

CYCLIN INHIBITORS

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application No. 63/467,651, filed May 19, 2023; U.S. Provisional Application No. 63/612,533, filed December 20, 2023; and U.S. Provisional Application No. 63/637,984, filed April 24, 2024, the disclosure of each is hereby incorporated by reference in their entirety for all purposes.

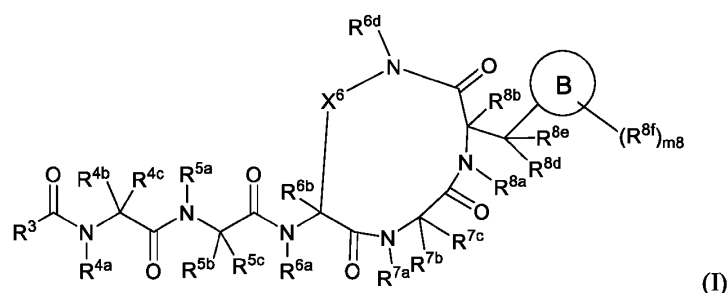
BACKGROUND

[0002] Cyclins are a family of proteins that play a central role in the regulation of the cell cycle. Specific cyclins, including Cyclins D, E, A and B, are expressed at the different stages of the cell cycle, during which they bind and activate their cognate cyclin dependent kinases (CDKs), including CDKs 1, 2, 4 and 6, to form cyclin-CDK complexes that orchestrate progression and transitions through the different stages of the cell cycle. Disruptions of the normal regulatory functions of cyclin-CDK complexes are common drivers of oncogenesis and the rapid proliferation of cancer cells. The central role of cyclins and CDKs in the cell cycle makes these proteins and their complexes attractive targets for treating proliferative disorders and cancer. To date, most inhibitors of cyclin-CDK complexes target the kinase activity of CDKs ("CDK inhibitors") and include therapeutics both in development and approved for clinical use. Alternative approaches could include disrupting the association of cyclins with CDKs or the interaction of a particular cyclin-CDK complex with its substrates or regulators.

[0003] Although CDK inhibitors have been developed and proven successful in certain cancers, they are currently limited by their relative lack of selectivity, small therapeutic window, and ultimately the development of resistance. As such, there is a need to develop agents that offer alternative approaches to inhibiting the function of cyclin-CDK complexes as a means to modulate the cell cycle. Such agents could provide new tools in the treatment of proliferative diseases. The present disclosure addresses this need by providing compounds that inhibit the binding of substrates to various cyclins, thereby disrupting the function of cyclin-CDK complexes.

BRIEF SUMMARY

[0004] In one embodiment, provided herein is a compound of Formula (I):



wherein

R^3 is

- 5
- (a) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{1-6} haloalkyl, each substituted with 0 to 5 R^{3a} ,
 - (b) C_{3-12} cycloalkyl substituted with 0 to 5 R^{3b} , or
 - (c) heterocycloalkyl having 3 to 12 ring members and 1 to 4 heteroatoms, each independently N, O, or S, wherein the heterocycloalkyl is substituted with 0 to 5 R^{3c} ;
 - 10 (g) heteroaryl having 5 to 6 ring members and 1 to 3 heteroatoms, each independently N, O, or S, wherein the heteroaryl is substituted with 0, 1, 2, 3, 4, or 5 R^{3g} ;

each R^{3a} is $-OH$, C_{1-6} alkoxy, C_{1-6} haloalkoxy, or $-O-C(O)C_{1-6}$ alkyl;

15 each R^{3b} is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $-OH$, C_{1-6} alkoxy, halo, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, or cyano;

each R^{3c} is independently C_{1-6} alkyl, halo, C_{1-6} haloalkyl, cyano, C_{3-6} cycloalkyl, or oxo;

each R^{3g} is independently C_{1-6} alkyl, halo, C_{1-6} haloalkyl, or C_{3-6} cycloalkyl;

R^{4a} is H or C_{1-6} alkyl;

20 R^{4b} and R^{4c} are each independently H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, $-C_{1-6}$ alkyl- C_{3-6} cycloalkyl, heterocycloalkyl, $-C_{1-6}$ alkyl-heterocycloalkyl, phenyl, $-C_{1-6}$ alkyl-phenyl, heteroaryl, or $-C_{1-6}$ alkyl-heteroaryl, wherein each heterocycloalkyl has 3 to 6 ring members and 1 to 3 heteroatoms, each independently N, O, or S, and each heteroaryl has 5 to 6 ring members and 1 to 3 heteroatoms, each independently N, O, or S;

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alternatively, R^{4c} and R^{4a} together with the carbon and nitrogen to which each is attached combine to form a heterocycloalkyl having 3 to 6 ring members and 1

- to 3 heteroatoms, each independently N, O, or S, wherein the heterocycloalkyl is substituted with 0 to 4 R^{4a1};
- each R^{4a1} is independently C₁₋₆ alkyl, -OH, C₁₋₆ alkyl-OH, C₁₋₆ alkoxy, or halo;
- R^{5a} is H or C₁₋₆ alkyl;
- 5 R^{5b} and R^{5c} are each independently H, C₁₋₆ alkyl, -C₁₋₆ alkyl-OH, C₂₋₆ alkoxyalkyl, C₁₋₆ haloalkyl, -C₁₋₆ alkyl-C(O)NR^{5b1}R^{5b2}, -C₁₋₆ alkyl-C(O)OR^{5b1}, C₃₋₆ cycloalkyl, C₁₋₆ alkyl-C₃₋₆ cycloalkyl, heterocycloalkyl, -C₁₋₆ alkyl-heterocycloalkyl, phenyl, -C₁₋₆ alkyl-phenyl, heteroaryl, or -C₁₋₆ alkyl-heteroaryl, wherein each heterocycloalkyl has 3 to 6 ring members and 1 to 3 heteroatoms, each independently N, O, or S, and each heteroaryl has 5 to 6 ring members and 1 to 3 heteroatoms, each independently N, O, or S, and wherein each cycloalkyl, heterocycloalkyl, phenyl, and heteroaryl is substituted with 0 to 3 R^{5b5};
- 10 each R^{5b1} and R^{5b2} are independently H, C₁₋₄ alkyl, or C₁₋₄ haloalkyl;
- 15 alternatively, R^{5b1} and R^{5b2} together with the nitrogen to which each is attached combine to form a heterocycloalkyl having 3 to 6 ring members and 0 to 1 additional heteroatoms, wherein the heterocycloalkyl is substituted with 0 to 2 R^{5b3};
- each R^{5b3} and R^{5b5} is independently C₁₋₆ alkyl, halo, C₁₋₆ haloalkyl, or cyano;
- 20 X⁶ is C₆₋₇ alkylene or C₆₋₇ alkenylene;
- R^{6a} is H, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₂₋₆ alkoxyalkyl, C₃₋₆ cycloalkyl, -C₁₋₆ alkyl-C₃₋₆ cycloalkyl, heterocycloalkyl, -C₁₋₆ alkyl-heterocycloalkyl, phenyl, -C₁₋₆ alkyl-phenyl, heteroaryl, or -C₁₋₆ alkyl-heteroaryl, wherein the heterocycloalkyl has 3 to 6 ring members and 1 to 3 heteroatoms, each
- 25 independently N, O, or S, and the heteroaryl has 5 to 6 ring members and 1 to 3 heteroatoms, each independently N, O, or S;
- R^{6b} and R^{6d} are each independently H or C₁₋₆ alkyl;
- R^{7a} is H or C₁₋₆ alkyl;
- R^{7b} and R^{7c} are each independently H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₁₋₆ haloalkyl, C₁₋₆ alkyl-OH, C₃₋₆ cycloalkyl, or -C₁₋₆ alkyl-C₃₋₆ cycloalkyl;
- 30 R^{8a} is H, C₁₋₆ alkyl, C₂₋₆ alkoxyalkyl, C₃₋₆ cycloalkyl or -C₁₋₆ alkyl-C₃₋₆ cycloalkyl;
- R^{8b}, R^{8d}, and R^{8e} are each independently H or C₁₋₆ alkyl;

ring B is C₆₋₁₂ aryl or heteroaryl having 5 to 12 ring members and 1 to 6 heteroatoms, each independently N, O or S;

the subscript m₈ is an integer from 0 to 5;

each R^{8f} is independently C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ alkoxy, C₁₋₆ deuterioalkoxy, halo, C₁₋₆ haloalkyl, cyano, -X^{8f}-cyano, C₃₋₁₂ cycloalkyl, -X^{8f}-C₃₋₆ cycloalkyl, -CH=CR^{8fi}R^{8f2}, heterocycloalkyl, -X^{8f}-heterocycloalkyl, C₆₋₁₂ aryl, -X^{8f}-C₆₋₁₂ aryl, heteroaryl, or -X^{8f}-heteroaryl, wherein each heterocycloalkyl has 3 to 12 ring members and 1 to 4 heteroatoms, each independently N, O, or S, and each heteroaryl has 5 to 10 ring members and 1 to 4 heteroatoms, each independently N, O, or S, wherein each alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is substituted with 0 to 3 R^{8f3};

alternatively, two R^{8f} groups on adjacent ring vertices combine to form a C₃₋₆ cycloalkyl or a heterocycloalkyl having 3 to 6 ring members and 1 to 3 heteroatoms, each independently N, O or S, wherein the cycloalkyl or heterocycloalkyl is substituted with 0 to 3 R^{8f3};

each X^{8f} is independently C₁₋₆ alkylene, C₂₋₆ alkenylene, -O-C₁₋₆ alkylene, C(O), O, or S;

each R^{8fi} and R^{8f2} are combined with the carbon to which they are attached to form a heterocycloalkyl having 3 to 10 ring members and 1 to 3 heteroatoms, each independently N, O or S, wherein the heterocycloalkyl is substituted with 0 to 3 R^{8f3};

each R^{8f3} is independently C₁₋₆ alkyl, -Y⁸-C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, -Y⁸-C₁₋₆ deuterioalkyl, -OH, -C₁₋₆ alkyl-OH, -Y⁸-C₁₋₆ alkyl-OH, -C₁₋₆ alkyl-Y⁸-C₁₋₆ alkyl, -(C₁₋₂ alkyl-O)₁₋₄-C₁₋₂ alkyl, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, -Y⁸-C₁₋₆ haloalkyl, cyano, -C₁₋₆ alkyl-cyano, -C₁₋₆ alkyl-NR^{8g}R^{8h}, oxo, C₃₋₆ cycloalkyl, -X^{8f3}-C₃₋₆ cycloalkyl, heterocycloalkyl, -X^{8f3}-heterocycloalkyl, phenyl, -X^{8f3}-phenyl, heteroaryl, or -X^{8f3}-heteroaryl, wherein each heterocycloalkyl has 3 to 12 members and 1 to 4 heteroatoms, each independently N, O, S, or S(O)₂, and each heteroaryl has 5 to 10 ring members and 1 to 4 heteroatoms, each independently N, O, or S, and wherein each heterocycloalkyl and heteroaryl are substituted with 0 to 2 C₁₋₄ alkyl or halo;

each X^{8f3} is independently C_{1-6} alkylene, O, C(O), or S(O)₂;
each Y^8 is independently C(O), C(O)O, N(R^{8f4})C(O), O, S, or S(O)₂;
each R^{8g} and R^{8h} is independently H, C_{1-3} alkyl, or C_{1-6} haloalkyl;
alternatively, two R^{8f3} groups on the same or adjacent ring vertices combine to form a
5 C_{3-6} cycloalkyl or a heterocycloalkyl having 3 to 6 ring members and 1 to 3
heteroatoms, each independently N, O or S, wherein nitrogen atom ring
members in the heterocycloalkyl are substituted with 0 to 1 C_{1-4} alkyl; and
each R^{8f4} is independently H or C_{1-6} alkyl;
or a pharmaceutically acceptable salt thereof.

10 **[0005]** In another embodiment, the present disclosure provides a pharmaceutical
composition comprising a compound of the present disclosure, and a pharmaceutically
acceptable excipient.

[0006] In another embodiment, the present disclosure provides a method of treating a
disease or disorder mediated at least in part by cyclin activity, the method comprising
15 administering to a subject in need thereof, a therapeutically effective amount of a compound
of the present disclosure, or a pharmaceutically acceptable salt thereof, or a pharmaceutical
composition of the present disclosure, thereby treating the disorder or condition.

[0007] In another embodiment, the present disclosure provides a method of treating a
cancer mediated at least in part by cyclin A, the method comprising administering to a subject
20 in need thereof, a therapeutically effective amount of a compound of the present disclosure,
or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of the present
disclosure, thereby treating the cancer.

[0008] In another embodiment, the present invention provides intermediates useful in the
preparation of compounds of Formula (I).

25 **[0009]** Other objects, features, and advantages of the present disclosure will be apparent to
one of skill in the art from the following detailed description and figures.

BRIEF DESCRIPTION OF THE DRAWINGS

[0010] NOT APPLICABLE

DETAILED DESCRIPTION

I. General

5 [0011] Provided herein are compounds and compositions that disrupt the typical cellular function of cyclins. Also provided herein are, for example, methods of treating or preventing a disease, disorder or condition, or a symptom thereof, mediated by cyclin activity.

[0012] Complexes between cyclins and cyclin dependent kinases (CDKs) are responsible for phosphorylating a wide range of substrates, thereby modulating the activity of the substrates. Many of these substrates are important in the cell cycle and the cyclin and CDKs that regulate these substrates therefore play key roles in regulating the cell cycle, including
10 Cyclins D, A, E and B, and CDKs 1, 2, 4 and 6. Without being bound to any particular theory, certain substrates, including p21, p27, Rb, E2F and CDC6, first bind to the cyclin-CDK complex via a conserved RxL motif within the substrate (Adams et al. Mol Cell Biol. 1996. 16(12):6223-33.) and bind to a region with the cyclin that is referred to as an RxL binding domain or a “hydrophobic patch” (Brown et al. Nat Cell Biol. 1999.1(7):438-43) and
15 contains a highly conserved MRAIL motif. Compounds that disrupt the binding of substrates to cyclins have been posited to be of potential therapeutic utility, including in the disruption of cancer cell proliferation (Chen et al. Proc Natl Acad Sci U S A. 1999. 96(8):4325-9).

[0013] Without being bound to any particular theory, it is believed that compounds of the present disclosure inhibit the binding of substrates to the hydrophobic patch region of cyclins
20 including, but not limited to, Cyclins A, E and B. Compounds of the present disclosure include compounds that bind more potently to one or more cyclins.

II. Definitions

[0014] As used herein, the term “about” means a range of values including the specified value, which a person of ordinary skill in the art would consider reasonably similar to the
25 specified value. In some embodiments, the term “about” means within a standard deviation using measurements generally acceptable in the art. In some embodiments, about means a range extending to +/- 10% of the specified value. In some embodiments, about means the specified value.

[0015] “Alkyl” refers to a straight or branched, saturated, aliphatic radical having the
30 number of carbon atoms indicated. Alkyl can include any number of carbons, such as C₁₋₂,

C₁₋₃, C₁₋₄, C₁₋₅, C₁₋₆, C₁₋₇, C₁₋₈, C₁₋₉, C₁₋₁₀, C₂₋₃, C₂₋₄, C₂₋₅, C₂₋₆, C₃₋₄, C₃₋₅, C₃₋₆, C₄₋₅, C₄₋₆ and C₅₋₆. For example, C₁₋₆ alkyl includes, but is not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, hexyl, etc. Alkyl can also refer to alkyl groups having up to 20 carbons atoms, such as, but not limited to heptyl, octyl, nonyl, decyl, etc. Alkyl groups can be substituted or unsubstituted.

[0016] “Alkylene” refers to a straight or branched, saturated, aliphatic radical having the number of carbon atoms indicated, and linking at least two other groups, *i.e.*, a divalent hydrocarbon radical. The two moieties linked to the alkylene can be linked to the same atom or different atoms of the alkylene group. For instance, a straight chain alkylene can be the bivalent radical of $-(CH_2)_n-$, where n is 1, 2, 3, 4, 5 or 6. Representative alkylene groups include, but are not limited to, methylene, ethylene, propylene, isopropylene, butylene, isobutylene, sec-butylene, pentylene and hexylene. Alkylene groups can be substituted or unsubstituted.

[0017] “Alkenyl” refers to a straight chain or branched hydrocarbon having at least 2 carbon atoms and at least one double bond. Alkenyl can include any number of carbons, such as C₂, C₂₋₃, C₂₋₄, C₂₋₅, C₂₋₆, C₂₋₇, C₂₋₈, C₂₋₉, C₂₋₁₀, C₃, C₃₋₄, C₃₋₅, C₃₋₆, C₄, C₄₋₅, C₄₋₆, C₅, C₅₋₆, and C₆. Alkenyl groups can have any suitable number of double bonds, including, but not limited to, 1, 2, 3, 4, 5 or more. Examples of alkenyl groups include, but are not limited to, vinyl (ethenyl), propenyl, isopropenyl, 1-butenyl, 2-butenyl, isobutenyl, butadienyl, 1-pentenyl, 2-pentenyl, isopentenyl, 1,3-pentadienyl, 1,4-pentadienyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 1,3-hexadienyl, 1,4-hexadienyl, 1,5-hexadienyl, 2,4-hexadienyl, or 1,3,5-hexatrienyl. Alkenyl groups can be substituted or unsubstituted.

[0018] “Alkenylene” refers to a straight or branched hydrocarbon having at least 2 carbon atoms, one double bond, and linking at least two other groups, *i.e.*, a divalent hydrocarbon radical. Alkenylene can include any number of carbons, such as C₂, C₂₋₃, C₂₋₄, C₂₋₅, C₂₋₆, C₂₋₇, C₂₋₈, C₂₋₉, C₂₋₁₀, C₃, C₃₋₄, C₃₋₅, C₃₋₆, C₃₋₇, C₄, C₄₋₅, C₄₋₆, C₄₋₇, C₆₋₇, C₅, C₆ and C₇. The two moieties linked to the alkenylene can be linked to the same atom or different atoms of the alkenylene group. Representative alkenylene groups include, but are not limited to, (E)-hex-2-enylene, (Z)-hex-2-enylene, (E)-hept-2-enylene, (Z)-hept-2-enylene, (E)-hept-3-enylene, and (Z)-hept-3-enylene. Alkenylene moieties can be in the E or Z isomer. Alkenylene groups can be substituted or unsubstituted.

[0019] “Alkynyl” refers to either a straight chain or branched hydrocarbon having at least 2 carbon atoms and at least one triple bond. Alkynyl can include any number of carbons, such as C₂, C₂₋₃, C₂₋₄, C₂₋₅, C₂₋₆, C₂₋₇, C₂₋₈, C₂₋₉, C₂₋₁₀, C₃, C₃₋₄, C₃₋₅, C₃₋₆, C₄, C₄₋₅, C₄₋₆, C₅, C₅₋₆, and C₆. Examples of alkynyl groups include, but are not limited to, acetylenyl, propynyl, 5 1-butynyl, 2-butynyl, butadiynyl, 1-pentynyl, 2-pentynyl, isopentynyl, 1,3-pentadiynyl, 1,4-pentadiynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 1,3-hexadiynyl, 1,4-hexadiynyl, 1,5-hexadiynyl, 2,4-hexadiynyl, or 1,3,5-hexatriynyl. Alkynyl groups can be substituted or unsubstituted.

[0020] “Alkoxy” refers to an alkyl group having an oxygen atom that connects the alkyl group to the point of attachment: alkyl-O-. As for alkyl group, alkoxy groups can have any 10 suitable number of carbon atoms, such as C₁₋₆. Alkoxy groups include, for example, methoxy, ethoxy, propoxy, iso-propoxy, butoxy, 2-butoxy, iso-butoxy, sec-butoxy, tert-butoxy, pentoxy, hexoxy, etc. The alkoxy groups can be substituted or unsubstituted.

[0021] “Alkoxyalkyl” refers to alkyl group connected to an oxygen atom that is further 15 connected to an second alkyl group, the second alkyl group being the point of attachment to the remainder of the molecule: alkyl-O-alkyl. The alkyl portion can have any suitable number of carbon atoms, such as C₂₋₆. Alkoxyalkyl groups include, for example, methoxymethyl, ethoxymethyl, methoxyethyl, ethoxyethyl, etc. The alkoxy groups can be substituted or unsubstituted.

20 [0022] “Halo” or “halogen” refers to fluorine, chlorine, bromine and iodine.

[0023] “Haloalkyl” refers to alkyl, as defined above, where some or all of the hydrogen atoms are replaced with halogen atoms. As for alkyl group, haloalkyl groups can have any suitable number of carbon atoms, such as C₁₋₆. For example, haloalkyl includes 25 trifluoromethyl, fluoromethyl, etc. In some instances, the term “perfluoro” can be used to define a compound or radical where all the hydrogens are replaced with fluorine. For example, perfluoromethyl refers to 1,1,1-trifluoromethyl.

[0024] “Haloalkoxy” refers to an alkoxy group where some or all of the hydrogen atoms are substituted with halogen atoms. As for an alkyl group, haloalkoxy groups can have any suitable number of carbon atoms, such as C₁₋₆. The alkoxy groups can be substituted with 1, 30 2, 3, or more halogens. When all the hydrogens are replaced with a halogen, for example by fluorine, the compounds are per-substituted, for example, perfluorinated. Haloalkoxy includes, but is not limited to, trifluoromethoxy, 2,2,2-trifluoroethoxy, perfluoroethoxy, etc.

[0025] “Cycloalkyl” refers to a saturated or partially unsaturated, monocyclic, spirocyclic, fused or bridged polycyclic ring assembly containing from 3 to 12 ring atoms, or the number of atoms indicated. Cycloalkyl can include any number of carbons, such as C₃₋₆, C₄₋₆, C₅₋₆, C₃₋₈, C₄₋₈, C₅₋₈, C₆₋₈, C₃₋₉, C₃₋₁₀, C₃₋₁₁, and C₃₋₁₂. Saturated monocyclic cycloalkyl rings include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cyclooctyl. Saturated bicyclic and polycyclic cycloalkyl rings include, for example, norbornane, [2.2.2] bicyclooctane, decahydronaphthalene and adamantane. Cycloalkyl groups can also be partially unsaturated, having one or more double or triple bonds in the ring, but cycloalkyl groups are not aromatic. Representative cycloalkyl groups that are partially unsaturated include, but are not limited to, cyclobutenyl, cyclopentenyl, cyclohexenyl, cyclohexadienyl (1,3- and 1,4-isomers), cycloheptenyl, cycloheptadienyl, cyclooctenyl, cyclooctadienyl (1,3-, 1,4- and 1,5-isomers), norbornenyl, and norbornadienyl. When cycloalkyl is a C₃₋₆ monocyclic cycloalkyl, exemplary groups include, but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, cyclohexadienyl (1,3- and 1,4-isomers). When cycloalkyl is a C₅₋₁₀ fused bicyclic cycloalkyl, exemplary groups include, but are not limited to bicyclo[3.1.0]hexanyl, bicyclo[4.1.0]heptanyl, bicyclo[4.2.0]octanyl, and octahydro-1H-indenyl. When cycloalkyl is a C₅₋₁₀ bridged polycyclic cycloalkyl, exemplary groups include, but are not limited to bicyclo[2.2.1]heptane, bicyclo[3.1.1]heptane, and bicyclo[2.1.1]hexane. When cycloalkyl is a C₅₋₁₀ spirocycloalkyl, exemplary groups include, but are not limited to spiro[3.3]heptane, spiro[3.4]octane, spiro[3.5]nonanyl, spiro[2.5]octane, and spiro[2.4]heptane. Cycloalkyl groups can be substituted or unsubstituted.

[0026] “Heterocycloalkyl” refers to a saturated or partially unsaturated, monocyclic, spirocyclic, fused or bridged polycyclic ring assembly having from 3 to 12 ring members and from 1 to 4 heteroatoms of N, O and S. The heteroatoms can also be oxidized, such as, but not limited to, -S(O)- and -S(O)₂-. Heterocycloalkyl groups can include any number of ring atoms, such as, 3 to 6, 4 to 6, 5 to 6, 3 to 8, 4 to 8, 5 to 8, 6 to 8, 3 to 9, 3 to 10, 3 to 11, or 3 to 12 ring members. Any suitable number of heteroatoms can be included in the heterocycloalkyl groups, such as 1, 2, 3, or 4, or 1 to 2, 1 to 3, 1 to 4, 2 to 3, 2 to 4, or 3 to 4. The heterocycloalkyl group can include groups such as aziridine, azetidine, pyrrolidine, piperidine, azepane, azocane, quinuclidine, pyrazolidine, imidazolidine, piperazine (1,2-, 1,3- and 1,4-isomers), oxirane, oxetane, tetrahydrofuran, oxane (tetrahydropyran), tetrahydropyridine, oxepane, thiirane, thietane, thiolane (tetrahydrothiophene), thiane

(tetrahydrothiopyran), oxazolidine, isoxazolidine, thiazolidine, isothiazolidine, dioxolane, dithiolane, morpholine, thiomorpholine, dioxane, or dithiane. Heterocycloalkyl groups can be unsubstituted or substituted.

[0027] The heterocycloalkyl groups can be linked via any position on the ring. For example, aziridine can be 1- or 2-aziridine, azetidine can be 1- or 2- azetidine, pyrrolidine can be 1-, 2- or 3-pyrrolidine, piperidine can be 1-, 2-, 3- or 4-piperidine, pyrazolidine can be 1-, 2-, 3-, or 4-pyrazolidine, imidazolidine can be 1-, 2-, 3- or 4-imidazolidine, piperazine can be 1-, 2-, 3- or 4-piperazine, tetrahydrofuran can be 1- or 2-tetrahydrofuran, oxazolidine can be 2-, 3-, 4- or 5-oxazolidine, isoxazolidine can be 2-, 3-, 4- or 5-isoxazolidine, thiazolidine can be 2-, 3-, 4- or 5-thiazolidine, isothiazolidine can be 2-, 3-, 4- or 5- isothiazolidine, and morpholine can be 2-, 3- or 4-morpholine.

[0028] When heterocycloalkyl is a monocyclic heterocycloalkyl having 3 to 6 ring members and 1 to 3 heteroatoms, representative members include, but are not limited to, pyrrolidine, piperidine, tetrahydrofuran, oxane, tetrahydrothiophene, thiane, pyrazolidine, imidazolidine, piperazine, oxazolidine, isoxazolidine, thiazolidine, isothiazolidine, morpholine, thiomorpholine, dioxane and dithiane. Heterocycloalkyl can also be monocyclic heterocycloalkyl having 5 to 6 ring members and 1 to 2 heteroatoms, with representative members including, but not limited to, pyrrolidine, piperidine, tetrahydrofuran, tetrahydrothiophene, pyrazolidine, imidazolidine, piperazine, oxazolidine, isoxazolidine, thiazolidine, isothiazolidine, and morpholine.

[0029] “Aryl” refers to an aromatic ring system having any suitable number of ring atoms and any suitable number of rings. Aryl groups can include any suitable number of ring atoms, such as, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16 ring atoms, as well as from 6 to 10, 6 to 12, or 6 to 14 ring members. Aryl groups can be monocyclic, fused to form bicyclic or tricyclic groups, or linked by a bond to form a biaryl group. Representative aryl groups include phenyl, naphthyl and biphenyl. Other aryl groups include benzyl, having a methylene linking group. Some aryl groups have from 6 to 12 ring members, such as phenyl, naphthyl or biphenyl. Other aryl groups have from 6 to 10 ring members, such as phenyl or naphthyl. Some other aryl groups have 6 ring members, such as phenyl. Aryl groups can be substituted or unsubstituted.

[0030] “Heteroaryl” refers to a monocyclic or fused bicyclic or tricyclic aromatic ring assembly containing 5 to 12 ring atoms, where from 1 to 6 of the ring atoms are a heteroatom

such as N, O or S. The heteroatoms can also be oxidized, such as, but not limited to, -S(O)- and -S(O)₂-. Heteroaryl groups can include any number of ring atoms, such as, 5 to 6, 5 to 8, 5 to 9, 5 to 10, 5 to 12, or 9 to 12 ring members. Any suitable number of heteroatoms can be included in the heteroaryl groups, such as 1, 2, 3, 4, 5, or 6, or 1 to 2, 1 to 3, 1 to 4, 1 to 5, 2 to 3, 2 to 4, 2 to 5, 2 to 6, 3 to 4, 3 to 5, or 3 to 6. Heteroaryl groups can have from 5 to 8 ring members and from 1 to 4 heteroatoms, or from 5 to 8 ring members and from 1 to 3 heteroatoms, or from 5 to 6 ring members and from 1 to 4 heteroatoms, or from 5 to 6 ring members and from 1 to 3 heteroatoms. The heteroaryl group can include groups such as pyrrole, pyridine, imidazole, pyrazole, triazole, tetrazole, pyrazine, pyrimidine, pyridazine, triazine (1,2,3-, 1,2,4- and 1,3,5-isomers), thiophene, furan, thiazole, isothiazole, oxazole, and isoxazole. The heteroaryl groups can also be fused to aromatic ring systems, such as a phenyl ring, to form members including, but not limited to, benzopyrroles such as indole and isoindole, benzopyridines such as quinoline and isoquinoline, benzopyrazine (quinoxaline), benzopyrimidine (quinazoline), benzopyridazines such as phthalazine and cinnoline, benzothiophene, and benzofuran. Other heteroaryl groups include heteroaryl rings linked by a bond, such as bipyridine. Heteroaryl groups can be substituted or unsubstituted.

[0031] The heteroaryl groups can be linked via any position on the ring. For example, pyrrole includes 1-, 2- and 3-pyrrole, pyridine includes 2-, 3- and 4-pyridine, imidazole includes 1-, 2-, 4- and 5-imidazole, pyrazole includes 1-, 3-, 4- and 5-pyrazole, triazole includes 1-, 4- and 5-triazole, tetrazole includes 1- and 5-tetrazole, pyrimidine includes 2-, 4-, 5- and 6- pyrimidine, pyridazine includes 3- and 4-pyridazine, 1,2,3-triazine includes 4- and 5-triazine, 1,2,4-triazine includes 3-, 5- and 6-triazine, 1,3,5-triazine includes 2-triazine, thiophene includes 2- and 3-thiophene, furan includes 2- and 3-furan, thiazole includes 2-, 4- and 5-thiazole, isothiazole includes 3-, 4- and 5-isothiazole, oxazole includes 2-, 4- and 5-oxazole, isoxazole includes 3-, 4- and 5-isoxazole, indole includes 1-, 2- and 3-indole, isoindole includes 1- and 2-isoindole, quinoline includes 2-, 3- and 4-quinoline, isoquinoline includes 1-, 3- and 4-isoquinoline, quinazoline includes 2- and 4-quinazoline, cinnoline includes 3- and 4-cinnoline, benzothiophene includes 2- and 3-benzothiophene, and benzofuran includes 2- and 3-benzofuran.

[0032] Some heteroaryl groups include those having from 5 to 10 ring members and from 1 to 3 ring atoms including N, O or S, such as pyrrole, pyridine, imidazole, pyrazole, triazole, pyrazine, pyrimidine, pyridazine, triazine (1,2,3-, 1,2,4- and 1,3,5-isomers), thiophene, furan,

thiazole, isothiazole, oxazole, isoxazole, indole, isoindole, quinoline, isoquinoline, quinoxaline, quinazoline, phthalazine, cinnoline, benzothiophene, and benzofuran. Other heteroaryl groups include those having from 5 to 8 ring members and from 1 to 3 heteroatoms, such as pyrrole, pyridine, imidazole, pyrazole, triazole, pyrazine, pyrimidine, pyridazine, triazine (1,2,3-, 1,2,4- and 1,3,5-isomers), thiophene, furan, thiazole, isothiazole, oxazole, and isoxazole. Some other heteroaryl groups include those having from 9 to 12 ring members and from 1 to 3 heteroatoms, such as indole, isoindole, quinoline, isoquinoline, quinoxaline, quinazoline, phthalazine, cinnoline, benzothiophene, benzofuran and bipyridine. Still other heteroaryl groups include those having from 5 to 6 ring members and from 1 to 2 ring atoms including N, O or S, such as pyrrole, pyridine, imidazole, pyrazole, pyrazine, pyrimidine, pyridazine, thiophene, furan, thiazole, isothiazole, oxazole, and isoxazole.

[0033] “Thiophenyl” refers to a thiophene radical.

[0034] As used herein, the term “oxo” refers to an oxygen atom connected to the point of attachment by a double bond (=O).

[0035] “Pharmaceutically acceptable excipient” refers to a substance that aids the formulation and/or administration of an active agent to a subject. Pharmaceutical excipients useful in the present disclosure include, but are not limited to, binders, fillers, disintegrants, lubricants, coatings, sweeteners, flavors and colors. One of skill in the art will recognize that other pharmaceutical excipients are useful in the present disclosure.

[0036] “Subject” refers to animals such as mammals, including, but not limited to, primates (e.g., humans), cows, sheep, goats, horses, dogs, cats, rabbits, rats, mice and the like. In some embodiments, the subject is a human.

[0037] “Administering” refers to oral administration, administration as a suppository, topical contact, parenteral, intravenous, intraperitoneal, intramuscular, intralesional, intranasal or subcutaneous administration, intrathecal administration, or the implantation of a slow-release device e.g., a mini-osmotic pump, to the subject.

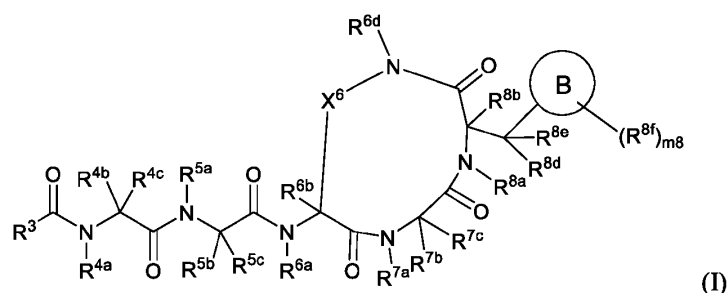
[0038] “Therapeutically effective amount” refers to a dose that produces therapeutic effects for which it is administered. The exact dose will depend on the purpose of the treatment, and will be ascertainable by one skilled in the art using known techniques (*see, e.g.*, Lieberman, *Pharmaceutical Dosage Forms* (vols. 1-3, 1992); Lloyd, *The Art, Science and Technology of Pharmaceutical Compounding* (1999); Pickar, *Dosage Calculations* (1999); and Remington:

The Science and Practice of Pharmacy, 20th Edition, 2003, Gennaro, Ed., Lippincott, Williams & Wilkins)

[0039] “Treat”, “treating” and “treatment” refers to any indicia of success in the treatment or amelioration of an injury, pathology, condition, or symptom (e.g., pain), including any objective or subjective parameter such as abatement; remission; diminishing of symptoms or making the symptom, injury, pathology or condition more tolerable to the patient; decreasing the frequency or duration of the symptom or condition. The treatment or amelioration of symptoms can be based on any objective or subjective parameter; including, e.g., the result of a physical examination.

