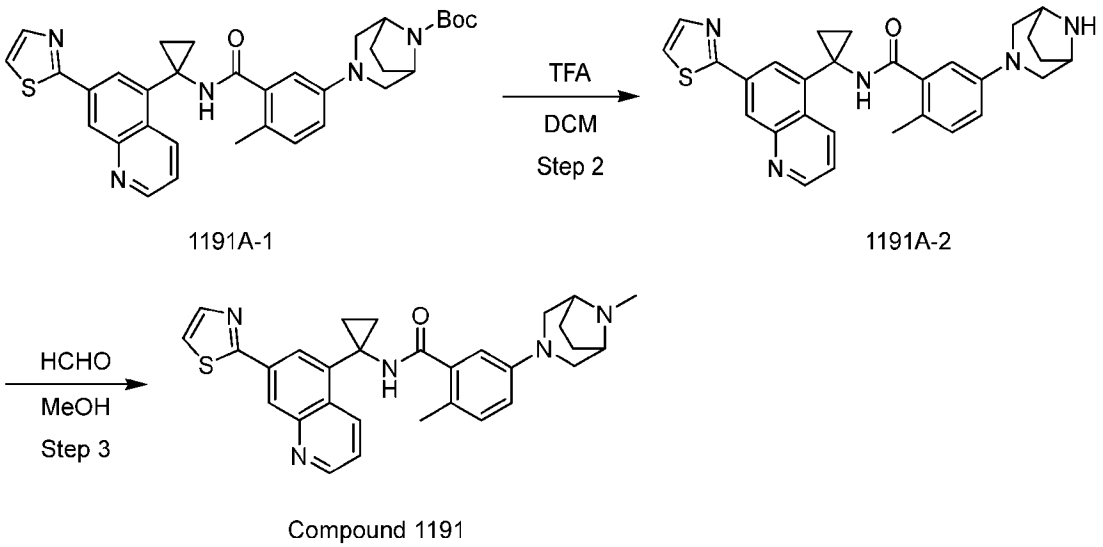
Step 3: 2-Methyl-*N*-(1-(2-methyl-7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)-5-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)benzamide (Compound 1185)

To a solution of 5-(3,8-diazabicyclo[3.2.1]octan-3-yl)-2-methyl-*N*-(1-(2-methyl-7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)benzamide (100 mg, 160 μmol, 1.0 eq, TFA salt) in MeOH (3.0 mL) was added TEA (16.2 mg, 161 μmol, 23.3 μL, 1.0 eq), followed by the addition of formaldehyde (26.1 mg, 321 μmol, 24.9 μL, 37% wt% in water, 2.0 eq). The resulting mixture was adjusted to pH 6 with a small amount of AcOH, then $NaBH_3CN$ (20.2 mg, 321 μmol, 2.0 eq) was added. The mixture was stirred at 20 °C for 3 h. LCMS indicated that the starting material was completely consumed, and the desired mass was detected. The mixture was concentrated under vacuum at 30 °C to give a residue which was purified by preparative HPLC (Phenomenex Luna C18 column (75 × 30 mm, 3 μm); flow rate: 25 mL/min; gradient: 10% – 40% B over 8 min; mobile phase A: 0.1% aqueous TFA, mobile phase B: acetonitrile). 2-Methyl-*N*-(1-(2-methyl-7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)-5-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)benzamide (67.3 mg, 105 μmol, 65% yield, TFA salt) was obtained as a yellow solid. M + H^+ = 524.3 (LCMS); ^1H NMR (400 MHz, DMSO-d_6) δ 9.76 (br d, *J* = 3.6 Hz, 1H), 9.14 – 9.08 (m, 2H), 8.43 (d, *J* = 1.6 Hz, 1H), 8.39 (s, 1H), 8.06 (d, *J* = 3.3 Hz, 1H), 7.94 (d, *J* = 3.1 Hz, 1H), 7.64 (d, *J* = 8.6 Hz, 1H), 6.99 (d, *J* = 8.5 Hz, 1H), 6.81 (dd, *J* = 2.6, 8.4 Hz, 1H), 6.60 (d, *J* = 2.6 Hz, 1H), 4.01 (br s, 2H), 3.60 (br d, *J* = 11.1 Hz, 2H), 2.97 (br d, *J* = 12.4 Hz, 2H), 2.81 – 2.68 (m, 6H), 2.23 – 2.07 (m, 2H), 1.98 – 1.81 (m, 5H), 1.41 (br s, 2H), 1.28 (br s, 2H).

Example 23: 5-(3,8-Diazabicyclo[3.2.1]octan-3-yl)-2-methyl-*N*-(1-(7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)benzamide (Compound 1191)



0954A-1



1191A-1 1191A-2

Compound 1191

Step 1: *tert*-Butyl 3-(4-methyl-3-((1-(7-(thiazol-2-yl)quinolin-5-yl) cyclopropyl) carbamoyl)phenyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1191A-1)

To a solution of *tert*-butyl 3-(4-methyl-3-((1-(7-(((trifluoromethyl)sulfonyl)oxy)quinolin-5-yl)cyclopropyl)carbamoyl)phenyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (155 mg, 235 µmol, 1.0 eq) and 2-(tributylstannyl)thiazole (176 mg, 470 µmol, 148 µL, 2.0 eq) in DMF (10 mL) was added $Pd(PPh_3)_2Cl_2$ (16.5 mg, 23.5 µmol, 0.1 eq). The mixture was degassed and purged with N_2 three times, then stirred at 60 °C for 3 h under a N_2 atmosphere. LCMS indicated that the starting material was completely consumed, and the desired mass was detected. The mixture was allowed to cool to room temperature, poured into water (5.0 mL) and extracted with EtOAc (5.0 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum to give a residue which was purified which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/0. *tert*-Butyl 3-(4-methyl-3-((1-(7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)carbamoyl)phenyl)-3,8-diazabicyclo [3.2.1]octane-8-carboxylate (150 mg, 252 µmol, 90% yield) was obtained as a yellow oil. M + H^+ = 596.4 (LCMS).

Step 2: 5-(3,8-Diazabicyclo[3.2.1]octan-3-yl)-2-methyl-*N*-(1-(7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)benzamide (1191A-2)

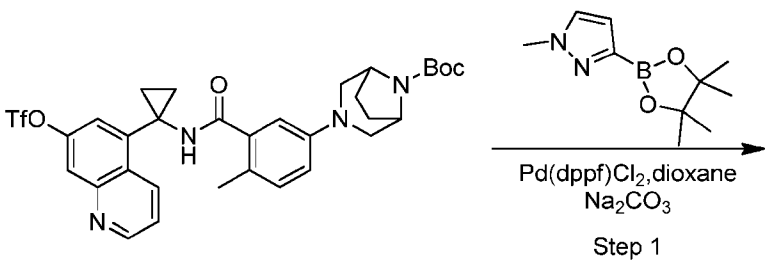
To a solution of *tert*-butyl 3-(4-methyl-3-((1-(7-(thiazol-2-yl)quinolin-5-yl) cyclopropyl) carbamoyl)phenyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (150 mg, 252 µmol, 1.0 eq) in DCM (10 mL) was added TFA (2.0 mL). The mixture was stirred at 20 °C for 30 min. LCMS indicated that the starting material was completely consumed. The reaction mixture was

concentrated under vacuum to give crude 5-(3,8-diazabicyclo[3.2.1]octan-3-yl)-2-methyl-*N*-(1-(7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl) benzamide(150 mg, TFA salt) as a yellow gum. M + H^+ = 496.4 (LCMS).

Step 3: 5-(3,8-Diazabicyclo[3.2.1]octan-3-yl)-2-methyl-*N*-(1-(7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)benzamide (Compound 1191)

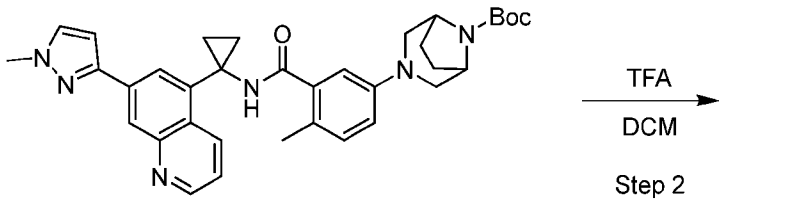
To a solution of 5-(3,8-diazabicyclo[3.2.1]octan-3-yl)-2-methyl-*N*-(1-(7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)benzamide (150 mg, 303 µmol, 1.0 eq, TFA salt) in MeOH (5.0 mL) was added TEA (30.2 mg, 303 µmol, 41.3 µL, 1.0 eq), followed by the addition of formaldehyde (49.1 mg, 606 µmol, 45.1 µL, 37% wt% in water, 2.0 eq). The resulting mixture was adjusted to pH 6 with a small amount of AcOH, then $NaBH_3CN$ (38.0 mg, 606 µmol, 2.0 eq) was added. The mixture was stirred at 20 °C for 1 h. LCMS indicated that the starting material was completely consumed, and the desired mass was detected. The mixture was concentrated under vacuum at 30 °C to give a residue which was purified by preparative HPLC (Phenomenex Luna C18 column (75 × 30 mm, 3 µm); flow rate: 25 mL/min; gradient: 10% – 40% B over 8 min; mobile phase A: 0.1% aqueous TFA, mobile phase B: acetonitrile). 5-(3,8-Diazabicyclo[3.2.1]octan-3-yl)-2-methyl-*N*-(1-(7-(thiazol-2-yl)quinolin-5-yl)cyclo propyl)benzamide (33.0 mg, 52.5 µmol, 17% yield, TFA salt) was obtained as a yellow solid. M + H^+ = 510.2 (LCMS); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.70 (br s, 1H), 9.18 – 9.09 (m, 2H), 9.00 (dd, *J* = 1.5, 4.1 Hz, 1H), 8.52 – 8.42 (m, 2H), 8.06 (d, *J* = 3.3 Hz, 1H), 7.94 (d, *J* = 3.3 Hz, 1H), 7.67 (dd, *J* = 4.2, 8.6 Hz, 1H), 7.00 (d, *J* = 8.6 Hz, 1H), 6.82 (dd, *J* = 2.8, 8.6 Hz, 1H), 6.59 (d, *J* = 2.6 Hz, 1H), 4.01 (br s, 2H), 3.59 (br d, *J* = 11.3 Hz, 2H), 2.96 (br d, *J* = 12.3 Hz, 2H), 2.74 (d, *J* = 4.9 Hz, 3H), 2.23 – 2.10 (m, 2H), 1.94 – 1.87 (m, 5H), 1.42 (br s, 2H), 1.32 – 1.26 (m, 2H).

Example 24: 2-Methyl-*N*-(1-(7-(1-methyl-1*H*-pyrazol-3-yl)quinolin-5-yl)cyclopropyl)-5-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)benzamide (Compound 1204)

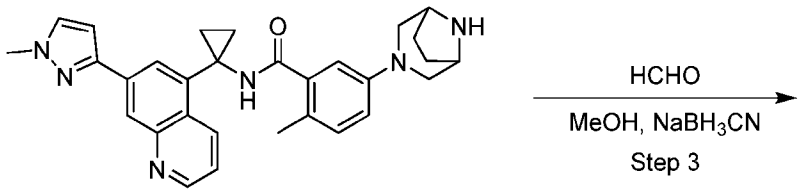


Step 1

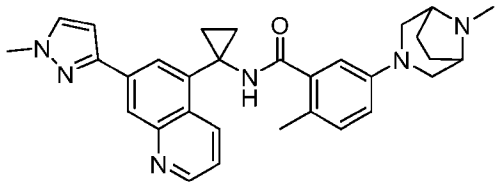
0954A-1



1204A-1



1204A-2



Compound 1204

Step 1: *tert*-Butyl 3-(4-methyl-3-((1-(7-(1-methyl-1*H*-pyrazol-3-yl)quinolin-5-yl)cyclopropyl)carbamoyl)phenyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1204A-1)

To a solution of *tert*-butyl 3-(4-methyl-3-((1-(7-(((trifluoromethyl)sulfonyl)oxy)quinolin-5-yl)cyclopropyl)carbamoyl)phenyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (130 mg, 197 μmol, 1.0 eq) and 1-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (82.0 mg, 394 μmol, 2.0 eq) in dioxane (4.0 mL) and H_2O (400 μL) were added Pd(dppf)Cl_2 (32.1 mg, 39.4 μmol, 0.2 eq) and Na_2CO_3 (41.7 mg, 393 μmol, 2.0 eq). The mixture was degassed and purged with N_2 three times, then stirred at 80 °C for 12 h under a N_2 atmosphere. LCMS indicated that the starting material was completely consumed. The mixture was cooled to room temperature, poured into water (5.0 mL), and extracted with EtOAc (3.0 mL x 4). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 10/7. *tert*-Butyl 3-(4-methyl-3-((1-(7-(1-methyl-1*H*-pyrazol-

3-yl)quinolin-5-yl)cyclopropyl)carbamoyl)phenyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (170 mg, 186 μmol, 95% yield) was obtained as a brown solid. M + H^+ = 593.4 (LCMS).

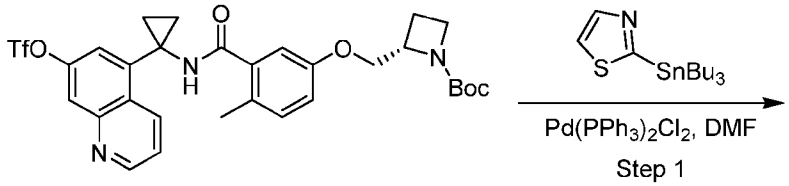
Step 2: 5-(3,8-Diazabicyclo[3.2.1]octan-3-yl)-2-methyl-*N*-(1-(7-(1-methyl-1*H*-pyrazol-3-yl)quinolin-5-yl)cyclopropyl)benzamide (1204A-2)

To a solution of *tert*-butyl 3-(4-methyl-3-((1-(7-(1-methyl-1*H*-pyrazol-3-yl)quinolin-5-yl)cyclopropyl)carbamoyl)phenyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (160 mg, 270 μmol, 1.0 eq) in DCM (3.0 mL) was added TFA (1.0 mL). The mixture was stirred at 20 °C for 2 h. LCMS indicated that the starting material was completely consumed, and the desired mass was detected. The mixture was concentrated under vacuum at 30 °C to give the crude product 5-(3,8-diazabicyclo[3.2.1]octan-3-yl)-2-methyl-*N*-(1-(7-(1-methyl-1*H*-pyrazol-3-yl)quinolin-5-yl)cyclopropyl)benzamide (190 mg, TFA salt) as a yellow oil. M + H^+ = 493.5 (LCMS).