10 III. Compounds

[0040] In some embodiments, the present disclosure provides a compound of Formula (I):



R³ is

- (a) C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, or C₁₋₆ haloalkyl, each substituted with 0 to 5 R^{3a},
- (b) C₃₋₁₂ cycloalkyl substituted with 0 to 5 R^{3b}, or
- (c) heterocycloalkyl having 3 to 12 ring members and 1 to 4 heteroatoms, each independently N, O, or S, wherein the heterocycloalkyl is substituted with 0 to 5 R^{3c};
- (g) heteroaryl having 5 to 6 ring members and 1 to 3 heteroatoms, each independently N, O, or S, wherein the heteroaryl is substituted with 0, 1, 2, 3, 4, or 5 R^{3g};

each R^{3a} is –OH, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, or –O–C(O)C₁₋₆ alkyl;

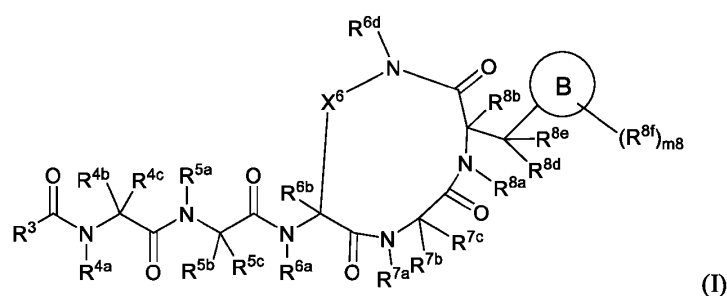
each R^{3b} is independently C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, –OH, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, or cyano;

- each R^{3c} is independently C₁₋₆ alkyl, halo, C₁₋₆ haloalkyl, cyano, C₃₋₆ cycloalkyl, or oxo;
- each R^{3g} is independently C₁₋₆ alkyl, halo, C₁₋₆ haloalkyl, or C₃₋₆ cycloalkyl;
- R^{4a} is H or C₁₋₆ alkyl;
- 5 R^{4b} and R^{4c} are each independently H, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, -C₁₋₆ alkyl-C₃₋₆ cycloalkyl, heterocycloalkyl, -C₁₋₆ alkyl-heterocycloalkyl, phenyl, -C₁₋₆ alkyl-phenyl, heteroaryl, or -C₁₋₆ alkyl-heteroaryl, wherein each heterocycloalkyl has 3 to 6 ring members and 1 to 3 heteroatoms, each independently N, O, or S, and each heteroaryl has 5 to 6 ring members and 1
- 10 to 3 heteroatoms, each independently N, O, or S;
- alternatively, R^{4c} and R^{4a} together with the carbon and nitrogen to which each is attached combine to form a heterocycloalkyl having 3 to 6 ring members and 1 to 3 heteroatoms, each independently N, O, or S, wherein the heterocycloalkyl is substituted with 0 to 4 R^{4a1};
- 15 each R^{4a1} is independently C₁₋₆ alkyl, -OH, C₁₋₆ alkyl-OH, C₁₋₆ alkoxy, or halo;
- R^{5a} is H or C₁₋₆ alkyl;
- R^{5b} and R^{5c} are each independently H, C₁₋₆ alkyl, -C₁₋₆ alkyl-OH, C₂₋₆ alkoxyalkyl, C₁₋₆ haloalkyl, -C₁₋₆ alkyl-C(O)NR^{5b1}R^{5b2}, -C₁₋₆ alkyl-C(O)OR^{5b1}, C₃₋₆ cycloalkyl, C₁₋₆ alkyl-C₃₋₆ cycloalkyl, heterocycloalkyl, -C₁₋₆ alkyl-
- 20 heterocycloalkyl, phenyl, -C₁₋₆ alkyl-phenyl, heteroaryl, or -C₁₋₆ alkyl-heteroaryl, wherein each heterocycloalkyl has 3 to 6 ring members and 1 to 3 heteroatoms, each independently N, O, or S, and each heteroaryl has 5 to 6 ring members and 1 to 3 heteroatoms, each independently N, O, or S, and wherein each cycloalkyl, heterocycloalkyl, phenyl, and heteroaryl is
- 25 substituted with 0 to 3 R^{5b5};
- each R^{5b1} and R^{5b2} are independently H, C₁₋₄ alkyl, or C₁₋₄ haloalkyl;
- alternatively, R^{5b1} and R^{5b2} together with the nitrogen to which each is attached combine to form a heterocycloalkyl having 3 to 6 ring members and 0 to 1 additional heteroatoms, wherein the heterocycloalkyl is substituted with 0 to 2
- 30 R^{5b3};
- each R^{5b3} and R^{5b5} is independently C₁₋₆ alkyl, halo, C₁₋₆ haloalkyl, or cyano;
- X⁶ is C₆₋₇ alkylene or C₆₋₇ alkenylene;

- R^{6a} is H, C_{1-6} alkyl, C_{1-6} deuterioalkyl, C_{2-6} alkoxyalkyl, C_{3-6} cycloalkyl, $-C_{1-6}$ alkyl- C_{3-6} cycloalkyl, heterocycloalkyl, $-C_{1-6}$ alkyl-heterocycloalkyl, phenyl, $-C_{1-6}$ alkyl-phenyl, heteroaryl, or $-C_{1-6}$ alkyl-heteroaryl, wherein the heterocycloalkyl has 3 to 6 ring members and 1 to 3 heteroatoms, each independently N, O, or S, and the heteroaryl has 5 to 6 ring members and 1 to 3 heteroatoms, each independently N, O, or S;
- R^{6b} and R^{6d} are each independently H or C_{1-6} alkyl;
- R^{7a} is H or C_{1-6} alkyl;
- R^{7b} and R^{7c} are each independently H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} haloalkyl, C_{1-6} alkyl-OH, C_{3-6} cycloalkyl, or $-C_{1-6}$ alkyl- C_{3-6} cycloalkyl;
- R^{8a} is H, C_{1-6} alkyl, C_{2-6} alkoxyalkyl, C_{3-6} cycloalkyl or $-C_{1-6}$ alkyl- C_{3-6} cycloalkyl;
- R^{8b} , R^{8d} , and R^{8e} are each independently H or C_{1-6} alkyl;
- ring B is C_{6-12} aryl or heteroaryl having 5 to 12 ring members and 1 to 6 heteroatoms, each independently N, O or S;
- the subscript m8 is an integer from 0 to 5;
- each R^{8f} is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, C_{1-6} deuterioalkoxy, halo, C_{1-6} haloalkyl, cyano, $-X^{8f}$ -cyano, C_{3-12} cycloalkyl, $-X^{8f}$ - C_{3-6} cycloalkyl, $-CH=CR^{8f1}R^{8f2}$, heterocycloalkyl, $-X^{8f}$ -heterocycloalkyl, C_{6-12} aryl, $-X^{8f}$ - C_{6-12} aryl, heteroaryl, or $-X^{8f}$ -heteroaryl, wherein each heterocycloalkyl has 3 to 12 ring members and 1 to 4 heteroatoms, each independently N, O, or S, and each heteroaryl has 5 to 10 ring members and 1 to 4 heteroatoms, each independently N, O, or S, wherein each alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is substituted with 0 to 3 R^{8f3} ;
- alternatively, two R^{8f} groups on adjacent ring vertices combine to form a C_{3-6} cycloalkyl or a heterocycloalkyl having 3 to 6 ring members and 1 to 3 heteroatoms, each independently N, O or S, wherein the cycloalkyl or heterocycloalkyl is substituted with 0 to 3 R^{8f3} ;
- each X^{8f} is independently C_{1-6} alkylene, C_{2-6} alkenylene, $-O-C_{1-6}$ alkylene, C(O), O, or S;
- each R^{8f1} and R^{8f2} are combined with the carbon to which they are attached to form a heterocycloalkyl having 3 to 10 ring members and 1 to 3 heteroatoms, each independently N, O or S, wherein the heterocycloalkyl is substituted with 0 to 3 R^{8f3} ;

- each R^{8f3} is independently C_{1-6} alkyl, $-Y^8-C_{1-6}$ alkyl, C_{1-6} deuterioalkyl, $-Y^8-C_{1-6}$ deuterioalkyl, $-OH$, $-C_{1-6}$ alkyl- OH , $-Y^8-C_{1-6}$ alkyl- OH , $-C_{1-6}$ alkyl- Y^8-C_{1-6} alkyl, $-(C_{1-2}$ alkyl- $O)_{1-4}-C_{1-2}$ alkyl, C_{1-6} alkoxy, halo, C_{1-6} haloalkyl, $-Y^8-C_{1-6}$ haloalkyl, cyano, $-C_{1-6}$ alkyl-cyano, $-C_{1-6}$ alkyl- $NR^{8g}R^{8h}$,
 5 oxo, C_{3-6} cycloalkyl, $-X^{8f3}-C_{3-6}$ cycloalkyl, heterocycloalkyl, $-X^{8f3}-$ heterocycloalkyl, phenyl, $-X^{8f3}-$ phenyl, heteroaryl, or $-X^{8f3}-$ heteroaryl, wherein each heterocycloalkyl has 3 to 12 members and 1 to 4 heteroatoms, each independently N, O, S, or $S(O)_2$, and each heteroaryl has 5 to 10 ring members and 1 to 4 heteroatoms, each independently N, O, or S, and wherein
 10 each heterocycloalkyl and heteroaryl are substituted with 0 to 2 C_{1-4} alkyl or halo;
 each X^{8f3} is independently C_{1-6} alkylene, O, $C(O)$, or $S(O)_2$;
 each Y^8 is independently $C(O)$, $C(O)O$, $N(R^{8f4})C(O)$, O, S, or $S(O)_2$;
 each R^{8g} and R^{8h} is independently H, C_{1-3} alkyl, or C_{1-6} haloalkyl;
 15 alternatively, two R^{8f3} groups on the same or adjacent ring vertices combine to form a C_{3-6} cycloalkyl or a heterocycloalkyl having 3 to 6 ring members and 1 to 3 heteroatoms, each independently N, O or S, wherein nitrogen atom ring members in the heterocycloalkyl are substituted with 0 to 1 C_{1-4} alkyl; and
 each R^{8f4} is independently H or C_{1-6} alkyl;
 20 or a pharmaceutically acceptable salt thereof.

[0041] In some embodiments, the present disclosure provides a compound of Formula (I):



wherein

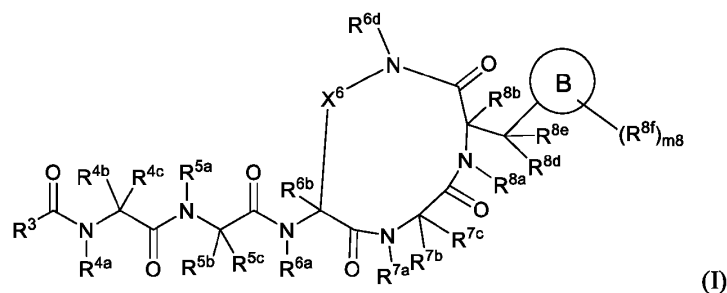
- R^3 is
- 25 (a) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{1-6} haloalkyl, each substituted with 0 to 5 R^{3a} ,
 (b) C_{3-12} cycloalkyl substituted with 0 to 5 R^{3b} , or

- (c) heterocycloalkyl having 3 to 12 ring members and 1 to 4 heteroatoms, each independently N, O, or S, wherein the heterocycloalkyl is substituted with 0 to 5 R^{3c};
- each R^{3a} is -OH, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, or -O-C(O)C₁₋₆ alkyl;
- 5 each R^{3b} is independently C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, -OH, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, or cyano;
- each R^{3c} is independently C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, or oxo;
- R^{4a} is H or C₁₋₆ alkyl;
- R^{4b} and R^{4c} are each independently H, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, -C₁₋₆ alkyl-C₃₋₆ cycloalkyl, heterocycloalkyl, -C₁₋₆ alkyl-heterocycloalkyl, phenyl, -C₁₋₆ alkyl-phenyl, heteroaryl, or -C₁₋₆ alkyl-heteroaryl, wherein each heterocycloalkyl has 3 to 6 ring members and 1 to 3 heteroatoms, each independently N, O, or S, and each heteroaryl has 5 to 6 ring members and 1 to 3 heteroatoms, each independently N, O, or S;
- 10 alternatively, R^{4c} and R^{4a} together with the carbon and nitrogen to which each is attached combine to form a heterocycloalkyl having 3 to 6 ring members, wherein the heterocycloalkyl is substituted with 0 to 4 R^{4a1};
- each R^{4a1} is independently C₁₋₆ alkyl, -OH, C₁₋₆ alkyl-OH, C₁₋₆ alkoxy, or halo;
- R^{5a} is H or C₁₋₆ alkyl;
- 20 R^{5b} and R^{5c} are each independently H, C₁₋₆ alkyl, -C₁₋₆ alkyl-OH, C₂₋₆ alkoxyalkyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, C₁₋₆ alkyl-C₃₋₆ cycloalkyl, heterocycloalkyl, -C₁₋₆ alkyl-heterocycloalkyl, phenyl, -C₁₋₆ alkyl-phenyl, heteroaryl, or -C₁₋₆ alkyl-heteroaryl, wherein each heterocycloalkyl has 3 to 6 ring members and 1 to 3 heteroatoms, each independently N, O, or S, and each heteroaryl has 5 to 6 ring members and 1 to 3 heteroatoms, each independently N, O, or S, and wherein each cycloalkyl, heterocycloalkyl, phenyl, and heteroaryl is substituted with 0 to 3 R^{5b5};
- 25 each R^{5b5} is independently C₁₋₆ alkyl, halo, or C₁₋₆ haloalkyl;
- X⁶ is C₆₋₇ alkylene or C₆₋₇ alkenylene;
- 30 R^{6a} is H, C₁₋₆ alkyl, C₂₋₆ alkoxyalkyl, C₃₋₆ cycloalkyl, -C₁₋₆ alkyl-C₃₋₆ cycloalkyl, heterocycloalkyl, -C₁₋₆ alkyl-heterocycloalkyl, phenyl, -C₁₋₆ alkyl-phenyl, heteroaryl, or -C₁₋₆ alkyl-heteroaryl, wherein the heterocycloalkyl has 3 to 6 ring members and 1 to 3 heteroatoms, each independently N, O, or S, and the

- heteroaryl has 5 to 6 ring members and 1 to 3 heteroatoms, each independently N, O, or S;
- R^{6b} and R^{6d} are each independently H or C_{1-6} alkyl;
- R^{7a} is H or C_{1-6} alkyl;
- 5 R^{7b} and R^{7c} are each independently H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} haloalkyl, C_{1-6} alkyl-OH, C_{3-6} cycloalkyl, or $-C_{1-6}$ alkyl- C_{3-6} cycloalkyl;
- R^{8a} is H, C_{1-6} alkyl, C_{2-6} alkoxyalkyl, C_{3-6} cycloalkyl or $-C_{1-6}$ alkyl- C_{3-6} cycloalkyl;
- R^{8b} , R^{8d} , and R^{8e} are each independently H or C_{1-6} alkyl;
- ring B is C_{6-12} aryl or heteroaryl having 5 to 12 ring members and 1 to 6 heteroatoms,
- 10 each independently N, O or S;
- the subscript m8 is an integer from 0 to 5;
- each R^{8f} is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, C_{1-6} deutoalkoxy, halo, C_{1-6} haloalkyl, cyano, $-X^{8f}$ -cyano, C_{3-6} cycloalkyl, $-X^{8f}$ - C_{3-6} cycloalkyl, $-CH=CR^{8f1}R^{8f2}$, heterocycloalkyl,
- 15 $-X^{8f}$ -heterocycloalkyl, C_{6-12} aryl, $-X^{8f}$ - C_{6-12} aryl, heteroaryl, or $-X^{8f}$ -heteroaryl, wherein each heterocycloalkyl has 3 to 12 ring members and 1 to 4 heteroatoms, each independently N, O, or S, and each heteroaryl has 5 to 10 ring members and 1 to 4 heteroatoms, each independently N, O, or S, wherein each alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is
- 20 substituted with 0 to 3 R^{8f3} ;
- alternatively, two R^{8f} groups on adjacent ring vertices combine to form a C_{3-6} cycloalkyl or a heterocycloalkyl having 3 to 6 ring members and 1 to 3 heteroatoms, each independently N, O or S, wherein the cycloalkyl or heterocycloalkyl is substituted with 0 to 3 R^{8f3} ;
- 25 each X^{8f} is independently C_{1-6} alkylene, C_{2-6} alkenylene, $-O-C_{1-6}$ alkylene, O, or S;
- each R^{8f1} and R^{8f2} are combined with the carbon to which they are attached to form a heterocycloalkyl having 3 to 10 ring members and 1 to 3 heteroatoms, each independently N, O or S, wherein the heterocycloalkyl is substituted with 0 to 3 R^{8f3} ;
- 30 each R^{8f3} is independently C_{1-6} alkyl, $-Y^8-C_{1-6}$ alkyl, C_{1-6} deutoalkyl, $-Y^8-C_{1-6}$ deutoalkyl, $-OH$, $-C_{1-6}$ alkyl-OH, $-Y^8-C_{1-6}$ alkyl-OH, $-C_{1-6}$ alkyl- $-Y^8-C_{1-6}$ alkyl, $-(C_{1-2}$ alkyl-O) $_{1-4}$ - C_{1-2} alkyl, C_{1-6} alkoxy, halo, C_{1-6} haloalkyl, $-Y^8-C_{1-6}$ haloalkyl, cyano, $-C_{1-6}$ alkyl-cyano, oxo, C_{3-6} cycloalkyl,

- 5 $-X^{8f3}-C_{3-6}$ cycloalkyl, heterocycloalkyl, $-X^{8f3}-$ heterocycloalkyl, phenyl, $-X^{8f3}$ -phenyl, heteroaryl, or $-X^{8f3}$ -heteroaryl, wherein each heterocycloalkyl has 3 to 12 members and 1 to 4 heteroatoms, each independently N, O, S, or S(O)₂, and each heteroaryl has 5 to 10 ring members and 1 to 4 heteroatoms, each independently N, O, or S, and wherein nitrogen atom ring members in each heterocycloalkyl and heteroaryl are substituted with 0 to 1 C₁₋₄ alkyl;
- each X^{8f3} is independently C₁₋₆ alkylene, O, C(O), or S(O)₂;
- each Y^8 is independently C(O), C(O)O, N(R^{8f4})C(O), O, S, or S(O)₂;
- alternatively, two R^{8f3} groups on the same or adjacent ring vertices combine to form a
- 10 C₃₋₆ cycloalkyl or a heterocycloalkyl having 3 to 6 ring members and 1 to 3 heteroatoms, each independently N, O or S, wherein nitrogen atom ring members in the heterocycloalkyl are substituted with 0 to 1 C₁₋₄ alkyl; and
- each R^{8f4} is independently H or C₁₋₆ alkyl;
- or a pharmaceutically acceptable salt thereof.

- 15 **[0042]** In some embodiments, the present disclosure provides a compound of Formula (I):



wherein

R³ is

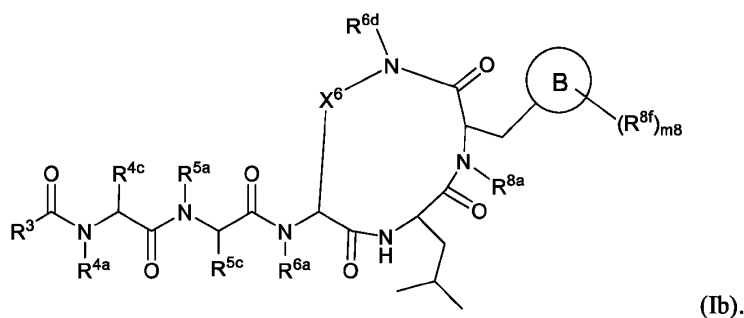
- 20 (a) C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, or C₁₋₆ haloalkyl, each substituted with 0 to 5 R^{3a},
- (b) C₃₋₁₂ cycloalkyl substituted with 0 to 5 R^{3b}, or
- (c) heterocycloalkyl having 3 to 12 ring members and 1 to 4 heteroatoms, each independently N, O, or S, wherein the heterocycloalkyl is substituted with 0 to 5 R^{3c};
- 25 each R^{3a} is -OH, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, or -O-C(O)C₁₋₆ alkyl;
- each R^{3b} is independently C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, -OH, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, or cyano;

- each R^{3c} is independently C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, or oxo;
R^{4a} is H or C₁₋₆ alkyl;
R^{4b} and R^{4c} are each independently H, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, -C₁₋₆ alkyl-C₃₋₆
cycloalkyl, heterocycloalkyl, -C₁₋₆ alkyl-heterocycloalkyl, phenyl, -C₁₋₆
5 alkyl-phenyl, heteroaryl, or -C₁₋₆ alkyl-heteroaryl, wherein each
heterocycloalkyl has 3 to 6 ring members and 1 to 3 heteroatoms, each
independently N, O, or S, and each heteroaryl has 5 to 6 ring members and 1
to 3 heteroatoms, each independently N, O, or S;
alternatively, R^{4c} and R^{4a} together with the carbon and nitrogen to which each is
10 attached combine to form a heterocycloalkyl having 3 to 6 ring members,
wherein the heterocycloalkyl is substituted with 0 to 4 R^{4a1};
each R^{4a1} is independently C₁₋₆ alkyl, -OH, C₁₋₆ alkyl-OH, C₁₋₆ alkoxy, or halo;
R^{5a} is H or C₁₋₆ alkyl;
R^{5b} and R^{5c} are each independently H, C₁₋₆ alkyl, -C₁₋₆ alkyl-OH, C₂₋₆ alkoxyalkyl,
15 C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, C₁₋₆ alkyl-C₃₋₆ cycloalkyl, heterocycloalkyl, -
C₁₋₆ alkyl-heterocycloalkyl, phenyl, -C₁₋₆ alkyl-phenyl, heteroaryl, or
-C₁₋₆ alkyl-heteroaryl, wherein each heterocycloalkyl has 3 to 6 ring members
and 1 to 3 heteroatoms, each independently N, O, or S, and each heteroaryl has
5 to 6 ring members and 1 to 3 heteroatoms, each independently N, O, or S,
20 and wherein each cycloalkyl, heterocycloalkyl, phenyl, and heteroaryl is
substituted with 0 to 3 R^{5b5};
each R^{5b5} is independently C₁₋₆ alkyl, halo, or C₁₋₆ haloalkyl;
X⁶ is C₆₋₇ alkylene or C₆₋₇ alkenylene;
R^{6a} is H, C₁₋₆ alkyl, C₂₋₆ alkoxyalkyl, C₃₋₆ cycloalkyl, -C₁₋₆ alkyl-C₃₋₆ cycloalkyl,
25 heterocycloalkyl, -C₁₋₆ alkyl-heterocycloalkyl, phenyl, -C₁₋₆ alkyl-phenyl,
heteroaryl, or -C₁₋₆ alkyl-heteroaryl, wherein the heterocycloalkyl has 3 to 6
ring members and 1 to 3 heteroatoms, each independently N, O, or S, and the
heteroaryl has 5 to 6 ring members and 1 to 3 heteroatoms, each independently
N, O, or S;
30 R^{6b} and R^{6d} are each independently H or C₁₋₆ alkyl;
R^{7a} is H or C₁₋₆ alkyl;
R^{7b} and R^{7c} are each independently H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₁₋₆ haloalkyl,
C₁₋₆ alkyl-OH, C₃₋₆ cycloalkyl, or -C₁₋₆ alkyl-C₃₋₆ cycloalkyl;

- R^{8a} is H, C_{1-6} alkyl, C_{2-6} alkoxyalkyl, C_{3-6} cycloalkyl or $-C_{1-6}$ alkyl- C_{3-6} cycloalkyl;
 R^{8b} , R^{8d} , and R^{8e} are each independently H or C_{1-6} alkyl;
 ring B is aryl or heteroaryl having 5 to 12 ring members and 1 to 6 heteroatoms, each
 independently N, O or S;
 5 the subscript m8 is an integer from 0 to 5;
 each R^{8f} is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, C_{1-6}
 deutoalkoxy, halo, C_{1-6} haloalkyl, cyano, $-X^{8f}$ -cyano, C_{3-12} cycloalkyl,
 $-X^{8f}$ - C_{3-6} cycloalkyl, $-CH=CR^{8f1}R^{8f2}$, heterocycloalkyl,
 $-X^{8f}$ -heterocycloalkyl, aryl, $-X^{8f}$ -aryl, heteroaryl, or $-X^{8f}$ -heteroaryl, wherein
 10 each heterocycloalkyl has 3 to 12 ring members and 1 to 4 heteroatoms, each
 independently N, O, or S, and each heteroaryl has 5 to 10 ring members and 1
 to 4 heteroatoms, each independently N, O, or S, wherein each alkynyl,
 cycloalkyl, heterocycloalkyl, phenyl, and heteroaryl is substituted with 0 to 3
 R^{8f3} ;
 15 alternatively, two R^{8f} groups on adjacent ring vertices combine to form a C_{3-6}
 cycloalkyl or a heterocycloalkyl having 3 to 6 ring members and 1 to 3
 heteroatoms, each independently N, O or S;
 each X^{8f} is independently C_{1-6} alkylene, C_{2-6} alkenylene, O, or S;
 each R^{8f1} and R^{8f2} are combined with the carbon to which they are attached to form a
 20 heterocycloalkyl having 3 to 10 ring members and 1 to 3 heteroatoms, each
 independently N, O or S, wherein the heterocycloalkyl is substituted with 0 to
 3 R^{8f3} ;
 each R^{8f3} is independently C_{1-6} alkyl, $-Y^8-C_{1-6}$ alkyl, C_{1-6} deutoalkyl,
 $-Y^8-C_{1-6}$ deutoalkyl, $-OH$, $-C_{1-6}$ alkyl- OH , $-Y^8-C_{1-6}$ alkyl- OH ,
 25 $-C_{1-6}$ alkyl- Y^8-C_{1-6} alkyl, C_{1-6} alkoxy, halo, C_{1-6} haloalkyl, $-Y^8-C_{1-6}$
 haloalkyl, cyano, $-C_{1-6}$ alkyl-cyano, oxo, C_{3-6} cycloalkyl, $-X^{8f3}-C_{3-6}$
 cycloalkyl, heterocycloalkyl, $-X^{8f3}$ -heterocycloalkyl, phenyl, $-X^{8f3}$ -phenyl,
 heteroaryl, or $-X^{8f3}$ -heteroaryl, wherein each heterocycloalkyl has 3 to 12
 members and 1 to 4 heteroatoms, each independently N, O, S, or $S(O)_2$, and
 30 each heteroaryl has 5 to 10 ring members and 1 to 4 heteroatoms, each
 independently N, O, or S, and wherein nitrogen atom ring members in each
 heterocycloalkyl and heteroaryl are substituted with 0 to 1 C_{1-4} alkyl;
 each X^{8f3} is independently C_{1-6} alkylene, O, $C(O)$, or $S(O)_2$;
 each Y^8 is independently $C(O)$, $C(O)O$, $N(R^{8f4})C(O)$, O, S, or $S(O)_2$;

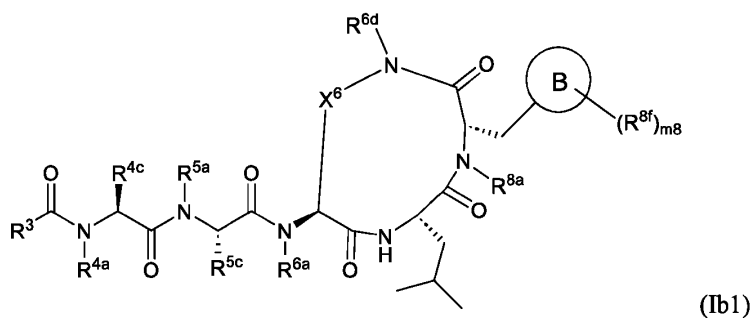
alternatively, two R^{8f3} groups on adjacent ring vertices combine to form a C_{3-6} cycloalkyl or a heterocycloalkyl having 3 to 6 ring members and 1 to 3 heteroatoms, each independently N, O or S; and
 each R^{8f4} is independently H or C_{1-6} alkyl;
 5 or a pharmaceutically acceptable salt thereof.

[0043] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I) having the structure of Formula (Ib):



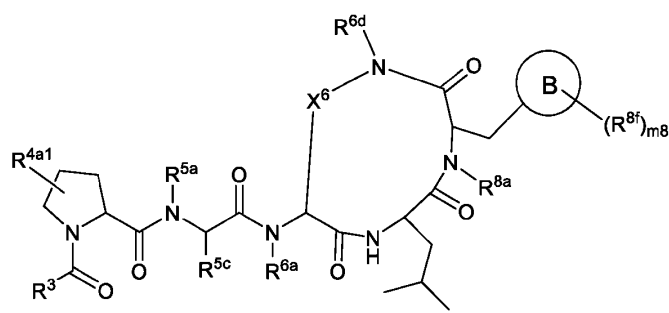
[0044] $R^3, R^{4a}, R^{4c}, R^{5a}, R^{5c}, R^{6a}, X^6, R^{6d}, R^{8a}, m8, R^{8f}$, and ring B can each independently
 10 be as defined for any embodiment of Formula (Ib) as described herein.

[0045] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I) having the structure of Formula (Ib1):



[0046] $R^3, R^{4a}, R^{4c}, R^{5a}, R^{5c}, R^{6a}, X^6, R^{6d}, R^{8a}, m8, R^{8f}$, and ring B can each independently
 15 be as defined for any embodiment of Formula (Ib1) as described herein.

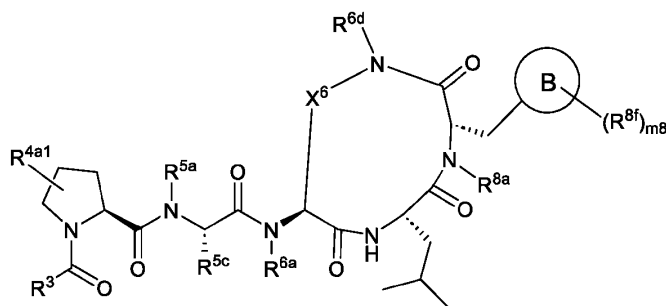
[0047] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I) having the structure of Formula (Ic):



(Ic).

[0048] R^3 , R^{4a1} , R^{5a} , R^{5c} , R^{6a} , X^6 , R^{6d} , R^{8a} , $m8$, R^{8f} , and ring B can each independently be as defined for any embodiment of Formula (Ic) as described herein.

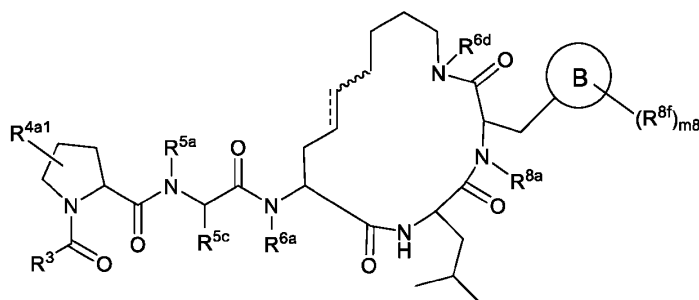
[0049] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I) having the structure of Formula (Ic1):



(Ic1)

[0050] R^3 , R^{4a1} , R^{5a} , R^{5c} , R^{6a} , X^6 , R^{6d} , R^{8a} , $m8$, R^{8f} , and ring B can each independently be as defined for any embodiment of Formula (Ic1) as described herein.

[0051] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I) having the structure of Formula (Id):

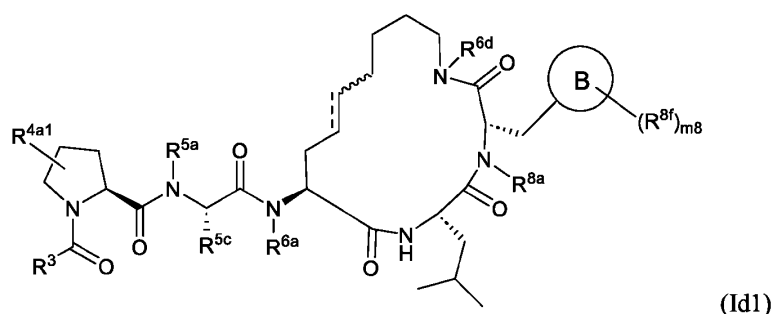


(Id),

wherein the dashed bond is absent or a single bond.

[0052] R^3 , R^{4a1} , R^{5a} , R^{5c} , R^{6a} , R^{6d} , R^{8a} , $m8$, R^{8f} , and ring B can each independently be as defined for any embodiment of Formula (Id) as described herein. When the dashed line is a single bond in Formula (Id), the wavy bond attached to the double bond indicates E, Z, or a mixture of both isomers.

- 5 [0053] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I) having the structure of Formula (Id1):



wherein the dashed bond is absent or a single bond.

- 10 [0054] R^3 , R^{4a1} , R^{5a} , R^{5c} , R^{6a} , R^{6d} , R^{8a} , $m8$, R^{8f} , and ring B can each independently be as defined for any embodiment of Formula (Id1) as described herein. When the dashed line is a bond in Formula (Id1), the wavy line attached to the double bond indicates E, Z, or a mixture or both linkages.

Residue 3

- 15 [0055] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein R^3 is (a) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{1-6} haloalkyl substituted with 0 to 5 R^{3a} . In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein R^3 is (a) C_{1-6} alkyl or C_{1-6} haloalkyl substituted with 0 to 2 R^{3a} . In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein R^3 is (a) C_{1-6} alkyl substituted with 0 to 2 R^{3a} . In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein R^3 is (a) C_{1-6} haloalkyl substituted with 0 to 2 R^{3a} . These embodiments of R^3 can be combined with any of
- 25 the embodiments described herein for R^{3a} .

[0056] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein each R^{3a} is –OH or C₁₋₆ alkoxy. In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1),
5 wherein each R^{3a} is –OH. These embodiments of R^{3a} can be combined with any of the relevant embodiments described herein for R³.