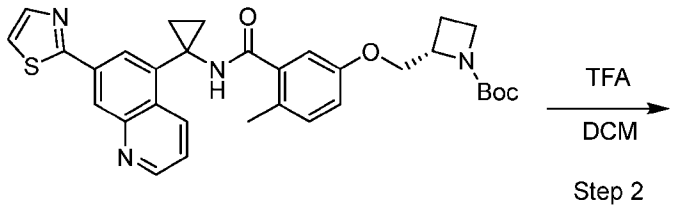
Step 3: 2-Methyl-*N*-(1-(7-(1-methyl-1*H*-pyrazol-3-yl)quinolin-5-yl)cyclopropyl)-5-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)benzamide (Compond 1204)

To a solution of 5-(3,8-diazabicyclo[3.2.1]octan-3-yl)-2-methyl-*N*-(1-(7-(1-methyl-1*H*-pyrazol-3-yl)quinolin-5-yl)cyclopropyl)benzamide (190 mg, 313 μmol, 1.0 eq, TFA salt) in MeOH (2.0 mL) was added TEA (0.1 mL), followed by the addition of formaldehyde (50.8 mg, 626 μmol, 46.6 μL, 37% wt% in water, 2.0 eq). The resulting mixture was adjusted to pH 6 with a small amount of AcOH, then $NaBH_3CN$ (39.4 mg, 626 μmol, 2.0 eq) was added. The resulting mixture was stirred at 20 °C for 2 h. LCMS indicated that the starting material was completely consumed, and the desired mass was detected. The mixture was concentrated under vacuum at 30 °C to give a residue which was purified by preparative HPLC (Phenomenex luna C18 column (80 × 40 mm, 3 μm); flow rate: 60 mL/min; gradient: 5% – 35% B over 8 min; mobile phase A: 0.1% aqueous TFA, mobile phase B: acetonitrile). 2-Methyl-*N*-(1-(7-(1-methyl-1*H*-pyrazol-3-yl)quinolin-5-yl)cyclopropyl)-5-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl) benzamide (75.2 mg, 120 μmol, 38% yield, TFA salt) was obtained as a yellow solid. M + H^+ = 507.3 (LCMS); ^1H NMR (400 MHz, DMSO-d_6) δ 9.87 – 9.70 (m, 1H), 9.25 – 9.13 (m, 1H), 9.12 – 9.05 (m, 1H), 9.02 – 8.92 (m, 1H), 8.44 – 8.39 (m, 1H), 8.34 – 8.27 (m, 1H), 7.87 – 7.82 (m, 1H), 7.69 – 7.59 (m, 1H), 7.04 – 6.97 (m, 1H), 6.91 (s, 1H), 6.84 – 6.77 (m, 1H), 6.62 – 6.55 (m, 1H), 4.03 – 3.99 (m, 2H), 3.99 – 3.95 (m, 3H), 3.62 – 3.55 (m, 2H), 3.01 – 2.93 (m, 2H), 2.77 – 2.72 (m, 3H), 2.20 – 2.10 (m, 2H), 1.94 – 1.91 (m, 2H), 1.91 – 1.87 (m, 3H), 1.43 – 1.36 (m, 2H), 1.31 – 1.24 (m, 2H).

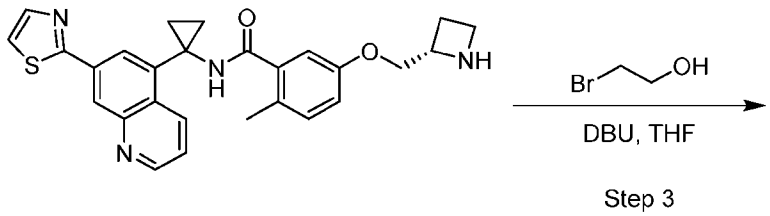
Example 25: (*S*)-5-((1-(2-Hydroxyethyl)azetidin-2-yl)methoxy)-2-methyl-*N*-(1-(7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)benzamide (Compound 1242)



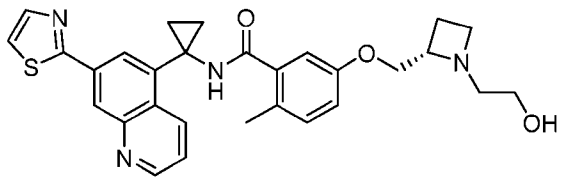
1242A-1



1242A-2



1242A-3



Compound 1242

Step 1: *tert*-Butyl (*S*)-2-((4-methyl-3-((1-(7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)carbamoyl)phenoxy)methyl)azetidine-1-carboxylate (1242A-2)

To a solution of *tert*-butyl (*S*)-2-((4-methyl-3-((1-(7-(((trifluoromethyl)sulfonyl)oxy) quinolin-5-yl)cyclopropyl)carbamoyl)phenoxy)methyl)azetidine-1-carboxylate (800 mg, 1.26 mmol, 45.5 µL, 1.0 eq) and 2-(tributylstannyl)thiazole (941 mg, 2.52 mmol, 2.0 eq) in DMF (40 mL) was added $Pd(PPh_3)_2Cl_2$ (88.3 mg, 125 µmol, 0.1 eq). The mixture was degassed and purged with N_2 three times, then stirred at 60 °C for 12 h under a N_2 atmosphere. LCMS indicated that the

starting material was completely consumed. The reaction mixture was allowed to cool to room temperature, poured into H_2O (40 mL), and extracted with EtOAc (20 mL x 5). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/0. *tert*-Butyl (*S*)-2-((4-methyl-3-((1-(7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)carbamoyl)phenoxy)methyl)azetidine-1-carboxylate (1.30 g, 2.28 mmol, 60% yield) was obtained as a white solid. M + H^+ = 571.4 (LCMS).

Step 2: (*S*)-5-(Azetidin-2-ylmethoxy)-2-methyl-*N*-(1-(7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)benzamide (1242A-3)

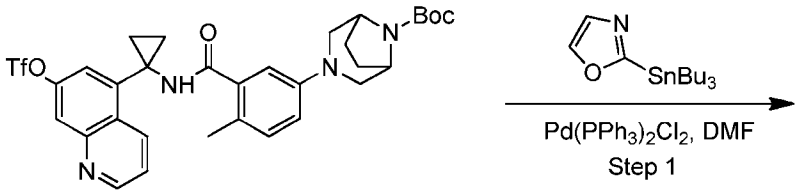
To a solution of *tert*-butyl (*S*)-2-((4-methyl-3-((1-(7-(thiazol-2-yl)quinolin-5-yl) cyclopropyl)carbamoyl)phenoxy)methyl) azetidine-1-carboxylate (100 mg, 175 µmol, 1.0 eq) in DCM (5.0 mL) was added TFA (0.5 mL). The mixture was stirred at 20 °C for 1 h. LCMS indicated that the starting material was completely consumed. The reaction mixture was concentrated under vacuum to give crude (*S*)-5-(azetidin-2-ylmethoxy)-2-methyl-*N*-(1-(7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)benzamide (100 mg, 171 µmol, 98% yield, TFA salt) as a white solid. M + H^+ = 471.3 (LCMS).

Step 3: (*S*)-5-((1-(2-Hydroxyethyl)azetidin-2-yl)methoxy)-2-methyl-*N*-(1-(7-(thiazo l-2-yl)quinolin-5-yl)cyclopropyl)benzamide (Compound 1242)

To a mixture of (*S*)-5-(azetidin-2-ylmethoxy)-2-methyl-*N*-(1-(7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)benzamide (90.0 mg, 154 µmol, 1.0 eq, TFA) and 2-bromoethan-1-ol (38.5 mg, 308 µmol, 21.8 µL, 2.0 eq) in THF (5.0 mL) was added DBU (70.3 mg, 462 µmol, 69.6 µL, 3.0 eq). The mixture was stirred at 60 °C for 5 h. LCMS indicated that some of the starting material remained, and the desired mass was detected. To the reaction mixture was added DBU (70.3 mg, 462 µmol, 69.6 µL, 3.0 eq) and the mixture was stirred at 60 °C for another 12 h. LCMS indicated that the starting material was completely consumed, and the desired mass was detected. The mixture was concentrated under vacuum at 30 °C to give a residue which was purified by preparative HPLC (Phenomenex Luna C18 column (75 × 30 mm, 3 µm); flow rate: 25 mL/min; gradient: 10% – 40% B over 8 min; mobile phase A: 0.1% aqueous TFA, mobile phase B: acetonitrile). ((*S*)-5-((1-(2-Hydroxyethyl)azetidin-2-yl)methoxy)-2-methyl-*N*-(1-(7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)benzamide (31.9 mg, 57.6 µmol, 37% yield, TFA salt) was obtained as a yellow solid. M + H^+ = 515.2 (LCMS); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.22 (s, 1H), 9.15 (d, *J* = 8.3 Hz, 1H), 9.01 (dd, *J* = 1.3, 4.3 Hz, 1H), 8.54 – 8.43 (m, 2H), 8.06 (d, *J* = 3.1 Hz, 1H), 7.92 (d, *J* = 3.3 Hz, 1H), 7.70 (dd, *J* = 4.3, 8.5 Hz, 1H), 7.09 (d, *J* = 8.5 Hz, 1H),

6.90 (dd, *J* = 2.7, 8.3 Hz, 1H), 6.70 (d, *J* = 2.5 Hz, 1H), 4.71 (dq, *J* = 2.2, 8.0 Hz, 1H), 4.34 – 4.13 (m, 2H), 4.06 – 3.93 (m, 2H), 3.57 (br dd, *J* = 4.1, 6.3 Hz, 2H), 3.32 – 3.22 (m, 2H), 2.41 – 2.31 (m, 2H), 1.94 (s, 3H), 1.42 (br s, 2H), 1.30 (br s, 2H).

Example 26: 2-Methyl-5-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)-*N*-(1-(7-(oxazol-2-yl)quinolin-5-yl)cyclopropyl)benzamide (Compound 1247)



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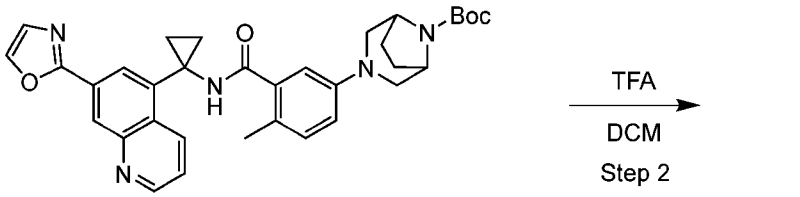
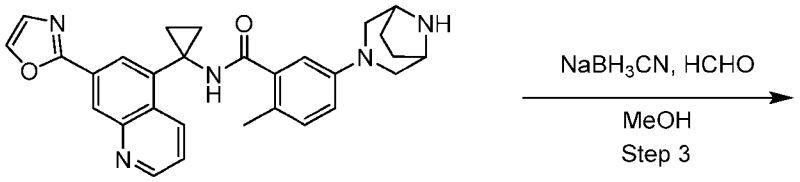
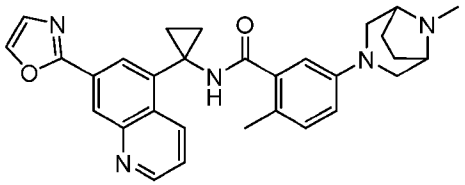


1247A-1



1247A-2



Compound 1247

Step 1: *tert*-Butyl 3-(4-methyl-3-((1-(7-(oxazol-2-yl)quinolin-5-yl)cyclopropyl) carbamoyl)phenyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1247A-1)

To a solution of *tert*-butyl 3-(4-methyl-3-((1-(7-(((trifluoromethyl)sulfonyl)oxy)quinolin-5-yl)cyclopropyl)carbamoyl)phenyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (130 mg, 196 µmol, 1.0 eq) and 2-(tributylstannyl)oxazole (140 mg, 393 µmol, 2.0 eq) in DMF (5.0 mL) was added $Pd(dppf)Cl_2$ (13.8 mg, 19.6 µmol, 0.1 eq). The mixture was degassed and purged with N_2 three times, then stirred at 60 °C for 12 h under a N_2 atmosphere. LCMS indicated that the starting material was completely consumed. The reaction mixture was allowed to cool to room temperature, poured into water (40 mL) and extracted with EtOAc (20 mL x 2). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/0. *tert*-Butyl 3-(4-methyl-3-((1-(7-(oxazol-2-yl)quinolin-5-yl)cyclopropyl)carbamoyl)phenyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (80.0 mg, 138 µmol, 70% yield) was obtained as a white solid. $M + H^+$ =580.4 (LCMS).

Step 2: 5-(3,8-Diazabicyclo[3.2.1]octan-3-yl)-2-methyl-*N*-(1-(7-(oxazol-2-yl)quinolin-5-yl)cyclopropyl)benzamide(1247A-2)

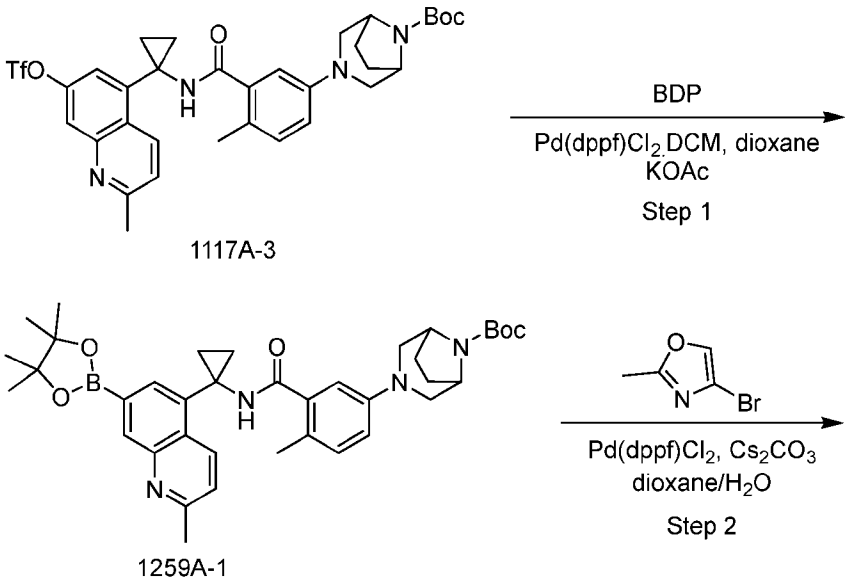
To a solution of *tert*-butyl 3-(4-methyl-3-((1-(7-(oxazol-2-yl)quinolin-5-yl)cyclopropyl) carbamoyl)phenyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (80.0 mg, 138 µmol, 1.0 eq) in EtOAc (3.0 mL) was added HCl/EtOAc (4 M, 3.0 mL). The mixture was stirred at 20 °C for 2 h. LCMS indicated that the starting material was completely consumed. The mixture was concentrated under vacuum at 20 °C to give crude 5-(3,8-diazabicyclo[3.2.1]octan-3-yl)-2-methyl-*N*-(1-(7-(oxazol-2-yl)quinolin-5-yl)cyclopropyl)benzamide (60.0 mg, HCl salt) as a yellow oil. $M + H^+$ = 480.3 (LCMS).

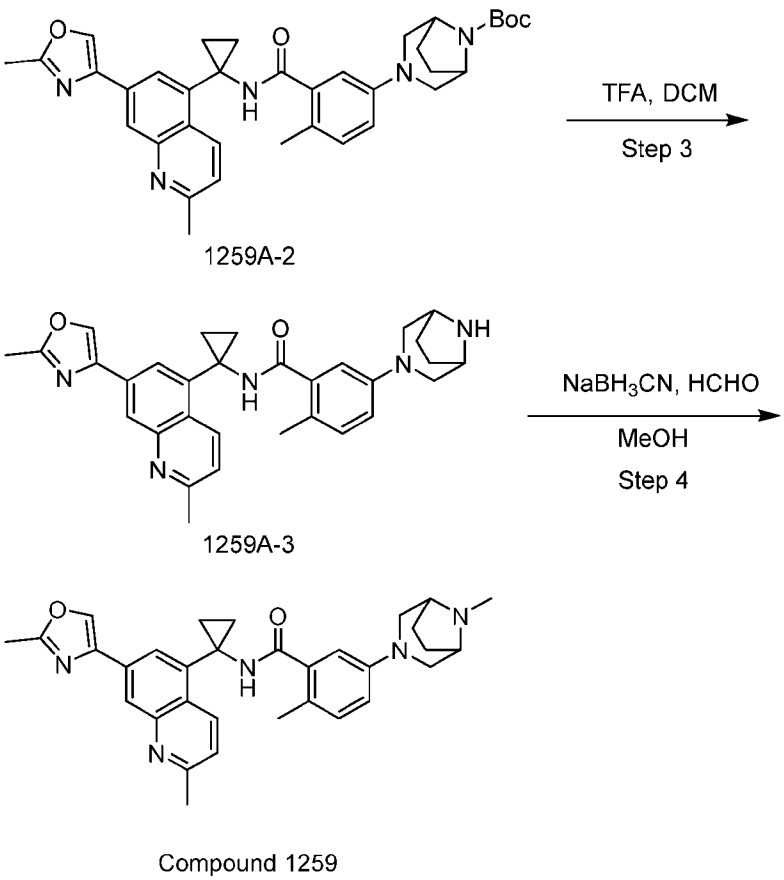
Step 3: 2-Methyl-5-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)-*N*-(1-(7-(oxazol-2-yl)quinolin-5-yl)cyclopropyl)benzamide (Compound 1247)

To a solution of 5-(3,8-diazabicyclo[3.2.1]octan-3-yl)-2-methyl-*N*-(1-(7-(oxazol-2-yl) quinolin-5-yl)cyclopropyl)benzamide (60.0 mg, 116 µmol, 1.0 eq, HCl salt) in MeOH (3.0 mL) was added TEA (11.7 mg, 116 µmol, 16.1 µL, 1.0 eq), followed by the addition of formaldehyde (18.8 mg, 232 µmol, 17.3 µL, 2.0 eq). The resulting mixture was adjusted to pH 6 with a small amount of AcOH. The mixture was stirred at 20 °C for 30 min, then $NaBH_3CN$ (14.6 mg, 232 µmol, 2.0 eq) was added. The resulting reaction mixture was stirred at 20 °C for another 16 h. LCMS indicated that the starting material was completely consumed. The reaction mixture was

poured into H_2O (5.0 mL) and extracted with EtOAc (5.0 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum to give a residue which was purified by preparative HPLC (Phenomenex Luna C18 column (75 × 30 mm, 3 μm); flow rate: 60 mL/min; gradient: 5% – 35% B over 8 min; mobile phase A: 0.04% aqueous HCl, mobile phase B: acetonitrile). 2-Methyl-5-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)-*N*-(1-(7-(oxazol-2-yl)quinolin-5-yl)cyclopropyl)benzamide (18.4 mg, 37.1 μmol, 32% yield, HCl salt) was obtained as a white solid. M + H^+ = 494.3 (LCMS); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.20 – 9.10 (m, 2H), 9.02 (dd, *J* = 1.5, 4.0 Hz, 1H), 8.54 – 8.42 (m, 2H), 8.31 (s, 1H), 7.72 (dd, *J* = 4.3, 8.8 Hz, 1H), 7.49 (s, 1H), 6.99 (d, *J* = 8.5 Hz, 1H), 6.81 (dd, *J* = 2.3, 8.3 Hz, 1H), 6.56 (d, *J* = 2.5 Hz, 1H), 3.97 (br s, 2H), 3.56 (br d, *J* = 11.5 Hz, 2H), 2.97 (br d, *J* = 12.5 Hz, 2H), 2.71 (s, 3H), 2.20 – 2.11 (m, 2H), 1.94 – 1.80 (m, 5H), 1.42 (br s, 2H), 1.28 (br s, 2H).

Example 27: 2-Methyl-*N*-(1-(2-methyl-7-(2-methyloxazol-4-yl)quinolin-5-yl)cyclopropyl)-5-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)benzamide (Compound 1259)





Step 1: *tert*-Butyl 3-(4-methyl-3-((1-(2-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinolin-5-yl)cyclopropyl)carbamoyl)phenyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1259A-1)

A solution of *tert*-butyl 3-(4-methyl-3-((1-(2-methyl-7-(((trifluoromethyl)sulfonyl)oxy) quinolin-5-yl)cyclopropyl)carbamoyl)phenyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (200 mg, 298 mmol, 1.0 eq), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (227 mg, 893 mmol, 3.0 eq), KOAc (73.0 mg, 74.4 mmol, 2.5 eq) and $Pd(dppf)Cl_2.CH_2Cl_2$ (24.3 mg, 30.0 μmol, 0.1 eq) in dioxane (5.0 mL) was degassed and purged with N_2 three times, then stirred at 80 °C for 12 h under a N_2 atmosphere. LCMS indicated that the starting material was completely consumed. The reaction mixture was allowed to cool to room temperature and concentrated under vacuum to give a residue which purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 1/100 to 1/0. *tert*-Butyl 3-(4-methyl-3-((1-(2-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-

2-yl)quinolin-5-yl)cyclopropyl)carbamoyl)phenyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (130 mg, 199 mmol, 65% yield) was obtained as a pale yellow solid.

Step 2: *tert*-Butyl 3-(4-methyl-3-((1-(2-methyl-7-(2-methyloxazol-4-yl)quinolin-5-yl)cyclopropyl)carbamoyl)phenyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1259A-2)

To a solution of *tert*-butyl 3-(4-methyl-3-((1-(2-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinolin-5-yl)cyclopropyl)carbamoyl)phenyl)-3,8-diazabicyclo[3.2.1] octane-8-carboxylate (130 mg, 199 mmol, 1.0 eq) and 4-bromo-2-methyloxazole (38.7 mg, 239 mmol, 1.2 eq) in dioxane (5.0 mL) and H_2O (500 µL) were added XPhos Pd G3 (15.2 mg, 17.9 µmol, 0.1 eq) and Cs_2CO_3 (163 mg, 498 µmol, 2.5 eq). The resulting mixture was degassed and purged with N_2 three times, then stirred at 90 °C for 12 h under a N_2 atmosphere. LCMS indicated that the starting material was completely consumed. The reaction mixture was allowed to cool to room temperature, poured into water (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/0. *tert*-Butyl 3-(4-methyl-3-((1-(2-methyl-7-(2-methyloxazol-4-yl)quinolin-5-yl)cyclopropyl)carbamoyl)phenyl)-3,8-diazabicyclo[3.2.1] octane-8-carboxylate (110 mg, 181 mmol, 91% yield) was obtained as a yellow solid. M + H^+ = 608.5 (LCMS).

Step 3: 5-(3,8-Diazabicyclo[3.2.1]octan-3-yl)-2-methyl-*N*-(1-(2-methyl-7-(2-methyloxazol-4-yl)quinolin-5-yl)cyclopropyl)benzamide (1259A-3)

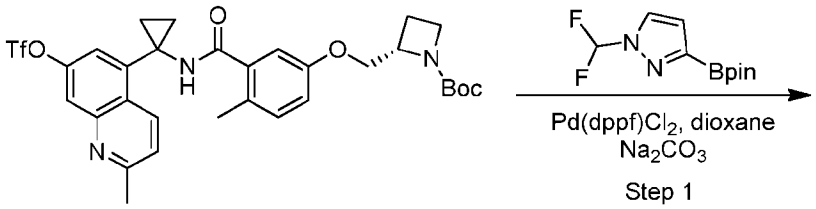
To a solution of *tert*-butyl 3-(4-methyl-3-((1-(2-methyl-7-(2-methyloxazol-4-yl)quinolin-5-yl)cyclopropyl)carbamoyl)phenyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (110 mg, 181 µmol, 1.0 eq) in DCM (2.0 mL) was added TFA (269 µL). The mixture was stirred at 20 °C for 1 h. LCMS indicated that the starting material was completely consumed. The reaction mixture was concentrated under vacuum to give crude 5-(3,8-diazabicyclo[3.2.1]octan-3-yl)-2-methyl-*N*-(1-(2-methyl-7-(2-methyloxazol-4-yl)quinolin-5-yl)cyclopropyl)benzamide (90.0 mg, crude, TFA salt) as a yellow solid. M + H^+ = 508.4 (LCMS).

Step 4: 2-Methyl-*N*-(1-(2-methyl-7-(2-methyloxazol-4-yl)quinolin-5-yl)cyclopropyl)-5-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)benzamide (Compound 1259)

To a solution of 5-(3,8-diazabicyclo[3.2.1]octan-3-yl)-2-methyl-*N*-(1-(2-methyl-7-(2-methyloxazol-4-yl)quinolin-5-yl)cyclopropyl)benzamide (90.0 mg, 209 µmol, 1.0 eq, TFA salt)

in MeOH (3.0 mL) was added TEA (21.2 mg, 209 µmol, 29 µL, 1.0 eq), followed by the addition of formaldehyde (34.0 mg, 341 µmol, 31.4 µL, 37% wt% in water, 2.0 eq). The resulting mixture was adjusted to pH 6 with a small amount of AcOH, then $NaBH_3CN$ (26.3 mg, 418 µmol, 2.0 eq) was added. The mixture was stirred at 20 °C for 3 h. LCMS indicated that the starting material was completely consumed, and the desired mass was detected. The mixture was concentrated under vacuum at 30 °C to give a residue which was purified by preparative HPLC (Phenomenex Luna C18 column (75 × 30 mm, 3 µm); flow rate: 25 mL/min; gradient: 10% – 40% B over 8 min; mobile phase A: 0.1% aqueous TFA, mobile phase B: acetonitrile). 2-Methyl-*N*-(1-(2-methyl-7-(2-methyloxazol-4-yl)quinolin-5-yl)cyclopropyl)-5-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)benzamide (50.0 mg, 77.4 µmol, 35% yield, TFA salt) was obtained as a yellow solid. M + H^+ = 522.3 (LCMS); ^1H NMR (400 MHz, DMSO-d_6) δ 9.39 (d, *J* = 8.8 Hz, 1H), 8.81 (s, 1H), 8.33 (d, *J* = 4.1 Hz, 2H), 7.84 (d, *J* = 8.9 Hz, 1H), 7.00 (d, *J* = 8.6 Hz, 1H), 6.82 (dd, *J* = 2.6, 8.7 Hz, 1H), 6.59 (d, *J* = 2.5 Hz, 1H), 3.97 (br s, 2H), 3.60 - 3.54 (m, 2H), 2.96 (br d, *J* = 12.3 Hz, 2H), 2.85 (s, 3H), 2.72 (s, 3H), 2.52 (s, 3H), 2.20 – 2.12 (m, 2H), 1.90 (br d, *J* = 8.5 Hz, 2H), 1.87 (s, 3H), 1.41 (br s, 2H), 1.33 (br s, 2H).

Example 28: (S)-*N*-(1-(7-(1-(Difluoromethyl)-1*H*-pyrazol-3-yl)-2-methylquinolin-5-yl)cyclopropyl)-2-methyl-5-((1-methylazetidin-2-yl)methoxy)benzamide (Compound 1265)



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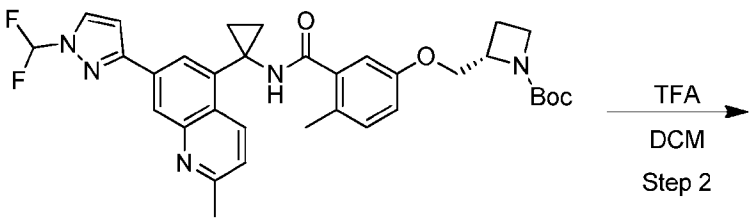
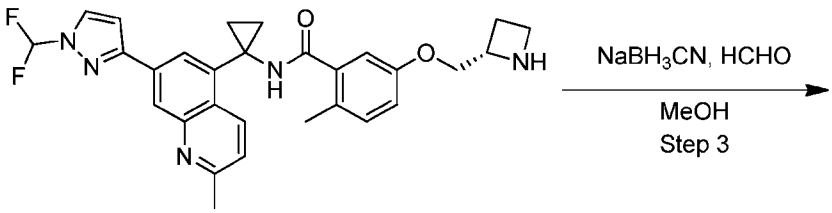
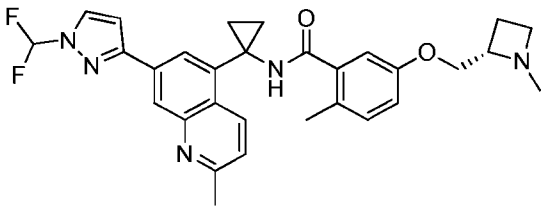


1265A-1



1265A-2



Compound 1265

Step 1: *tert*-Butyl (S)-2-((3-((1-(7-(1-(difluoromethyl)-1*H*-pyrazol-3-yl)-2-methylquinolin-5-yl)cyclopropyl)carbamoyl)-4-methylphenoxy)methyl)azetidine-1-carboxylate (1265A-1)

To a mixture of 1-(difluoromethyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (169 mg, 693 μmol, 3.0 eq) and *tert*-butyl(*S*)-2-((4-methyl-3-((1-(2-methyl-7-(((trifluoromethyl)sulfonyl)oxy)quinolin-5-yl)cyclopropyl)carbamoyl)phenoxy)methyl) azetidine-1-carboxylate (150 mg, 231 μmol, 1.0 eq) in dioxane (5.0 mL) and H_2O (1.0 mL) were added Na_2CO_3 (73.4 mg, 693 μmol, 3.0 eq) and $Pd(dppf)Cl_2$ (16. 9 mg, 23.1 μmol, 0.1 eq). The mixture was degassed and purged with N_2 three times, then stirred at 80 °C for 1 h under a N_2 atmosphere. LCMS indicated that the starting material was completely consumed, and the desired mass was detected. The reaction mixture was allowed to cool to room temperature, poured into H_2O (10 mL) and extracted with DCM (4.0 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/0. *tert*-Butyl (*S*)-2-((3-((1-(7-(1-(difluoromethyl)-1*H*-pyrazol-3-yl)-2-methylquinolin-5-yl)cyclopropyl)carbamoyl)-4-methylphenoxy)methyl) azetidine-1-carboxylate (100 mg, 162 μmol, 70% yield) was obtained as a yellow oil. $M + H^+$ = 618.4 (LCMS).

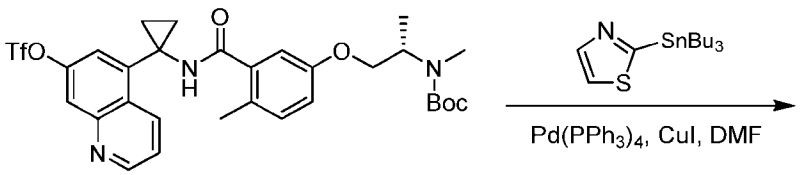
Step 2: (*S*)-5-(Azetidin-2-ylmethoxy)-*N*-(1-(7-(1-(difluoromethyl)-1*H*-pyrazol-3-yl)-2-methylquinolin-5-yl)cyclopropyl)-2-methylbenzamide (1265A-2)

To a solution of *tert*-butyl (*S*)-2-((3-((1-(7-(1-(difluoromethyl)-1*H*-pyrazol-3-yl)-2-methyl quinolin-5-yl)cyclopropyl)carbamoyl)-4-methylphenoxy)methyl)azetidine-1-carboxylate (100 mg, 162 μmol, 1.0 eq) in DCM (5.0 mL) was added TFA (1.54 g, 13.5 mmol, 1.0 mL). The resulting mixture was stirred at 25 °C for 1 h. LCMS indicated that the starting material was completely consumed, and the desired mass was detected. The reaction mixture was concentrated under vacuum to give (*S*)-5-(azetidin-2-ylmethoxy)-*N*-(1-(7-(1-(difluoromethyl)-1*H*-pyrazol-3-yl)-2-methylquinolin-5-yl)cyclopropyl)-2-methylbenzamide (100 mg, TFA salt) as a yellow oil, which was used in the next step without any further purification. M + H^+ = 518.3 (LCMS).