[0057] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein R³ is (b) C₃₋₁₂ cycloalkyl substituted with 0 to 3 R^{3b}. In some embodiments, the compound, or the
10 pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein R³ is (b) C₃₋₇ cycloalkyl substituted with 0 to 3 R^{3b}. In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein R³ is (b) C₅₋₆ cycloalkyl substituted with 0 to 2 R^{3b}. In some embodiments, the compound, or the
15 pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein R³ is (b) C₃₋₄ cycloalkyl substituted with 0 to 2 R^{3b}. These embodiments of R³ can be combined with any of the embodiments described herein for R^{3b}.

[0058] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein each
20 R^{3b} is halo, C₁₋₄ haloalkyl, or cyano. In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein each R^{3b} is halo or C₁₋₄ haloalkyl. In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein each R^{3b} is fluoro or trifluoromethyl. These
25 embodiments of R^{3b} can be combined with any of the relevant embodiments described herein for R³.

[0059] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein R³ is (c) heterocycloalkyl having 3 to 6 ring members and 1 to 3 heteroatoms, each independently
30 N, O, or S, wherein the heterocycloalkyl is substituted with 0 to 5 R^{3c}. In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein R³ is (c)

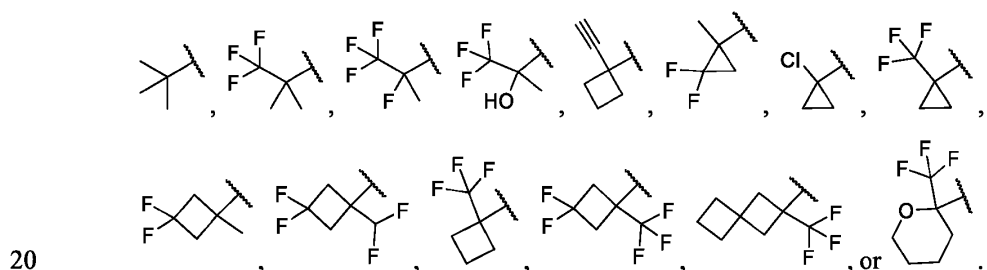
heterocycloalkyl having 6 ring members and 1 to 3 heteroatoms, each independently N, O, or S, wherein the heterocycloalkyl is substituted with 0 to 2 R^{3c}. These embodiments of R³ can be combined with any of the relevant embodiments described herein for R^{3c}.

5 [0060] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein R^{3c} is halo or C₁₋₄ haloalkyl. In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein each R^{3c} is fluoro or trifluoromethyl. These embodiments of R^{3c} can be combined with any of the embodiments described herein for R³.

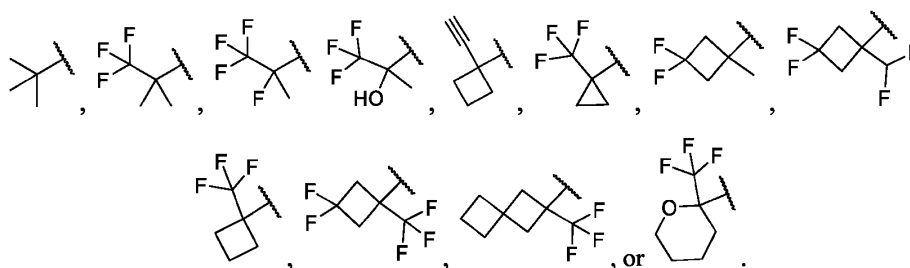
10 [0061] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein R³ is (g) heteroaryl having 5 to 6 ring members and 1 to 3 heteroatoms, each independently N, O, or S, wherein the heteroaryl is substituted with 0, 1, 2, 3, 4, or 5 R^{3g}.

15 [0062] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein R^{3g} is independently C₁₋₆ alkyl, halo, C₁₋₆ haloalkyl, or C₃₋₆ cycloalkyl.

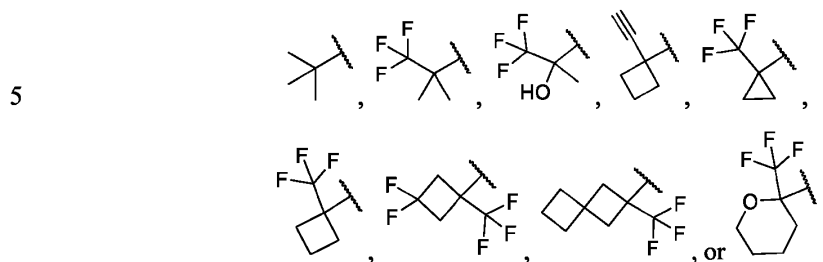
[0063] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein R³ is



[0064] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein R³ is



[0065] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein R³ is



[0066] Any of the embodiments described herein for residue 3 can be combined with any of the embodiments described herein for residues 4, 5, 6, 7, and 8. For example, any of the embodiments of R³ as described herein, can be combined with any of the embodiments described herein for R^{4a}, R^{4b}, R^{4c}, R^{5a}, R^{5b}, R^{5c}, X⁶, R^{6a}, R^{6b}, R^{6d}, R^{7a}, R^{7b}, R^{7c}, R^{8a}, R^{8b}, R^{8d}, R^{8e}, ring B, m8, and R^{8f}.

10

Residue 4

[0067] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), or (Ib1), wherein

15 R^{4a}, R^{4b}, and R^{4c} are each independently H or C₁₋₆ alkyl;
 alternatively, R^{4c} and R^{4a} together with the carbon and nitrogen to which each is attached combine to form a heterocycloalkyl having 4 to 6 ring members and 1 to 3 heteroatoms, each independently N, O, or S, wherein the heterocycloalkyl is substituted with 0 to 2 R^{4a1}; and

20 each R^{4a1} is independently halo.

[0068] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), or (Ib1), wherein R^{4a}, R^{4b}, and R^{4c} are each independently H or C₁₋₆ alkyl;

alternatively, R^{4c} and R^{4a} together with the carbon and nitrogen to which each is attached combine to form a heterocycloalkyl having 4 to 6 ring members, wherein the heterocycloalkyl is substituted with 0 to 2 R^{4a1}; and each R^{4a1} is independently halo.

5 **[0069]** In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), or (Ib1), wherein R^{4a}, R^{4b}, and R^{4c} are each independently H or C₁₋₆ alkyl.

[0070] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), or (Ib1), wherein

10 R^{4b} is H or C₁₋₆ alkyl; and

R^{4c} and R^{4a} together with the carbon and nitrogen to which each is attached combine to form a heterocycloalkyl having 4 to 6 ring members and 1 to 3 heteroatoms, each independently N, O, or S, wherein the heterocycloalkyl is substituted with 0 to 3 R^{4a1}.

[0071] In some embodiments, the compound, or the pharmaceutically acceptable salt

15 thereof, is the compound of Formula (I), (Ib), or (Ib1), wherein

R^{4b} is H or C₁₋₆ alkyl; and

R^{4c} and R^{4a} together with the carbon and nitrogen to which each is attached combine to form a heterocycloalkyl having 4 to 6 ring members, wherein the heterocycloalkyl is substituted with 0 to 3 R^{4a1}.

20 **[0072]** In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), or (Ib1), wherein

R^{4a} and R^{4b} are each H; and

R^{4c} is ethyl;

alternatively, R^{4c} and R^{4a} together with the carbon and nitrogen to which each is attached

25 combine to form a pyrrolidinyl, substituted with 0 to 2 fluoro.

[0073] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), or (Ib1), wherein

R^{4b} is H; and

R^{4c} and R^{4a} together with the carbon and nitrogen to which each is attached combine to form

30 a pyrrolidinyl, substituted with 0 to 2 R^{4a1}.

[0074] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), (Id1), wherein R^{4a1} is C₁₋₆ alkyl or halo. In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), (Id1), wherein R^{4a1} is halo. In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), (Id1), wherein R^{4a1} is fluoro. These embodiments of R^{4a1} can be combined with any of the relevant embodiments described herein for R⁴.

[0075] The embodiments described herein for R^{4a}, R^{4b} and R^{4c} can be present in any combination. In addition, the embodiments described herein for residue 4 can be present in combination with any of the embodiments described herein for residues 3, 5, 6, 7, and 8. For example, any of the embodiments of R^{4a}, R^{4b} and R^{4c} as described herein, can be combined with any of the embodiments described herein for R³, R^{5a}, R^{5b}, R^{5c}, X⁶, R^{6a}, R^{6b}, R^{6d}, R^{7a}, R^{7b}, R^{7c}, R^{8a}, R^{8b}, R^{8d}, R^{8e}, ring B, m8, and R^{8f}.

15 Residue 5

[0076] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein R^{5a} is H or C₁₋₆ alkyl; R^{5b} and R^{5c} are each independently H, C₁₋₆ alkyl, -C₁₋₆ alkyl-OH, C₂₋₆ alkoxyalkyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, or C₁₋₄ alkyl-C₃₋₆ cycloalkyl, wherein each cycloalkyl is substituted with 0 to 3 R^{5b5}; and each R^{5b5} is independently C₁₋₄ alkyl, halo, or C₁₋₄ haloalkyl.

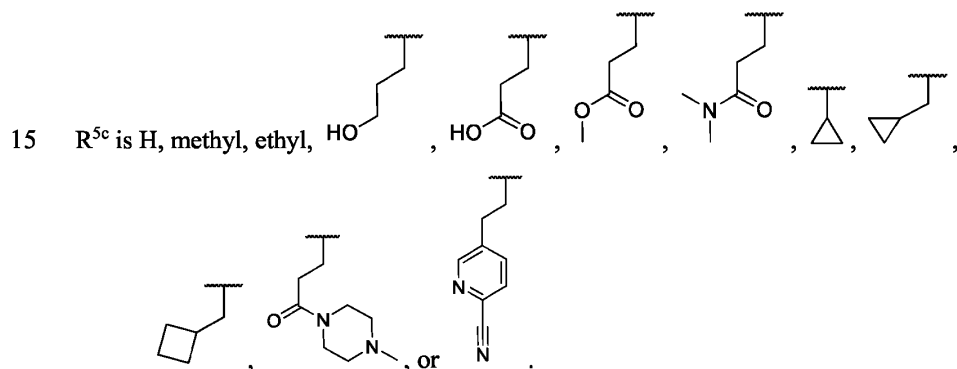
[0077] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein R^{5a} is H or C₁₋₆ alkyl; R^{5b} and R^{5c} are each independently H, -C₁₋₆ alkyl-C(O)NR^{5b1}R^{5b2}, or -C₁₋₆ alkyl-C(O)OR^{5b1}; each R^{5b1} and R^{5b2} are independently H, C₁₋₄ alkyl, or C₁₋₄ haloalkyl; alternatively, R^{5b1} and R^{5b2} together with the nitrogen to which each is attached combine to form a heterocycloalkyl having 3 to 6 ring members and 0 to 1 additional heteroatoms, wherein the heterocycloalkyl is substituted with 0 to 2 R^{5b3}; and

each R^{5b3} is independently C_{1-6} alkyl, halo, C_{1-6} haloalkyl, or cyano; each R^{5b5} is independently C_{1-4} alkyl, halo, or C_{1-4} haloalkyl.

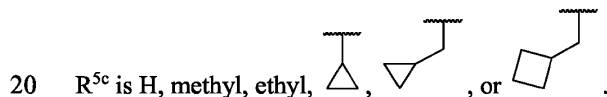
- [0078]** In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein
- 5 R^{5a} is H or C_{1-6} alkyl; and
- R^{5b} and R^{5c} are each independently H, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-4} alkyl- C_{3-6} cycloalkyl.

- [0079]** In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein
- R^{5a} is H or C_{1-6} alkyl;
- 10 R^{5b} is H; and
- R^{5c} is C_{3-6} cycloalkyl or C_{1-4} alkyl- C_{3-6} cycloalkyl.

[0080] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein R^{5a} and R^{5b} are each H; and



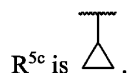
[0081] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein R^{5a} and R^{5b} are each H; and



[0082] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein

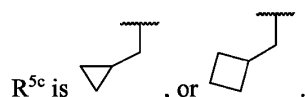
R^{5a} is H or C_{1-6} alkyl;

R^{5b} is H; and



[0083] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein R^{5a} is H or C₁₋₆ alkyl;

5 R^{5b} is H; and

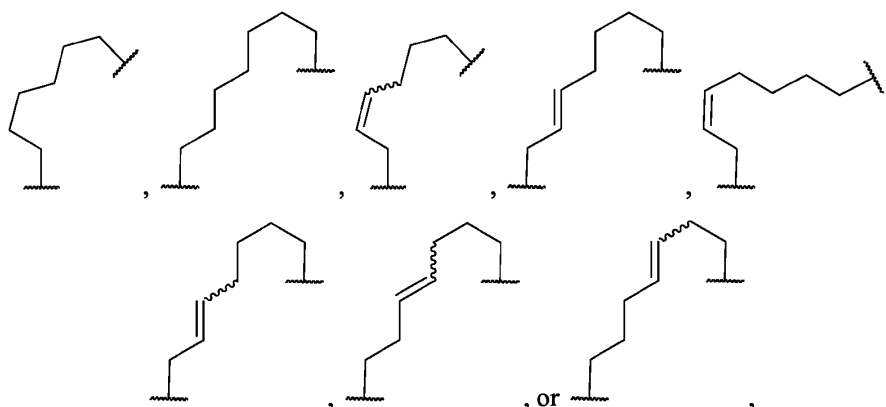


[0084] The embodiments described herein for R^{5a}, R^{5b} and R^{5c} can be present in any combination. In addition, the embodiments described herein for residue 5 can be present in combination with any of the embodiments described herein for residues 3, 4, 6, 7, and 8. For example, any of the embodiments of R^{5a}, R^{5b} and R^{5c} as described herein, can be combined with any of the embodiments described herein for R³, R^{4a}, R^{4b}, R^{4c}, X⁶, R^{6a}, R^{6b}, R^{6d}, R^{7a}, R^{7b}, R^{7c}, R^{8a}, R^{8b}, R^{8d}, R^{8e}, ring B, m8, and R^{8f}.

Residue 6

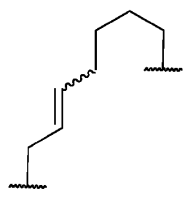
[0085] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), or (Ic1), wherein X⁶ is C₆₋₇ alkylene. In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), or (Ic1), wherein X⁶ is C₆₋₇ alkenylene. These embodiments of X⁶ can be combined with any of the embodiments described herein for R^{6a}, R^{6b} and R^{6d}.

20 **[0086]** In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), or (Ic1), wherein X⁶ is



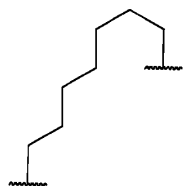
wherein the wavy bond attached to the double bond indicates E, Z, or a mixture of both isomers. These embodiments of X^6 can be combined with any of the embodiments described
 5 herein for R^{6a} , R^{6b} and R^{6d} .

[0087] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), or (Ic1), wherein X^6 is



wherein the wavy bond attached to the double bond indicates E, Z, or a mixture of both
 10 isomers. This embodiment of X^6 can be combined with any of the embodiments described herein for R^{6a} , R^{6b} and R^{6d} .

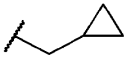
[0088] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), or (Ic1), wherein X^6 is



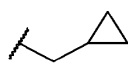
15 This embodiment of X^6 can be combined with any of the embodiments described herein for R^{6a} , R^{6b} and R^{6d} .

- [0089]** In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein R^{6a} is H, C_{1-4} alkyl, C_{1-4} deuterioalkyl, or $-C_{1-4}$ alkyl- C_{3-6} cycloalkyl; and R^{6b} and R^{6d} are each independently H or C_{1-6} alkyl. In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein R^{6a} is H, C_{1-4} alkyl, or $-C_{1-4}$ alkyl- C_{3-6} cycloalkyl; and R^{6b} and R^{6d} are each independently H or C_{1-6} alkyl. In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein R^{6a} is C_{1-4} alkyl; R^{6b} is H; and R^{6d} is C_{1-4} alkyl. In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein R^{6a} is C_{1-4} alkyl; and R^{6b} and R^{6d} are each H. In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein R^{6a} , R^{6b} , and R^{6d} are each H. These embodiments of R^{6a} , R^{6b} and R^{6d} can be combined with any of the embodiments described herein for X^6 .

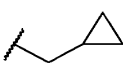
[0090] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein

- R^{6a} is H, methyl, ethyl, , or ; R^{6b} is H; and R^{6d} is H, methyl, or ethyl.
- This embodiment of R^{6a} , R^{6b} and R^{6d} can be combined with any of the embodiments described herein for X^6 .

[0091] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein

- R^{6a} is H, methyl, ethyl, or ; R^{6b} is H; and R^{6d} is H, methyl, or ethyl. This embodiment of R^{6a} , R^{6b} and R^{6d} can be combined with any of the embodiments described herein for X^6 .

[0092] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein

R^{6a} is H, methyl, ethyl, or ; R^{6b} is H; and R^{6d} is H or methyl. This embodiment of R^{6a} , R^{6b} and R^{6d} can be combined with any of the embodiments described herein for X^6 .

- [0093] The embodiments described herein for X^6 , R^{6a} , R^{6b} and R^{6d} can be present in any combination. In addition, the embodiments described herein for residue 6 can be present in combination with any of the embodiments described herein for residues 3, 4, 5, 7, and 8. For example, any of the embodiments of X^6 , R^{6a} , R^{6b} and R^{6d} as described herein, can be combined with any of the embodiments described herein for R^3 , R^{4a} , R^{4b} , R^{4c} , R^{5a} , R^{5b} , R^{5c} , R^{7a} , R^{7b} , R^{7c} , R^{8a} , R^{8b} , R^{8d} , R^{8e} , ring B, m8, and R^{8f} .

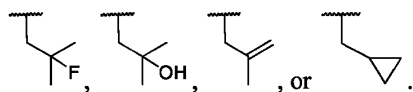
Residue 7

- 10 [0094] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), wherein R^{7a} and R^{7b} are each independently H or C_{1-6} alkyl; and R^{7c} is C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} haloalkyl, C_{1-6} alkyl-OH, or $-C_{1-6}$ alkyl- C_{3-6} cycloalkyl.

- 15 [0095] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), wherein R^{7a} and R^{7b} are each independently H or C_{1-6} alkyl; and R^{7c} is C_{1-6} alkyl or C_{1-6} haloalkyl.

[0096] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), wherein R^{7a} and R^{7b} are each H; and R^{7c} is C_{1-6} alkyl.

- 20 [0097] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), wherein R^{7a} and R^{7b} are each H; and R^{7c} is isobutyl,



[0098] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), wherein R^{7a} and R^{7b} are each H; and R^{7c} is isobutyl.

- 25 [0099] The embodiments described herein for R^{7a} , R^{7b} and R^{7c} can be present in any combination. In addition, the embodiments described herein for residue 7 can be present in combination with any of the embodiments described herein for residues 3, 4, 5, 6, and 8. For example, any of the embodiments of R^{7a} , R^{7b} and R^{7c} as described herein, can be combined

with any of the embodiments described herein for R³, R^{4a}, R^{4b}, R^{4c}, R^{5a}, R^{5b}, R^{5c}, X⁶, R^{6a}, R^{6b}, R^{6d}, R^{8a}, R^{8b}, R^{8d}, R^{8e}, ring B, m8, and R^{8f}.

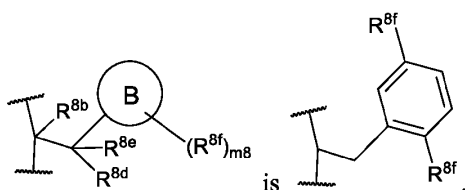
Residue 8

[0100] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein R^{8a}, R^{8b}, R^{8d}, and R^{8e} are each independently H or C₁₋₆ alkyl. In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein R^{8a} is H or methyl; and R^{8b}, R^{8d} and R^{8e} are each H. These embodiments of R^{8a}, R^{8b}, R^{8d}, and R^{8e} can be combined with any of the
10 embodiments described herein for m8, ring B, R^{8f}, and R^{8g}.

[0101] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein ring B is phenyl or heteroaryl having 5 to 6 ring members and 1 to 3 heteroatoms, wherein each heteroatom is N, O, or S. In some embodiments, the compound, or the pharmaceutically
15 acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein ring B is phenyl. In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein ring B is naphthyl. In some embodiments, the compound, or the pharmaceutically
20 acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein ring B is biphenyl. In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein ring B is a heteroaryl having 5 to 6 ring members and 1 to 3 heteroatoms, wherein
25 each heteroatom is N, O, or S. In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein ring B is thiophenyl. In some embodiments, the compound, or the pharmaceutically
30 acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein ring B is a heteroaryl having 5 to 6 ring members and 1 to 3 heteroatoms, wherein each heteroatom is N. In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein ring B is pyridyl. In some embodiments, the compound, or the pharmaceutically
 acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein ring B is benzofuranyl. In some embodiments, the compound, or the

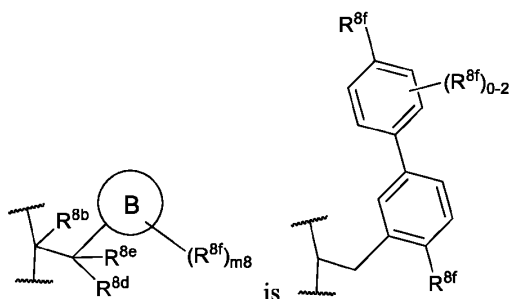
- pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein ring B is indolyl. In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein ring B is indazolyl. In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein ring B is quinoliny. In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein ring B is pyrid-3-yl. In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein ring B is phenyl or pyridyl. In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein ring B is phenyl or pyrid-3-yl. These embodiments of ring B can be combined with any of the embodiments described herein for R^{8a} , R^{8b} , R^{8d} , R^{8e} , m8, R^{8f} , and R^{8f3} .
- 15 **[0102]** In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein the subscript m8 is 1, 2, or 3. In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein the subscript m8 is 0. In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein the subscript m8 is 1. In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein the subscript m8 is 2. In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein the subscript m8 is 3. In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein the subscript m8 is 4. In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein the subscript m8 is 5. These embodiments of m8 can be combined with any of the embodiments described herein for R^{8a} , R^{8b} , R^{8d} , R^{8e} , R^{8f} , R^{8f3} , and ring B.
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[0103] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein the moiety



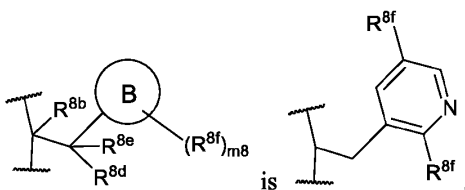
These embodiments can be combined with any of the embodiments described herein for R^{8a}, R^{8b}, R^{8d}, R^{8e}, R^{8f}, R^{8f3}, m8 and ring B.

- [0104]** In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein the moiety



These embodiments can be combined with any of the embodiments described herein for R^{8a}, R^{8b}, R^{8d}, R^{8e}, R^{8f}, R^{8f3}, m8 and ring B.

- [0105]** In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein the moiety



- [0106]** In some embodiments, at least one R^{8f} is halo. In some embodiments, at least one R^{8f} is fluoro or chloro. These embodiments of R^{8f} can be combined with any of the embodiments described herein for R^{8a}, R^{8b}, R^{8d}, R^{8e}, m8, ring B, and R^{8f3}.

[0107] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein each R^{8f} is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} alkoxy, C_{1-6} deutoalkoxy, halo, C_{1-6} haloalkyl, cyano, or $-X^{8f}$ -cyano. These embodiments of R^{8f} can be combined with any of the
 5 embodiments described herein for R^{8a} , R^{8b} , R^{8d} , R^{8e} , m8, ring B, and R^{8f3} .

[0108] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein each R^{8f} is independently halo, C_{3-6} cycloalkyl, $-X^{8f}$ - C_{3-6} cycloalkyl, $-CH=CR^{8f1}R^{8f2}$, heterocycloalkyl, $-X^{8f}$ -heterocycloalkyl, phenyl, $-X^{8f}$ -phenyl, heteroaryl, or $-X^{8f}$ -heteroaryl,
 10 wherein each heterocycloalkyl has 3 to 10 ring members and 1 to 3 heteroatoms, each independently N, O, or S, and each heteroaryl has 5 to 10 ring members and 1 to 3 heteroatoms, each independently N, O, or S, wherein each cycloalkyl, heterocycloalkyl, phenyl, and heteroaryl is substituted with 0 to 3 R^{8f3} ; each X^{8f} is independently C_{1-6} alkylene, C_{2-6} alkenylene, O, or S; and each R^{8f1} and R^{8f2} are combined with the carbon to which they
 15 are attached to form a heterocycloalkyl having 3 to 10 ring members and 1 to 3 heteroatoms, each independently N, O or S, wherein the heterocycloalkyl is substituted with 0 to 3 R^{8f3} . These embodiments of R^{8f} can be combined with any of the embodiments described herein for R^{8a} , R^{8b} , R^{8d} , R^{8e} , m8, ring B, and R^{8f3} .

[0109] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein each R^{8f} is independently halo, C_{3-6} cycloalkyl, $-X^{8f}$ - C_{3-6} cycloalkyl, $-CH=CR^{8f1}R^{8f2}$, heterocycloalkyl, $-X^{8f}$ -heterocycloalkyl, heteroaryl, or $-X^{8f}$ -heteroaryl, wherein each heterocycloalkyl has 3 to 10 ring members and 1 to 3 heteroatoms, each independently N, O, or S, and each heteroaryl has 5 to 10 ring members and 1 to 3 heteroatoms, each
 20 independently N, O, or S, wherein each cycloalkyl, heterocycloalkyl, and heteroaryl is substituted with 0 to 3 R^{8f3} ; each X^{8f} is independently C_{1-6} alkylene, C_{2-6} alkenylene, O, or S; and each R^{8f1} and R^{8f2} are combined with the carbon to which they are attached to form a heterocycloalkyl having 3 to 10 ring members and 1 to 3 heteroatoms, each independently N, O or S, wherein the heterocycloalkyl is substituted with 0 to 3 R^{8f3} . These embodiments of
 25 R^{8f} can be combined with any of the embodiments described herein for R^{8a} , R^{8b} , R^{8d} , R^{8e} , m8, ring B, and R^{8f3} .
 30

[0110] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein each X^{8f} is independently C_{1-6} alkylene. In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein each X^{8f} is independently C_{2-6} alkenylene. In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein each X^{8f} is independently $-O-C_{1-6}$ alkylene. In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein each X^{8f} is independently $C(O)$. In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein each X^{8f} is independently O. In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein each X^{8f} is independently S. In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein each X^{8f} is independently C_{1-6} alkylene or O. These embodiments of R^{8f} can be combined with any of the embodiments described herein for R^{8a} , R^{8b} , R^{8d} , R^{8e} , m8, ring B, and R^{8f3} .

[0111] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein each R^{8f} is independently halo, C_{3-6} cycloalkyl, $-CH=CR^{8f1}R^{8f2}$, heterocycloalkyl, phenyl, or heteroaryl, wherein each heterocycloalkyl has 3 to 10 ring members and 1 to 3 heteroatoms, each independently N, O, or S, and each heteroaryl has 5 to 10 ring members and 1 to 3 heteroatoms, each independently N, O, or S, wherein each cycloalkyl, heterocycloalkyl, phenyl, and heteroaryl is substituted with 0 to 3 R^{8f3} ; each R^{8f1} and R^{8f2} are combined with the carbon to which they are attached to form a heterocycloalkyl having 3 to 10 ring members and 1 to 3 heteroatoms, each independently N, O or S, wherein the heterocycloalkyl is substituted with 0 to 3 R^{8f3} . These embodiments of R^{8f} can be combined with any of the embodiments described herein for R^{8a} , R^{8b} , R^{8d} , R^{8e} , m8, ring B, and R^{8f3} .

[0112] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein each R^{8f} is independently C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-4} alkoxy, C_{1-4} deutoalkoxy, halo, C_{1-4}

haloalkyl, cyano, or $-C_{1-2}$ alkyl-cyano. These embodiments of R^{8f} can be combined with any of the embodiments described herein for R^{8a} , R^{8b} , R^{8d} , R^{8e} , m8, ring B, and R^{8f3} .

[0113] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein each R^{8f} is independently halo, C_{3-6} cycloalkyl, $-O-C_{3-6}$ cycloalkyl, heterocycloalkyl, $-C_{2-4}$ alkenyl-heterocycloalkyl, $-O$ -heterocycloalkyl, $-CH=CR^{8f1}R^{8f2}$, phenyl, $-O$ -phenyl, heteroaryl, or $-O$ -heteroaryl, wherein each heterocycloalkyl has 3 to 9 ring members and 1 to 3 heteroatoms, each independently N, O, or S, and each heteroaryl has 5 to 9 ring members and 1 to 3 heteroatoms, each independently N, O, or S, wherein each cycloalkyl, heterocycloalkyl, phenyl, and heteroaryl is substituted with 0 to 3 R^{8f3} ; and R^{8f1} and R^{8f2} are combined with the carbon to which they are attached to form a heterocycloalkyl having 3 to 10 ring members and 1 to 3 heteroatoms, each independently N, O or S, wherein the heterocycloalkyl is substituted with 0 to 3 R^{8f3} . These embodiments of R^{8f} can be combined with any of the embodiments described herein for R^{8a} , R^{8b} , R^{8d} , R^{8e} , m8, ring B, and R^{8f3} .

[0114] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein each R^{8f} is independently halo, C_{3-6} cycloalkyl, $-O-C_{3-6}$ cycloalkyl, heterocycloalkyl, $-C_{2-4}$ alkenyl-heterocycloalkyl, $-O$ -heterocycloalkyl, phenyl, $-O$ -phenyl, heteroaryl, or $-O$ -heteroaryl, wherein each heterocycloalkyl has 3 to 6 ring members and 1 to 2 heteroatoms, each independently N, O, or S, and each heteroaryl has 5 to 6 ring members and 1 to 3 heteroatoms, each independently N, O, or S, wherein each cycloalkyl, heterocycloalkyl, phenyl, and heteroaryl is substituted with 0 to 3 R^{8f3} . These embodiments of R^{8f} can be combined with any of the embodiments described herein for R^{8a} , R^{8b} , R^{8d} , R^{8e} , m8, ring B, and R^{8f3} .

[0115] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein each R^{8f} is independently halo, C_{3-6} cycloalkyl, $-O-C_{3-6}$ cycloalkyl, heteroaryl, or $-O$ -heteroaryl, wherein each heteroaryl has 5 to 6 ring members and 1 to 3 heteroatoms, each independently N, O, or S, wherein each cycloalkyl, and heteroaryl is substituted with 0 to 3 R^{8f3} . These embodiments of R^{8f} can be combined with any of the embodiments described herein for R^{8a} , R^{8b} , R^{8d} , R^{8e} , m8, ring B, and R^{8f3} .

[0116] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein each R^{8f} is independently halo, heterocycloalkyl, $-O$ -heterocycloalkyl, phenyl, or $-O$ -phenyl, wherein each heterocycloalkyl has 3 to 6 ring members and 1 to 2 heteroatoms, each
 5 independently N, O, or S, wherein each heterocycloalkyl and phenyl is substituted with 0 to 3 R^{8f3} . These embodiments of R^{8f} can be combined with any of the embodiments described herein for R^{8a} , R^{8b} , R^{8d} , R^{8e} , m8, ring B, and R^{8f3} .

[0117] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein each
 10 R^{8f} is independently halo, heterocycloalkyl, or $-O$ -heterocycloalkyl, wherein each heterocycloalkyl has 3 to 6 ring members and 1 to 2 heteroatoms, each independently N, O, or S, wherein each heterocycloalkyl is substituted with 0 to 3 R^{8f3} . These embodiments of R^{8f} can be combined with any of the embodiments described herein for R^{8a} , R^{8b} , R^{8d} , R^{8e} , m8, ring B, and R^{8f3} .

[0118] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein each R^{8f3} is independently C_{1-6} alkyl, $-Y^8-C_{1-6}$ alkyl, C_{1-6} deuterioalkyl, $-Y^8-C_{1-6}$ deuterioalkyl, $-OH$, $-C_{1-6}$ alkyl- OH , $-Y^8-C_{1-6}$ alkyl- OH , $-C_{1-6}$ alkyl- Y^8-C_{1-6} alkyl, halo, C_{1-6} haloalkyl, $-Y^8-C_{1-6}$ haloalkyl, or oxo; each Y^8 is
 20 independently $C(O)$, $C(O)O$, $N(R^{8f4})C(O)$, O, S, or $S(O)_2$; and each R^{8f4} is independently H or C_{1-6} alkyl. These embodiments of R^{8f3} can be combined with any of the embodiments described herein for R^{8a} , R^{8b} , R^{8d} , R^{8e} , m8, ring B, and R^{8f} .

[0119] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein each
 25 R^{8f3} is independently C_{1-6} alkyl, $-Y^8-C_{1-6}$ alkyl, C_{1-6} deuterioalkyl, $-Y^8-C_{1-6}$ deuterioalkyl, $-OH$, $-C_{1-6}$ alkyl- OH , $-Y^8-C_{1-6}$ alkyl- OH , $-C_{1-6}$ alkyl- Y^8-C_{1-6} alkyl, halo, C_{1-6} haloalkyl, $-Y^8-C_{1-6}$ haloalkyl, $-C_{1-6}$ alkyl- $NR^{8g}R^{8h}$, or oxo; each Y^8 is independently $C(O)$, $C(O)O$, $N(R^{8f4})C(O)$, O, S, or $S(O)_2$; and each R^{8f4} is independently H or C_{1-6} alkyl. These embodiments of R^{8f3} can be combined with any of the
 30 embodiments described herein for R^{8a} , R^{8b} , R^{8d} , R^{8e} , m8, ring B, and R^{8f} .

[0120] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein each R^{8g} and R^{8h} is independently H, C_{1-3} alkyl, or C_{1-3} haloalkyl.

[0121] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein each Y^8 is independently $-Y^8-C_{1-6}$ alkyl. In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein each Y^8 is independently $-Y^8$ -methyl. In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein each Y^8 is independently C(O). In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein each Y^8 is independently C(O)O. In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein each Y^8 is independently NHC(O). In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein each Y^8 is independently O. In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein each Y^8 is independently S. In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein each Y^8 is independently S(O)₂. These embodiments of Y^8 can be combined with any of the embodiments described herein for R^{8a} , R^{8b} , R^{8d} , R^{8e} , m8, ring B, R^{8f} , and R^{8f3} .