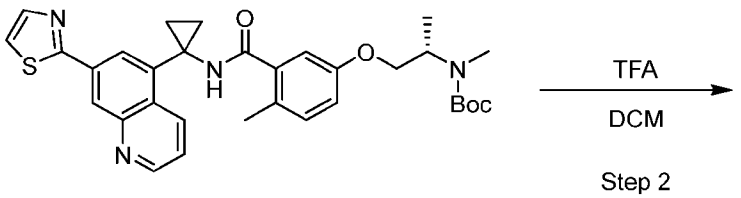
Step 3: (*S*)-*N*-(1-(7-(1-(Difluoromethyl)-1*H*-pyrazol-3-yl)-2-methylquinolin-5-yl)cyclo propyl)-2-methyl-5-((1-methylazetidin-2-yl)methoxy)benzamide(Compound 1265)

To a solution of (*S*)-5-(azetidin-2-ylmethoxy)-*N*-(1-(7-(1-(difluoromethyl)-1*H*-pyrazol-3-yl)-2-methylquinolin-5-yl)cyclopropyl)-2-methylbenzamide (100 mg, TFA salt) in MeOH (2.0 mL) was added TEA (50.0 μL), followed by the addition of formaldehyde (25.7 mg, 317 μmol, 23.6 μL, 37% wt% in water, 2.0 eq). The resulting mixture was adjusted to pH 6 with a small amount of AcOH. The mixture was stirred at 20 °C for 30 min, then $NaBH_3CN$ (19.9 mg, 317 μmol, 2.0 eq) was added. The resulting reaction mixture was stirred at 20 °C for another 16 h. LCMS indicated that the starting material was completely consumed, and the desired mass was detected. The mixture was poured into H_2O (5.0 mL) and extracted with DCM (1.0 mL x 5). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum to give a residue which was purified by preparative HPLC (Phenomenex Luna C18 column (75 × 30 mm, 3 μm); flow rate: 25 mL/min; gradient: 5% – 35% B over 8 min; mobile phase A: 0.1% aqueous TFA, mobile phase B: acetonitrile). (*S*)-*N*-(1-(7-(1-(Difluoromethyl)-1*H*-pyrazol-3-yl)-2-methylquinolin-5-yl)cyclopropyl)-2-methyl-5-((1-methylazetidin-2-yl)methoxy)benzamide (74.9 mg, 115 μmol, 73% yield, TFA salt) was obtained as a white solid. M + H^+ = 532.4 (LCMS); ^1H NMR (400 MHz, DMSO-d_6) δ 9.95 – 9.76 (m, 1H), 9.23 – 9.05 (m, 2H), 8.47 – 8.33 (m, 3H), 7.95 (t, *J* = 59.1 Hz, 1H), 7.67 – 7.55 (m, 1H), 7.29 (d, *J* = 2.4 Hz, 1H), 7.17 – 7.05 (m, 1H), 6.92 (dd, *J* = 2.3, 8.6 Hz, 1H), 6.72 (d, *J* = 2.1 Hz, 1H), 4.66 – 4.54 (m, 1H), 4.28 – 4.15 (m, 2H), 4.06 – 3.96 (m, 1H), 3.86 (br dd, *J* = 6.5, 10.0 Hz, 1H), 2.89 – 2.80 (m, 3H), 2.74 (s, 3H), 2.37 (br s, 2H), 1.97 (s, 3H), 1.40 (br s, 2H), 1.28 (br s, 2H).

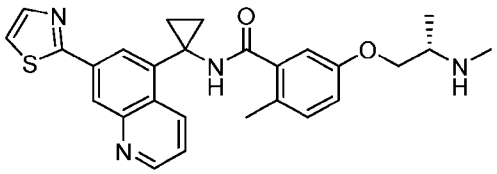
Example 29: (*S*)-2-Methyl-5-(2-(methylamino)propoxy)-*N*-(1-(7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)benzamide (Compound 1023)



0839A-1



1023A-1



Compound 1023

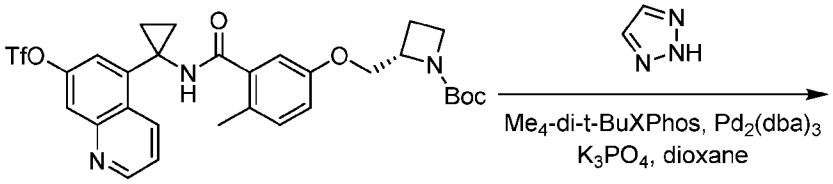
Step 1: *tert*-Butyl (*S*)-methyl(1-(4-methyl-3-((1-(7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)carbamoyl)phenoxy)propan-2-yl)carbamate (1023A-1)

A mixture of (*S*)-5-(1-(5-(2-((*tert*-butoxycarbonyl)(methyl)amino)propoxy)-2-methylbenzamido)cyclopropyl)quinolin-7-yl trifluoromethanesulfonate (200 mg, 313 µmol, 1.0 eq), 2-(tributylstannyl)thiazole (176 mg, 470 µmol, 148 µL, 1.5 eq), $Pd(PPh_3)_4$ (72.5 mg, 62.7 µmol, 0.2 eq), and CuI (59.7 mg, 314 µmol, 1.0 eq) in DMF (2.0 mL) was degassed and purged with N_2 three times. The resulting mixture was stirred at 120 °C under a N_2 atmosphere for 16 h. LCMS indicated that the starting material was completely consumed, and the desired mass was detected. The reaction was allowed to cool to room temperature, poured into water (10 mL), and extracted with DCM (10 mL x 2). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum to give the crude *tert*-butyl (*S*)-methyl(1-(4-methyl-3-((1-(7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)carbamoyl)phenoxy)propan-2-yl)carbamate (200 mg) as a yellow oil. M + H^+ = 573.3 (LCMS).

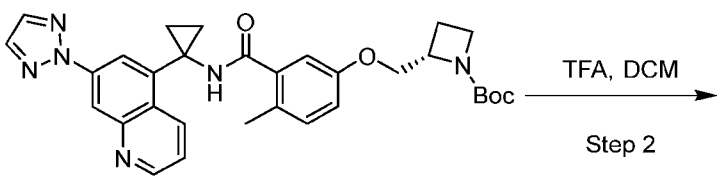
Step 2: (*S*)-2-Methyl-5-(2-(methylamino)propoxy)-*N*-(1-(7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)benzamide (Compound 1023)

To a solution of *tert*-butyl (*S*)-methyl(1-(4-methyl-3-((1-(7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)carbamoyl)phenoxy)propan-2-yl)carbamate (200 mg, 349 μmol, 1.0 eq) in DCM (1.0 mL) was added TFA (1.1 mL). The mixture was stirred at 20 °C for 30 min. LCMS indicated that the starting material was completely consumed, and the desired mass was detected. The mixture was concentrated under vacuum to give a residue which was purified by preparative HPLC ((Phenomenex Gemini C18 column (100 × 40 mm, 3.0 μm); flow rate: 60 mL/min; gradient: 10% – 40% B over 8 min; mobile phase A: 0.1% aqueous TFA, mobile phase B: acetonitrile)). (*S*)-2-Methyl-5-(2-(methylamino)propoxy)-*N*-(1-(7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)benzamide (96.8 mg, 47% yield, TFA salt) was obtained as a white solid. M + H^+ = 473.3 (LCMS); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.23 (s, 1H), 9.15 (d, *J* = 8.5 Hz, 1H), 9.06 – 9.00 (m, 1H), 8.71 – 8.54 (m, 2H), 8.52 – 8.45 (m, 2H), 8.06 (d, *J* = 3.3 Hz, 1H), 7.94 (d, *J* = 3.1 Hz, 1H), 7.70 (dd, *J* = 4.2, 8.6 Hz, 1H), 7.09 (d, *J* = 8.4 Hz, 1H), 6.91 (dd, *J* = 2.6, 8.4 Hz, 1H), 6.70 (d, *J* = 2.6 Hz, 1H), 4.11 (dd, *J* = 3.6, 10.6 Hz, 1H), 3.97 (dd, *J* = 6.3, 10.6 Hz, 1H), 3.53 (br d, *J* = 5.6 Hz, 1H), 2.57 (t, *J* = 5.3 Hz, 3H), 1.96 (s, 3H), 1.43 (br s, 2H), 1.31 (br s, 2H), 1.27 – 1.23 (m, 3H).

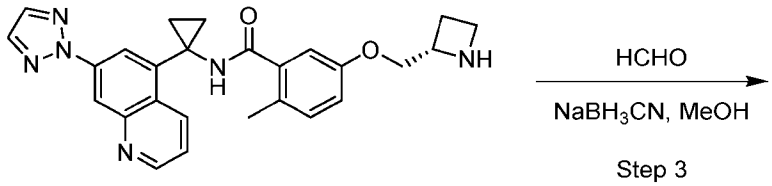
Example 30: (*S*)-*N*-(1-(7-(2*H*-1,2,3-Triazol-2-yl)quinolin-5-yl)cyclopropyl)-2-methyl-5-((1-methylazetidin-2-yl)methoxy)benzamide (Compound 1219)



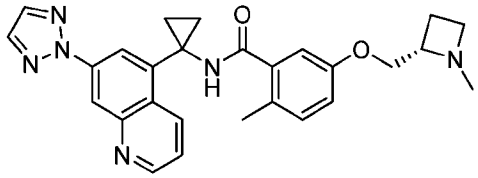
1242A-1



1219A-1



1219A-2



Compoud 1219

Step 1: *tert*-Butyl (*S*)-2-((3-((1-(7-(2*H*-1,2,3-triazol-2-yl)quinolin-5-yl)cyclopropyl)carbamoyl)-4-methylphenoxy)methyl)azetidine-1-carboxylate (1219A-1)

To a solution of *tert*-butyl (*S*)-2-((4-methyl-3-((1-(7-(((trifluoromethyl)sulfonyl)oxy)quinolin-5-yl)cyclopropyl)carbamoyl)phenoxy)methyl)azetidine-1-carboxylate (150 mg, 235 μmol, 1.0 eq) and 2*H*-1,2,3-triazole (16.4 mg, 238 μmol, 13.0 μL, 1.0 eq) in dioxane (5.0 mL) were added K_3PO_4 (55.1 mg, 259 μmol, 1.1 eq), $Pd_2(dba)_3$ (43.2 mg, 47.2 μmol, 0.2 eq), and Me_4-di-*t*-BuXPhos (11.3 mg, 23.6 μmol, 0.1 eq) at 20 °C. The mixture was degassed and purged with N_2 three times, then stirred at 90 °C for 12 h under a N_2 atmosphere. LCMS indicated that the starting material was completely consumed. The reaction was allowed to cool to room temperature, poured into H_2O (10 mL), and extracted with EtOAc (10 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered, and the filtrate was concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 7/10. *tert*-Butyl (*S*)-2-((3-((1-(7-(2*H*-1,2,3-triazol-2-yl)quinolin-5-yl)cyclopropyl)carbamoyl)-4-methylphenoxy)methyl)azetidine-1-carboxylate (90.0 mg, 162 μmol, 68% yield) was obtained as a yellow solid. M + H^+ = 555.4 (LCMS).

Step 2: (*S*)-*N*-(1-(7-(2*H*-1,2,3-Triazol-2-yl)quinolin-5-yl)cyclopropyl)-5-(azetidin-2-ylmethoxy)-2-methylbenzamide (1219A-2)

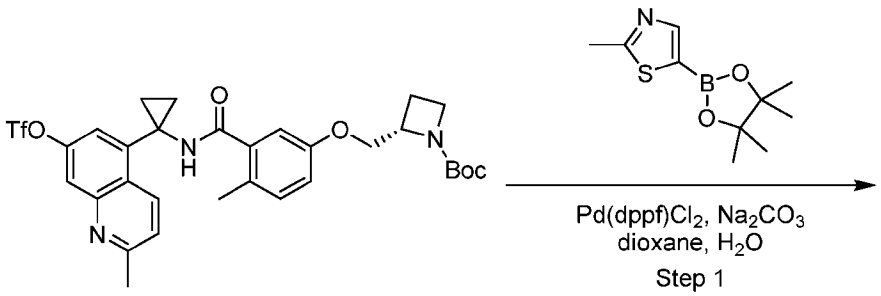
To a solution of *tert*-butyl (*S*)-2-((3-((1-(7-(2*H*-1,2,3-triazol-2-yl)quinolin-5-yl)cyclopropyl)carbamoyl)-4-methylphenoxy)methyl)azetidine-1-carboxylate (90.0 mg, 162 μmol, 1.0 eq) in DCM (3.0 mL) was added TFA (305 μL). The mixture was stirred at 20 °C for

1 h. LCMS indicated that the starting material was completely consumed, and the desired mass was detected. The mixture was concentrated under vacuum to give crude (*S*)-*N*-(1-(7-(2*H*-1,2,3-triazol-2-yl)quinolin-5-yl)cyclopropyl)-5-(azetidin-2-ylmethoxy)-2-methylbenzamide (90 mg, TFA salt) as a yellow oil. M + H^+ = 455.2 (LCMS).

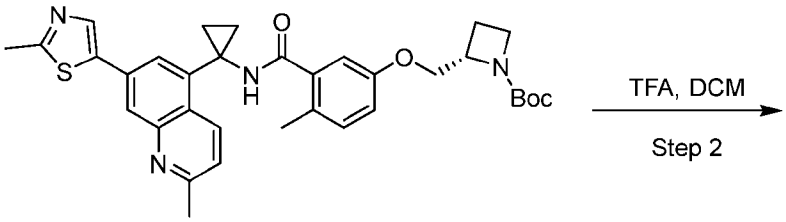
Step 3: (*S*)-*N*-(1-(7-(2*H*-1,2,3-Triazol-2-yl)quinolin-5-yl)cyclopropyl)-2-methyl-5-((1-methylazetidin-2-yl)methoxy)benzamide (Compound 1219)

To a solution of (*S*)-*N*-(1-(7-(2*H*-1,2,3-triazol-2-yl)quinolin-5-yl)cyclopropyl)-5-(azetidin-2-ylmethoxy)-2-methylbenzamide (90.0 mg, 198 μmol, 1.0 eq, TFA salt) in MeOH (3.0 mL) was added TEA (20.0 mg, 198 μmol, 27.5 μL, 1.0 eq), followed by the addition of formaldehyde (32.1 mg, 396 μmol, 29.4 μL, 37% wt% in water, 2.0 eq). The resulting mixture was adjusted to pH 6 with a small amount of AcOH. The mixture was stirred at 20 °C for 30 min, then $NaBH_3CN$ (37.3 mg, 594 μmol, 3.0 eq) was added. The resulting reaction mixture was stirred at 20 °C for another 12 h. LCMS indicated starting material was completely consumed, and the desired mass was detected. The reaction was filtered, and the filtrate was purified by preparative HPLC (Phenomenex Gemini C18 column (75 × 30 mm, 3 μm); flow rate: 25 mL/min; gradient: 5% – 35% B over 8 min; mobile phase A: 0.1% aqueous TFA, mobile phase B: acetonitrile). (*S*)-*N*-(1-(7-(2*H*-1,2,3-Triazol-2-yl)quinolin-5-yl)cyclopropyl)-2-methyl-5-((1-methylazetidin-2-yl)methoxy)benzamide (59.7 mg, 102 μmol, 51% yield, TFA salt) was obtained as a white solid. M + H^+ = 469.3 (LCMS); ^1H NMR (400 MHz, DMSO-d_6) δ 9.91 – 9.80 (m, 1H), 9.28 – 9.22 (m, 1H), 9.14 (d, *J* = 8.3 Hz, 1H), 9.02 (dd, *J* = 1.6, 4.2 Hz, 1H), 8.64 (d, *J* = 2.1 Hz, 1H), 8.49 (d, *J* = 1.9 Hz, 1H), 8.26 (s, 2H), 7.67 (dd, *J* = 4.2, 8.6 Hz, 1H), 7.13 – 7.07 (m, 1H), 6.92 (dd, *J* = 2.8, 8.4 Hz, 1H), 6.73 (d, *J* = 2.6 Hz, 1H), 4.64 – 4.57 (m, 1H), 4.26 – 4.18 (m, 2H), 4.05 – 3.97 (m, 1H), 3.91 – 3.80 (m, 1H), 2.83 (d, *J* = 5.0 Hz, 3H), 2.41 – 2.30 (m, 2H), 1.96 (s, 3H), 1.44 (br s, 2H), 1.32 (br s, 2H).