[0122] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein each R^{8f3} is independently C_{1-6} alkyl, C_{1-6} deutoalkyl, $-OH$, $-C_{1-6}$ alkyl- OH , halo, C_{1-6} haloalkyl, or oxo. These embodiments of R^{8f3} can be combined with any of the embodiments described herein for R^{8a} , R^{8b} , R^{8d} , R^{8e} , m8, ring B, and R^{8f} .

[0123] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein each R^{8f3} is independently C_{1-6} alkyl or $-Y^8-C_{1-6}$ alkyl. In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic),

(Ic1), (Id), or (Id1), wherein each Y⁸ is independently a C(O) or C(O)O. These embodiments of R^{8f3} and Y⁸ can be combined with any of the embodiments described herein for R^{8a}, R^{8b}, R^{8d}, R^{8e}, m8, ring B, and R^{8f}.

5 [0124] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein each R^{8f3} is independently C₃₋₆ cycloalkyl, -X^{8f3}-C₃₋₆ cycloalkyl, heterocycloalkyl, or -X^{8f3}-heterocycloalkyl, wherein each heterocycloalkyl has 3 to 6 members and 1 to 2 heteroatoms, each independently N, O, S, or S(O)₂; and each X^{8f3} is independently C₁₋₆ alkylene, C(O), or S(O)₂. These embodiments of R^{8f3} can be combined with any of the
10 embodiments described herein for R^{8a}, R^{8b}, R^{8d}, R^{8e}, m8, ring B, and R^{8f}.

[0125] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein each X^{8f3} is independently C₁₋₆ alkylene. In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic),
15 (Ic1), (Id), or (Id1), wherein each X^{8f3} is independently C(O). In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein each X^{8f3} is independently S(O)₂. These embodiments of X^{8f3} can be combined with any of the embodiments described herein for R^{8a}, R^{8b}, R^{8d}, R^{8e}, m8, ring B, R^{8f}, and R^{8f3}.

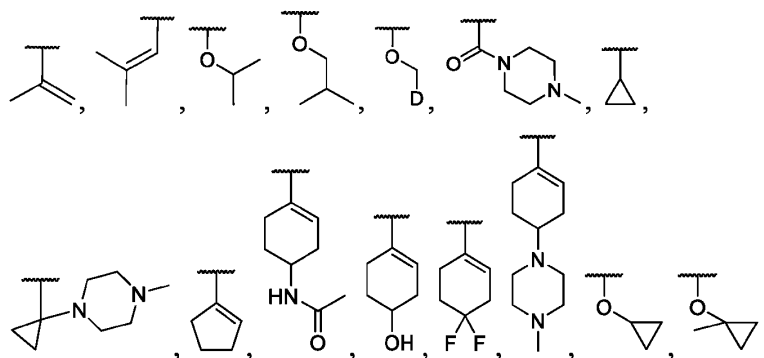
20 [0126] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein each R^{8f3} is independently C₃₋₆ cycloalkyl or heterocycloalkyl, wherein each heterocycloalkyl has 3 to 6 members and 1 to 2 heteroatoms, each independently N, O, S, or S(O)₂. These embodiments of R^{8f3} can be combined with any of the embodiments described herein for R^{8a},
25 R^{8b}, R^{8d}, R^{8e}, m8, ring B, and R^{8f}.

[0127] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein two R^{8f3} groups on adjacent ring vertices combine to form a heterocycloalkyl having 3 to 6 ring members and 1 to 3 heteroatoms, each independently N, O or S. These embodiments of R^{8f3}
30 can be combined with any of the embodiments described herein for R^{8a}, R^{8b}, R^{8d}, R^{8e}, m8, ring B, and R^{8f}.

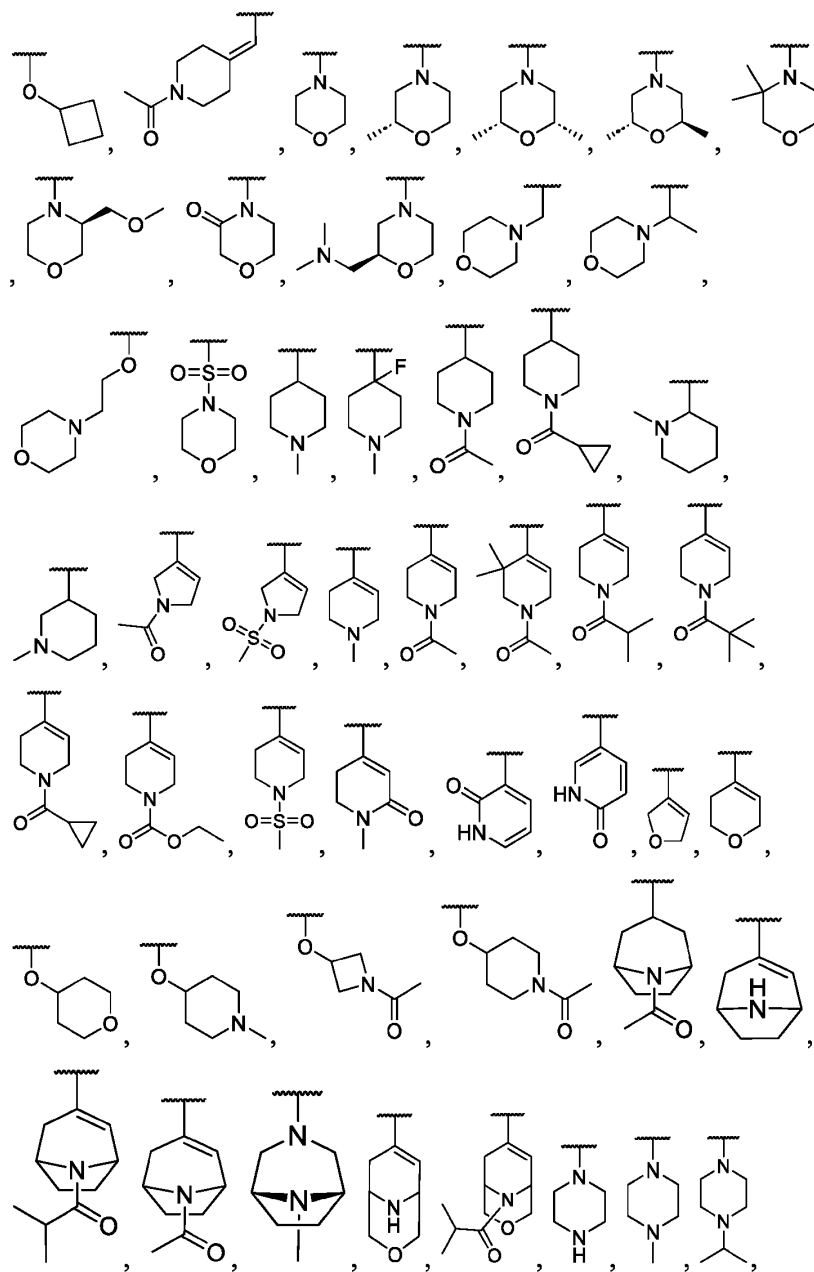
[0128] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein each R^{8f3} is independently C₁₋₄ alkyl, C₁₋₄ alkoxy, C₂₋₆ alkoxyalkyl, -S(O)₂-C₁₋₄ alkyl, -C₁₋₄ alkyl-S(O)₂-C₁₋₄ alkyl, halo, C₁₋₄ haloalkyl, oxo, -C(O)-C₁₋₄ alkyl, or -C(O)O-C₁₋₄ alkyl. These embodiments of R^{8f3} can be combined with any of the embodiments described herein for R^{8a} , R^{8b} , R^{8d} , R^{8e} , m8, ring B, and R^{8f} .

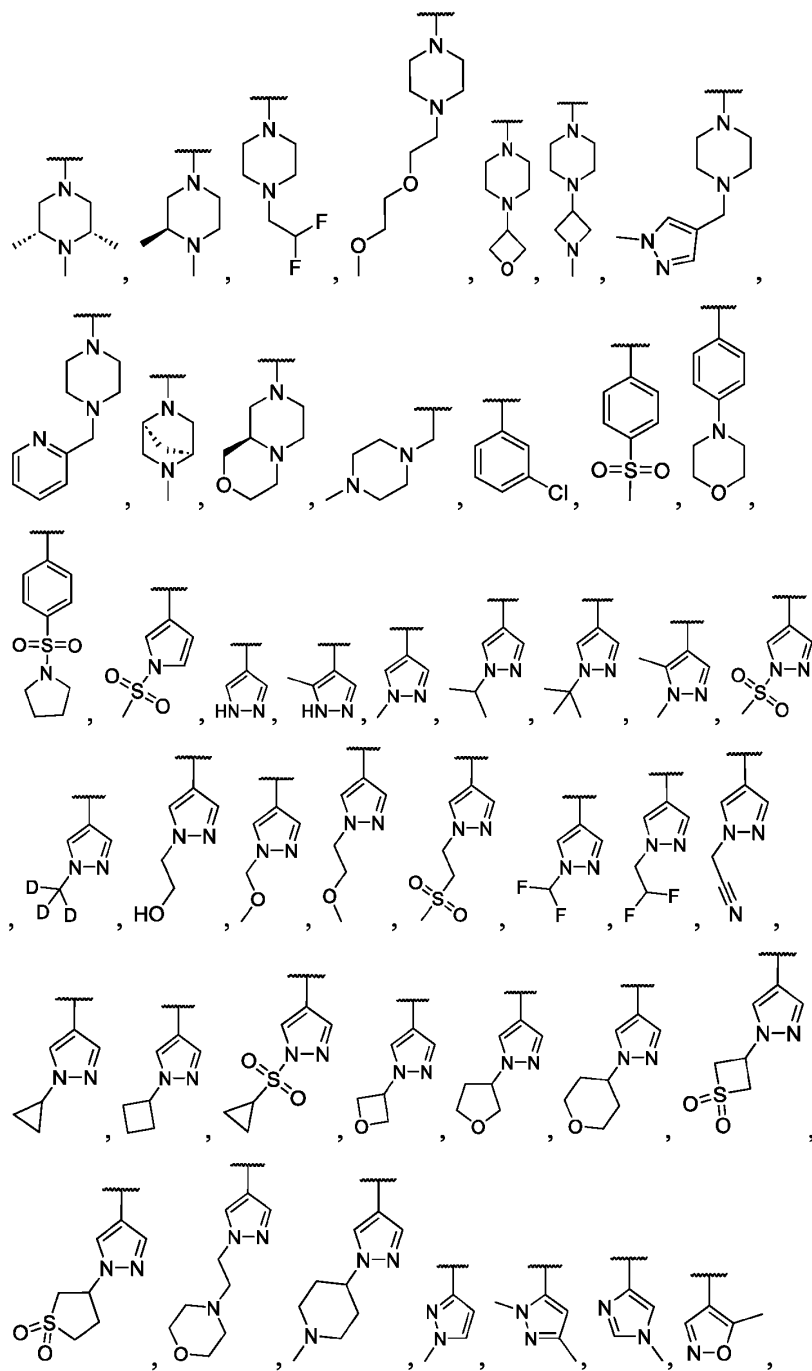
[0129] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein each R^{8f3} is independently C₁₋₄ alkyl, C₁₋₄ alkoxy, C₂₋₆ alkoxyalkyl, halo, C₁₋₄ haloalkyl, oxo, -S(O)₂-C₁₋₄ alkyl, -C₁₋₄ alkyl-S(O)₂-C₁₋₄ alkyl, -C(O)-C₁₋₄ alkyl, -C(O)O-C₁₋₄ alkyl, C₃₋₆ cycloalkyl, -C(O)-C₃₋₆ cycloalkyl, -S(O)₂-C₃₋₆ cycloalkyl, heterocycloalkyl, -C₁₋₄ alkyl-heterocycloalkyl, or -S(O)₂-heterocycloalkyl, wherein each heterocycloalkyl has 4 to 6 members and 1 to 2 heteroatoms, each independently N, O, S, or S(O)₂; alternatively, two R^{8f3} groups on adjacent ring vertices combine to form a non-aromatic cyclic moiety having 3 to 6 ring members and 0 to 2 additional heteroatoms, each independently N, O or S. These embodiments of R^{8f3} can be combined with any of the embodiments described herein for R^{8a} , R^{8b} , R^{8d} , R^{8e} , m8, ring B, and R^{8f} .

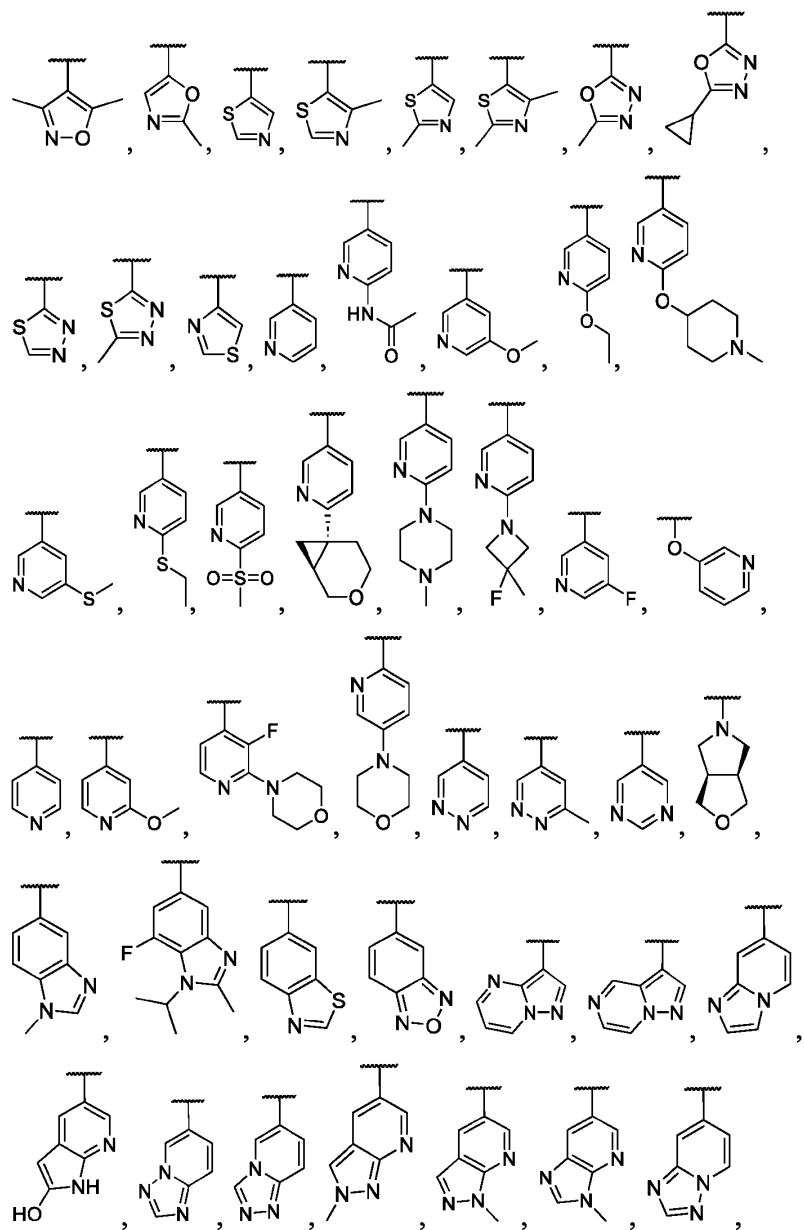
[0130] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein m8 is 1, 2, or 3; and each R^{8f} is independently methyl, isopropyl, isobutyl, methoxy, ethoxy, fluoro, chloro, cyano,

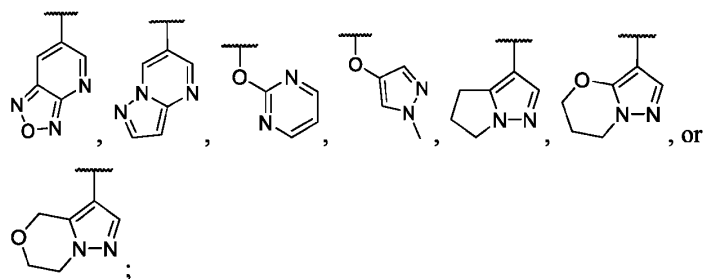


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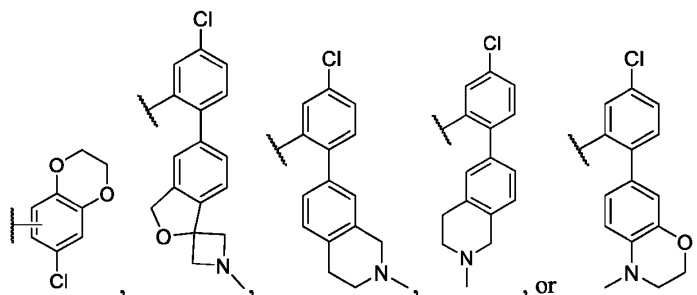








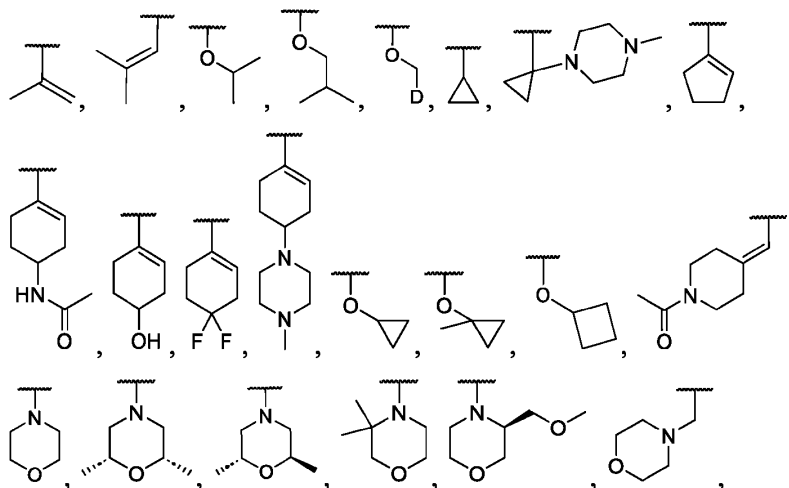
alternatively, ring B and three R^{8f} groups form the moiety

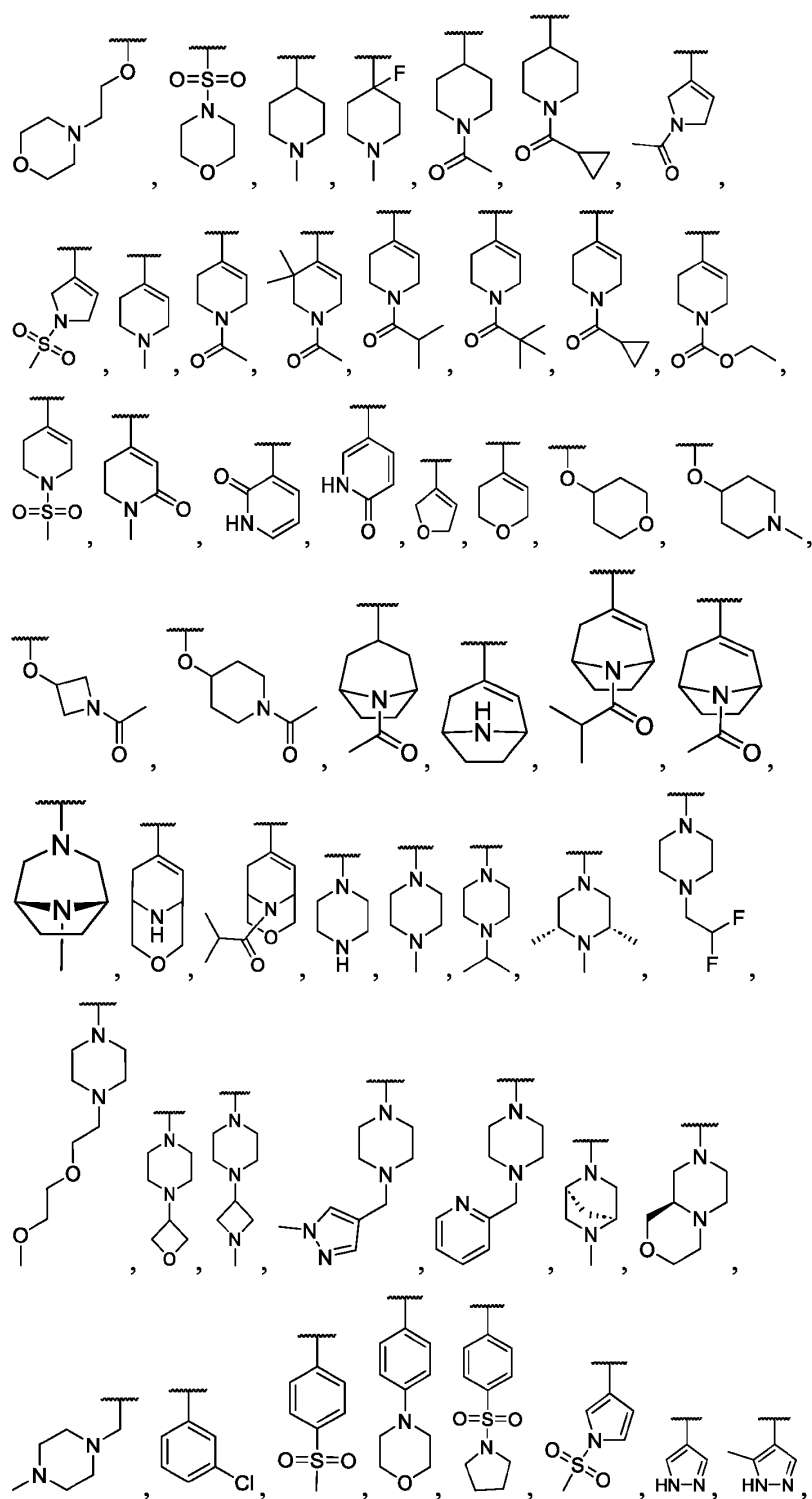


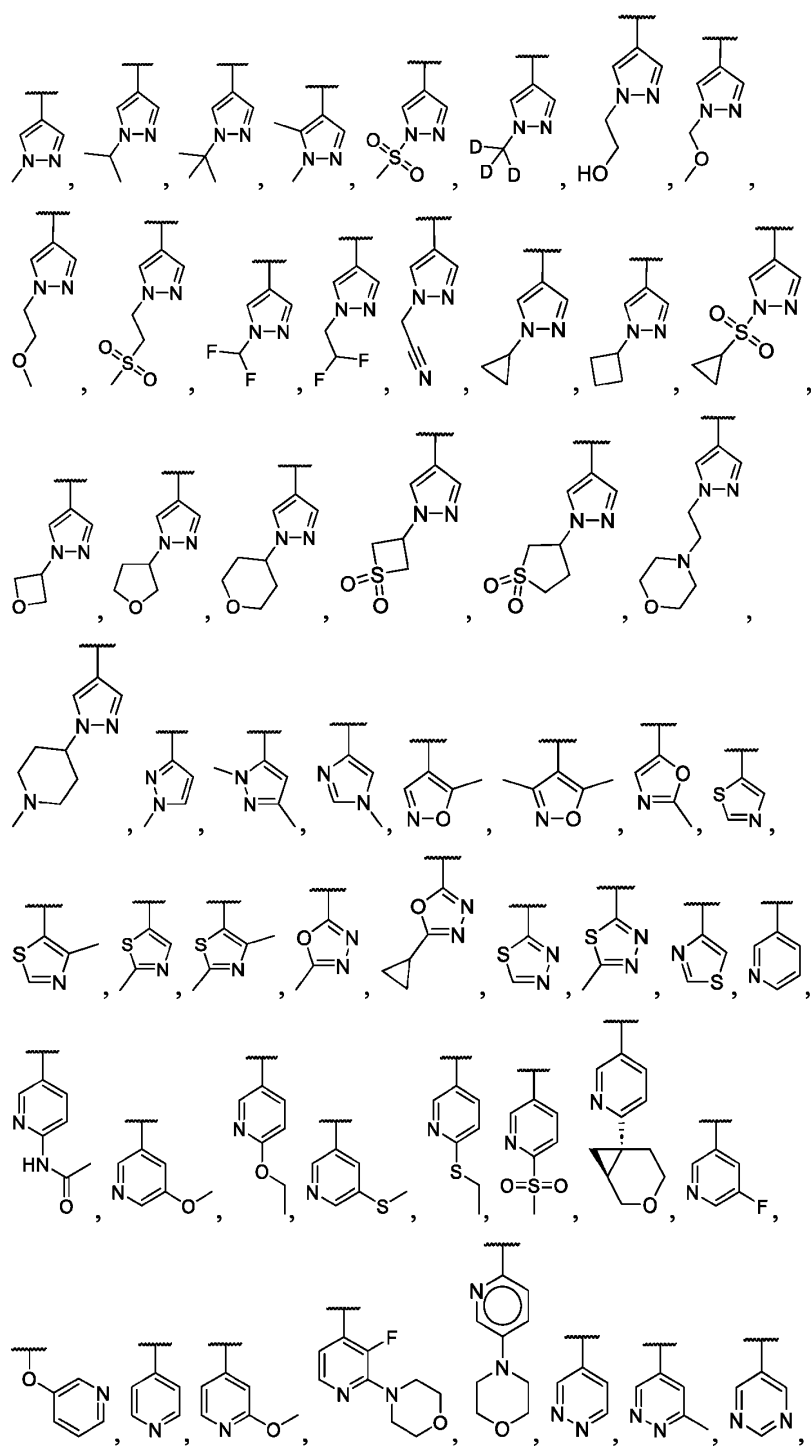
5 wherein the wavy line identifies attachment to the remainder of the molecule.

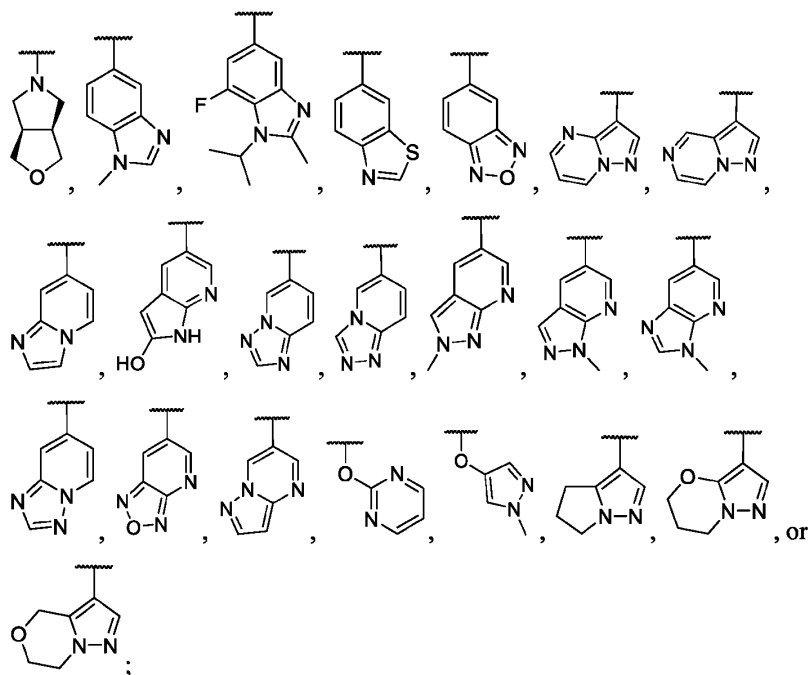
[0131] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein m8 is 1, 2, or 3; and

each R^{8f} is independently methyl, isopropyl, isobutyl, methoxy, ethoxy, fluoro, chloro, cyano,

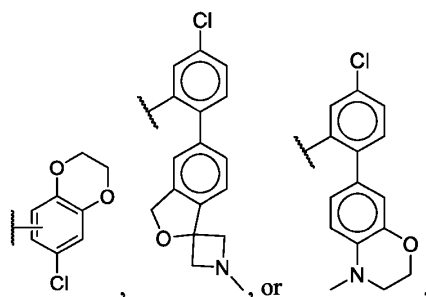








5 alternatively, ring B and three R^{8f} groups form the moiety

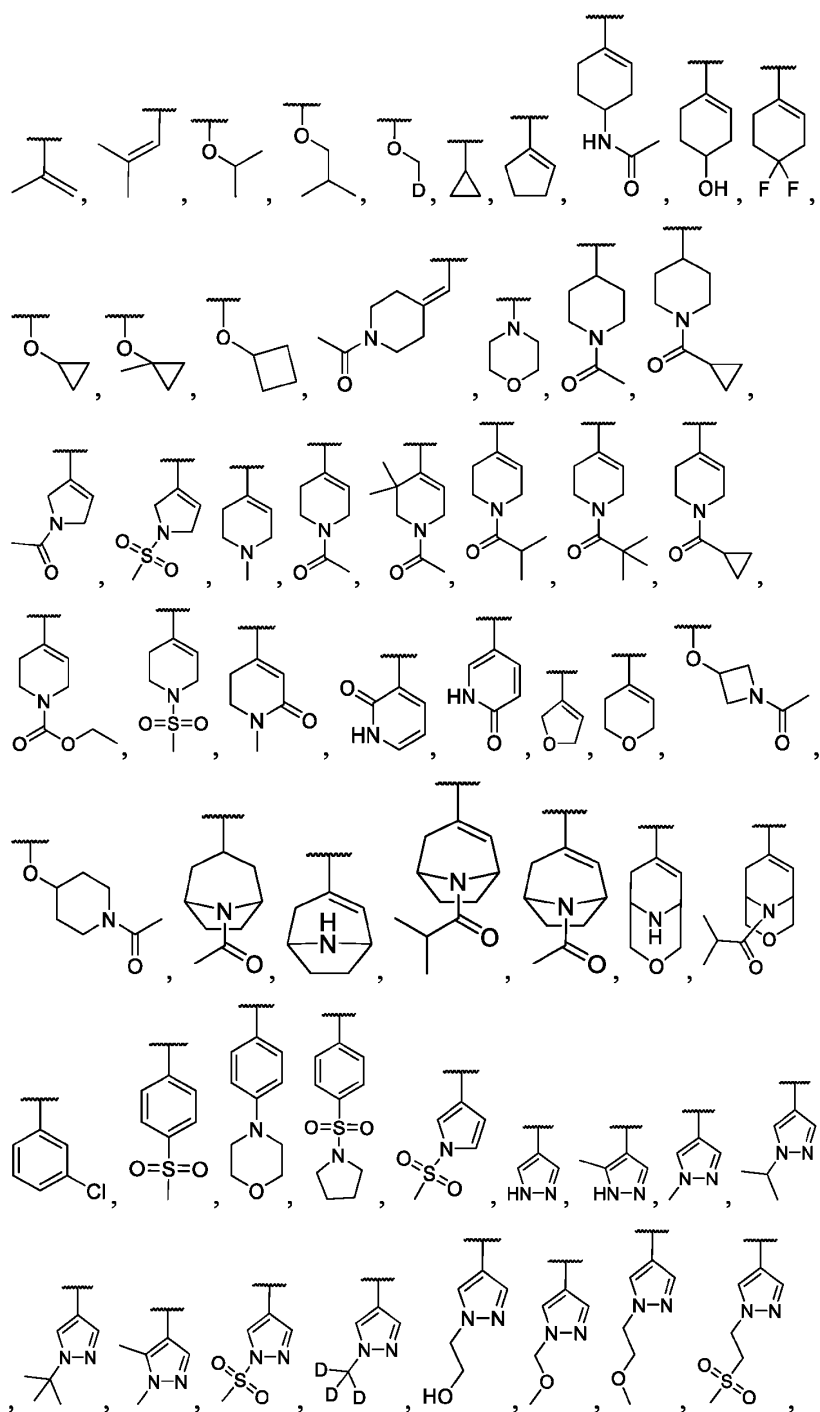


wherein the wavy line identifies attachment to the remainder of the molecule.

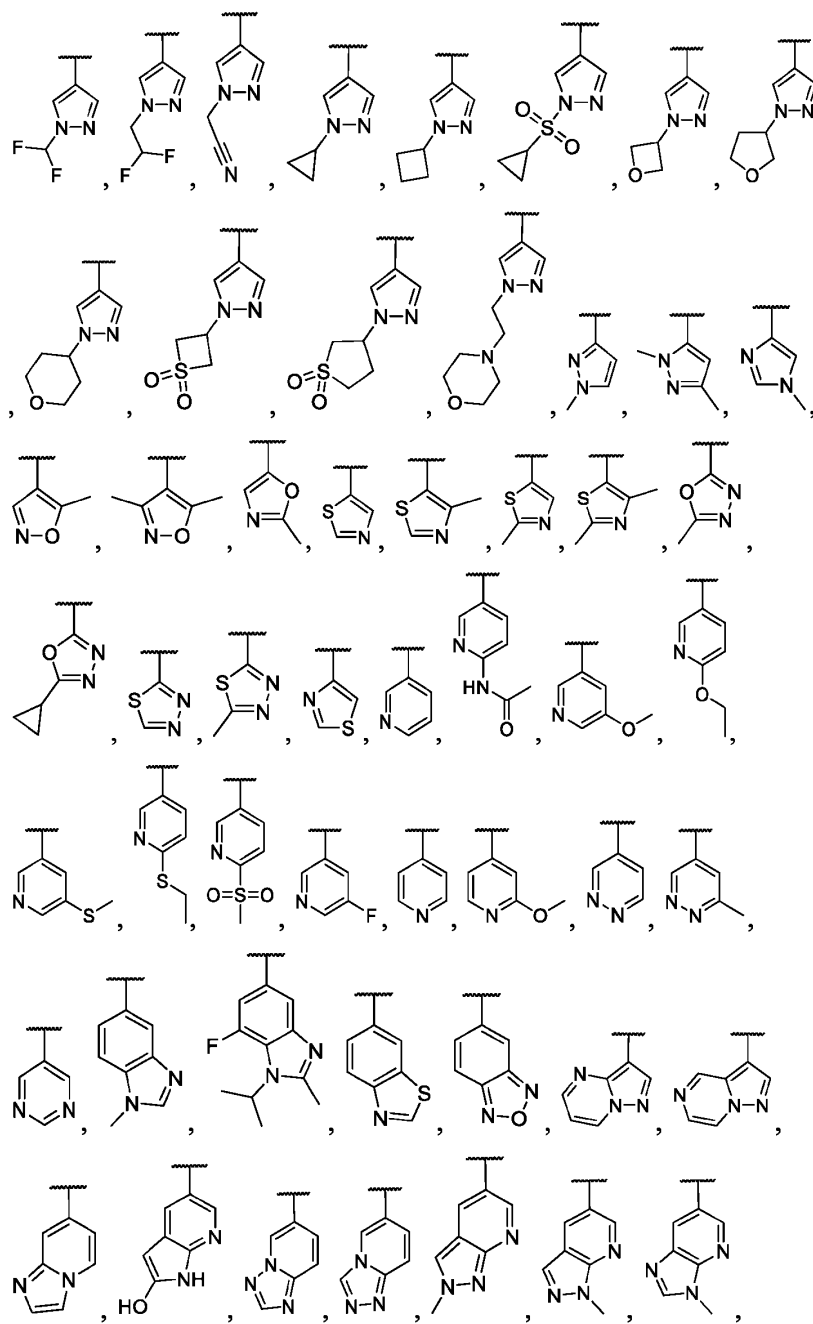
[0132] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ic), (Id), or (Id1), wherein

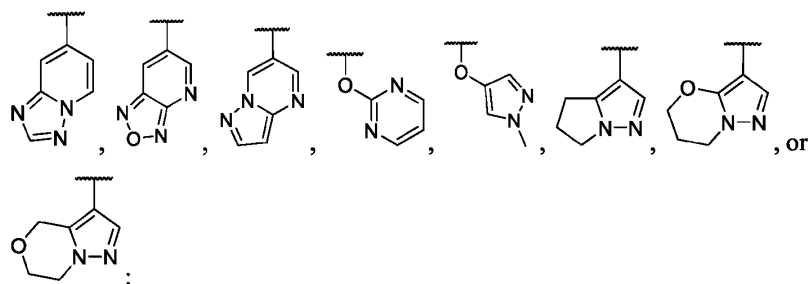
10 m8 is 1, 2, or 3; and

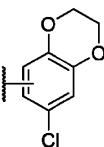
each R^{8f} is independently methyl, isopropyl, isobutyl, methoxy, ethoxy, fluoro, chloro,



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alternatively, ring B and three R^{8f} groups form the moiety , wherein the wavy line identifies attachment to the remainder of the molecule.

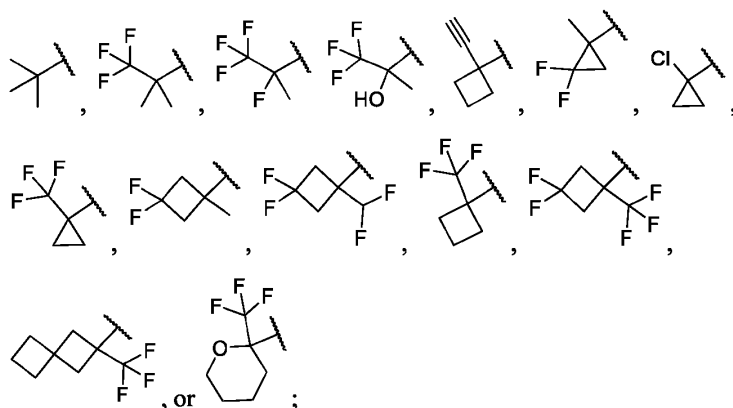
- 5 **[0133]** The embodiments described herein for R^{8a} , R^{8b} , R^{8d} , R^{8e} , m8, R^{8f} , and ring B can be present in any combination. In addition, the embodiments described herein for residue 8 can be present in combination with any of the embodiments described herein for residues 3, 4, 5, 6, and 7. For example, any of the embodiments of R^{8a} , R^{8b} , R^{8d} , R^{8e} , m8, R^{8f} , and ring B as described herein, can be combined with any of the embodiments described herein for R^3 , R^{4a} ,
 10 R^{4b} , R^{4c} , R^{5a} , R^{5b} , R^{5c} , X^6 , R^{6a} , R^{6b} , R^{6d} , R^{7a} , R^{7b} , and R^{7c} .

Residues 3 to 8

[0134] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein

R^3 is

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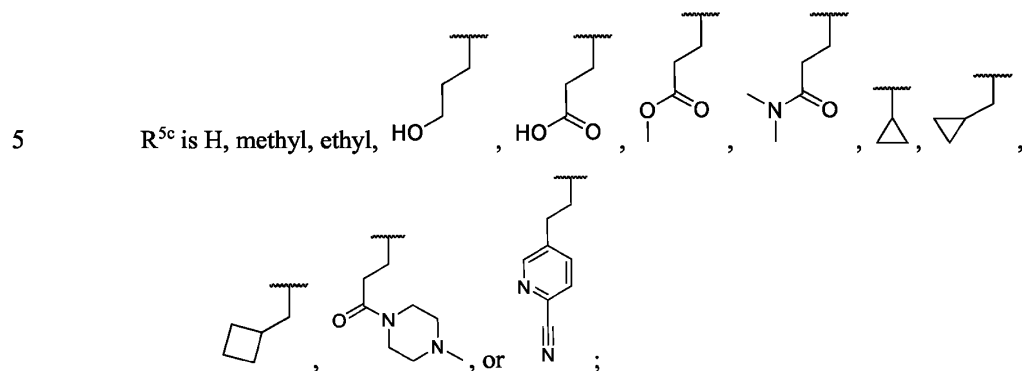


R^{4a} and R^{4b} are each H;

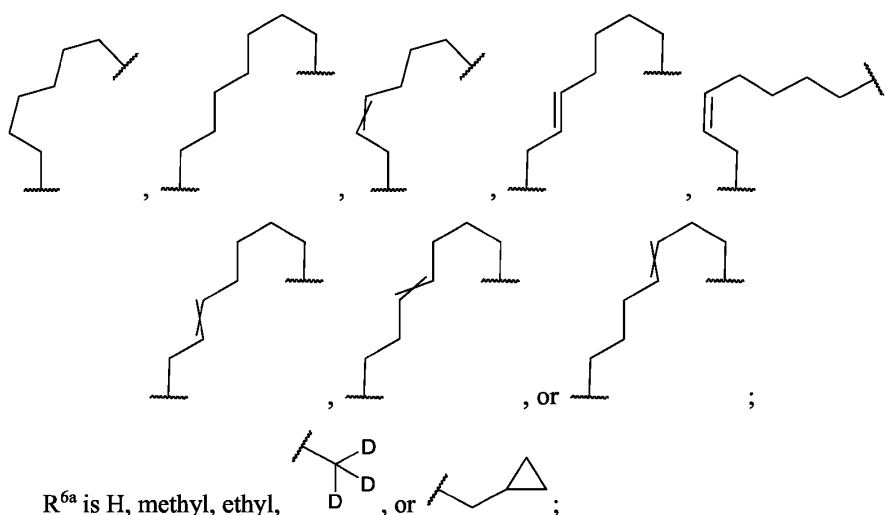
R^{4c} is ethyl;

alternatively, R^{4c} and R^{4a} together with the carbon and nitrogen to which each is attached combine to form a pyrrolidinyl, substituted with 0 to 2 fluoro;

R^{5a} and R^{5b} are each H;



X^6 is

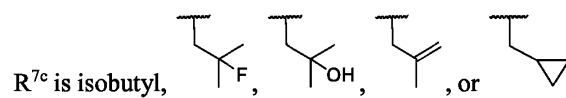


10 R^{6a} is H, methyl, ethyl,

R^{6b} is H;

R^{6d} is H, methyl, or ethyl;

R^{7a} and R^{7b} are each H;



15 R^{8a} is H or methyl;

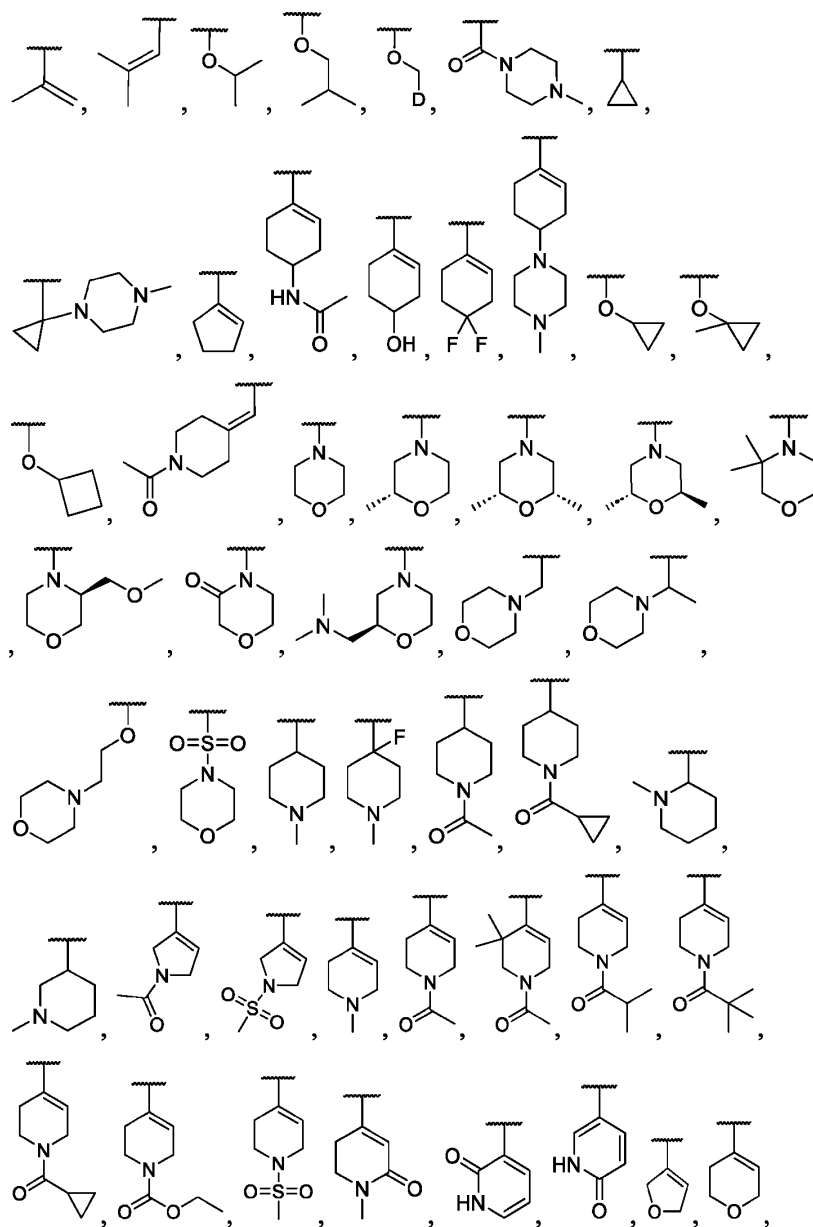
R^{8b} , R^{8d} and R^{8e} are each H;

ring B is phenyl, naphthyl, biphenyl, thiophenyl, pyridyl, benzofuranyl, indolyl, indazolyl, or quinolinyl;

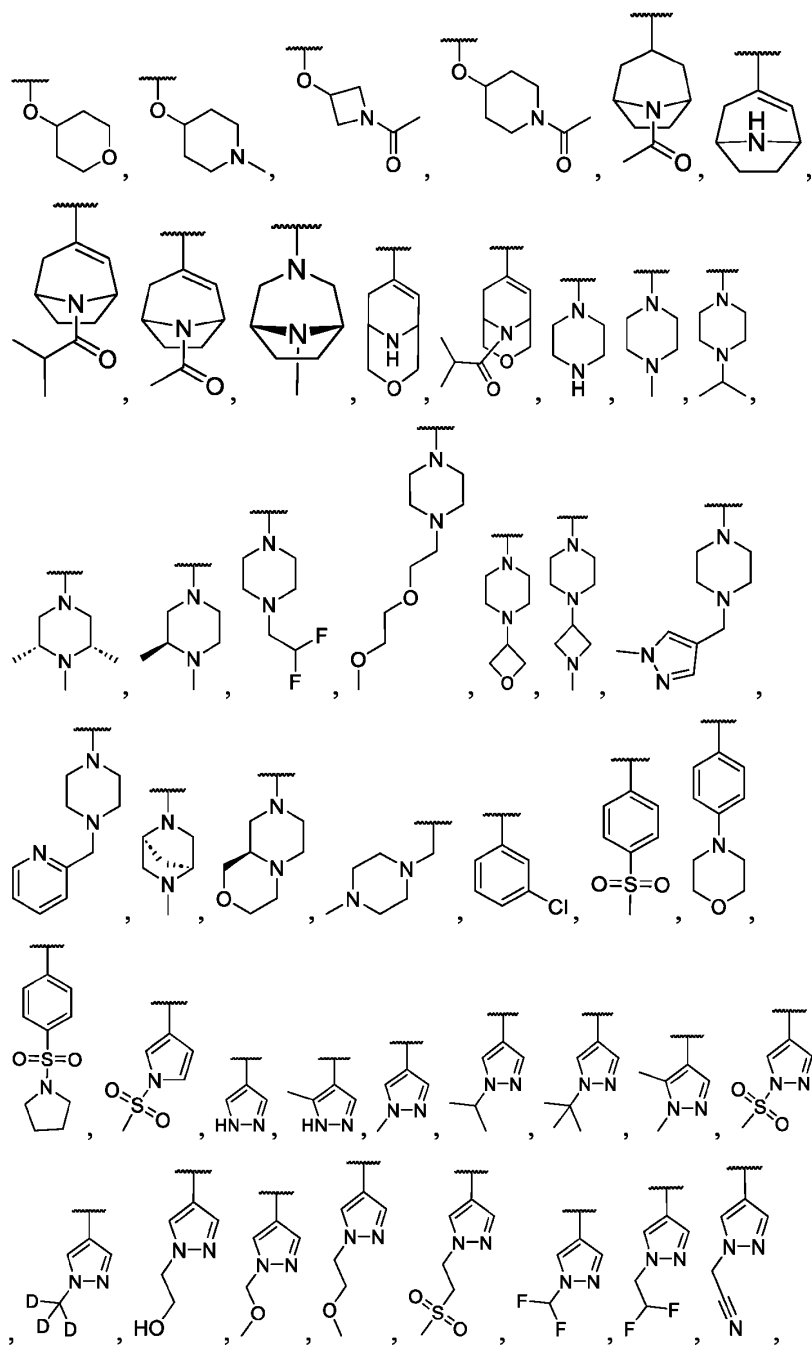
m8 is 1, 2, or 3; and

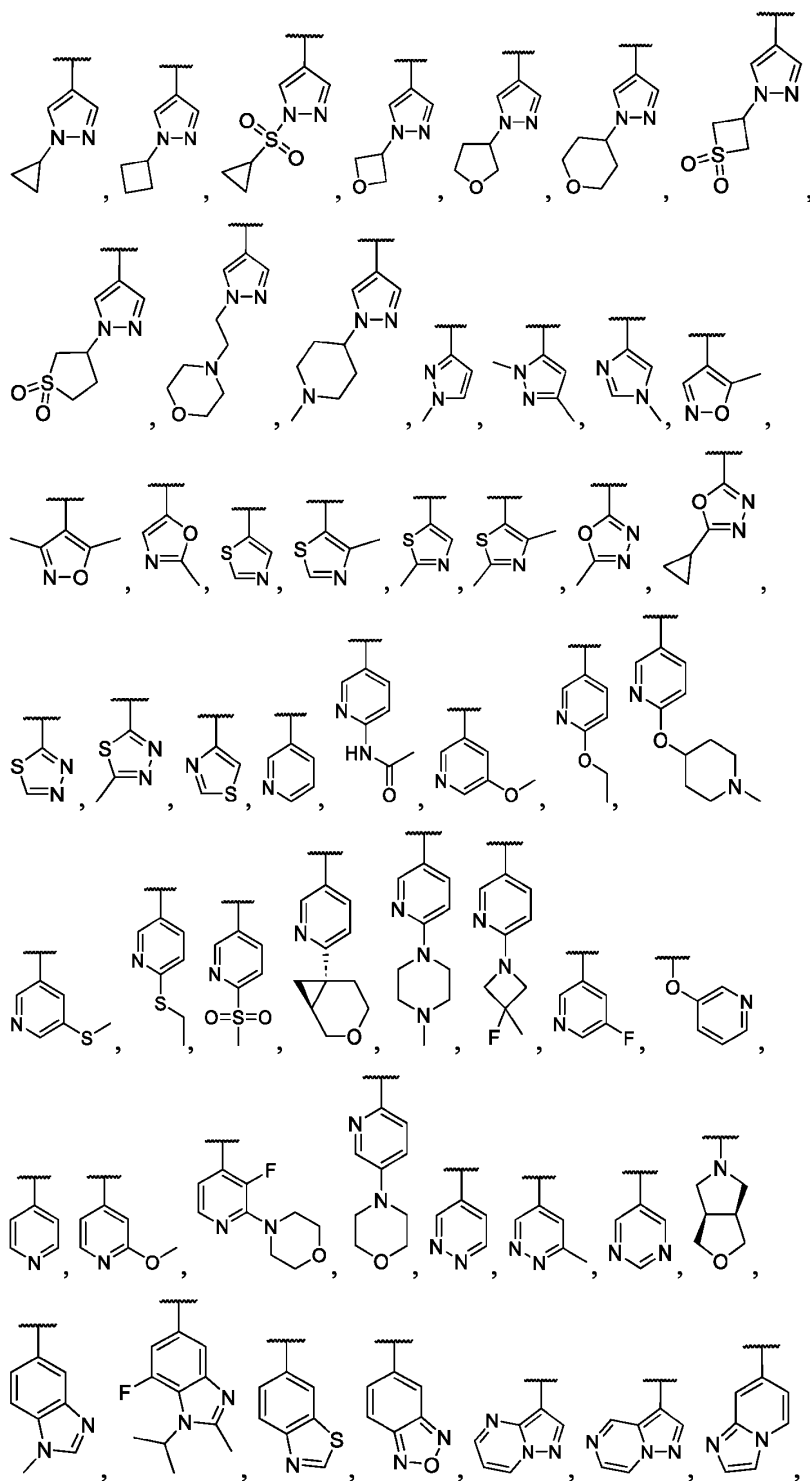
each R^{8f} is independently methyl, isopropyl, isobutyl, methoxy, ethoxy, fluoro, chloro, cyano,

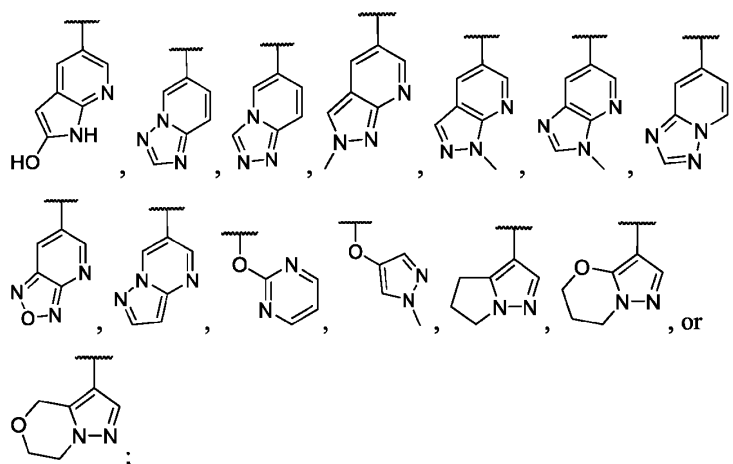
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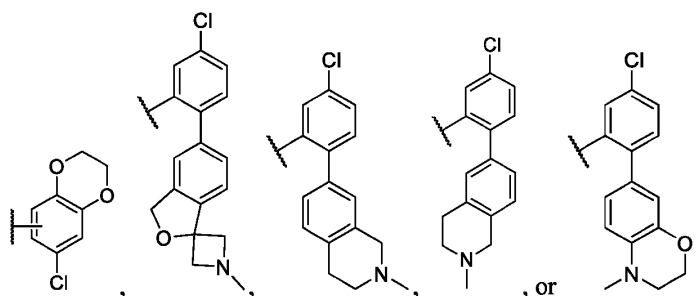
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alternatively, ring B and three R^{8f} groups form the moiety

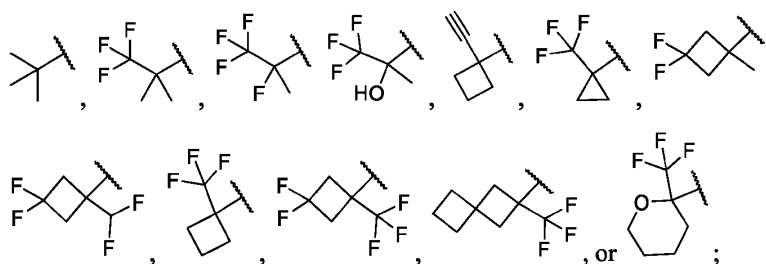


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wherein the wavy line identifies attachment to the remainder of the molecule.

[0135] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein

R³ is



10

R^{4a} and R^{4b} are each H;

R^{4c} is ethyl;

alternatively, R^{4c} and R^{4a} together with the carbon and nitrogen to which each is

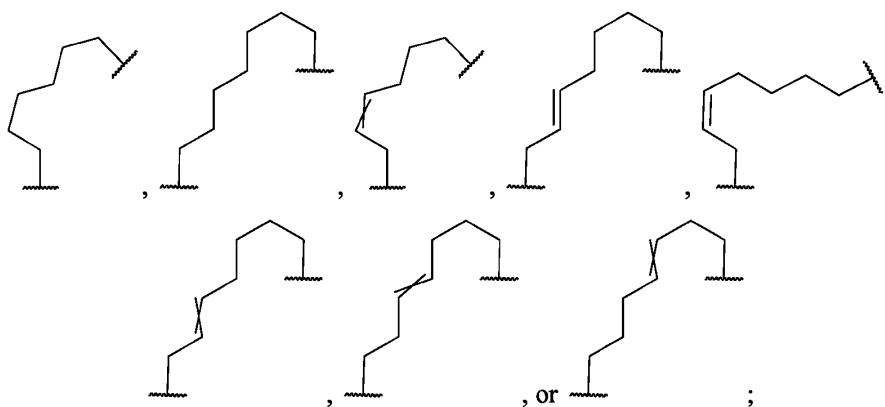
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attached combine to form a pyrrolidiny, substituted with 0 to 2 fluoro;

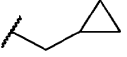
R^{5a} and R^{5b} are each H;

R^{5c} is H, methyl, ethyl, , , or  ;

X⁶ is



5

R^{6a} is H, methyl, ethyl, or  ;

R^{6b} is H;

R^{6d} is H, methyl, or ethyl;

R^{7a} and R^{7b} are each H;

10 R^{7c} is isobutyl, , , , , or  ;

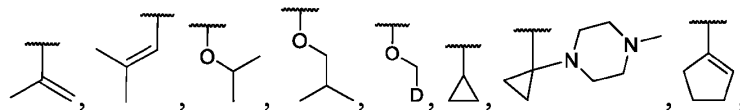
R^{8a} is H or methyl;

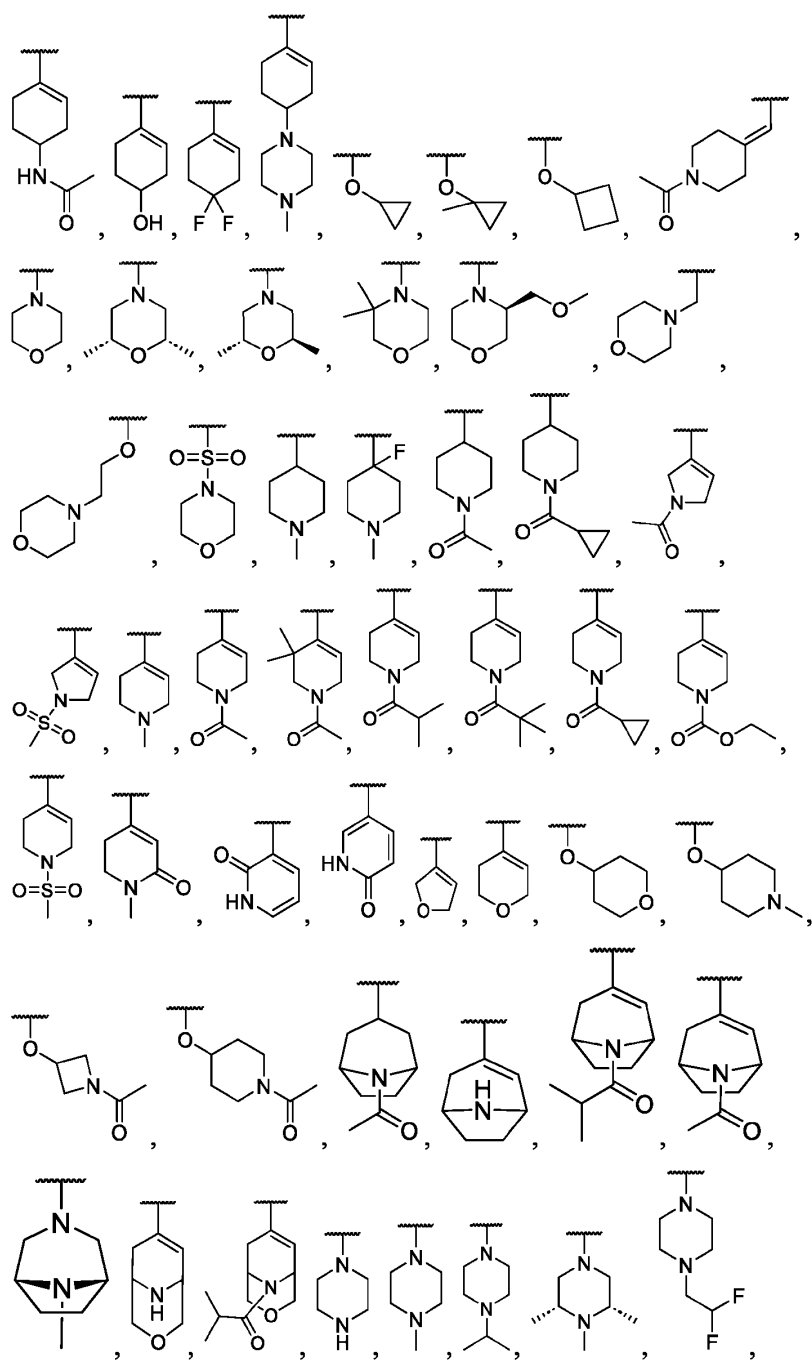
R^{8b}, R^{8d} and R^{8e} are each H;

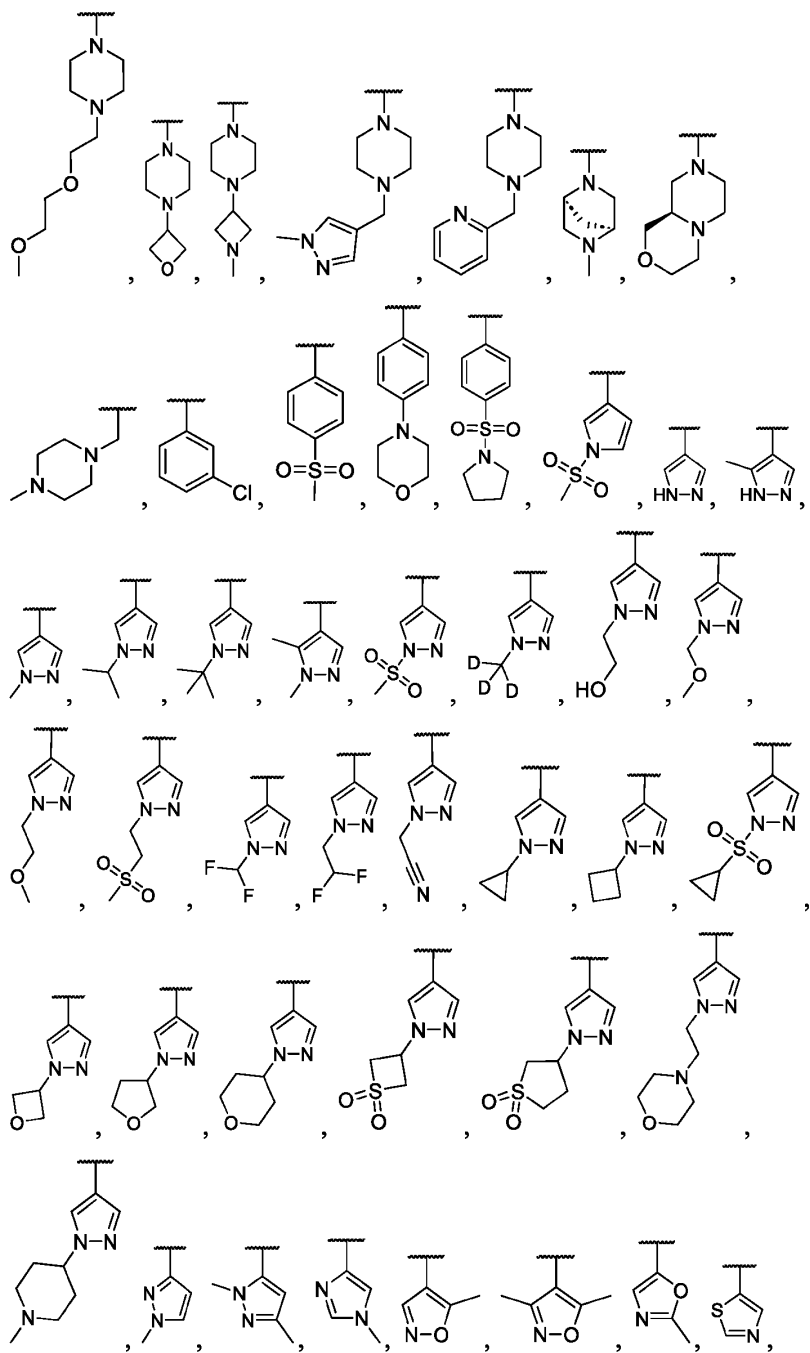
ring B is phenyl, biphenyl, or pyrid-3-yl;

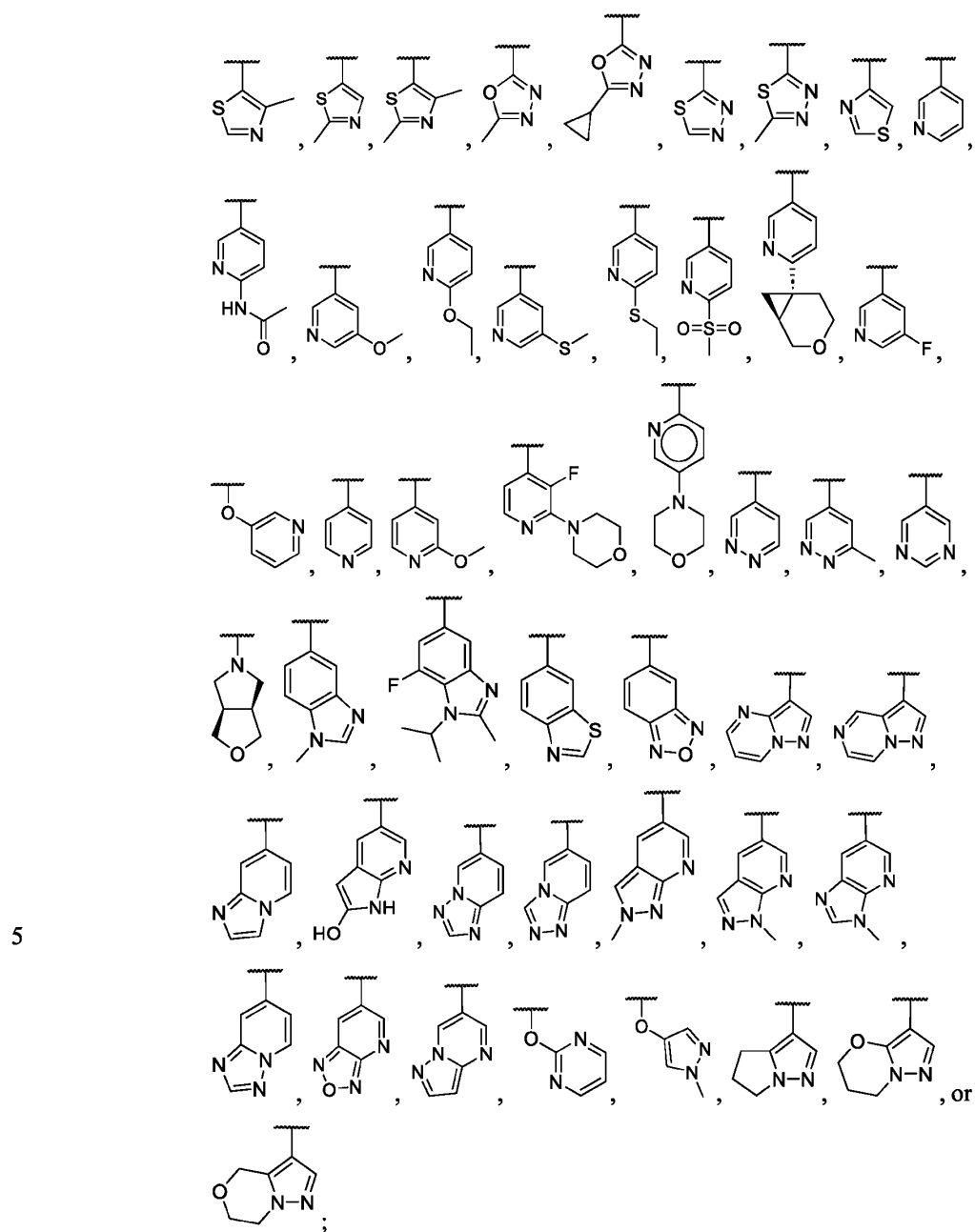
m8 is 1, 2, or 3; and

15 each R^{8f} is independently methyl, isopropyl, isobutyl, methoxy, ethoxy, fluoro, chloro, cyano,

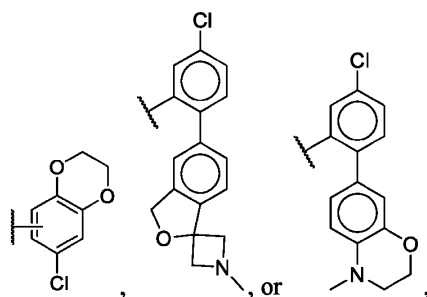








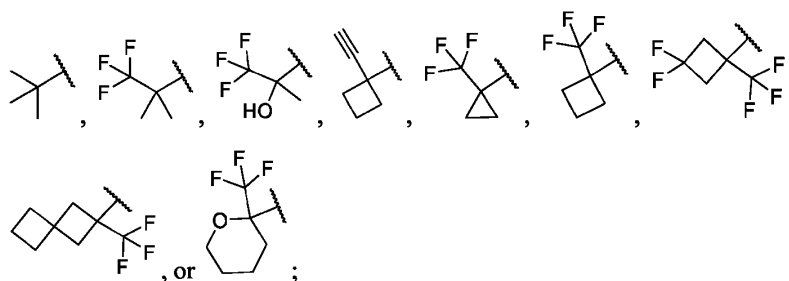
alternatively, ring B and three R^{8f} groups form the moiety



wherein the wavy line identifies attachment to the remainder of the molecule.