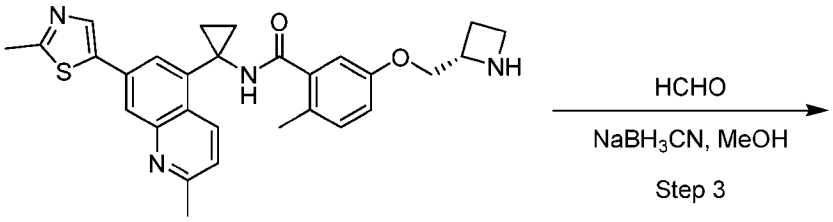
Example 31: (*S*)-2-Methyl-*N*-(1-(2-methyl-7-(2-methylthiazol-5-yl)quinolin-5-yl)cyclopropyl)-5-((1-methylazetidin-2-yl)methoxy)benzamide (Compound 1226)



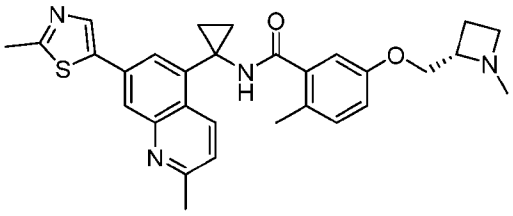
1159A-1



1226A-1



1226A-2



Compound 1226

Step 1: *tert*-Butyl (*S*)-2-((4-methyl-3-((1-(2-methyl-7-(2-methylthiazol-5-yl)quinolin-5-yl)cyclopropyl)carbamoyl)phenoxy)methyl)azetidine-1-carboxylate (1226A-1)

To a solution of *tert*-butyl (*S*)-2-((4-methyl-3-((1-(2-methyl-7-(((trifluoromethyl)sulfonyl)oxy)quinolin-5-yl)cyclopropyl)carbamoyl)phenoxy)methyl)azetidine-

1-carboxylate (250 mg, 384 μmol, 1.0 eq) in dioxane (2.0 mL) and H_2O (200 μL) were added 2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiazole (129 mg, 577 μmol, 1.5 eq), $Pd(dppf)Cl_2$ (28.1 mg, 38.4 μmol, 0.1 eq), and Na_2CO_3 (122 mg, 1.15 mmol, 3.0 eq). The mixture was degassed and purged with N_2 three times, then stirred at 80 °C for 12 h under a N_2 atmosphere. LCMS indicated that the starting material was completely consumed, and the desired mass was detected. The reaction was allowed to cool to room temperature, diluted with H_2O (5.0 mL), and extracted with EtOAc (5.0 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 3/10. *tert*-Butyl (*S*)-2-((4-methyl-3-((1-(2-methyl-7-(2-methylthiazol-5-yl)quinolin-5-yl)cyclopropyl)carbamoyl)phenoxy)methyl)azetidine-1-carboxylate (200 mg, 303 μmol, 78% yield) was obtained as a yellow oil. M + H^+ = 599.4 (LCMS).

Step 2: (*S*)-5-(Azetidin-2-ylmethoxy)-2-methyl-*N*-(1-(2-methyl-7-(2-methylthiazol-5-yl)quinolin-5-yl)cyclopropyl)benzamide (1226A-2)

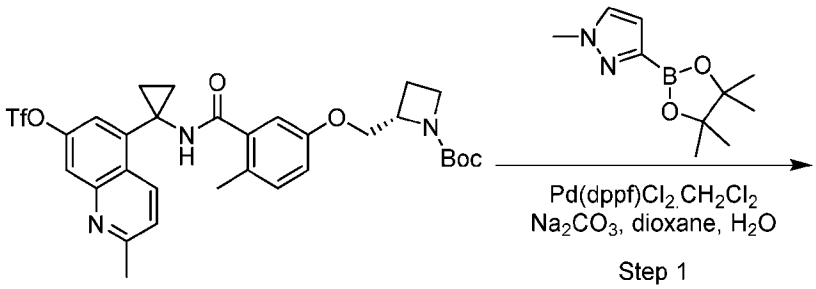
To a solution of *tert*-butyl (*S*)-2-((4-methyl-3-((1-(2-methyl-7-(2-methylthiazol-5-yl)quinolin-5-yl)cyclopropyl)carbamoyl)phenoxy)methyl)azetidine-1-carboxylate (300 mg, 501 μmol, 1.0 eq) in DCM (5.0 mL) was added TFA (1.1 mL) at 20 °C. The mixture was stirred at 20 °C for 1 h. LCMS indicated that the starting material was completely consumed, and the desired mass was detected. The reaction mixture was concentrated under vacuum to give crude (*S*)-5-(azetidin-2-ylmethoxy)-2-methyl-*N*-(1-(2-methyl-7-(2-methylthiazol-5-yl)quinolin-5-yl)cyclopropyl)benzamide (300 mg, TFA salt) as a yellow oil. M + H^+ = 499.4 (LCMS).

Step 3: (*S*)-2-Methyl-*N*-(1-(2-methyl-7-(2-methylthiazol-5-yl)quinolin-5-yl)cyclopropyl)-5-((1-methylazetidin-2-yl)methoxy)benzamide (Compound 1226)

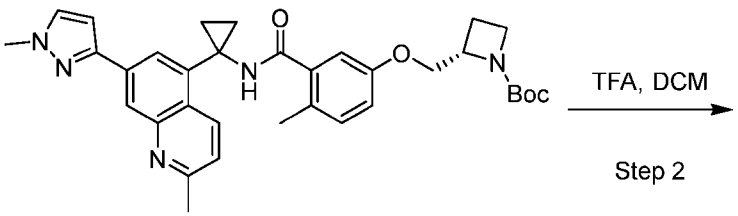
To a solution of (*S*)-5-(azetidin-2-ylmethoxy)-2-methyl-*N*-(1-(2-methyl-7-(2-methylthiazol-5-yl)quinolin-5-yl)cyclopropyl)benzamide (300 mg, 601 μmol, 1.0 eq) in MeOH (5.0 mL) was added TEA (60.8 mg, 601 μmol, 83.7 μL, 1.0 eq), followed by the addition of formaldehyde (97.6 mg, 1.20 mmol, 89.5 μL, 37% wt% in water, 2.0 eq). The resulting mixture was adjusted to pH 6 with a small amount of AcOH. The mixture was stirred at 20 °C for 30 min, then $NaBH_3CN$ (113 mg, 1.80 mmol, 3.0 eq) was added. The resulting reaction mixture was stirred at 20 °C for another 12 h. LCMS indicated that the starting material was completely consumed, and the desired compound was detected. The reaction was filtered, and the filtrate was purified by preparative HPLC (Phenomenex Gemini C18 column (75 × 30 mm, 3 μm); flow rate: 25 mL/min; gradient: 5% – 35% B over 8 min; mobile phase A: 0.1% aqueous TFA, mobile phase

B: acetonitrile). (*S*)-2-Methyl-*N*-(1-(2-methyl-7-(2-methylthiazol-5-yl)quinolin-5-yl)cyclopropyl)-5-((1-methylazetidin-2-yl)methoxy)benzamide (101 mg, 161 µmol, 26% yield, TFA salt) was obtained as a yellow solid. M + H^+ = 513.3 (LCMS); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.16 – 9.96 (m, 1H), 9.20 (s, 2H), 8.34 (s, 1H), 8.19 – 8.08 (m, 2H), 7.71 (br d, *J* = 7.1 Hz, 1H), 7.14 – 7.06 (m, 1H), 6.96 – 6.88 (m, 1H), 6.77 – 6.70 (m, 1H), 4.61 (br d, *J* = 5.6 Hz, 1H), 4.23 (d, *J* = 5.3 Hz, 2H), 4.09 – 3.98 (m, 1H), 3.94 – 3.81 (m, 1H), 2.84 (d, *J* = 4.8 Hz, 3H), 2.80 – 2.71 (m, 6H), 2.43 – 2.29 (m, 2H), 1.98 (s, 3H), 1.37 (br d, *J* = 18.9 Hz, 4H).

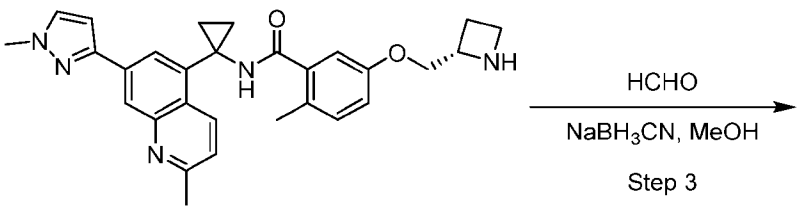
Example 32: (*S*)-2-Methyl-*N*-(1-(2-methyl-7-(1-methyl-1*H*-pyrazol-3-yl)quinolin-5-yl)cyclopropyl)-5-((1-methylazetidin-2-yl)methoxy)benzamide (Compound 1227)



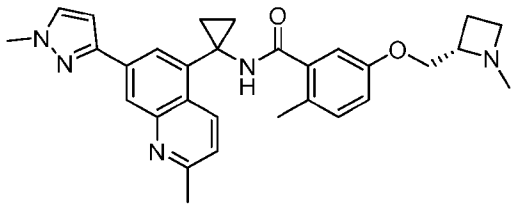
1159A-1



1227A-1



1227A-2



Compound 1227

Step 1: *tert*-Butyl (*S*)-2-((4-methyl-3-((1-(2-methyl-7-(1-methyl-1*H*-pyrazol-3-yl)quinolin-5-yl)cyclopropyl)carbamoyl)phenoxy)methyl)azetidine-1-carboxylate (1227A-1)

To a solution of *tert*-butyl (*S*)-2-((4-methyl-3-((1-(2-methyl-7-(((trifluoromethyl)sulfonyl)oxy)quinolin-5-yl)cyclopropyl)carbamoyl)phenoxy)methyl)azetidine-1-carboxylate (250 mg, 384 μmol, 1.0 eq) and 1-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (120 mg, 577 μmol, 1.5 eq) in dioxane (3.0 mL) and H_2O (100 μL) were added $Pd(dppf)Cl_2.CH_2Cl_2$ (31.4 mg, 38.4 μmol, 0.1 eq) and Na_2CO_3 (95.8 mg, 1.15 mmol, 3.0 eq). The mixture was degassed and purged with N_2 three times, then stirred at 80 °C under a N_2 atmosphere for 12 h. LCMS indicated that the starting material was completely consumed. The reaction was allowed to cool to room temperature, poured into H_2O (10 mL), and extracted with DCM (5.0 mL x 4). The combined organic layers were dried over Na_2SO_4, filtered, and the filtrate was concentrated under vacuum to give crude *tert*-butyl (*S*)-2-((4-methyl-3-((1-(2-methyl-7-(1-methyl-1*H*-pyrazol-3-yl)quinolin-5-yl)cyclopropyl)carbamoyl)phenoxy)methyl)azetidine-1-carboxylate (300 mg) as a yellow oil. M + H^+ = 582.5 (LCMS).

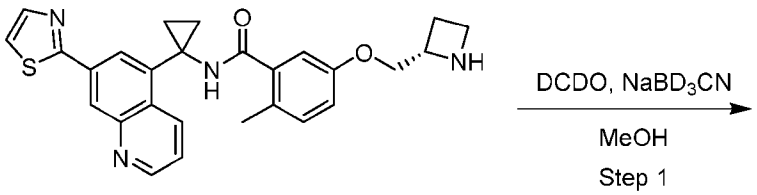
Step 2: (*S*)-5-(Azetidin-2-ylmethoxy)-2-methyl-*N*-(1-(2-methyl-7-(1-methyl-1*H*-pyrazol-3-yl)quinolin-5-yl)cyclopropyl)benzamide (1227A-2)

To a solution of *tert*-butyl (*S*)-2-((4-methyl-3-((1-(2-methyl-7-(1-methyl-1*H*-pyrazol-3-yl)quinolin-5-yl)cyclopropyl)carbamoyl)phenoxy)methyl)azetidine-1-carboxylate (230 mg, 395 μmol, 1.0 eq) in DCM (5.0 mL) was added TFA (881 μL). The mixture was stirred at 20 °C for 1 h. LCMS indicated that the starting material was completely consumed, and the desired mass was detected. The mixture was concentrated under vacuum to give crude (*S*)-5-(azetidin-2-ylmethoxy)-2-methyl-*N*-(1-(2-methyl-7-(1-methyl-1*H*-pyrazol-3-yl)quinolin-5-yl)cyclopropyl)benzamide (230 mg, TFA salt) as a yellow oil. M + H^+ = 482.3 (LCMS).

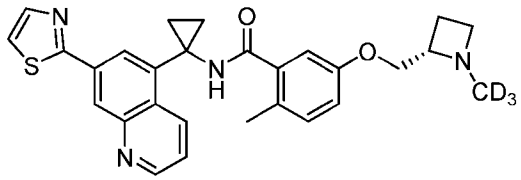
Step 3: (*S*)-2-Methyl-*N*-(1-(2-methyl-7-(1-methyl-1*H*-pyrazol-3-yl)quinolin-5-yl)cyclopropyl)-5-((1-methylazetidin-2-yl)methoxy)benzamide (Compound 1227)

To a solution of (*S*)-5-(azetidin-2-ylmethoxy)-2-methyl-*N*-(1-(2-methyl-7-(1-methyl-1*H*-pyrazol-3-yl)quinolin-5-yl)cyclopropyl)benzamide (230 mg, 477 μmol, 1.0 eq) in MeOH (4.0 mL) was added TEA (48.3 mg, 477 μmol, 66.5 μL, 1.0 eq), followed by the addition of formaldehyde (77.5 mg, 955 μmol, 71.1 μL, 37% wt% in water, 2.0 eq). The resulting mixture was adjusted to pH 6 with a small amount of AcOH. The mixture was stirred at 20 °C for 30 min, then $NaBH_3CN$ (90.0 mg, 1.43 mmol, 3.0 eq) was added. The resulting reaction mixture was stirred at 20 °C for another 12 h. LCMS indicated that the starting material was completely consumed, and the desired mass was detected. The reaction was filtered, and the filtrate was purified by preparative HPLC (Phenomenex Gemini C18 column (75 × 30 mm, 3 μm); flow rate: 25 mL/min; gradient: 5% – 35% B over 8 min; mobile phase A: 0.1% aqueous TFA, mobile phase B: acetonitrile). (*S*)-2-Methyl-*N*-(1-(2-methyl-7-(1-methyl-1*H*-pyrazol-3-yl)quinolin-5-yl)cyclopropyl)-5-((1-methylazetidin-2-yl)methoxy)benzamide (99.3 mg, 162 μmol, 34% yield, TFA salt) was obtained as a pale yellow solid. M + H^+ = 496.4 (LCMS); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.09 – 9.97 (m, 1H), 9.35 – 9.15 (m, 2H), 8.48 (s, 1H), 8.33 (s, 1H), 7.88 (d, *J* = 2.1 Hz, 1H), 7.75 (br d, *J* = 8.0 Hz, 1H), 7.10 (d, *J* = 8.4 Hz, 1H), 6.98 – 6.89 (m, 2H), 6.77 – 6.70 (m, 1H), 4.61 (br d, *J* = 5.4 Hz, 1H), 4.23 (br d, *J* = 5.3 Hz, 2H), 4.00 – 3.84 (m, 5H), 2.90 – 2.76 (m, 6H), 2.40 – 2.31 (m, 2H), 1.97 (s, 3H), 1.42 (br s, 2H), 1.30 (br s, 2H).