[0136] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1), (Id), or (Id1), wherein

5 R^3 is



R^{4a} and R^{4b} are each H;

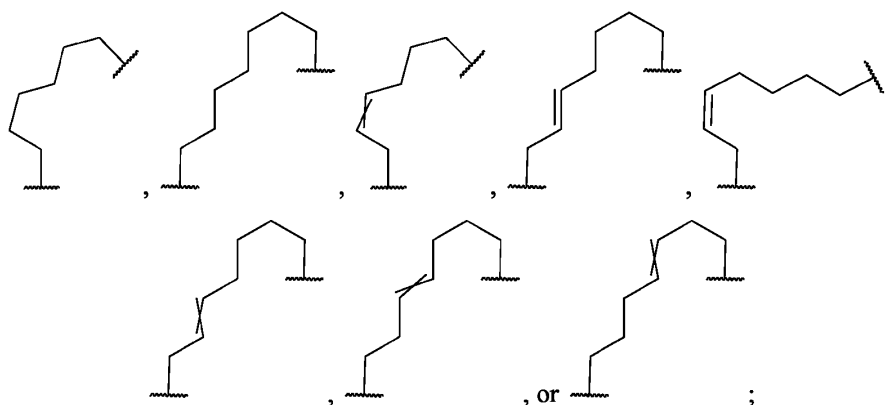
R^{4c} is ethyl;

10 alternatively, R^{4c} and R^{4a} together with the carbon and nitrogen to which each is attached combine to form a pyrrolidinyl, substituted with 0 to 2 fluoro;

R^{5a} and R^{5b} are each H;

R^{5c} is H, methyl, ethyl, , , or  ;

X^6 is

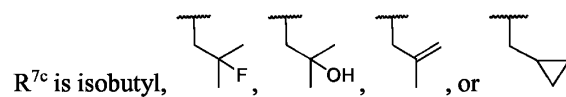


R^{6a} is H, methyl, ethyl, or  ;

R^{6b} is H;

5 R^{6d} is H or methyl;

R^{7a} and R^{7b} are each H;



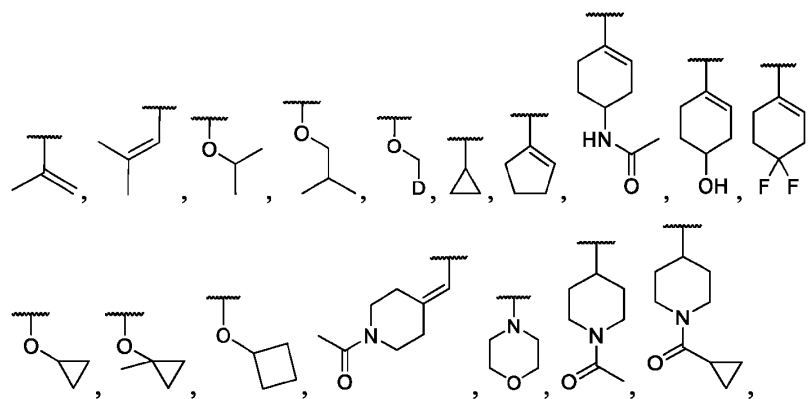
R^{8a} is H or methyl;

R^{8b} , R^{8d} and R^{8e} are each H;

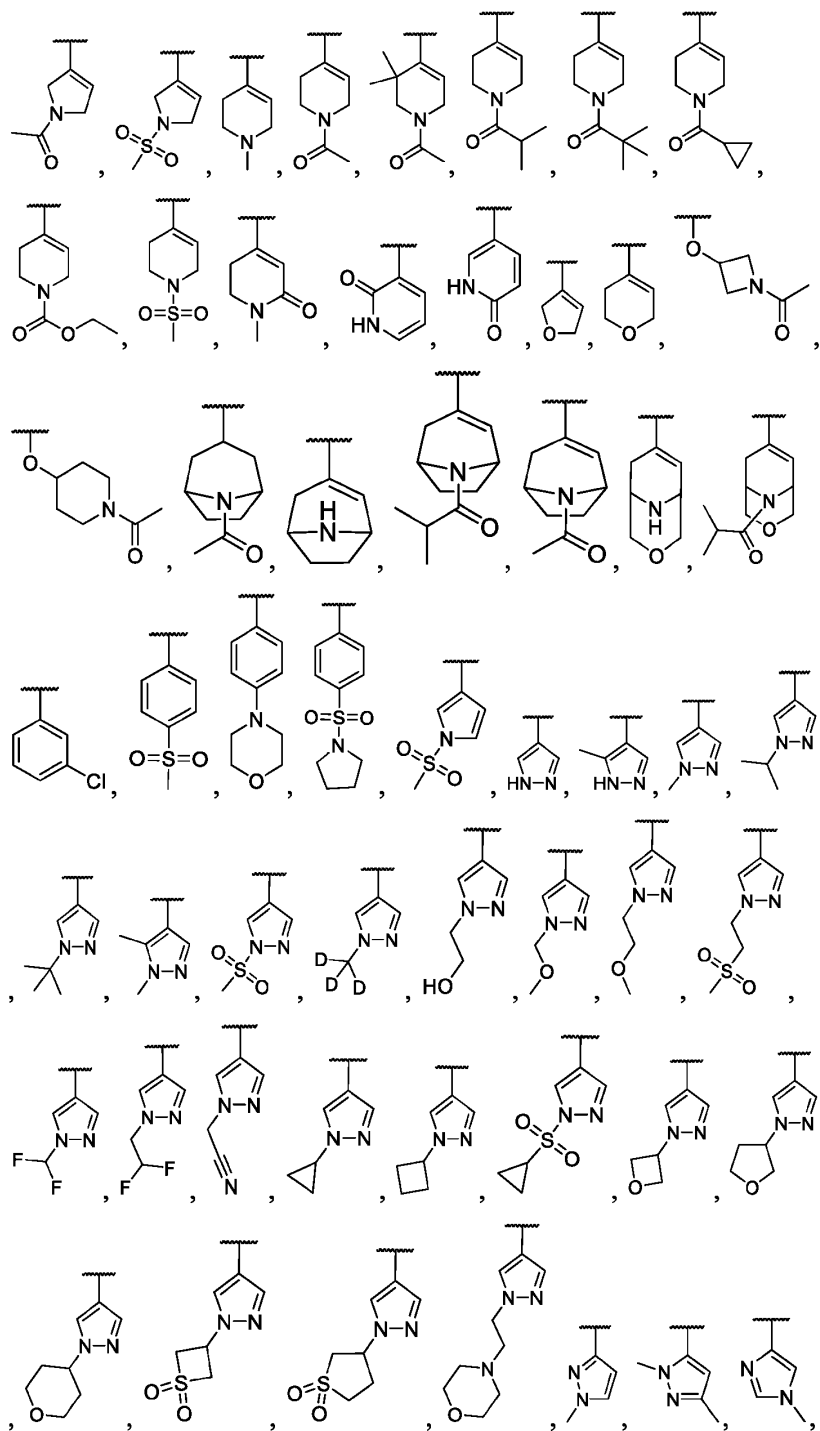
10 ring B is phenyl or pyrid-3-yl;

m8 is 1, 2, or 3; and

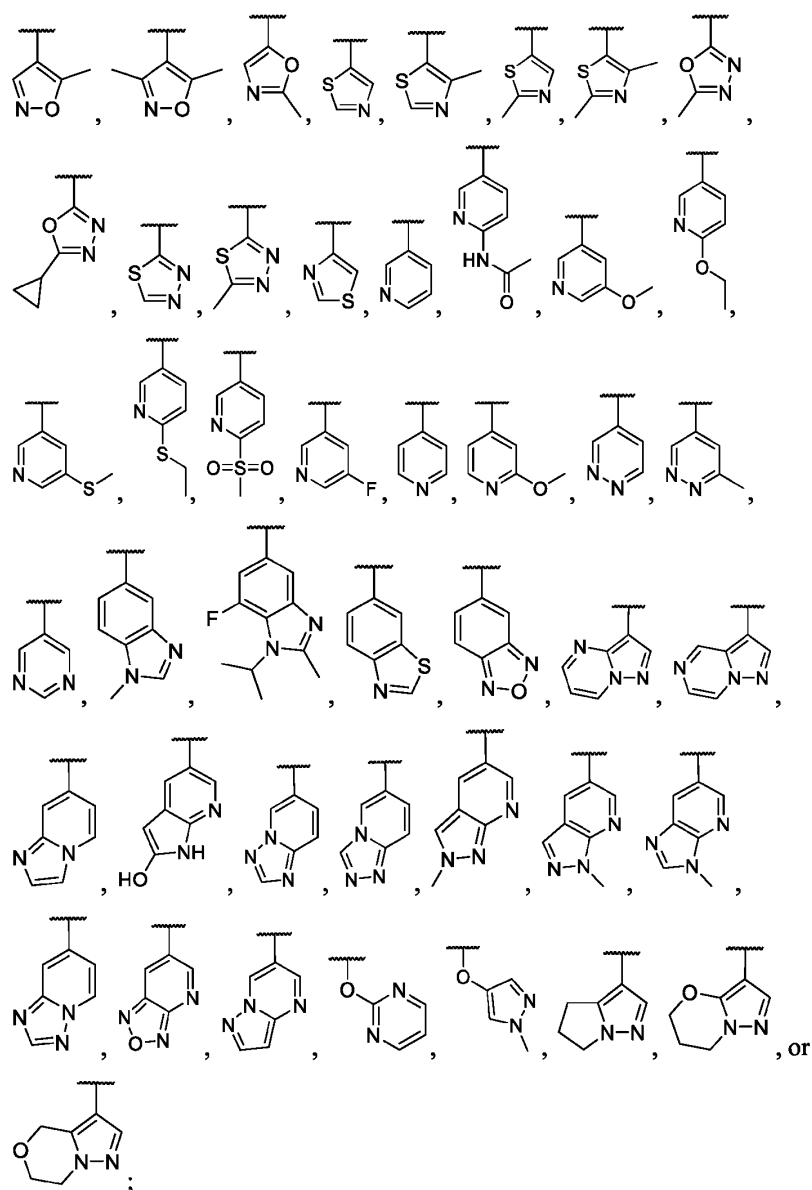
each R^{8f} is independently methyl, isopropyl, isobutyl, methoxy, ethoxy, fluoro, chloro,

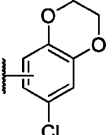


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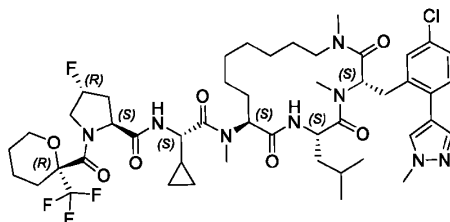


alternatively, ring B and three R^{8f} groups form the moiety , wherein the wavy line identifies attachment to the remainder of the molecule.

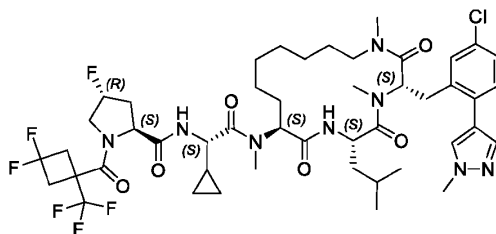
[0137] For the above embodiment, R³, R^{4a}, R^{4b}, R^{4c}, R^{5a}, R^{5b}, R^{5c}, X⁶, R^{6a}, R^{6b}, R^{6d}, R^{7a}, R^{7b}, R^{7c}, R^{8a}, R^{8b}, R^{8d}, R^{8e}, ring B, m8, and R^{8f} can each independently be as defined for any embodiment of Formula (I), (Ib), (Ib1), (Ic), (Ic1) (Id), or (Id1) as described herein.

[0138] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1) (Id), or (Id1) having the structure of any one of Examples 1-426. In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1) (Id), or (Id1) having the structure of any one of Examples 1-389. In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1) (Id), or (Id1) having the structure of any one of Examples 1-334. In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1) (Id), or (Id1) having the structure of any one of Examples 1-50. In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1) (Id), or (Id1) having the structure of any one of Examples 51-100. In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1) (Id), or (Id1) having the structure of any one of Examples 101-150. In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1) (Id), or (Id1) having the structure of any one of Examples 151-200. In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1) (Id), or (Id1) having the structure of any one of Examples 201-250. In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1) (Id), or (Id1) having the structure of any one of Examples 251-300. In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1) (Id), or (Id1) having the structure of any one of Examples 301-334. In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1) (Id), or (Id1) having the structure of any one of Examples 335-389. In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1) (Id), or (Id1) having the structure of any one of Examples 390-426.

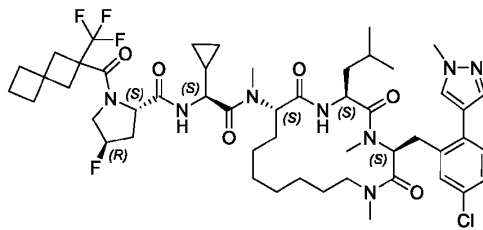
[0139] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I) having the structure



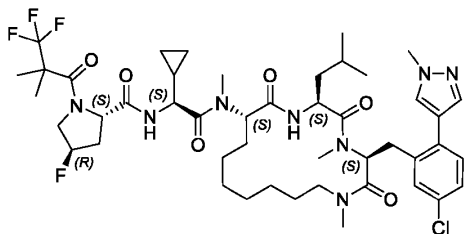
5 [0140] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I) having the structure



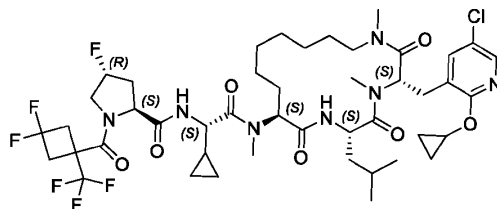
[0141] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I) having the structure



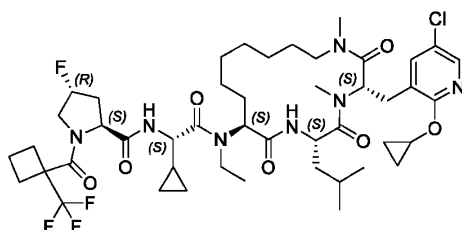
10 [0142] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I) having the structure



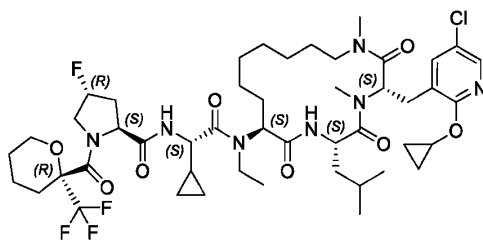
[0143] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I) having the structure



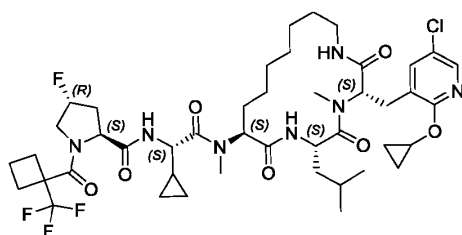
[0144] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I) having the structure



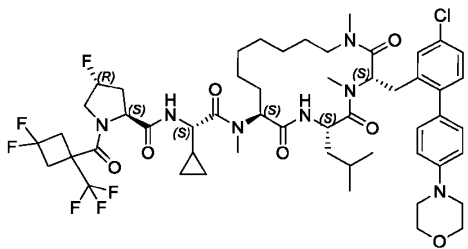
[0145] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I) having the structure



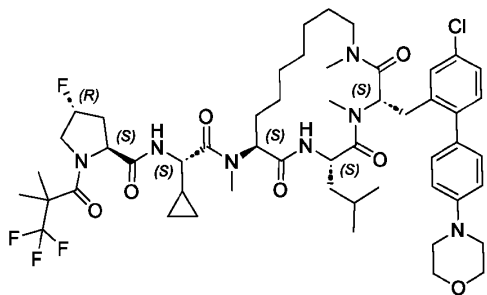
10 **[0146]** In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I) having the structure



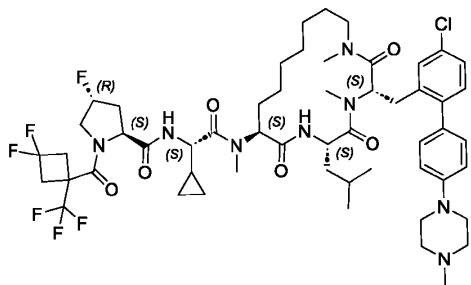
[0147] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I) having the structure



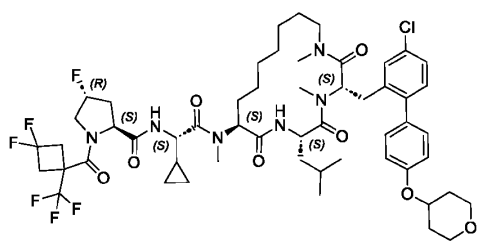
5 [0148] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I) having the structure



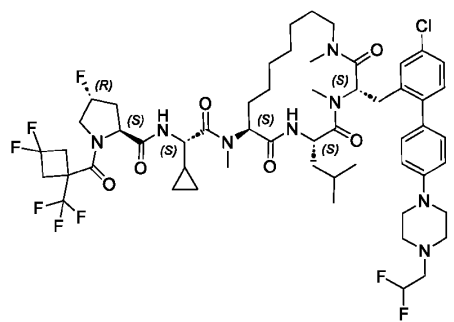
[0149] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I) having the structure



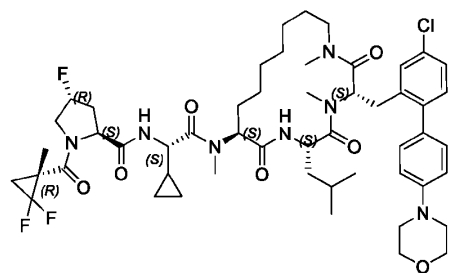
10 [0150] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I) having the structure



[0151] In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I) having the structure



5 **[0152]** In some embodiments, the compound, or the pharmaceutically acceptable salt thereof, is the compound of Formula (I) having the structure



[0153] The present disclosure includes all tautomers and stereoisomers of the compounds described herein, either in admixture or in pure or substantially pure form. The compounds of Formula (I), (Ib), (Ib1), (Ic), (Ic1) (Id), or (Id1) can have asymmetric centers at one or more carbon atoms, and therefore compounds of Formula (I), (Ib), (Ib1), (Ic), (Ic1) (Id), or (Id1) can exist in diastereomeric or enantiomeric forms or mixtures thereof. All 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, as well as solvates, hydrates, and tautomers are within the scope of the present disclosure. Compounds of Formula (I), (Ib), (Ib1), (Ic), (Ic1) (Id), or (Id1) can be prepared using diastereomers,

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enantiomers or racemic mixtures as starting materials. Furthermore, diastereomer and enantiomer products can be separated by chromatography, fractional crystallization or other methods known to those of skill in the art. Unless otherwise indicated, when a stereochemical depiction is shown, it is meant that the isomer with the depicted stereochemistry is present and substantially free of the other isomer(s). “Substantially free of” another isomer indicates at least an 80/20 ratio of the two isomers, more preferably 90/10, or 95/5 or more. When a structure includes a wavy bond attached to a double bond, this indicates E, Z, or a mixture of both isomers.

[0154] The compounds of Formula (I), (Ib), (Ib1), (Ic), (Ic1) (Id), or (Id1) can also be in the salt forms, such as acid or base salts of the compounds of Formula (I), (Ib), (Ib1), (Ic), (Ic1) (Id), or (Id1). Illustrative examples of pharmaceutically acceptable salts are mineral acid (hydrochloric acid, hydrobromic acid, phosphoric acid, and the like) salts, organic acid (acetic acid, propionic acid, glutamic acid, citric acid and the like) salts, quaternary ammonium (methyl iodide, ethyl iodide, and the like) salts. It is understood that the pharmaceutically acceptable salts are non-toxic. Additional information on suitable pharmaceutically acceptable salts can be found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, Pa., 1985, which is incorporated herein by reference.

[0155] Pharmaceutically acceptable salts of the acidic compounds of Formula (I), (Ib), (Ib1), (Ic), (Ic1) (Id), or (Id1) are salts formed with bases, namely cationic salts such as alkali and alkaline earth metal salts, such as sodium, lithium, potassium, calcium, magnesium, as well as ammonium salts, such as ammonium, trimethyl-ammonium, diethylammonium, and tris-(hydroxymethyl)-methyl-ammonium salts.

[0156] Similarly acid addition salts, such as of mineral acids, organic carboxylic and organic sulfonic acids, e.g., hydrochloric acid, methanesulfonic acid, maleic acid, are also possible provided a basic group, such as pyridyl, constitutes part of the structure.

[0157] The neutral forms of the compounds can be regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents, but otherwise the salts are equivalent to the parent form of the compound for the purposes of the present disclosure.

[0158] The present disclosure also includes isotopically-labeled compounds of Formula(I), (Ib), (Ib1), (Ic), (Ic1) (Id), or (Id1), wherein one or more atoms are replaced by one or more atoms having specific atomic mass or mass numbers. Examples of isotopes that can be incorporated into compounds of Formula (I), (Ib), (Ib1), (Ic), (Ic1) (Id), or (Id1) include, but are not limited to, isotopes of hydrogen, carbon, nitrogen, oxygen, fluorine, sulfur, and chlorine (such as ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{18}F , ^{35}S and ^{36}Cl). Isotopically-labeled compounds of Formula (I), (Ib), (Ib1), (Ic), (Ic1) (Id), or (Id1) can be useful in assays of the tissue distribution of the compounds and their prodrugs and metabolites; preferred isotopes for such assays include ^3H and ^{14}C . In addition, in certain circumstances substitution with heavier isotopes, such as deuterium (^2H), can provide increased metabolic stability, which offers therapeutic advantages such as increased in vivo half-life or reduced dosage requirements. Isotopically-labeled compounds of Formula (I), (Ib), (Ib1), (Ic), (Ic1) (Id), or (Id1) can generally be prepared according to methods known in the art.

IV. Compositions

[0159] The compounds of Formula (I), (Ib), (Ib1), (Ic), (Ic1) (Id), or (Id1) described herein are useful in the manufacture of a pharmaceutical composition or a medicament for modulating one or more cyclins (e.g. cyclin A, cyclin B, cycline E). In some embodiments, the present disclosure provides a pharmaceutical composition comprising a compound of the present disclosure, and a pharmaceutically acceptable excipient. In some embodiments, a pharmaceutical composition or medicament comprising one or more compounds of Formula (I), (Ib), (Ib1), (Ic), (Ic1) (Id), or (Id1) can be administered to a subject for the treatment of a cancer.

[0160] Pharmaceutical compositions or medicaments for use in the present disclosure can be formulated by standard techniques or methods well-known in the art of pharmacy using one or more physiologically acceptable carriers or excipients. Suitable pharmaceutical carriers are described herein and in, e.g., "Remington's Pharmaceutical Sciences" by E.W. Martin. Compounds of Formula (I), (Ib), (Ib1), (Ic), (Ic1) (Id), or (Id1) and their physiologically acceptable salts and solvates can be formulated for administration by any suitable route, including, but not limited to, orally, topically, nasally, rectally, pulmonary, parenterally (e.g., intravenously, subcutaneously, intramuscularly, etc.), and combinations thereof. In some embodiments, the compounds of Formula (I), (Ib), (Ib1), (Ic), (Ic1) (Id), or (Id1) is dissolved in a liquid, for example, water. The most suitable route of administration

for a compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1) (Id), or (Id1) in any given case will depend, in part, on the nature, severity, and optionally, and the stage of the cancer.

5 [0161] The pharmaceutical compositions or medicaments of the present disclosure can include a compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1) (Id), or (Id1) with as an active ingredient and a pharmaceutically acceptable carrier and/or excipient or diluent. Any carrier and/or excipient suitable for the form of preparation desired for administration is contemplated for use with the compounds of Formula (I), (Ib), (Ib1), (Ic), (Ic1) (Id), or (Id1) disclosed herein.

10 [0162] In some embodiments, the pharmaceutical compositions or medicaments described herein are suitable for systemic administration. Systemic administration includes enteral administration (*e.g.*, absorption of the compound through the gastrointestinal tract) or parenteral administration (*e.g.*, injection, infusion, or implantation). In some embodiments, the pharmaceutical compositions or medicaments can be administered via a syringe or intravenously. In preferred embodiments, the pharmaceutical compositions or medicaments
15 are injected subcutaneously.

[0163] For oral administration, a pharmaceutical composition or a medicament can take the form of, *e.g.*, a tablet or a capsule prepared by conventional means with a pharmaceutically acceptable excipient. Preferred are tablets and gelatin capsules comprising the active ingredient(s), together with (a) diluents or fillers, *e.g.*, lactose, dextrose, sucrose, mannitol,
20 sorbitol, cellulose (*e.g.*, ethyl cellulose, microcrystalline cellulose), glycine, pectin, polyacrylates and/or calcium hydrogen phosphate, calcium sulfate, (b) lubricants, *e.g.*, silica, anhydrous colloidal silica, talcum, stearic acid, its magnesium or calcium salt (*e.g.*, magnesium stearate or calcium stearate), metallic stearates, colloidal silicon dioxide, hydrogenated vegetable oil, corn starch, sodium benzoate, sodium acetate and/or
25 polyethyleneglycol; for tablets also (c) binders, *e.g.*, magnesium aluminum silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, polyvinylpyrrolidone and/or hydroxypropyl methylcellulose; if desired (d) disintegrants, *e.g.*, starches (*e.g.*, potato starch or sodium starch), glycolate, agar, alginic acid or its sodium salt, or effervescent mixtures; (e) wetting agents, *e.g.*, sodium lauryl sulfate, and/or (f) absorbents,
30 colorants, flavors and sweeteners. In some embodiments, the tablet contains a mixture of hydroxypropyl methylcellulose, polyethyleneglycol 6000 and titanium dioxide. Tablets can be either film coated or enteric coated according to methods known in the art.

[0164] Liquid preparations for oral administration can take the form of, for example, solutions, syrups, or suspensions, or they can be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations can be prepared by conventional means with pharmaceutically acceptable additives, for example, suspending agents, for example, sorbitol syrup, cellulose derivatives, or hydrogenated edible fats; emulsifying agents, for example, lecithin or acacia; non-aqueous vehicles, for example, almond oil, oily esters, ethyl alcohol, or fractionated vegetable oils; and preservatives, for example, methyl or propyl-p-hydroxybenzoates or sorbic acid. The preparations can also contain buffer salts, flavoring, coloring, and/or sweetening agents as appropriate. If desired, preparations for oral administration can be suitably formulated to give controlled release of the active compound.

[0165] Typical formulations for topical administration include creams, ointments, sprays, lotions, and patches. The pharmaceutical composition can, however, be formulated for any type of administration, *e.g.*, intradermal, subdermal, intravenous, intramuscular, intranasal, intracerebral, intratracheal, intraarterial, intraperitoneal, intravesical, intrapleural, intracoronary or intratumoral injection, with a syringe or other devices. Formulation for administration by inhalation (*e.g.*, aerosol), or for oral, rectal, or vaginal administration is also contemplated.

[0166] Pharmaceutical compositions for pulmonary administration include, but are not limited to, dry powder compositions consisting of the powder of a compound described herein, or a salt thereof, and the powder of a suitable carrier and/or lubricant. The compositions for pulmonary administration can be inhaled from any suitable dry powder inhaler device known to a person skilled in the art. In certain instances, the compositions can be conveniently delivered in the form of an aerosol spray from pressurized packs or a nebulizer, with the use of a suitable propellant, for example, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide, or other suitable gas. In the case of a pressurized aerosol, the dosage unit can be determined by providing a valve to deliver a metered amount. Capsules and cartridges of, for example, gelatin for use in an inhaler or insufflator can be formulated containing a powder mix of the compound(s) and a suitable powder base, for example, lactose or starch.

[0167] The compounds of Formula (I), (Ib), (Ib1), (Ic), (Ic1) (Id), or (Id1) can also be formulated in rectal compositions, for example, suppositories or retention enemas, for

example, containing conventional suppository bases, for example, cocoa butter or other glycerides.

[0168] The compounds of Formula (I), (Ib), (Ib1), (Ic), (Ic1) (Id), or (Id1) set forth herein can be formulated for parenteral administration by injection, for example by bolus injection.

- 5 Formulations for injection can be presented in unit dosage form, for example, in ampoules or in multi-dose containers, with an added preservative. Injectable compositions are preferably aqueous isotonic solutions or suspensions, and suppositories are preferably prepared from fatty emulsions or suspensions. The compositions can be sterilized and/or contain adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for
- 10 regulating the osmotic pressure and/or buffers. Alternatively, the compound(s) can be in powder form for reconstitution with a suitable vehicle, for example, sterile pyrogen-free water, before use. In addition, they may also contain other therapeutically valuable substances. The compositions are prepared according to conventional mixing, granulating or coating methods, respectively, and contain about 0.1 to 75%, preferably about 1 to 50%, of
- 15 the compound(s).

[0169] In some embodiments, the compositions described herein are prepared with a polysaccharide such as chitosan or derivatives thereof (*e.g.*, chitosan succinate, chitosan phthalate, *etc.*), pectin and derivatives thereof (*e.g.*, amidated pectin, calcium pectinate, *etc.*), chondroitin and derivatives thereof (*e.g.*, chondroitin sulfate), and alginates.

- 20 [0170] In some embodiments, the compositions described herein further include a pharmaceutical surfactant. In other embodiments, the compositions further include a cryoprotectant. Non-limiting examples of cryoprotectants include glucose, sucrose, trehalose, lactose, sodium glutamate, PVP, cyclodextrin, 2-hydroxypropyl-13-cyclodextrin (HPI3CD) glycerol, maltose, mannitol, saccharose, and mixtures thereof.

25 V. Methods

- [0171] The present disclosure contemplates the use of the compounds of Formula (I), (Ib), (Ib1), (Ic), (Ic1) (Id), or (Id1) described herein in the treatment or prevention of diseases or disorders modulated, at least in part, by one or more cyclins. In some embodiments, the cyclin mediated disease is a proliferative condition or disorder, including cancer. In some
- 30 embodiments, the present disclosure provides a method of treating a cancer mediated at least in part by cyclin activity, the method comprising administering to a subject in need thereof, a

therapeutically effective amount of a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of the present disclosure, thereby treating the cancer.

5 [0172] In some embodiments, provided herein are compounds of Formula (I), (Ib), (Ib1), (Ic), (Ic1) (Id), or (Id1) for use in therapy.

[0173] The present disclosure contemplates the use of the compounds of Formula (I), (Ib), (Ib1), (Ic), (Ic1) (Id), or (Id1) described herein in the treatment or prevention of diseases or disorders modulated, at least in part, by cyclin A. In some embodiments, the cyclin A mediated disease is a proliferative condition or disorder, including cancer. In some
10 embodiments, the present disclosure provides a method of treating a cancer mediated at least in part by cyclin A, the method comprising administering to a subject in need thereof, a therapeutically effective amount of a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of the present disclosure, thereby treating the cancer.

15 [0174] In some embodiments, provided herein are methods of treating a proliferative condition or disorder mediated at least in part by cyclin A comprising administering a compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1) (Id), or (Id1) described herein.

[0175] In some embodiments, provided herein are compounds of Formula (I), (Ib), (Ib1), (Ic), (Ic1) (Id), or (Id1) for use in a method for treating a proliferative condition or disorder
20 mediated at least in part by cyclin A.

[0176] In some embodiments, provided herein are uses of compounds of Formula (I), (Ib), (Ib1), (Ic), (Ic1) (Id), or (Id1) for the manufacture of a medicament for the treatment of a proliferative condition or disorder mediated at least in part by cyclin A.

[0177] The present disclosure contemplates the use of the compounds of Formula (I), (Ib), (Ib1), (Ic), (Ic1) (Id), or (Id1) described herein in the treatment or prevention of diseases or disorders modulated, at least in part, by cyclin B. In some embodiments, the cyclin B mediated disease is a proliferative condition or disorder, including cancer. In some
25 embodiments, the present disclosure provides a method of treating a cancer mediated at least in part by cyclin B, the method comprising administering to a subject in need thereof, a therapeutically effective amount of a compound of the present disclosure, or a
30

pharmaceutically acceptable salt thereof, or a pharmaceutical composition of the present disclosure, thereby treating the cancer.

5 **[0178]** In some embodiments, provided herein are methods of treating a proliferative condition or disorder mediated at least in part by cyclin B comprising administering a compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1) (Id), or (Id1) described herein.

[0179] In some embodiments, provided herein are compounds of Formula (I), (Ib), (Ib1), (Ic), (Ic1) (Id), or (Id1) for use in a method for treating a proliferative condition or disorder mediated at least in part by cyclin B.

10 **[0180]** In some embodiments, provided herein are uses of compounds of Formula (I), (Ib), (Ib1), (Ic), (Ic1) (Id), or (Id1) for the manufacture of a medicament for the treatment of a proliferative condition or disorder mediated at least in part by cyclin B.

[0181] The present disclosure contemplates the use of the compounds of Formula (I), (Ib), (Ib1), (Ic), (Ic1) (Id), or (Id1) described herein in the treatment or prevention of diseases or disorders modulated, at least in part, by cyclin E. In some embodiments, the cyclin E
15 mediated disease is a proliferative condition or disorder, including cancer. In some embodiments, the present disclosure provides a method of treating a cancer mediated at least in part by cyclin E, the method comprising administering to a subject in need thereof, a therapeutically effective amount of a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of the present
20 disclosure, thereby treating the cancer.