Example 33: (*S*)-2-Methyl-5-((1-(methyl-d_3)azetidin-2-yl)methoxy)-*N*-(1-(7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)benzamide (Compound 905)



1242A-3

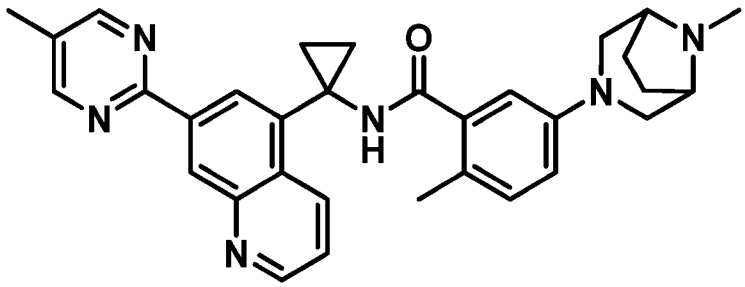


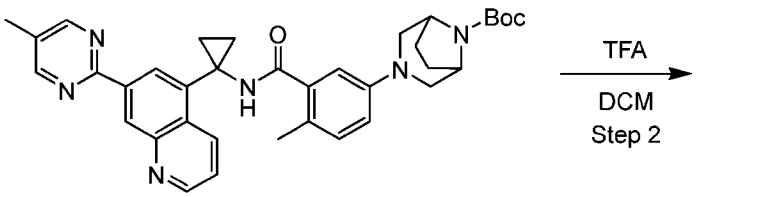
Compound 0905

Step 1: (*S*)-2-Methyl-5-((1-(methyl-d_3)azetidin-2-yl)methoxy)-*N*-(1-(7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)benzamide (Compound 0905)

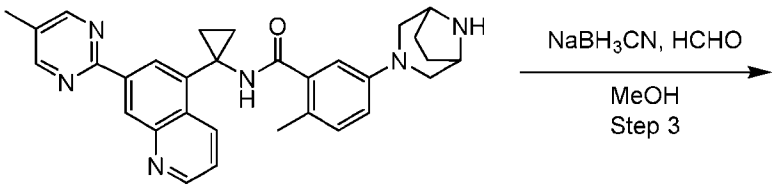
To a solution of (*S*)-5-(azetidin-2-ylmethoxy)-2-methyl-*N*-(1-(7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)benzamide (90.0 mg, 154 µmol, 1.0 eq, TFA salt) in MeOH (3.0 mL) was added TEA (61.5 mg, 607 µmol, 84.0 µL, 1.0 eq), followed by formaldehyde-d_2 (69.3 mg, 462 µmol, 20% purity in D_2O, 3.0 eq). The resulting mixture was adjusted to pH 6 with a small amount of AcOH, then $NaBD_3CN$ (19.3 mg, 308 µmol, 2.0 eq) was added. The mixture was stirred at 20 °C for another 0.5 h. LCMS indicated that the starting material was completely consumed, and the desired mass was detected. The reaction was filtered, and the filtrate was purified by preparative HPLC (Phenomenex Luna C18 column (100 × 40 mm, 5 µm); flow rate: 25 mL/min; gradient: 1% – 35% B over 8 min; mobile phase A: 0.1% aqueous TFA, mobile phase B: acetonitrile). (*S*)-2-Methyl-5-((1-(methyl-d_3)azetidin-2-yl)methoxy)-*N*-(1-(7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)benzamide (74.3 mg, 123 µmol, 80% yield, TFA salt) was obtained as a yellow solid. M + H^+ = 488.4 (LCMS); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.95 (br s, 1H), 9.22 (s, 1H), 9.15 (br d, *J* = 8.6 Hz, 1H), 9.01 (d, *J* = 3.0 Hz, 1H), 8.50 (d, *J* = 1.4 Hz, 1H), 8.47 (s, 1H), 8.06 (d, *J* = 3.1 Hz, 1H), 7.94 (d, *J* = 3.1 Hz, 1H), 7.69 (dd, *J* = 4.3, 8.5 Hz, 1H), 7.10 (d, *J* = 8.4 Hz, 1H), 6.91 (dd, *J* = 2.6, 8.4 Hz, 1H), 6.73 (d, *J* = 2.5 Hz, 1H), 4.60 (br d, *J* = 4.9 Hz, 1H), 4.22 (br d, *J* = 5.0 Hz, 2H), 4.10 – 3.96 (m, 1H), 3.86 (br dd, *J* = 6.6, 9.4 Hz, 1H), 2.45 – 2.24 (m, 2H), 1.97 (s, 3H), 1.43 (br s, 2H), 1.31 (br s, 2H).

Example 34: 2-Methyl-5-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)-*N*-(1-(7-(5-methylpyrimidin-2-yl)quinolin-5-yl)cyclopropyl)benzamide (Compound 1188)

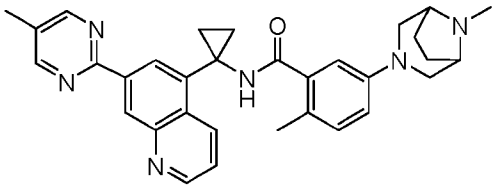




1188A-1



1188A-2



Compound 1188

Step 1: *tert*-Butyl 3-(4-methyl-3-((1-(7-(5-methylpyrimidin-2-yl)quinolin-5-yl)cyclopropyl)carbamoyl)phenyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1188A-1)

To a solution of *tert*-butyl 3-(4-methyl-3-((1-(7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinolin-5-yl)cyclopropyl)carbamoyl)phenyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (100 mg, 157 µmol, 1.0 eq) and 2-chloro-5-methylpyrimidine (24.2 mg, 188 µmol, 1.2 eq) in dioxane (5.0 mL) and H_2O (1.0 mL) were added $Pd(dppf)Cl_2$ (9.17 mg, 12.5 µmol, 0.08 eq)

and Cs_2CO_3 (86.7 mg, 266 μmol, 1.7 eq). The mixture was degassed and purged with N_2 three times, then stirred at 100 °C for 16 h under a N_2 atmosphere. LCMS indicated that the starting material was completely consumed. The reaction mixture was allowed to cool to room temperature, poured into water (10 mL), and extracted with EtOAc (5.0 mL x 5). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/0. *tert*-Butyl 3-(4-methyl-3-((1-(7-(5-methylpyrimidin-2-yl)quinolin-5-yl)cyclopropyl)carbamoyl)phenyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (80.0 mg, 132 μmol, 84% yield) was obtained as a white solid. M + H^+ = 605.4 (LCMS).

Step 2: 5-(3,8-Diazabicyclo[3.2.1]octan-3-yl)-2-methyl-*N*-(1-(7-(5-methylpyrimidin-2-yl)quinolin-5-yl)cyclopropyl)benzamide (1188A-2)

To a solution of *tert*-butyl 3-(4-methyl-3-((1-(7-(5-methylpyrimidin-2-yl)quinolin-5-yl)cyclopropyl)carbamoyl)phenyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (80.0 mg, 132 μmol, 1.0 eq) in DCM (3.0 mL) was added TFA (196 μL). The mixture was stirred at 20 °C for 1 h. LCMS indicated that the starting material was completely consumed. The reaction mixture was concentrated under vacuum to give the crude 5-(3,8-diazabicyclo[3.2.1]octan-3-yl)-2-methyl-*N*-(1-(7-(5-methylpyrimidin-2-yl)quinolin-5-yl)cyclopropyl)benzamide (80.0 mg, TFA salt) as a yellow gum. M + H^+ = 505.4 (LCMS).

Step 3: 2-Methyl-5-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)-*N*-(1-(7-(5-methyl pyrimidin-2-yl)quinolin-5-yl)cyclopropyl)benzamide (Compound 1188)

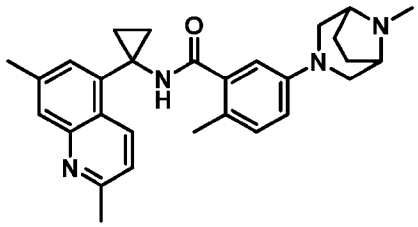
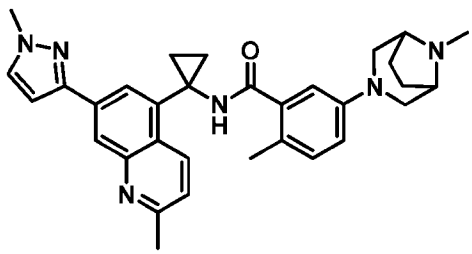
To a solution of 5-(3,8-diazabicyclo[3.2.1]octan-3-yl)-2-methyl-*N*-(1-(7-(5-methylpyrimidin-2-yl)quinolin-5-yl)cyclopropyl)benzamide (80.0 mg, 129 μmol, 1.0 eq, TFA salt) in MeOH (3.0 mL) was added TEA (13.1 mg, 129 μmol, 18.0 μL, 1.0 eq), followed by the addition of formaldehyde (21.0 mg, 259 μmol, 19.3 μL, 37 weight % in water, 2.0 eq). The resulting mixture was adjusted to pH 6 with a small amount of AcOH, then $NaBH_3CN$ (16.3 mg, 259 μmol, 2.0 eq) was added. The mixture was stirred at 20 °C for 3 h. LCMS indicated that the starting material was completely consumed, and the desired mass was detected. The mixture was concentrated under vacuum at 30 °C to give a residue which was purified by preparative HPLC (Phenomenex Luna C18 column (75 × 30 mm, 3 μm); flow rate: 25 mL/min; gradient: 10% – 40% B over 8 min; mobile phase A: 0.1% aqueous TFA, mobile phase B: acetonitrile). 2-Methyl-5-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)-*N*-(1-(7-(5-methylpyrimidin-2-yl) quinolin-5-yl)cyclopropyl)benzamide (46.7 mg, 73.6 μmol, 57% yield, TFA salt) was obtained

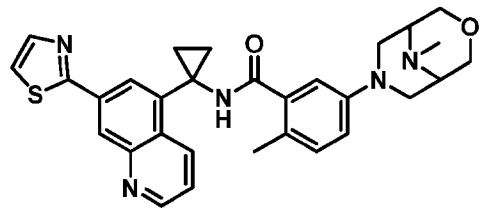
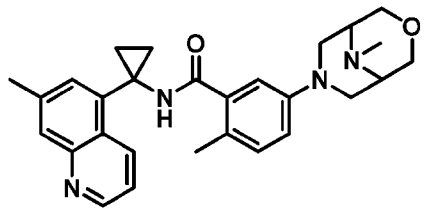
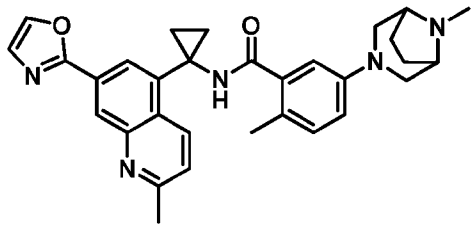
as a yellow solid. M + H^+ = 519.4 (LCMS); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (br d, J = 4.1 Hz, 1H), 9.22 (d, J = 8.4 Hz, 1H), 9.14 (s, 1H), 9.04 (dd, J = 1.3, 4.2 Hz, 1H), 8.95 (s, 1H), 8.91 (d, J = 1.5 Hz, 1H), 8.88 (s, 1H), 7.72 (dd, J = 4.3, 8.5 Hz, 1H), 6.99 (d, J = 8.5 Hz, 1H), 6.81 (dd, J = 2.6, 8.4 Hz, 1H), 6.59 (d, J = 2.4 Hz, 1H), 4.00 (br s, 2H), 3.59 (br d, J = 11.3 Hz, 2H), 2.99 (br d, J = 12.5 Hz, 2H), 2.74 (d, J = 4.9 Hz, 3H), 2.37 (s, 3H), 2.21 – 2.08 (m, 2H), 1.95 – 1.86 (m, 5H), 1.44 (br s, 2H), 1.29 (br s, 2H).

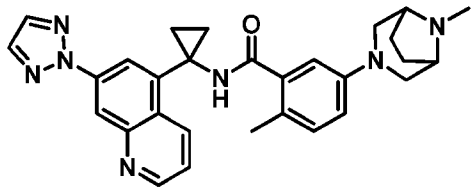
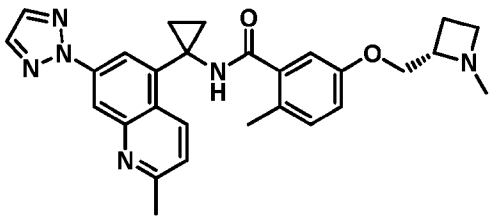
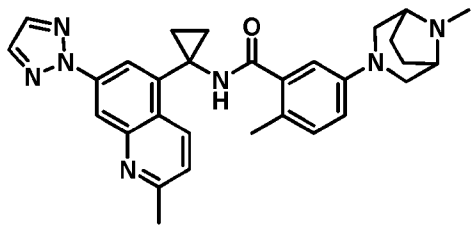
Prophetic Examples:

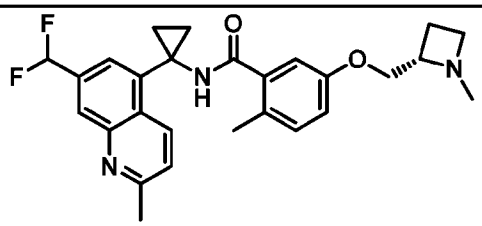
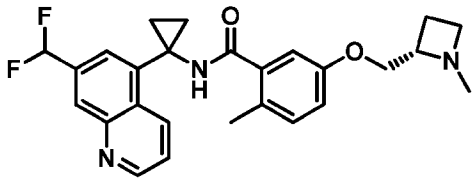
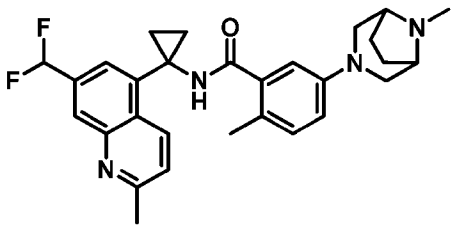
The following compounds as disclosed in Embodiment E18, reproduced below, are prophetic examples not currently prepared but are expected to have similar activity,

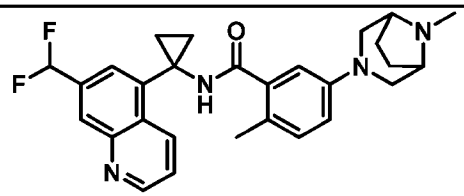
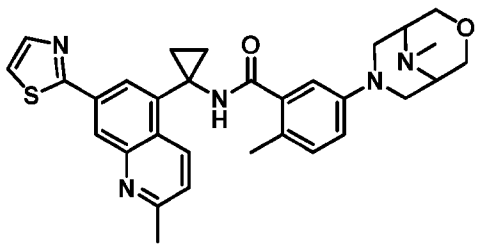
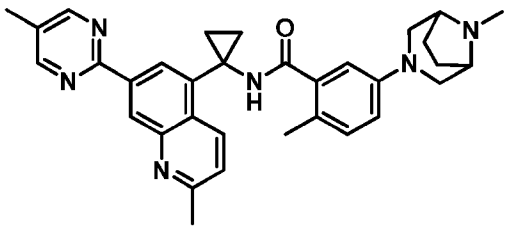
Table 1: Prophetic Examples

Example Number	Structure / Compound Name	Preparation Method
35	 N-(1-(2,7-dimethylquinolin-5-yl)cyclopropyl)-2-methyl-5-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)benzamide	Example **35** is synthesized by an analogous procedure to that described for Example **9.**
36		Example **36** is synthesized by an analogous procedure to that described for Example **24.**

	2-methyl-N-(1-(2-methyl-7-(1-methyl-1H-pyrazol-3-yl)quinolin-5-yl)cyclopropyl)-5-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)benzamide	
37	 2-methyl-5-(9-methyl-3-oxa-7,9-diazabicyclo[3.3.1]nonan-7-yl)-N-(1-(7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)benzamide	Example **37** is synthesized by an analogous procedure to that described for Example **23.**
38	 2-methyl-5-(9-methyl-3-oxa-7,9-diazabicyclo[3.3.1]nonan-7-yl)-N-(1-(7-methylquinolin-5-yl)cyclopropyl)benzamide	Example **38** is synthesized by an analogous procedure to that described for Example **9.**
39	 2-methyl-N-(1-(2-methyl-7-(oxazol-2-yl)quinolin-5-yl)cyclopropyl)-5-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)benzamide	Example **39** is synthesized by an analogous procedure to that described for Example **26.**

40	 N-(1-(7-(2H-1,2,3-triazol-2-yl)quinolin-5-yl)cyclopropyl)-2-methyl-5-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)benzamide	Example **40** is synthesized by an analogous procedure to that described for Example **30.**
41	 (S)-2-methyl-N-(1-(2-methyl-7-(2H-1,2,3-triazol-2-yl)quinolin-5-yl)cyclopropyl)-5-((1-methylazetidin-2-yl)methoxy)benzamide	Example **41** is synthesized by an analogous procedure to that described for Example **30.**
42	 2-methyl-N-(1-(2-methyl-7-(2H-1,2,3-triazol-2-yl)quinolin-5-yl)cyclopropyl)-5-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)benzamide	Example **42** is synthesized by an analogous procedure to that described for Example **30.**
43		Example **43** is synthesized by an analogous procedure to that described for Example **31.**

	 (S)-N-(1-(7-(difluoromethyl)-2-methylquinolin-5-yl)cyclopropyl)-2-methyl-5-((1-methylazetidin-2-yl)methoxy)benzamide	
44	 (S)-N-(1-(7-(difluoromethyl)quinolin-5-yl)cyclopropyl)-2-methyl-5-((1-methylazetidin-2-yl)methoxy)benzamide	Example **44** is synthesized by an analogous procedure to that described for Example **33.**
45	 N-(1-(7-(difluoromethyl)-2-methylquinolin-5-yl)cyclopropyl)-2-methyl-5-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)benzamide	Example **45** is synthesized by an analogous procedure to that described for Example **22.**
46		Example **46** is synthesized by an analogous procedure to that described for Example **14.**

	 N-(1-(7-(difluoromethyl)quinolin-5-yl)cyclopropyl)-2-methyl-5-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)benzamide	
47	 2-methyl-N-(1-(2-methyl-7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)-5-(9-methyl-3-oxa-7,9-diazabicyclo[3.3.1]nonan-7-yl)benzamide	Example **47** is synthesized by an analogous procedure to that described for Example **23.**
48	 2-methyl-N-(1-(2-methyl-7-(5-methylpyrimidin-2-yl)quinolin-5-yl)cyclopropyl)-5-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)benzamide	Example **48** is synthesized by an analogous procedure to that described for Example **2.**

Evaluation of in vitro inhibitory activity of compounds against SARS-CoV-2 Papain-like Protease

Recombinant SARS-CoV-2 PLpro was prepared by WuXi (Gene ID: QHD43415). The substrate RLRGG⬇-AMC was synthesized by Genscript. The assay buffer contained 50 mM HEPES (pH 7.5), 0.01% Triton-X 100, 0.1mg/ml BSA and 5mM DTT.

Test compounds were 3-fold serially diluted for 10 doses and added to an assay plate (384w format) using ECHO, in duplicate wells. 20 µL of 1.25 nM of wild-type PLpro protein was added to an assay plate containing compounds using a Multidrop. The compounds and PLpro protein were pre-incubated at room temperature for 30 min. Then 5 µL of 125 µM of substrate (RLRGG⬇-AMC) was added to an assay plate using a Multidrop. The final concentrations of PLpro and substrate were 1 nM and 25 µM, respectively. For 100% inhibition control (HPE, hundred percent effect), high concentration of positive compound was added. For no inhibition control (ZPE, zero percent effect), no compound was added. The final DMSO concentration is 1%.

After 60 min incubation at 25°C, the fluorescence signal (RFU) was detected using a microplate reader SpectraMax M2e (Molecular Devices) at Ex/Em=360nm/460nm.

The inhibitory activity (Inhibition%) was calculated using the formula below, IC50 values was calculated using the Inhibition% data.

Inhibition% =[(Sample- Average ZPE)/(Average HPE-Average ZPE)] * 100% #

HEP: Hundred percent effect controls. Containing substrate + assay buffer, no compound.

ZPE: Zero percent effective controls. Containing enzyme + substrate, no compound.

Sample: Compound activity testing wells. Containing compound + enzyme + substrate.

IC_{50} values of compounds were calculated with the GraphPad Prism software using the nonlinear regression model of log(inhibitor) vs. response -- Variable slope (four parameters). The results are seen in Table 2.

Evaluation of antiviral activity of compounds in SARS CoV-2 Nanoluciferase Reporter Virus Assay

Method for measuring antiviral effect of compounds: A549 cells expressing ACE-2 (obtained from Ralph Baric at UNC) were grown in DMEM high glucose supplemented with 20% HI FBS, 1% NEAA, 100 µg/ml Blasticidin and split 1:6 every three days (remove Blasticidin from the

media one passage before using the cells in the assay). On the day of assay, the cells were harvested in DMEM supplemented with 2% HI FBS, 1% HEPES, 1% Pen/Strep. Assay ready plates pre-drugged with test compounds were prepared in the BSL-2 lab by adding 5µL assay media to each well. The plates and cells were then passed into the BSL-3 facility. A working stock of SARS CoV-2 nanoluciferase reporter virus (NLRV) passaged five times in A549 cells expressing ACE2 was diluted 6000-fold in media containing 160,000 cells per mL (MOI ~ 0.002) and stirred at 200 RMP for approximately 10 minutes. A 25µL aliquot of virus inoculated cells (4000 cells) was added to each well in columns 3-24 of the assay plates. The wells in columns 23-24 did not contain test compounds, only virus infected cells for the 0% inhibition controls. Prior to virus inoculation, a 25µL aliquot of cells was added to columns 1-2 (no test compounds) of each plate for the cell only 100% inhibition controls. After incubating plates at 37°C/5%CO2 and 90% humidity for 72 hours, 30µL of NanoGlo (Promega) was added to each well. Luminescence was read using a BMG CLARIOstar plate reader (bottom read) following incubation at room temperature for 10 minutes to measure luciferase activity as an index of virus titer. Plates were sealed with a clear cover and surface decontaminated prior to luminescence reading.

Data analysis:

The raw data from plate readers were imported into ActivityBase where values were associated with compound IDs and test concentrations.

Raw signal values were converted to % inhibition by the following formula:

% inhibition = 100 x (test compound value – mean value infected cell controls)/(mean value uninfected cell controls – mean value infected cell controls).

EC_{90} values were calculated from a four parameter logistic fit of data using the XLfit module of ActivityBase with top and bottom constrained to 100 and 0%, respectively.

The results are seen in Table 2.

Table 2

Example Number	Molecule Number	Biochemical Papain-like Protease Inhibition Assay		A549 SARS CoV-2 Nanoluciferase Reporter Virus Assay	
		Geometric mean IC_{50} (μM)	Replicates (n)	Geometric mean EC_{90} (μM)	Replicates (n)
1	1134	0.00086	1	0.166	2
2	1159	0.00062	1	0.0592	2
3	1164	0.00041	1	0.0345	2
4	1167	0.00041	1	0.0365	2
5	1160	0.00053	1	0.0544	2
6	842	0.000555	2	0.0582	3
7	1145	0.00051	1	0.029	2
8	1117	0.00037	1	0.0273	2
9	1120	0.00038	1	0.0277	2
10	1049	0.00056	2	0.176	2
11	1139	0.00075	1	0.113	2
12	1168	0.00058	1	0.114	2
13	839	0.00117	3	0.289	3
14	1077	0.00037	1	0.0503	2
15	1083	0.00087	1	0.154	2
16	1091	0.00094	1	0.137	2
17	1096	0.0004	1	0.0285	2
18	1128	0.00095	1	0.281	1
19	1170	0.00041	1	0.125	2
20	1172	0.00074	1	0.111	2
21	954	0.00032	1	0.035	2
22	1185	0.0002	1	0.005	1
23	1191	0.00031	1	0.009	1
24	1204	0.0003	1	0.016	1
25	1242	0.001	1	NA*	NA
26	1247	< 0.00051	1	NA	NA
29	1023	0.000715	2	0.132	2
30	1219	0.00064	1	0.081	1
31	1226	0.0006	1	NA	NA
32	1227	0.00062	1	NA	NA
33	905	0.000465	2	0.0338	2
34	1188	0.00031	1	0.023	1

*NA means “not available”

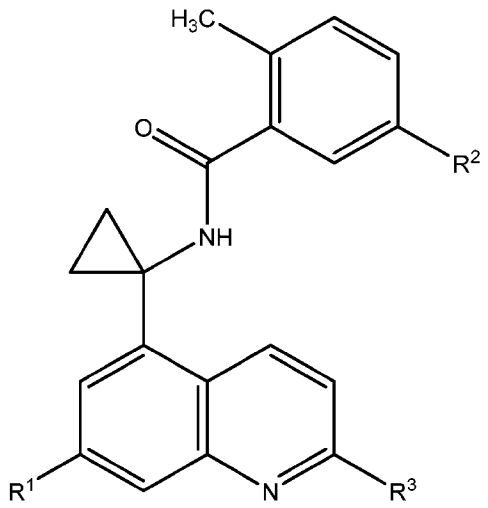
It will be apparent to those skilled in the art that various modifications and variations may be made in the present invention without departing from the scope or spirit of the invention. Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims.

All references cited herein, including patents, patent applications, papers, textbooks, and the like, and the references cited therein, to the extent that they are not already, are hereby incorporated by reference in their entireties. In the event that one or more of the incorporated literature and similar materials differs from or contradicts this application, including but not limited to defined terms, term usage, described techniques, or the like, this application controls.

CLAIMS

We claim:

1. A compound of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, C_2-C_6 alkenyl, C_3-C_6 cycloalkyl, 3- to 6- membered heterocycloalkyl with one to three heteroatoms independently selected from N, O, or S, and 5- to 6-membered heteroaryl with one to three heteroatoms independently selected from N, O, or S; wherein said heterocycloalkyl or heteroaryl is optionally substituted with C_1-C_3 alkyl, C_1-C_3 fluoroalkyl, cyano, deuterium, halo (e.g., F, Cl, Br, and/or I), or C_1-C_3 alkoxy optionally substituted with 1 to 3 fluoro;

R^2 is selected from:

-NR^4R^5, wherein R^4 and R^5 taken together with the nitrogen atom (i.e., first ring nitrogen atom) to which they are attached form a 4- to 10-membered heterocycloalkyl ring containing a second ring nitrogen atom, wherein the second ring nitrogen atom is optionally substituted with (C_1-C_3)alkyl; and wherein the 4- to 10-membered heterocycloalkyl ring optionally contains a third heteroatom selected from O or S; wherein the 4- to 10-membered heterocycloalkyl ring is monocyclic, or the 4- to 10-membered heterocycloalkyl ring is bicyclic and optionally bridged, fused, or spirocyclic; or

R^2 is selected from -O-(C_1-C_6 alkyl) substituted with -NR^6R^7; wherein one of the carbon atoms of said -O-(C_1-C_6 alkyl) moiety may optionally interconnect with another carbon atom of said -O-(C_1-C_6 alkyl) moiety to form a C_3-C_4 cycloalkyl ring;

wherein R^6 is H or C_1-C_3 alkyl optionally substituted with hydroxy, 1 to 3 deuteriums, or 1 to 3 fluoro;

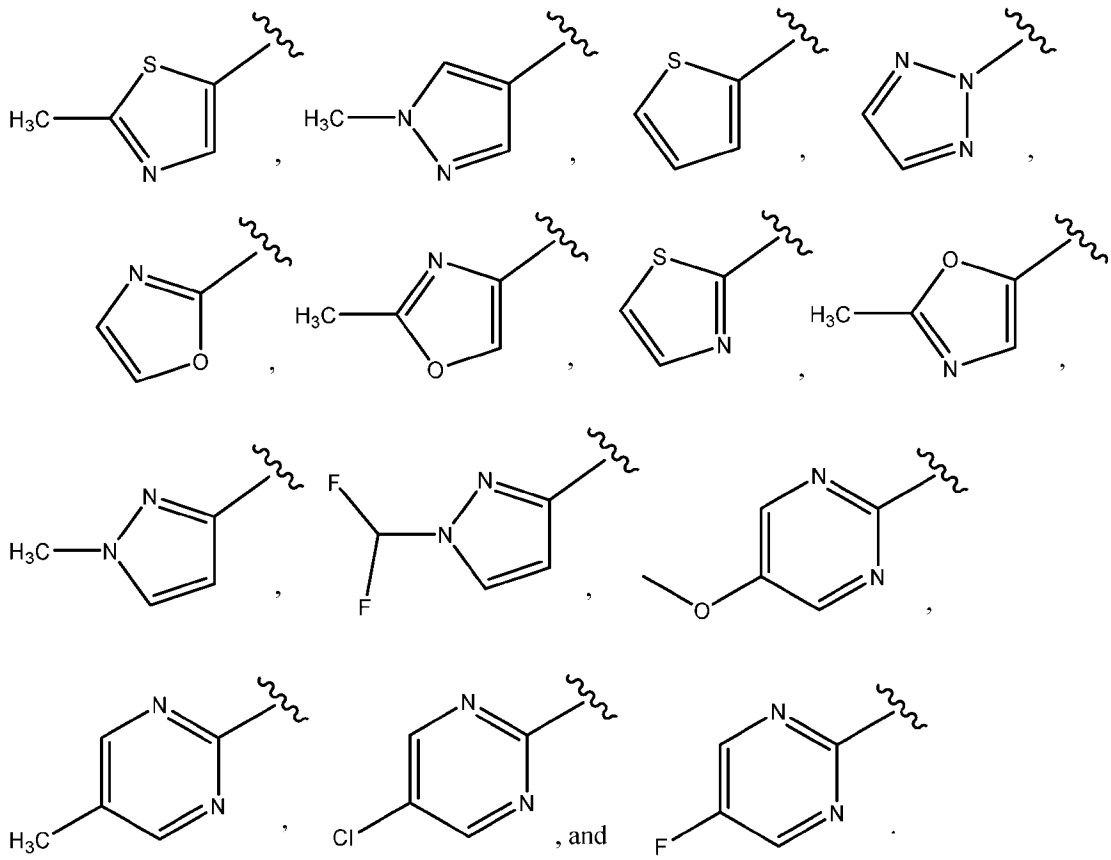
wherein R^7 is H or C_1-C_3 alkyl optionally substituted with hydroxy; wherein said C_1-C_3 alkyl moiety may optionally interconnect with one of the carbon atoms of said -O-(C_1-C_6 alkyl) moiety of R^2 to form a 4- or 5-membered heterocycloalkyl;

and wherein one to three hydrogens in R^2 may optionally be replaced by deuterium; and

R^3 is selected from the group consisting of H, D, -CD_3, C_1-C_6 alkyl, and C_1-C_6 fluoroalkyl.