[0182] In some embodiments, provided herein are methods of treating a proliferative condition or disorder mediated at least in part by cyclin E comprising administering a compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1) (Id), or (Id1) described herein.

25 **[0183]** In some embodiments, provided herein are compounds of Formula (I), (Ib), (Ib1), (Ic), (Ic1) (Id), or (Id1) for use in a method for treating a proliferative condition or disorder mediated at least in part by cyclin E.

[0184] In some embodiments, provided herein are uses of compounds of Formula (I), (Ib), (Ib1), (Ic), (Ic1) (Id), or (Id1) for the manufacture of a medicament for the treatment of a proliferative condition or disorder mediated at least in part by cyclin E.

[0185] In some embodiments, the compounds of Formula (I), (Ib), (Ib1), (Ic), (Ic1) (Id), or (Id1) described herein can be used to treat or prevent a proliferative condition or disorder, including a cancer, for example, cancer of the uterus, cervix, breast, prostate, testes, gastrointestinal tract (e.g., esophagus, oropharynx, stomach, small or large intestines, colon, or rectum), kidney, renal cell, bladder, bone, bone marrow, skin, head or neck, liver, gall bladder, bile ducts, heart, lung (e.g., non-small-cell lung carcinoma, small cell lung cancer), pancreas, salivary gland, adrenal gland, thyroid, brain, ganglia, central nervous system (CNS) and peripheral nervous system (PNS), and cancers of the hematopoietic system and the immune system (e.g., spleen or thymus).

10 [0186] The present disclosure also provides methods of treating or preventing other cancer-related diseases, disorders or conditions, including, for example, virus-induced cancers (e.g., epithelial cell cancers, endothelial cell cancers, squamous cell carcinomas and papillomavirus), adenocarcinomas, lymphomas, carcinomas, melanomas, leukemias, myelomas, sarcomas, teratocarcinomas, chemically-induced cancers, metastasis, and
15 angiogenesis.

[0187] In some embodiments, the tumor or cancer is colon cancer, ovarian cancer, breast cancer, melanoma, lung cancer, glioblastoma, or leukemia.

[0188] In some embodiments, the tumor or cancer is small cell lung cancer (SCLC).

[0189] The use of the term(s) cancer-related diseases, disorders and conditions is meant to
20 refer broadly to conditions that are associated, directly or indirectly, with cancer, and includes, e.g., angiogenesis and precancerous conditions such as dysplasia.

[0190] In some embodiments, the cancer is a blood cancer (e.g., leukemia, lymphoma, multiple myeloma).

[0191] In some embodiments, the leukemia is acute lymphocytic leukemia, chronic
25 lymphocytic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, or hairy cell leukemia.

[0192] In some embodiments, the lymphoma is non-Hodgkin's lymphoma, Hodgkin's lymphoma, B-cell lymphoma, or Burkitt's lymphoma.

[0193] In some embodiments, the cancer is an Rb mutated cancer. In some embodiments,
30 the cancer has a mutation in the Rb/E2F pathway.

VI. Administration

[0194] The present disclosure contemplates the administration of compounds of Formula (I), (Ib), (Ib1), (Ic), (Ic1) (Id), or (Id1) and compositions thereof, in any appropriate manner. Suitable routes of administration include oral, parenteral (e.g., intramuscular, intravenous, subcutaneous (e.g., injection or implant), intraperitoneal, intracisternal, intraarticular, intraperitoneal, intracerebral (intraparenchymal) and intracerebroventricular), nasal, vaginal, sublingual, intraocular, rectal, topical (e.g., transdermal), buccal and inhalation.

[0195] Pharmaceutical compositions comprising compounds of Formula (I), (Ib), (Ib1), (Ic), (Ic1) (Id), or (Id1) are preferably in unit dosage form. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

[0196] Compounds of Formula (I), (Ib), (Ib1), (Ic), (Ic1) (Id), or (Id1) or pharmaceutical compositions or medicaments thereof can be administered to a subject diagnosed or suspected of having a disease or disorder mediated at least in part by cyclin A in an amount sufficient to elicit an effective therapeutic response in the subject.

[0197] The dosage of compounds administered is dependent on a variety of factors including the subject's body weight, age, individual condition, and/or on the form of administration. The size of the dose will also be determined by the existence, nature, and extent of any adverse effects that accompany the administration of a particular compound in a particular subject. Typically, a dosage of the active compounds is a dosage that is sufficient to achieve the desired effect. Optimal dosing schedules can be calculated from measurements of compound accumulation in the body of a subject. In general, dosage can be given once or more daily, weekly, or monthly. Persons of ordinary skill in the art can easily determine optimum dosages, dosing methodologies, and repetition rates.

[0198] In some embodiments, a unit dosage for oral administration of a compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1) (Id), or (Id1) described herein to a subject (e.g., a human) of about 50 to about 70 kg may contain between about 1 and about 5,000 mg, about 1 and about 3,000 mg, about 1 and about 2,000 mg, or about 1 to about 1,000 mg of the compound(s).

- 5 **[0199]** In some embodiments, a unit dosage for subcutaneous administration of a compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1) (Id), or (Id1) described herein to a subject (*e.g.*, human) of about 50 to about 70 kg may contain between about 0.1 and about 500 mg, about 0.5 and about 300 mg, about 0.5 and about 200 mg, about 0.5 and about 100 mg, or about 0.5 and about 50 mg.
- [0200]** The dose can be administered once per day or divided into sub-doses and administered in multiple doses, *e.g.*, twice, three times, or four times per day. However, as will be appreciated by a skilled artisan, depending on the route of administration different amounts can be administered at different times.
- 10 **[0201]** In some embodiments, the compounds are administered for about 1 to 31 days, or for about 1 to 12 months. In some embodiments, the compounds are administered for one or more weeks, *e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or more weeks. In some embodiments, the compounds are administered for one or more months, *e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or more months.
- 15 **[0202]** Optimum dosages, toxicity, and therapeutic efficacy of such compounds may vary depending on the relative potency of individual compounds and can be determined by standard pharmaceutical procedures in experimental animals, for example, by determining the LD₅₀ (the dose lethal to 50% of the population) and the ED₅₀ (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index
- 20 and can be expressed as the ratio, LD₅₀/ED₅₀. Compounds that exhibit large therapeutic indices are preferred. While compounds that exhibit toxic side-effects can be used, care should be taken to design a delivery system that targets such compounds to the affected site to minimize potential damage to normal cells and, thereby, reduce side-effects.
- [0203]** The dosage of a pharmaceutical composition or medicament of the present
- 25 disclosure can be monitored and adjusted throughout treatment, depending on severity of symptoms, frequency of recurrence, and/or the physiological response to the therapeutic regimen. Those of skill in the art commonly engage in such adjustments in therapeutic regimens.
- [0204]** Single or multiple administrations of the pharmaceutical compositions or
- 30 medicaments can be administered depending on the dosage and frequency as required and tolerated by the patient. In any event, the composition or medicament should provide a sufficient quantity of the compounds of the disclosure to effectively treat the patient.

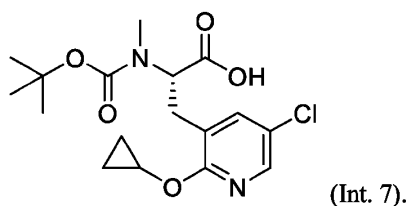
Generally, when treating cancer, the dose is sufficient to stop tumor growth or cause tumor regression without producing unacceptable toxicity or side-effects to the patient.

VII. Intermediates

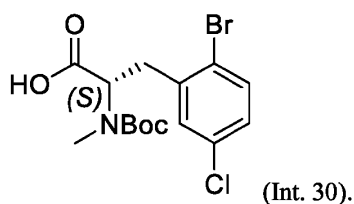
[0205] In some embodiments, the present disclosure provides intermediates useful in the preparation of compounds of Formula (I). Certain intermediates useful in the preparation of a compound of Formula (I) can be found, for example, in the Examples section of the current disclosure.

[0206] In some embodiments, the intermediate is an External Building Block described herein. In some embodiments the intermediate is a compound produced in one of Methods A-D or Methods 1-14 for any one of the compounds exemplified herein. In some
10 embodiments, the intermediate is one of Int. 1-438. In some embodiments, the intermediate is one of Int. 1-405. In some embodiments, the intermediate is one of Int. 1-154.

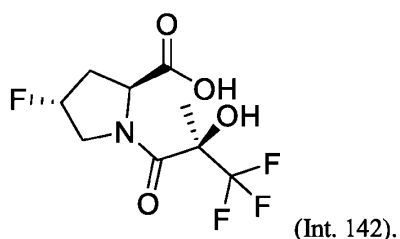
[0207] In some embodiments, the intermediate is Int. 7



15 **[0208]** In some embodiments, the intermediate is Int. 30



[0209] In some embodiments, the intermediate is Int. 142



[0210] In some embodiments, the intermediate is a combination of one or more covalently linked External Building Blocks.

VIII. Kits

- 5 **[0211]** The present disclosure contemplates kits comprising a compound of Formula (I), (Ib), (Ib1), (Ic), (Ic1) (Id), or (Id1) described herein, and pharmaceutical compositions thereof. The kits are generally in the form of a physical structure housing various components, as described below, and can be utilized, for example, in practicing the methods described above.
- 10 **[0212]** A kit can include one or more of the compounds disclosed herein (provided in, e.g., a sterile container), which may be in the form of a pharmaceutical composition suitable for administration to a subject. The compounds described herein can be provided in a form that is ready for use (e.g., a tablet, capsule, syringe) or in a form requiring, for example, reconstitution or dilution (e.g., a powder) prior to administration. When the compounds
- 15 described herein are in a form that needs to be reconstituted or diluted by a user, the kit may also include diluents (e.g., sterile water), buffers, pharmaceutically acceptable excipients, and the like, packaged with or separately from the compounds described herein. Each component of the kit can be enclosed within an individual container, and all of the various containers can be within a single package. A kit of the present disclosure can be designed for conditions
- 20 necessary to properly maintain the components housed therein (e.g., refrigeration or freezing).
- [0213]** A kit may contain a label or packaging insert including identifying information for the components therein and instructions for their use (e.g., dosing parameters, clinical pharmacology of the active ingredient(s), including mechanism of action, pharmacokinetics
- 25 and pharmacodynamics, adverse effects, contraindications, etc.). Labels or inserts can include manufacturer information such as lot numbers and expiration dates. The label or packaging insert may be, e.g., integrated into the physical structure housing the components,

contained separately within the physical structure, or affixed to a component of the kit (e.g., an ampule, tube or vial).

- [0214] Labels or inserts can additionally include, or be incorporated into, a computer readable medium, such as a disk (e.g., hard disk, card, memory disk), optical disk such as CD- or DVD-ROM/RAM, DVD, MP3, magnetic tape, or an electrical storage media such as RAM and ROM or hybrids of these such as magnetic/optical storage media, FLASH media or memory-type cards. In some embodiments, the actual instructions are not present in the kit, but means for obtaining the instructions from a remote source, e.g., via the internet, are provided.

IX. Examples

[0215] The following examples illustrate how various intermediates and exemplary compounds of Formula (I) are prepared. The following examples are offered to illustrate, but not to limit the current disclosure.

A. External Building Blocks

- [0216] The compounds of Formula (I) described herein are prepared by covalently linking the external building blocks described in this section. The external building blocks of the present disclosure are identified in Table 1, below, by intermediate number (INT #), IUPAC name, and CAS number, if known. For those without a CAS number, an experimental write-up is provided herein. The order and details related to covalently linking these external building blocks are described in another section.

Table 1: External Building Blocks of the Present Disclosure

INT #	IUPAC	CAS Number, if known
Int. 1	hex-5-en-1-amine	34825-70-2
Int. 2	4-Penten-1-amine	22537-07-1
Int. 3	N-Methylhex-5-en-1-amine	55863-02-0
Int. 4	N-Methyl-4-penten-1-amine	5831-72-1
Int. 5	3-Buten-1-amine	2524-49-4
Int. 6	(S)-2-((tert-butoxycarbonyl)(methyl)amino)-3-(2,5-dichlorophenyl)propanoic acid	
Int. 7	(S)-2-((tert-butoxycarbonyl)(methyl)amino)-3-(5-chloro-2-cyclopropoxy-pyridin-3-yl)propanoic acid	

INT #	IUPAC	CAS Number, if known
Int. 8	(S)-2-((tert-butoxycarbonyl)(methyl)amino)-3-(5-chloro-2-(5-methyl-1,3,4-oxadiazol-2-yl)phenyl)propanoic acid	
Int. 9	(S)-2-((tert-butoxycarbonyl)(methyl)amino)-3-(2-cyclopropoxy-5-fluoropyridin-3-yl)propanoic acid	
Int. 10	(S)-2-((tert-butoxycarbonyl)(methyl)amino)-3-(5-chloro-2-isopropoxypyridin-3-yl)propanoic acid	
Int. 11	(S)-2-((tert-butoxycarbonyl)(methyl)amino)-3-(5-chloro-2-(pyrimidin-2-yloxy)phenyl)propanoic acid	
Int. 12	(S)-2-((tert-butoxycarbonyl)(methyl)amino)-3-(5-chloro-2-cyclobutoxypyridin-3-yl)propanoic acid	
Int. 13	(S)-2-((tert-butoxycarbonyl)(methyl)amino)-3-(5-chloro-2-methoxypyridin-3-yl)propanoic acid	
Int. 14	(S)-2-((tert-butoxycarbonyl)(methyl)amino)-3-(5-chloro-2-ethoxypyridin-3-yl)propanoic acid	
Int. 15	(S)-2-((tert-butoxycarbonyl)(methyl)amino)-3-(5-chloro-2-isobutoxypyridin-3-yl)propanoic acid	
Int. 16	(S)-2-((tert-butoxycarbonyl)(methyl)amino)-3-(5-chloro-2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)phenyl)propanoic acid	
Int. 17	(S)-3-(2-((1-acetylpiperidin-4-yl)oxy)-5-chlorophenyl)-2-((tert-butoxycarbonyl)(methyl)amino)propanoic acid	
Int. 18	(S)-2-((tert-butoxycarbonyl)(methyl)amino)-3-(5-fluoro-2-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)propanoic acid	
Int. 19	(S)-2-((tert-butoxycarbonyl)(methyl)amino)-3-(5-chloro-2-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)propanoic acid	
Int. 20	(S)-2-((tert-butoxycarbonyl)(methyl)amino)-3-(5-chloro-2-(1-methylcyclopropoxy)phenyl)propanoic acid	
Int. 21	(S)-2-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)pent-4-enoic acid	146549-21-5
Int. 22	(S)-3-(1'-acetyl-5-chloro-1',2',3',6'-tetrahydro-[2,4'-bipyridin]-3-yl)-2-((tert-butoxycarbonyl)(methyl)amino)propanoic acid	
Int. 23	(S)-2-((tert-butoxycarbonyl)(methyl)amino)-3-(5-chloro-2-cyclopropoxyphenyl)propanoic acid	
Int. 24	(S)-2-((tert-butoxycarbonyl)(methyl)amino)-3-(5-chloro-2-morpholinophenyl)propanoic acid	
Int. 25	(S)-2-((tert-butoxycarbonyl)(methyl)amino)-3-(5-chloro-2-morpholinopyridin-3-yl)propanoic acid	

INT #	IUPAC	CAS Number, if known
Int. 26	(S)-2-((tert-butoxycarbonyl)(methyl)amino)-3-(7-chloro-2,3-dihydrobenzo[b][1,4]dioxin-5-yl)propanoic acid	
Int. 27	(S)-2-((tert-butoxycarbonyl)(methyl)amino)-3-(5-chloro-2-methylpyridin-3-yl)propanoic acid	
Int. 28	(S)-2-((tert-butoxycarbonyl)(methyl)amino)-3-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)oxy)pyridin-3-yl)propanoic acid	
Int. 29	(S)-3-(2-((1-acetylazetidin-3-yl)oxy)-5-chloropyridin-3-yl)-2-((tert-butoxycarbonyl)(methyl)amino)propanoic acid	
Int. 30	(S)-3-(2-bromo-5-chlorophenyl)-2-((tert-butoxycarbonyl)(methyl)amino)propanoic acid	
Int. 31	(S)-3-(2-bromo-5-fluorophenyl)-2-((tert-butoxycarbonyl)(methyl)amino)propanoic acid	
Int. 32	(tert-butoxycarbonyl)-L-alanine	15761-38-3
Int. 33	((2S,4R)-4-fluoro-1-(1-(trifluoromethyl)cyclopropane-1-carbonyl)pyrrolidine-2-carbonyl)glycine	
Int. 34	((S)-2-(1-(trifluoromethyl)cyclopropane-1-carboxamido)butanoyl)-L-alanine	
Int. 35	(S)-2-((2S,4R)-4-fluoro-1-(1-(trifluoromethyl)cyclopropane-1-carbonyl)pyrrolidine-2-carboxamido)butanoic acid	
Int. 36	ethyl carbonochloridate	541-41-3
Int. 37	isobutyryl chloride	79-30-1
Int. 38	pivaloyl chloride	3282-30-2
Int. 39	(2S,4R)-4-fluoro-1-(2-(trifluoromethyl)tetrahydro-2H-pyran-2-carbonyl)pyrrolidine-2-carboxylic acid	
Int. 40	1-(4-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methylene)piperidin-1-yl)ethan-1-one	
Int. 41	(S)-2-((tert-butoxycarbonyl)(ethyl)amino)pent-4-enoic acid	
Int. 42	(S)-2-((tert-butoxycarbonyl)(methyl)amino)hex-5-enoic acid	
Int. 43	(S)-2-((tert-butoxycarbonyl)(methyl)amino)hept-6-enoic acid	
Int. 44	1-(methylsulfonyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,5-dihydro-1H-pyrrole	
Int. 45	1-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-8-azabicyclo[3.2.1]oct-2-en-8-yl)ethan-1-one	
Int. 46	2-(3,6-dihydro-2H-pyran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane	287944-16-5

INT #	IUPAC	CAS Number, if known
Int. 47	1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridin-1(2H)-yl)ethan-1-one	1227068-67-8
Int. 48	(3-chlorophenyl)boronic acid	63503-60-6
Int. 49	2-(4,4-difluorocyclohex-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane	1227068-84-9
Int. 50	1-(methylsulfonyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine	1382137-67-8
Int. 51	4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-en-1-ol	1310384-24-7
Int. 52	1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole	761446-44-0
Int. 53	1-(oxetan-3-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole	1339890-99-1
Int. 54	2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)ethan-1-ol	1040377-08-9
Int. 55	pyrimidin-5-ylboronic acid	109299-78-7
Int. 56	1-(2-methoxyethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole	847818-71-7
Int. 57	2-(cyclopent-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane	287944-10-9
Int. 58	1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine	454482-11-2
Int. 59	1-cyclopropyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole	1151802-22-0
Int. 60	1-(methoxymethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole	1301198-65-1
Int. 61	1-(2,2-difluoroethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole	1048730-40-6
Int. 62	1-(tetrahydro-2H-pyran-4-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole	1040377-03-4
Int. 63	1-(tetrahydrofuran-3-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole	1029715-63-6
Int. 64	1-(methylsulfonyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole	944994-03-0
Int. 65	1-cyclobutyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole	1002309-48-9
Int. 66	cyclopropyl(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridin-1(2H)-yl)methanone	1616388-38-5
Int. 67	4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine hydrochloride	1121057-75-7
Int. 68	4,4,5,5-tetramethyl-2-(prop-1-en-2-yl)-1,3,2-dioxaborolane	126726-62-3

INT #	IUPAC	CAS Number, if known
Int. 69	4,4,5,5-tetramethyl-2-(2-methylprop-1-en-1-yl)-1,3,2-dioxaborolane	126689-00-7
Int. 70	2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiazole	1218791-01-5
Int. 71	1-isopropyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole	879487-10-2
Int. 72	cyclopropylboronic acid	411235-57-9
Int. 73	3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole	1314138-13-0
Int. 74	1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-imidazole	1083180-01-1
Int. 75	4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole	269410-08-4
Int. 76	benzo[c][1,2,5]oxadiazol-5-ylboronic acid	426268-09-9
Int. 77	6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,5]oxadiazolo[3,4-b]pyridine	1218790-54-5
Int. 78	6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyrimidine	1416437-27-8
Int. 79	3-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3H-imidazo[4,5-b]pyridine	1257554-02-1
Int. 80	6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[4,3-a]pyridine	1314137-24-0
Int. 81	7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-a]pyridine	1210048-18-2
Int. 82	(6-(ethylthio)pyridin-3-yl)boronic acid	1217501-38-6
Int. 83	(6-ethoxypyridin-3-yl)boronic acid	612845-44-0
Int. 84	1-(tert-butyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole	1256359-15-5
Int. 85	3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6,7-dihydro-5H-pyrazolo[5,1-b][1,3]oxazine	1383675-83-9
Int. 86	pyridin-4-ylboronic acid hydrate	1692-15-5
Int. 87	(2-methoxypyridin-4-yl)boronic acid	762262-09-9
Int. 88	(5-fluoropyridin-3-yl)boronic acid	872041-86-6
Int. 89	5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3-dihydro-2H-pyrrolo[2,3-b]pyridin-2-one	1207623-97-9
Int. 90	1-(difluoromethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole	1206640-82-5
Int. 91	(6-(methylsulfonyl)pyridin-3-yl)boronic acid	1088496-41-6
Int. 92	(5-(methylthio)pyridin-3-yl)boronic acid	477251-98-2
Int. 93	1-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole	1020174-04-2
Int. 94	2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oxazole	1192056-62-4

INT #	IUPAC	CAS Number, if known
Int. 95	2,4-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiazole	859833-13-9
Int. 96	(2-oxo-1,2-dihydropyridin-3-yl)boronic acid	951655-49-5
Int. 97	2-(2,5-dihydrofuran-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane	212127-80-5
Int. 98	(3,5-dimethylisoxazol-4-yl)boronic acid	16114-47-9
Int. 99	3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole	936250-20-3
Int. 100	5-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoxazole	1346808-41-0
Int. 101	2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)acetonitrile	1093307-35-7
Int. 102	4-fluoro-1-isopropyl-2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d]imidazole	1231930-37-2
Int. 103	6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-a]pyridine	1160790-18-0
Int. 104	1,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole	1036991-40-8
Int. 105	1,3-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole	847818-79-5
Int. 106	7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)imidazo[1,2-a]pyridine	908268-52-0
Int. 107	1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyridin-2(1H)-one	1227068-65-6
Int. 108	1-(methyl-d3)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole	1022151-50-3
Int. 109	(2-methyl-2H-pyrazolo[3,4-b]pyridin-5-yl)boronic acid	2304634-03-3
Int. 110	1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazolo[3,4-b]pyridine	1312312-78-9
Int. 111	1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d]imidazole	1107627-02-0
Int. 112	1-(cyclopropylsulfonyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole	1612172-62-9
Int. 113	3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)tetrahydrothiophene 1,1-dioxide	1233526-31-2
Int. 114	3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)thietane 1,1-dioxide	1776065-66-7
Int. 115	4-(2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)ethyl)morpholine	864754-18-7
Int. 116	1-(2-(methylsulfonyl)ethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole	1339892-52-2

INT #	IUPAC	CAS Number, if known
Int. 117	4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)morpholine	568577-88-8
Int. 118	(4-(methylsulfonyl)phenyl)boronic acid	149104-88-1
Int. 119	(6-acetamidopyridin-3-yl)boronic acid	947533-21-3
Int. 120	(4-(pyrrolidin-1-ylsulfonyl)phenyl)boronic acid	486422-57-5
Int. 121	pyridin-3-ylboronic acid	1692-25-7
Int. 122	1-(3,3-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridin-1(2H)-yl)ethan-1-one	
Int. 123	4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridazine	863422-41-7
Int. 124	3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridazine	1350543-95-1
Int. 125	3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyrimidine	1169690-88-3
Int. 126	pyrazolo[1,5-a]pyrazin-3-ylboronic acid	2304634-86-2
Int. 127	(S)-2-cyclopropyl-2-((2S,4R)-1-(3,3-difluoro-1-(trifluoromethyl)cyclobutane-1-carbonyl)-4-fluoropyrrolidine-2-carboxamido)acetic acid	
Int. 128	tert-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,5-dihydro-1H-pyrrole-1-carboxylate	212127-83-8
Int. 129	(S)-2-cyclopropyl-2-((2S,4R)-4-fluoro-1-(1-(trifluoromethyl)cyclopropane-1-carbonyl)pyrrolidine-2-carboxamido)acetic acid	
Int. 130	Methylboronic acid	13061-96-6
Int. 131	5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[d]thiazole	1073354-91-2
Int. 132	5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1H)-one	1054483-78-1
Int. 133	3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine	329214-79-1
Int. 134	tert-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate	900503-08-4
Int. 135	tert-butyl 7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-oxa-9-azabicyclo[3.3.1]non-6-ene-9-carboxylate	1313034-29-5
Int. 137	tert-butyl (4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-en-1-yl)carbamate	1251732-64-5
Int. 138	tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate	286961-14-6

INT #	IUPAC	CAS Number, if known
Int. 140	(2S,4R)-4-fluoro-1-(1-(trifluoromethyl)cyclopropane-1-carbonyl)pyrrolidine-2-carboxylic acid	
Int. 141	(2S,4R)-1-(3,3-difluoro-1-(trifluoromethyl)cyclobutane-1-carbonyl)-4-fluoropyrrolidine-2-carboxylic acid	
Int. 142	(2S,4R)-4-fluoro-1-((R)-3,3,3-trifluoro-2-hydroxy-2-methylpropanoyl)pyrrolidine-2-carboxylic acid	
Int. 143	(2S,4R)-4-fluoro-1-(2-(trifluoromethyl)spiro[3.3]heptane-2-carbonyl)pyrrolidine-2-carboxylic acid	
Int. 144	(2S,4R)-4-fluoro-1-(1-(trifluoromethyl)cyclobutane-1-carbonyl)pyrrolidine-2-carboxylic acid	
Int. 145	(1-(trifluoromethyl)cyclobutane-1-carbonyl)-L-proline	
Int. 146	(3,3-difluoro-1-(trifluoromethyl)cyclobutane-1-carbonyl)-L-proline	
Int. 147	(2S,4R)-1-(1-cyanocyclobutane-1-carbonyl)-4-fluoropyrrolidine-2-carboxylic acid	
Int. 148	(2S,4R)-4-fluoro-1-((R)-2-(trifluoromethyl)tetrahydro-2H-pyran-2-carbonyl)pyrrolidine-2-carboxylic acid	
Int. 149	(2S,4R)-4-fluoro-1-((S)-2-(trifluoromethyl)tetrahydro-2H-pyran-2-carbonyl)pyrrolidine-2-carboxylic acid	
Int. 150	(2S,4R)-4-fluoro-1-(3,3,3-trifluoro-2,2-dimethylpropanoyl)pyrrolidine-2-carboxylic acid	
Int. 151	(tert-butoxycarbonyl)-L-leucine	13139-15-6
Int. 152	(S)-2-((tert-butoxycarbonyl)(methyl)amino)pent-4-enoic acid	136092-76-7
Int. 153	(S)-2-((tert-butoxycarbonyl)amino)-2-cyclopropylacetic acid	155976-13-9
Int. 154	tert-butyl (S)-2-(((9H-fluoren-9-yl)methoxy)carbonyl)(methyl)amino)pent-4-enoate	
Int. 155	4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)morpholine	364794-79-6
Int. 156	1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)piperazine	938043-30-2
Int. 157	1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazine	747413-21-4
Int. 158	3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyridine	929203-04-3

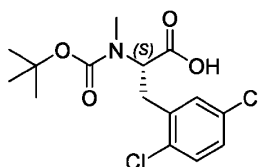
INT #	IUPAC	CAS Number, if known
Int. 159	1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazine	747413-21-4
Int. 160	4-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)sulfonyl)morpholine	1401222-64-7
Int. 161	1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1H-pyrazole	1607838-14-1
Int. 162	(S)-1-(3,3-difluoro-1-(trifluoromethyl)cyclobutane-1-carbonyl)-4,4-difluoropyrrolidine-2-carboxylic acid	
Int. 163	(3-methyl-4-morpholinophenyl)boronic acid	1426245-63-7
Int. 164	4-(2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)ethyl)morpholine	690636-28-3
Int. 165	4-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydro-2H-benzo[b][1,4]oxazine	519054-54-7
Int. 166	(3-chloro-4-morpholinophenyl)boronic acid	1426246-59-4
Int. 167	(4-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)boronic acid	279261-92-6
Int. 168	1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazine	912369-50-7
Int. 169	1-isopropyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazine	1073354-18-3
Int. 170	1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidine	1247000-92-5
Int. 171	(3-fluoro-4-morpholinophenyl)boronic acid	279262-09-8
Int. 172	1-methyl-5'-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3'H-spiro[azetidine-3,1'-isobenzofuran]	
Int. 173	4-(3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)morpholine	957198-29-7
Int. 174	(2S,4R)-1-(1-(difluoromethyl)-3,3-difluorocyclobutane-1-carbonyl)-4-fluoropyrrolidine-2-carboxylic acid	
Int. 175	1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine	124700-48-9
Int. 176	2-((1S,6R)-3-oxabicyclo[4.1.0]heptan-6-yl)-5-(4,4,5,5-tetraethyl-1,3,2-dioxaborolan-2-yl)pyridine	
Int. 177	1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1,2,3,6-tetrahydropyridine	1447696-00-5
Int. 178	8-methyl-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-3,8-diazabicyclo[3.2.1]octane	

INT #	IUPAC	CAS Number, if known
Int. 179	(1S,4S)-2-methyl-5-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-2,5-diazabicyclo[2.2.1]heptane	
Int. 180	(2S,4R)-1-(3,3-difluoro-1-methylcyclobutane-1-carbonyl)-4-fluoropyrrolidine-2-carboxylic acid	
Int. 181	2,2-dimethyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)morpholine	
Int. 182	4-(2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)morpholine	
Int. 183	1-(pyridin-2-ylmethyl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazine	
Int. 184	(S)-3-(methoxymethyl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)morpholine	
Int. 185	1-methyl-4-(2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazine	1310704-51-8
Int. 186	4-fluoro-1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidine	
Int. 187	2-morpholino-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile	
Int. 188	1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-en-1-yl)piperazine	1046793-62-7
Int. 189	(2S,4R)-4-fluoro-1-(2,3,3,3-tetrafluoro-2-methylpropanoyl)pyrrolidine-2-carboxylic acid	
Int. 190	3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-6,7-dihydro-4H-pyrazolo[5,1-c][1,4]oxazine...	
Int. 191	1-methyl-4-(4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1H-pyrazol-1-yl)piperidine...	
Int. 192	(2R,6R)-2,6-dimethyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)morpholine	
Int. 193	tert-butyl 3-(4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazin-1-yl)azetidine-1-carboxylate	
Int. 194	(4-(1-(4-Methylpiperazin-1-yl)cyclopropyl)phenyl)boronic acid pinacol ester	1643923-77-6
Int. 195	N-ethylhex-5-en-1-amine	
Int. 196	(2R,6S)-1,2,6-trimethyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazine...	
Int. 197	3-[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenoxy]-pyridine	1362703-30-7
Int. 198	2,3-Difluoro-4-morpholinophenylboronic acid	2377609-97-5
Int. 199	1-(oxetan-3-yl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazine	

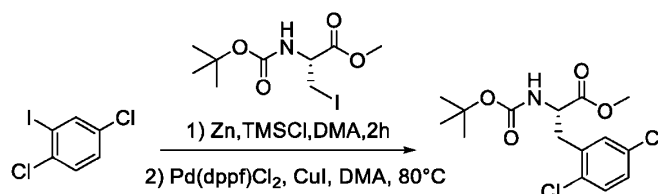
INT #	IUPAC	CAS Number, if known
Int. 400	(3aR,6aS)-5-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)hexahydro-1H-furo[3,4-c]pyrrole	
Int. 401	(R)-8-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)octahydropyrazino[2,1-c][1,4]oxazine	
Int. 402	4-(3-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)morpholine	1366131-51-2
Int. 403	1-(2-(2-methoxyethoxy)ethyl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazine	
Int. 404	1-(2,2-difluoroethyl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazine	
Int. 405	1-((1-methyl-1H-pyrazol-4-yl)methyl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazine	
Int. 406	(S)-2-((tert-butoxycarbonyl)(methyl)amino)-4-methoxy-4-oxobutanoic acid	
Int. 407	(S)-2-((tert-butoxycarbonyl)amino)-5-methoxy-5-oxopentanoic acid	45214-91-3
Int. 408	(S)-2-((tert-butoxycarbonyl)(methyl-d3)amino)pent-4-enoic acid	
Int. 409	[4-(4-Methylpiperazine-1-carbonyl)phenyl]boronic acid pinacol ester	832114-06-4
Int. 410	1-methyl-4-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)piperazine	918524-63-7
Int. 411	7-bromo-5-chloro-1-methyl-1H-indole	
Int. 412	4-bromo-6-chloro-1-methyl-1H-indole	
Int. 413	7-bromo-5-chlorobenzofuran	286836-07-5
Int. 414	2-((1-methylpiperidin-4-yl)oxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine	
Int. 415	(2S,4R)-1-(1-chlorocyclopropane-1-carbonyl)-4-fluoropyrrolidine-2-carboxylic acid	
Int. 416	(2S,4R)-1-((R)-2,2-difluoro-1-methylcyclopropane-1-carbonyl)-4-fluoropyrrolidine-2-carboxylic acid	
Int. 417	(2S,4R)-1-((S)-2,2-difluoro-1-methylcyclopropane-1-carbonyl)-4-fluoropyrrolidine-2-carboxylic acid...	
Int. 418	1-(2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-4-methylpiperazine	1408088-34-5
Int. 419	2-(3-fluoro-3-methylazetidin-1-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine	
Int. 420	4-(1-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)morpholine	1206594-12-8

INT #	IUPAC	CAS Number, if known
Int. 421	2-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,4-tetrahydroisoquinoline	
Int. 422	2-Methyl-1,2,3,4-tetrahydroisoquinoline-6-boronicacid pinacol ester	922718-57-8
Int. 423	4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]morpholin-3-one	928631-04-3
Int. 424	2-methyl-6-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-2,6-diazaspiro[3.4]octane...	
Int. 425	(S)-1,2-dimethyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazine...	
Int. 426	(S)-N,N-dimethyl-1-(4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)morpholin-2-yl)methanamine	
Int. 427	(R)-1-methyl-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidine...	
Int. 428	(S)-1-methyl-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidine	
Int. 429	1-(2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-4-isopropylpiperazine...	
Int. 430	(R)-2-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)morpholine	
Int. 431	(S)-1-methyl-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidine	
Int. 432	8-Bromo-6-fluoroquinoline	22960-18-5
Int. 433	4-bromo-6-chloro-1-methyl-1H-indazole	
Int. 434	1-Bromo-3-chloronaphthalene	51671-06-8
Int. 435	2-bromo-4-chlorothiophene	32431-92-8
Int. 436	5-Bromo-2-cyanopyridine	97483-77-7
Int. 437	1-Methylpiperazine	109-01-3
Int. 438	(S)-3-(2-bromo-5-chlorophenyl)-2-((tert-butoxycarbonyl)amino)propanoic acid	

Int. 6: Preparation of (S)-2-((tert-butoxycarbonyl)(methyl)amino)-3-(2,5-dichlorophenyl)propanoic acid

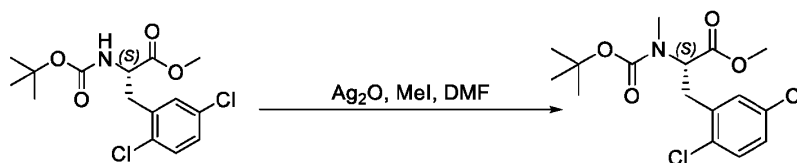


Step 1: Methyl (2S)-2-[(tert-butoxycarbonyl)amino]-3-(2,5-dichlorophenyl)propanoate:



- [0217]** To a stirred mixture of Zn (29.95 g, 458.06 mmol, 2.5 eq) and TMSCl (1.33 g, 12.28 mmol, 0.067 eq) in DMA was added methyl (2R)-2-[(tert-butoxycarbonyl)amino]-3-iodopropanoate (1.03 g, 3.11 mmol, 1.7 eq) dropwise below
- 5 45 °C under nitrogen atmosphere. The resulting mixture was stirred for 16 h at rt under nitrogen atmosphere. The above mixture was added into a solution of 1,4-dichloro-2-iodo-benzene (50 g, 183.22 mmol, 1 eq), CuI (6.96 g, 36.64 mmol, 0.2 eq) and Pd(dppf)Cl₂.CH₂Cl₂ (14.93 g, 18.32 mmol, 0.10 eq) at rt under nitrogen. The resulting mixture was stirred for additional 16 h at 85 °C. Desired product could be detected
- 10 by LCMS. The reaction was quenched by the addition of water (1.5 L) at rt. The aqueous layer was extracted with EtOAc (3 x 500 mL). The combined organics were washed with (5 x 300 mL) of water and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (25:1) to afford methyl (2S)-2-[(tert-butoxycarbonyl)amino]-3-(2,5-dichlorophenyl)propanoate (40 g, 63 %) as a white solid.
- 15 **LCMS** (ESI+): *m/z* 292.15 (M-56⁺). **¹H NMR** (300 MHz, DMSO-*d*₆): δ 1.11 – 1.47 (m, 12H), 2.89 (dd, 1H), 3.22 (dd, 1H), 3.64 (d, 4H), 3.91 – 4.37 (m, 1H), 6.87 – 7.89 (m, 4H).