2. The compound of claim 1 wherein R^1 is selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, C_2-C_6 alkenyl, and 5- to 6-membered heteroaryl with one to three heteroatoms independently selected from N, O, or S; wherein said heteroaryl is optionally substituted with C_1-C_3 alkyl, C_1-C_3 fluoroalkyl, halo, or C_1-C_3 alkoxy optionally substituted with 1 to 3 fluoro.

3. The compound of any of claims 1 to 2 wherein R^1 is selected from the group consisting of methyl, difluoromethyl,



4. The compound of any of claims 1 to 3 wherein R^2 is selected from the group consisting of:

$-NR^4R^5$, wherein R^4 and R^5 taken together with the nitrogen atom (i.e., first ring nitrogen atom) to which they are attached form a 4- to 10-membered heterocycloalkyl ring containing a second ring nitrogen atom, wherein the second ring nitrogen atom is optionally substituted with $(C_1\text{-}C_3)$alkyl; and wherein the 4- to 10-membered heterocycloalkyl ring optionally contains a third heteroatom selected from O or S; wherein the 4- to 10-membered heterocycloalkyl ring is monocyclic or may be bicyclic and optionally bridged; or

R^2 is selected from -O-(C_1-C_6 alkyl) substituted with $-NR^6R^7$; wherein one of the carbon atoms of said -O-(C_1-C_6 alkyl) moiety may optionally interconnect with another carbon atom of said -O-(C_1-C_6 alkyl) moiety to form a C_3-C_4 cycloalkyl ring;

wherein R^6 is H or C_1-C_3 alkyl optionally substituted with hydroxy, or 1 to 3 deuteriums;

wherein R^7 is H or C_1-C_3 alkyl optionally substituted with hydroxy; wherein said C_1-C_3 alkyl moiety may optionally interconnect with one of the carbon atoms of said -O-(C_1-C_6 alkyl) moiety of R^2 to form a 4- or 5-membered heterocycloalkyl.

5. The compound of any of claims 1 to 4 wherein R^2 is selected from the group consisting of is selected from the group consisting of:

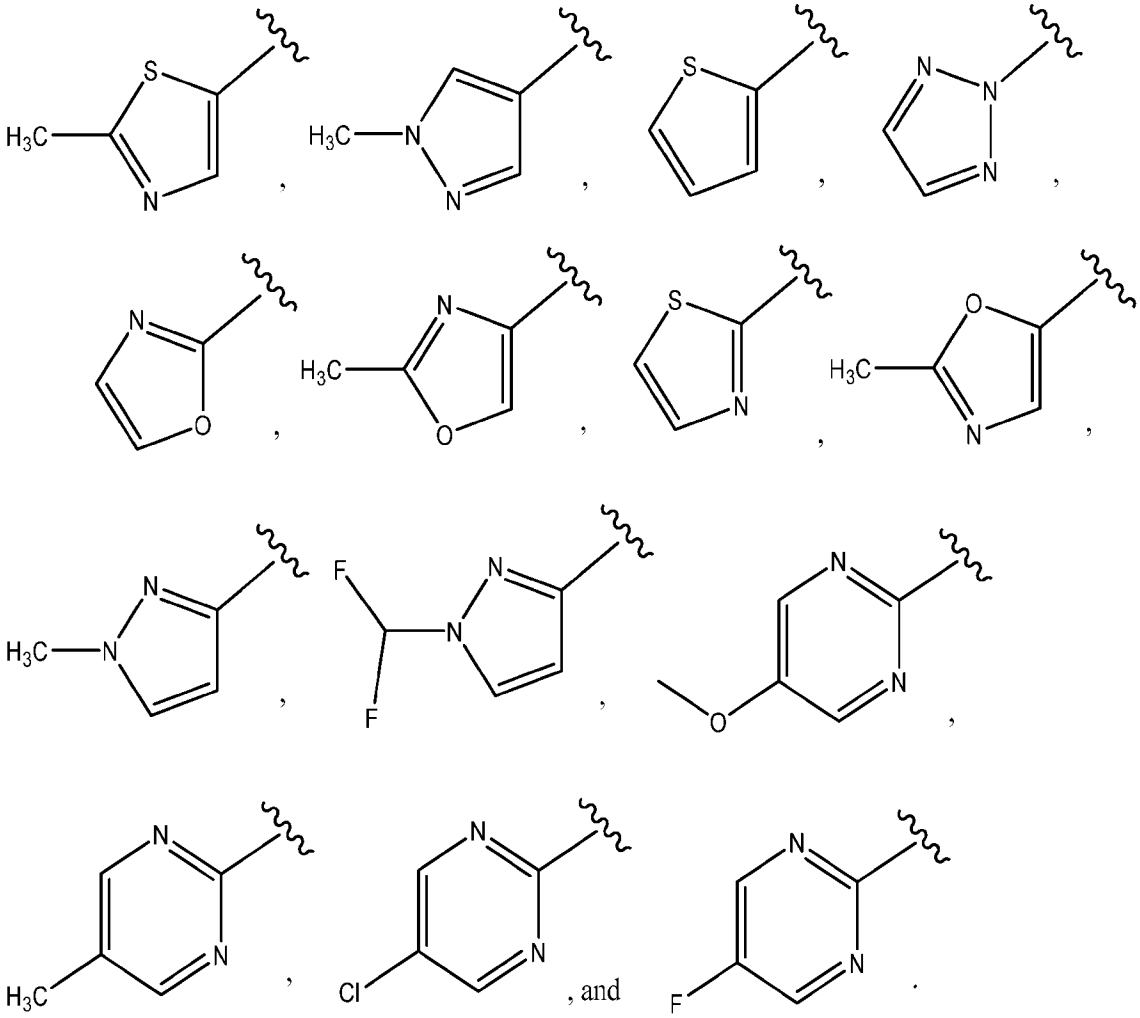
$-NR^4R^5$, wherein R^4 and R^5 taken together with the nitrogen atom (i.e., first ring nitrogen atom) to which they are attached form a 6- to 9-membered heterocycloalkyl ring containing a second ring nitrogen atom, wherein the second ring nitrogen atom is optionally substituted with (C_1-C_3)alkyl; and wherein the 6- to 9-membered heterocycloalkyl ring optionally contains a third heteroatom that is O; wherein the 6- to 9-membered heterocycloalkyl ring is monocyclic or may be bicyclic and optionally bridged; or

R^2 is selected from -O-(C_1-C_6 alkyl) substituted with $-NR^6R^7$; wherein one of the carbon atoms of said -O-(C_1-C_6 alkyl) moiety may optionally interconnect with another carbon atom of said -O-(C_1-C_6 alkyl) moiety to form a C_3-C_4 cycloalkyl ring;

wherein R^6 is H or C_1-C_3 alkyl optionally substituted with hydroxy, or 1 to 3 deuteriums;

wherein R^7 is H or C_1-C_3 alkyl optionally substituted with hydroxy; wherein said C_1-C_3 alkyl moiety may optionally interconnect with one of the carbon atoms of said -O-(C_1-C_6 alkyl) moiety of R^2 to form a 4-membered heterocycloalkyl.

6. The compound of any of the claims 1 to 5, or a pharmaceutically acceptable salt thereof, wherein R^2 is selected from the group consisting of:



7. The compound of any of claims 1 to 6, or a pharmaceutically acceptable salt thereof, wherein R^3 is selected from the group consisting of H, C_1-C_6 alkyl, and C_1-C_6 fluoroalkyl.

8. The compound of any of claims 1 to 7, or a pharmaceutically acceptable salt thereof, wherein R^3 is selected from the group consisting of H, methyl, and difluoromethyl.

9. The compound of claim 1, or a pharmaceutically acceptable salt thereof, selected from the group consisting of

(*S*)-2-methyl-5-(2-(methylamino)propoxy)-*N*-(1-(7-(2-methylthiazol-5-yl)quinolin-5-yl)cyclopropyl)benzamide;

(*S*)-2-methyl-*N*-(1-(2-methyl-7-(oxazol-2-yl)quinolin-5-yl)cyclopropyl)-5-((1-methylazetidin-2-yl)methoxy)benzamide;

(*S*)-2-methyl-5-((1-(methyl-d_3)azetidin-2-yl)methoxy)-*N*-(1-(7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)benzamide;

2-methyl-5-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)-*N*-(1-(7-(2-methyloxazol-5-yl)quinolin-5-yl)cyclopropyl)benzamide;

(*S*)-2-methyl-5-(2-(methylamino)propoxy)-*N*-(1-(7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)benzamide;

2-methyl-5-(6-methyl-3,6-diazabicyclo[3.1.1]heptan-3-yl)-*N*-(1-(7-(2-methyloxazol-5-yl)quinolin-5-yl)cyclopropyl)benzamide;

2-methyl-*N*-(1-(7-(1-methyl-1*H*-pyrazol-4-yl)quinolin-5-yl)cyclopropyl)-5-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)benzamide;

2-methyl-*N*-(1-(7-(1-methyl-1*H*-pyrazol-4-yl)quinolin-5-yl)cyclopropyl)-5-(4-methylpiperazin-1-yl)benzamide;

2-methyl-*N*-(1-(7-(2-methyloxazol-4-yl)quinolin-5-yl)cyclopropyl)-5-(4-methylpiperazin-1-yl)benzamide;

2-methyl-5-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)-*N*-(1-(7-(2-methyloxazol-4-yl)quinolin-5-yl)cyclopropyl)benzamide;

2-methyl-*N*-(1-(2-methyl-7-(2-methyloxazol-5-yl)quinolin-5-yl)cyclopropyl)-5-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)benzamide;

2-methyl-*N*-(1-(2-methyl-7-(1-methyl-1*H*-pyrazol-4-yl)quinolin-5-yl)cyclopropyl)-5-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)benzamide;

(*S*)-5-(2-aminopropoxy)-2-methyl-*N*-(1-(7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)benzamide;

(*S*)-*N*-(1-(2-(difluoromethyl)-7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)-2-methyl-5-(2-(methylamino)propoxy)benzamide;

2-methyl-*N*-(1-(2-methyl-7-(2-methyloxazol-5-yl)quinolin-5-yl)cyclopropyl)-5-(4-methylpiperazin-1-yl)benzamide;

(*S*)-2-methyl-*N*-(1-(2-methyl-7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)-5-((1-methylazetidin-2-yl)methoxy)benzamide;

(*S*)-2-methyl-*N*-(1-(2-methyl-7-(5-methylpyrimidin-2-yl)quinolin-5-yl)cyclopropyl)-5-((1-methylazetidin-2-yl)methoxy)benzamide;

(*S*)-N-(1-(7-(5-fluoropyrimidin-2-yl)-2-methylquinolin-5-yl)cyclopropyl)-2-methyl-5-((1-methylazetidin-2-yl)methoxy)benzamide;

(*S*)-N-(1-(7-(5-chloropyrimidin-2-yl)-2-methylquinolin-5-yl)cyclopropyl)-2-methyl-5-((1-methylazetidin-2-yl)methoxy)benzamide;

(*S*)-N-(1-(7-(5-methoxypyrimidin-2-yl)-2-methylquinolin-5-yl)cyclopropyl)-2-methyl-5-((1-methylazetidin-2-yl)methoxy)benzamide;

5-((1-aminocyclobutyl)methoxy)-2-methyl-*N*-(1-(7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)benzamide;

(*S*)-5-(2-aminopropoxy)-2-methyl-*N*-(1-(2-methyl-7-(thiophen-2-yl)quinolin-5-yl)cyclopropyl)benzamide;

(*S*)-5-(2-aminopropoxy)-2-methyl-*N*-(1-(2-methyl-7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)benzamide;

2-methyl-*N*-(1-(2-methyl-7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)-5-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)benzamide;

2-methyl-5-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)-*N*-(1-(7-(5-methylpyrimidin-2-yl)quinolin-5-yl)cyclopropyl)benzamide;

2-methyl-5-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)-*N*-(1-(7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)benzamide;

2-methyl-*N*-(1-(7-(1-methyl-1*H*-pyrazol-3-yl)quinolin-5-yl)cyclopropyl)-5-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)benzamide;

(*S*)-*N*-(1-(7-(2H-1,2,3-triazol-2-yl)quinolin-5-yl)cyclopropyl)-2-methyl-5-((1-methylazetidin-2-yl)methoxy)benzamide;

(*S*)-2-methyl-*N*-(1-(2-methyl-7-(2-methylthiazol-5-yl)quinolin-5-yl)cyclopropyl)-5-((1-methylazetidin-2-yl)methoxy)benzamide;

(*S*)-2-methyl-*N*-(1-(2-methyl-7-(1-methyl-1*H*-pyrazol-3-yl)quinolin-5-yl)cyclopropyl)-5-((1-methylazetidin-2-yl)methoxy)benzamide;

(*S*)-5-((1-(2-hydroxyethyl)azetidin-2-yl)methoxy)-2-methyl-*N*-(1-(7-(thiazol-2-yl)quinolin-5-yl)cyclopropyl)benzamide;

2-methyl-5-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)-*N*-(1-(7-(oxazol-2-yl)quinolin-5-yl)cyclopropyl)benzamide;

2-methyl-*N*-(1-(2-methyl-7-(2-methyloxazol-4-yl)quinolin-5-yl)cyclopropyl)-5-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)benzamide; and

(*S*)-*N*-(1-(7-(1-(difluoromethyl)-1*H*-pyrazol-3-yl)-2-methylquinolin-5-yl)cyclopropyl)-2-methyl-5-((1-methylazetidin-2-yl)methoxy)benzamide.

10. A pharmaceutical composition comprising the compound according to any of claims 1 to 9, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.

11. A method for treating coronavirus infections, comprising administering to a subject in need thereof a therapeutically effective amount of the compound of any of claims 1 to 9, or a pharmaceutically acceptable salt thereof.

12. A method for treating COVID-19, comprising administering to a subject in need thereof a therapeutically effective amount of the compound of any of claims 1 to 9, or a pharmaceutically acceptable salt thereof.

13. A method for treating coronavirus infections, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any of claims 1 to 9, or a pharmaceutically acceptable salt thereof, and further comprising administering a therapeutically effective amount of an additional therapeutic agent.

14. The method of claim 7 wherein the additional therapeutic agent is an Mpro inhibitor, a nucleoside, or a polymerase inhibitor.

15. A compound according to any of claims 1 to 9 for use as a medicament.

16. A compound according to any of claims 1 to 9 for use in the treatment of coronavirus infections.

17. A compound according to any of claims 1 to 9 for use in the treatment of COVID-19 infections.

18. Use of a compound according to any of claims 1 to 9 for the manufacture of a medicament for the treatment of coronavirus infections.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2024/023951

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D401/12 C07D401/14 C07D409/14 C07D413/14 C07D417/14
C07D471/08 C07D498/08 A61P31/14

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, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CN 114 957 165 A (UNIV TSINGHUA) 30 August 2022 (2022-08-30) abstract claims 1, 22	1-18
A	CN 114 957 110 A (UNIV TSINGHUA) 30 August 2022 (2022-08-30) abstract claims 1, 12	1-18

☐ Further documents are listed in the continuation of Box C.

☒ 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

"E" earlier application or patent but published on or after the international filing date

"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)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"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

"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

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Date of the actual completion of the international search	Date of mailing of the international search report
12 July 2024	23/07/2024

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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