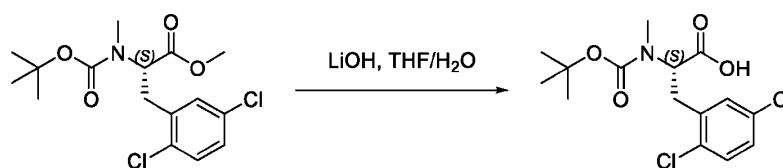
Step 2: Methyl (2S)-2-[(tert-butoxycarbonyl)(methyl)amino]-3-(2,5-dichlorophenyl)propanoate:



- 20 **[0218]** To a stirred solution of methyl (2S)-2-[(tert-butoxycarbonyl)amino]-3-(2,5-dichlorophenyl)propanoate (200 mg, 0.574 mmol, 1 eq) and methyl iodide (214.00 g, 1507.67 mmol, 15 eq) in DMF (350 mL) was added (argenticooxy)silver (93.17 g, 402.04 mmol, 4 eq) in portions at 25 °C under nitrogen atmosphere. The reaction mixture was stirred for 16 h at 25 °C. Desired product could be detected by LCMS. The resulting mixture was
- 25 filtered, the filter cake was washed with EtOAc (3 x 100 mL). The filtrate was diluted water

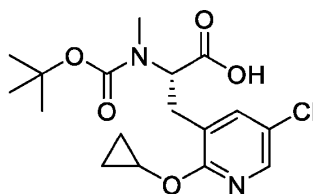
- (500 mL) and extracted with EtOAc (3 x 300 mL). The combined organic layers were washed with water (4 x 200 mL) and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (0.05% TFA), 10% to 50% gradient in 10 min; detector, UV 220 nm.
- This resulted in methyl (2S)-2-[(tert-butoxycarbonyl)(methyl)amino]-3-(2,5-dichlorophenyl)propanoate as a white solid. LCMS (ESI+): *m/z* 262.20 (M+Na⁺).

Step 3: Int. 6:

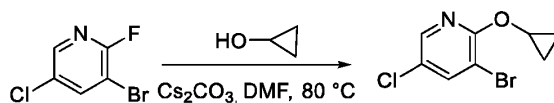


- [0219]** A solution of methyl (2S)-2-[(tert-butoxycarbonyl)(methyl)amino]-3-(2,5-dichlorophenyl)propanoate (35 g, 96.62 mmol, 1 eq) and LiOH (4.63 g, 193.24 mmol, 2 eq) in THF (500 mL)/ H₂O (300 mg) was stirred for 16 h at 25 °C. Desired product could be detected by LCMS. The mixture was acidified to pH=4 with diluted HCl (aq.). The aqueous layer was extracted with EtOAc (3 x 500 mL). The combined organics was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (0.1% FA), 10% to 50% gradient in 10 min; detector, UV 220 nm. This resulted in **Int. 6** (25.26 g, 75.07%) as a light-yellow solid. LCMS (ESI+): *m/z* 346.00 (M-H⁻). ¹H NMR (400 MHz, DMSO-*d*₆): δ 1.23 (d, 9H), 2.66 (d, 3H), 3.06 – 3.39 (m, 2H), 7.24 – 7.56 (m, 3H), 13.00 (s, 1H).

Int. 7: Preparation of (S)-2-[(tert-butoxycarbonyl)(methyl)amino]-3-(5-chloro-2-cyclopropoxyphenyl)propanoic acid

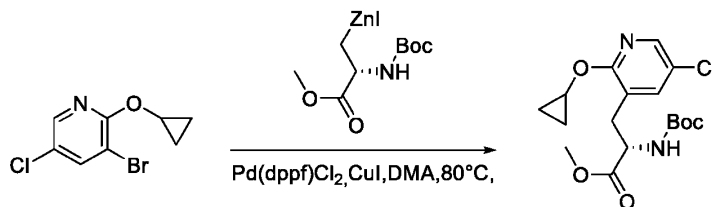


Step 1: 3-Bromo-5-chloro-2-cyclopropoxyphenylpyridine:



- [0220] Into a 1000 mL round-bottom flask were added 3-bromo-5-chloro-2-fluoropyridine (50 g, 237.61 mmol, 1 eq) in DMF (400 mL), Cs₂CO₃ (232.97 g, 712.83 mmol, 3 eq) was added at rt under nitrogen atmosphere. The mixture was stirred at rt for 50 min.
- 5 cyclopropanol (9.94 g, 171.08 mmol, 1.2 eq) was added dropwise over 2 min at rt. The resulting mixture was stirred at 80 °C for 16 h. The reaction was quenched with ice-water (700 mL) and extracted with EA (3 x 100 mL). The organic layer combined and washed with brine (300 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography,
- 10 eluted with PE/EA (0~20%). This resulted in 3-bromo-5-chloro-2-cyclopropoxypyridine (40 g, 68 %) as a colorless oil. LCMS (ESI⁺): *m/z* 249.95. ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.76 (ddd, *J* = 5.7, 4.5, 3.1 Hz, 2H), 0.96 – 0.78 (m, 2H), 4.32 (tt, *J* = 6.4, 3.1 Hz, 1H), 8.17 (d, *J* = 2.5 Hz, 1H), 8.26 (d, *J* = 2.4 Hz, 1H).

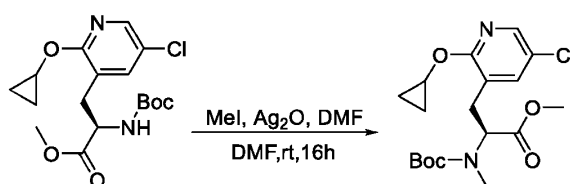
- Step 2: Methyl (2S)-2-[(tert-butoxycarbonyl)amino]-3-(5-chloro-2-cyclopropoxypyridin-**
- 15 **3-yl)propanoate:**



- [0221] To a mixture of Zn (26.84 g, 410.46 mmol, 1.7 eq) in DMA (135 mL) was added 1,2-dibromoethane (6.80 g, 36.22 mmol, 0.15 eq) in one portion under N₂. Then chlorotrimethylsilane (2.62 g, 24.15 mmol, 0.1 eq) was added slowly and the mixture was
- 20 stirred for 30 min at 25 °C. A solution of methyl 2-[(tert-butoxycarbonyl)amino]-3-iodopropanoate (95.36 g, 289.74 mmol, 1.2 eq) in DMA (135 mL) was added dropwise slowly (60 min) to maintain temperature below 50 °C, the resulting mixture was stirred at rt for 2 h and then added 1000 mL 3-necked round-bottom flask a cannula to a solution of 3-bromo-5-chloro-2-cyclopropoxypyridine (60 g, 241.45 mmol, 1 eq), Pd(dppf)Cl₂·CH₂Cl₂
- 25 (19.67 g, 24.14 mmol, 0.1 eq) and CuI (9.20 g, 48.29 mmol, 0.2 eq) in DMA (135 mL) under N₂, the color of the mixture turned brown, then the mixture was heated and stirred at 80 °C

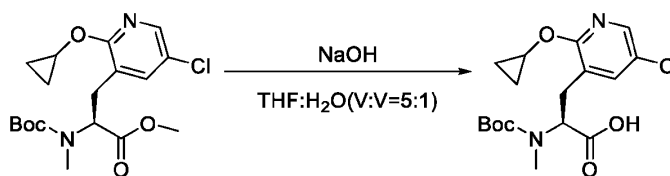
for 2 h under N₂. The mixture was quenched with ice-water (700 ml) and extracted with EA (3 x 500 ml). The organic layer was combined and washed with brine (300 ml), dried with anhydrous Na₂SO₄, filtered, and concentrated in vacuum to give the crude product. The crude product was purified by silica gel chromatography eluted with PE/EA (0~50%) to afford methyl (2S)-2-[(tert-butoxycarbonyl)amino]-3-(5-chloro-2-cyclopropoxy)pyridin-3-yl)propanoate (30 g, 34 %) as a white solid. LCMS (ESI⁺): *m/z* 371.10.

Step 3: Methyl (2S)-2-[(tert-butoxycarbonyl)(methyl)amino]-3-(5-chloro-2-cyclopropoxy)pyridin-3-yl)propanoate:



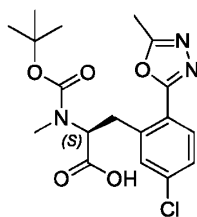
[0222] Into a 1000 mL round-bottom flask were added methyl (2S)-2-[(tert-butoxycarbonyl)amino]-3-(5-chloro-2-cyclopropoxy)pyridin-3-yl)propanoate (25 g, 67.42 mmol, 1 eq) in DMF (400 mL), Ag₂O (78.11 g, 337.08 mmol, 5 eq) was added at 0 °C under nitrogen atmosphere. The mixture was stirred at 0 °C for 30 min, CH₃I (95.69 g, 674.16 mmol, 10 eq) was added dropwise over 2 min at 0 °C. The resulting mixture was stirred at rt for 16 h. The reaction was quenched with ice-water (500 mL) and extracted with EtOAc (3 x 500 mL). The organic layer was combined and washed with brine (300 mL) and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (7:1) to afford methyl (2S)-2-[(tert-butoxycarbonyl)(methyl)amino]-3-(5-chloro-2-cyclopropoxy)pyridin-3-yl)propanoate (22 g, 85 %) as a colorless oil. LCMS (ESI⁺): *m/z* 385.10. ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.83 – 0.62(m, 2H), 1.19 (t, *J* = 7.1 Hz, 2H), 1.28 (s, 9H), 2.65 (d, *J* = 3.3 Hz, 3H), 2.95 (dd, *J* = 13.6, 10.4 Hz, 1H), 3.07(ddd, *J* = 14.2, 4.9, 1.9 Hz, 2H), 3.73 – 3.61 (m, 3H), 4.69 (dd, *J* = 10.5, 4.6 Hz, 1H), 8.12 (dd, *J* = 17.7, 2.6 Hz, 2H).

Step 4: Int. 7:

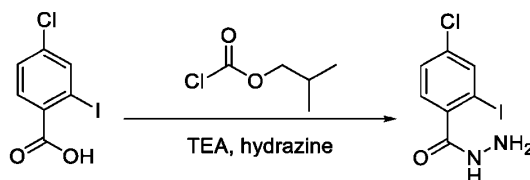


[0223] Into a 1000 mL round-bottom flask were added methyl (2S)-2-[(tert-butoxycarbonyl)(methyl)amino]-3-(5-chloro-2-cyclopropoxypyridin-3-yl)propanoate (20 g, 51.97 mmol, 1 eq) in THF (250 ml) and NaOH (10.39 g, 259.84 mmol, 5 eq) in water (50 ml) was added dropwise at 0 °C under nitrogen atmosphere. The resulting mixture was stirred at rt for 2 h. The solvent was removed by reduce pressure and the residue was purified by reverse flash chromatography with the following conditions: column, C18; mobile phase, ACN in water (0.5% FA), 0% to 100% gradient in 40 min; detector, UV 254 nm. This resulted in **Int. 7** (13.95 g, 72%) as a yellow oil. LCMS (ESI+): m/z 371.00. ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.79 – 0.61 (m, 4H), 1.21 (s, 9H), 2.95 – 2.84 (m, 2H), 3.00 (s, 3H), 3.09 – 3.01 (m, 1H), 4.86 (dd, *J* = 11.3, 4.6 Hz, 1H), 7.67 (d, *J* = 2.6 Hz, 1H), 8.11 (dd, *J* = 18.4, 2.6 Hz, 1H).

Int. 8: Preparation of (S)-2-((tert-butoxycarbonyl)(methyl)amino)-3-(5-chloro-2-(5-methyl-1,3,4-oxadiazol-2-yl)phenyl)propanoic acid



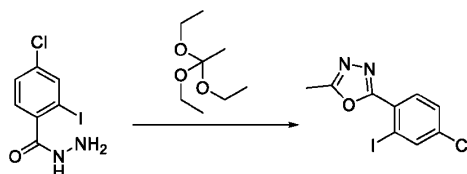
Step 1: 4-chloro-2-iodobenzohydrazide:



[0224] Into a stirred mixture of 4-chloro-2-iodobenzoic acid (10 g, 35.40 mmol, 1 eq) and 2-methylpropyl carbonochloridate (4.84 g, 35.40 mmol, 1 eq) in THF (100mL) were added TEA (10.75 g, 106.21 mmol, 3 eq) and hydrazine (5.67 g, 177.02 mmol, 5 eq) dropwise at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for an additional 4 h at rt. Desired product could be detected by LCMS. The resulting mixture was diluted with water (100 mL). The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with 0.5N HCl solution (3 x 50 mL). The combined aqueous layers were basified to pH 8 with NaOH (0.5N). The resulting mixture

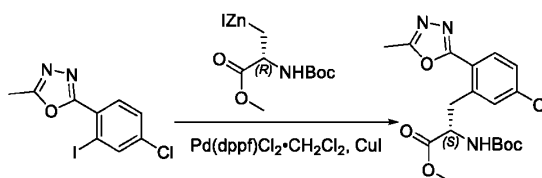
was extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water (0.1% FA), 5% to 100% gradient in 30 min; detector, UV 254 nm. This resulted in 4-chloro-2-iodobenzohydrazide (7.5 g, 72 %) as a white solid. LCMS (ESI⁺): *m/z* 296.90 (M+H⁺).

Step 2: 2-(4-chloro-2-iodophenyl)-5-methyl-1,3,4-oxadiazole:



[0225] Into a 200 mL vial were added 4-chloro-2-iodobenzohydrazide (8 g, 26.98 mmol, 1 eq) and triethyl orthoacetate (80 mL) at rt. The resulting mixture was stirred overnight at 140 °C. Desired product could be detected by LCMS. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water (0.1% TFA), 5% to 100% gradient in 30 min; detector, UV 254 nm. This resulted in 2-(4-chloro-2-iodophenyl)-5-methyl-1,3,4-oxadiazole (10.2 g, 118 %) as a yellow solid. LCMS (ESI⁺): *m/z* 320.85 (M+H⁺).

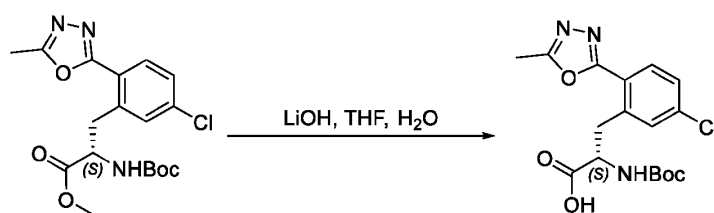
Step 3: methyl (2S)-2-[(tert-butoxycarbonyl) amino]-3-[5-chloro-2-(5-methyl-1,3,4-oxadiazol-2-yl) phenyl] propanoate:



[0226] Into a stirred solution of Zn (3.84 g, 58.73 mmol, 2 eq) DMA (30 mL) were added 1,2-dibromoethane (0.55 g, 2.937 mmol, 0.1 eq) and TMSCl (0.21 g, 1.967 mmol, 0.067 eq) dropwise at rt under nitrogen atmosphere. To the above mixture was added methyl (2R)-2-[(tert-butoxycarbonyl) amino]-3-iodopropanoate (9.66 g, 29.37 mmol, 1 eq) in DMA (30 mL) dropwise. The resulting mixture was stirred for an additional 3 h at rt. To a stirred mixture of 2-(4-chloro-2-iodophenyl)-1,3,4-oxadiazole (9 g, 29.37 mmol, 1 eq) in DMA (30 mL) were added Pd(dppf)Cl₂CH₂Cl₂ (2.39 g, 2.94 mmol, 0.10 eq) and CuI

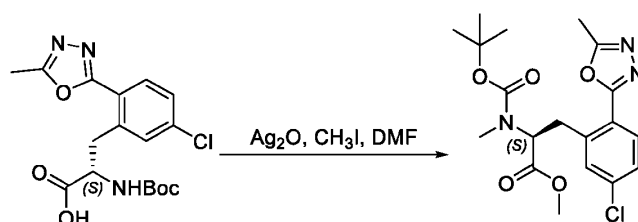
(1.12 g, 5.87 mmol, 0.2 eq) in portions at rt under nitrogen atmosphere. Then, two mixtures were added together. The resulting mixture was stirred for an additional 16h at rt. The resulting mixture was stirred for additional 3 h at 80 °C. Desired product could be detected by LCMS. The reaction was quenched with water 100 mL) at rt. The resulting mixture was
 5 filtered, and the filter cake was washed with EtOAc (3 x 150 mL). The filtrate was concentrated under reduced pressure. The resulting mixture was extracted with EtOAc (3 x 100mL). The combined organic layers were dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile
 10 phase, MeCN in water (0.1% FA), 5% to 100% gradient in 30 min; detector, UV 254 nm. This resulted in methyl (2S)-2-[(tert-butoxycarbonyl) amino]-3-[5-chloro-2-(5-methyl-1,3,4-oxadiazol-2-yl) phenyl] propanoate (4.5 g, 39 %) as a yellow solid. LCMS (ESI+): *m/z* 396.1 (M+H⁺).

Step 4: (2S)-2-[(tert-butoxycarbonyl) amino]-3-[5-chloro-2-(5-methyl-1,3,4-oxadiazol-2-yl) phenyl] propanoic acid:
 15



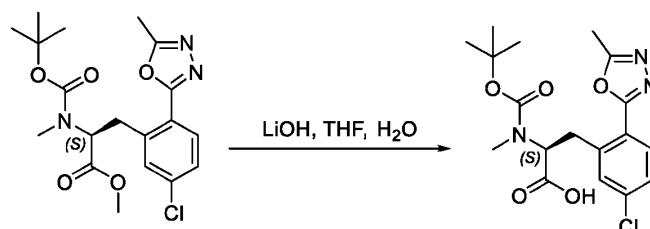
[0227] A solution of methyl (2S)-2-[(tert-butoxycarbonyl) amino]-3-[5-chloro-2-(5-methyl-1,3,4-oxadiazol-2-yl) phenyl] propanoate (5 g, 12.63 mmol, 1 eq) in THF (40 mL) and water (10 mL) was treated with LiOH (1.51 g, 63.16 mmol, 5 eq) for 4 h at rt. Desired product
 20 could be detected by LCMS. The mixture was diluted with water and EA. The water phase was acidified by diluted HCl (0.5N) and extracted with EA. The organic layer was dried over anhydrous Na₂SO₄ and concentrated in vacuo. This resulted in (2S)-2-[(tert-butoxycarbonyl) amino]-3-[5-chloro-2-(5-methyl-1,3,4-oxadiazol-2-yl) phenyl] propanoic acid (4.5 g) as a light-yellow solid. LCMS (ESI+): *m/z* 404.0 (M+Na⁺).

Step 5: methyl (2S)-3-[5-chloro-2-(5-methyl-1,3,4-oxadiazol-2-yl)phenyl]-2-[(isopropoxycarbonyl)(methyl)amino]propanoate:
 25



- [0228]** A solution of (2S)-2-[(tert-butoxycarbonyl)amino]-3-[5-chloro-2-(5-methyl-1,3,4-oxadiazol-2-yl)phenyl]propanoic acid (4.5 g, 11.79 mmol, 1 eq) in DMF (50 mL) was treated with Ag_2O (13.66 g, 58.93 mmol, 5 eq) for 20 min at rt under nitrogen atmosphere followed by the addition of CH_3I (25.09 g, 176.79 mmol, 15 eq) dropwise at rt. The resulting mixture was stirred for 4 h at rt. The resulting mixture was diluted with water (50 mL). The resulting mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (3 x 50 mL), dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water (0.1% TFA), 5% to 100% gradient in 50 min; detector, UV 220 nm. This resulted in methyl (2S)-2-[(tert-butoxycarbonyl)(methyl)amino]-3-[5-chloro-2-(5-methyl-1,3,4-oxadiazol-2-yl)phenyl]propanoate (3.7 g, 79 %) as a yellow solid. LCMS (ESI⁺): m/z 410.1 ($\text{M}+\text{H}^+$).

Step 6: Int. 8:

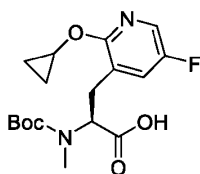


- [0229]** A solution of methyl (2S)-2-[(tert-butoxycarbonyl)(methyl)amino]-3-[5-chloro-2-(5-methyl-1,3,4-oxadiazol-2-yl)phenyl]propanoate (2.6 g, 6.34 mmol, 1 eq) in THF (40 mL) and H_2O (10 mL) was treated with LiOH (1.08 g, 45.14 mmol, 5 eq) for 4 h at rt under nitrogen atmosphere. Desired product could be detected by LCMS. The resulting mixture was diluted with water (20 mL) and acidified to pH 6 with HCl (0.5 mol/L). The mixture was concentrated under reduced pressure and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 . After filtration, the filtrate was

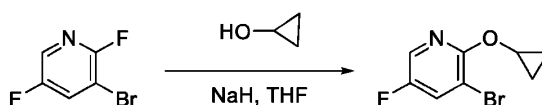
concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water (0.1% TFA), 5% to 100% gradient in 30 min; detector, UV 254 nm. This resulted in **Int. 8** (3.4289 g, 96 %) as a yellow solid. **LCMS** (ESI+): m/z 390.10

5 (M+H⁺). **¹H NMR** (300 MHz, DMSO-*d*₆): δ 1.26 (s, 4H), 1.39 (s, 5H) 2.67 (d, J = 1.9 Hz, 3H), 2.84 (d, J = 8.8 Hz, 3H), 3.33 (ddd, J = 14.3, 10.9, 3.4 Hz, 1H), 3.91 (dt, J = 14.6, 2.9 Hz, 1H), 5.06 (ddd, J = 18.1, 10.8, 3.8 Hz, 1H), 7.34 – 7.26 (m, 1H), 7.40 (ddd, J = 8.5, 6.1, 2.1 Hz, 1H), 7.90 (dd, J = 8.4, 3.8 Hz, 1H), 10.00 (s, 1H).

10 **Int. 9: Preparation of (S)-2-((tert-butoxycarbonyl)(methyl)amino)-3-(2-cyclopropoxy-5-fluoropyridin-3-yl)propanoic acid**

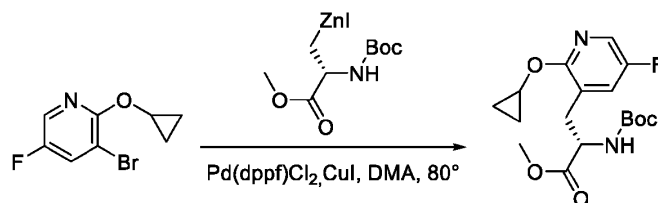


Step 1: 3-bromo-2-cyclopropoxy-5-fluoropyridine:



15 **[0230]** To a solution of cyclopropanol (15.55 g, 268.10 mmol, 1.3 eq) in THF (500 mL) was added sodium hydride (16.6 g, 691.67 mmol, 2 eq) portion wise at 0 °C under nitrogen atmosphere. The mixture was stirred at 0 °C for 1 h. 3-bromo-2,5-difluoropyridine (40 g, 206.21 mmol, 1 eq) was added dropwise over 30 min at 0 °C. The resulting mixture was stirred at rt for 16 h. The reaction was quenched with ice-water (700 mL) and extracted with DCM (3 x 100 mL). The organic layer combined and washed with brine (300 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure to afford 3-bromo-2-cyclopropoxy-5-fluoropyridine (34 g, crude) as a yellow oil. The crude product was used in the next step directly without further purification. **LCMS** (ESI+): m/z 233.90 (M+H⁺).

25 **Step 2: Methyl (2S)-2-[(tert-butoxycarbonyl)amino]-3-(2-cyclopropoxy-5-fluoropyridin-3-yl)propanoate:**



- [0231]** To a mixture of Zn (15.94 g, 249.06 mmol, 1.7 eq) in DMA (80 mL) was added 1,2-dibromoethane (4.13 g, 21.98 mmol, 0.15 eq) in one portion under N₂. Then chlorotrimethylsilane (1.58 g, 14.66 mmol, 0.1 eq) was added slowly and the mixture was stirred for 30 min at 25 °C. A solution of methyl 2-[(tert-butoxycarbonyl)amino]-3-iodopropanoate (57.86 g, 175.86 mmol, 1.2 eq) in DMA (80 mL) was added dropwise slowly (60 min) to maintain temperature below 50 °C, the resulting mixture was stirred at rt for 2 h and then added 250 mL 3-necked round-bottom flask a cannula to a solution of 3-bromo-2-cyclopropoxy-5-fluoropyridine (34 g, 146.55 mmol, 1equiv), Pd(dppf)Cl₂.CH₂Cl₂ (23.94 g, 29.31 mmol, 0.2 eq) and CuI (5.57 g, 29.31 mmol, 0.2 eq) in DMA (80 mL) under N₂, the color of the mixture turned brown, then the mixture was heated and stirred at 80 °C for 2 h under N₂. The mixture was quenched with ice-water (400 ml) and extracted with EA (3 x 500 ml). The organic layer was combined and washed with brine (300 ml), dried with anhydrous Na₂SO₄, filtered, and concentrated in vacuum to give the crude product. The crude product was purified by silica gel chromatography eluted with PE/EtOAc = 0~50% to afford methyl (2S)-2-[(tert-butoxycarbonyl)amino]-3-(2-cyclopropoxy-5-fluoropyridin-3-yl)propanoate (11.2 g, 23 %) as a yellow oil. LCMS (ESI+): *m/z* 355.10 (M+H⁺).

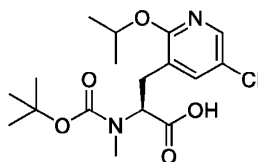
Step 3: Int. 9:



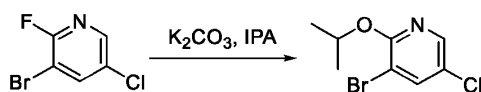
- [0232]** Into a 1000 mL round-bottom flask were added methyl (2S)-2-[(tert-butoxycarbonyl)amino]-3-(2-cyclopropoxy-5-fluoropyridin-3-yl)propanoate (11 g, 31.07 mmol, 1 eq) in DMF (150 mL), Ag₂O (35.89 g, 155.37 mmol, 5 eq) was added at 0 °C under nitrogen atmosphere. The mixture was stirred at 0 °C for 30 min, methyl iodide (44.12 g, 310.73 mmol, 10 eq) was added dropwise over 2 min at 0 °C. The resulting mixture was

stirred at rt for 16 h. The reaction was quenched with ice-water (100 mL) and extracted with EtOAc (3 x 300 mL). The organic layer was combined and washed with brine (3 x 200 mL) and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (7:1) to afford **Int. 9** (10.8 g, 94 %) as a yellow oil. **LCMS** (ESI⁺): *m/z* 369.15 (M+H⁺). **¹H NMR** (400 MHz, DMSO-*d*₆): δ 8.06 (dd, *J* = 18.7, 3.0 Hz, 1H), 7.55 (ddd, *J* = 18.5, 8.7, 3.0 Hz, 1H), 4.68 (dd, *J* = 10.6, 4.5 Hz, 1H), 4.24 (ddt, *J* = 11.7, 8.6, 4.0 Hz, 1H), 3.68 (d, *J* = 7.6 Hz, 3H), 3.13 – 2.84 (m, 2H), 2.63 (d, *J* = 7.7 Hz, 3H), 1.24 (d, *J* = 18.3 Hz, 9H), 0.80 – 0.63 (m, 4H).

10 Int. 10: Preparation of (S)-2-((tert-butoxycarbonyl)(methyl)amino)-3-(5-chloro-2-isopropoxyipyridin-3-yl)propanoic acid

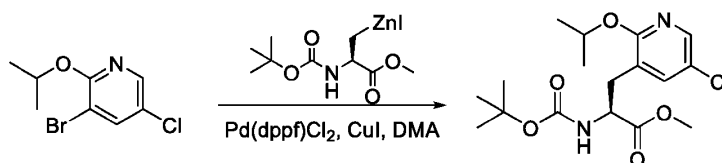


Step 1: 3-bromo-5-chloro-2-isopropoxyipyridine:



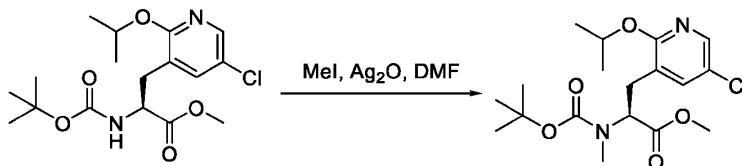
15 [0233] To a stirred mixture of 3-bromo-5-chloro-2-fluoropyridine (50 g, 237.61 mmol, 1 eq) and K₂CO₃ (98.52 g, 712.83 mmol, 3 eq) in IPA (500 mL, 5261.52 mmol, 22.14 eq) at 20 °C. The resulting mixture was stirred for 48 h at 80 °C. The resulting mixture was concentrated under vacuum and the mixture was dissolved in DCM (300 mL). The resulting mixture was filtered, and the filter cake was washed with DCM (3 x 50 mL). The filtrate was concentrated under reduced pressure. This resulted in 3-bromo-5-chloro-2-isopropoxyipyridine (50 g, 84.0%) as a yellow oil. **LCMS** (ESI⁺): *m/z* 252.05 (M+H⁺).

Step 2: Methyl (2S)-2-[(tert-butoxycarbonyl)amino]-3-(5-chloro-2-isopropoxyipyridin-3-yl) propanoate:



[0234] To a stirred mixture of 3-bromo-5-chloro-2-isopropoxy-4-methylpyridine (50 g, 199.59 mmol, 1 eq) and Pd(dppf)Cl₂ DCM adduct (16.26 g, 19.96 mmol, 0.1 eq), CuI (7.60 g, 39.92 mmol, 0.2 eq) in DMA (500 mL) was added methyl (2S)-2-[(tert-butoxycarbonyl)amino]-2-(iodozincio)acetate (162.6 mL, 199.59 mmol, 10 eq) dropwise at 20 °C under nitrogen atmosphere. The resulting mixture was stirred for 16 h at 80 °C under nitrogen atmosphere. The resulting mixture was filtered, the filter cake was washed with EtOAc (3 x 500 mL). The filtrate was extracted with EtOAc (3 x 800 mL). The combined organic layers were washed with H₂O (3 x 1000 mL) and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH₂Cl₂ / PE (5:1) to afford methyl (2S)-2-[(tert-butoxycarbonyl)amino]-3-(5-chloro-2-isopropoxy-4-methylpyridin-3-yl)propanoate (110g) as a yellow oil. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (0.1% FA), 10% to 80% gradient in 35 min; detector, UV 280 nm. The resulting mixture was concentrated under vacuum. This resulted in methyl (2S)-2-[(tert-butoxycarbonyl)amino]-3-(5-chloro-2-isopropoxy-4-methylpyridin-3-yl) propanoate (53g, 77 %) as a white solid. LCMS (ESI⁺): *m/z* 373.25 (M+H⁺).

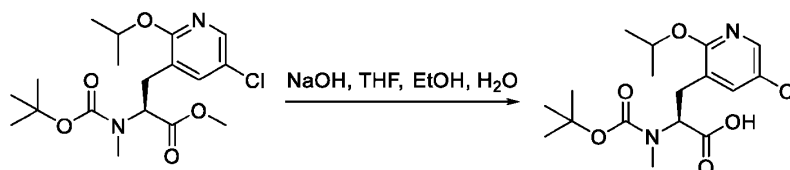
Step 3: Methyl (2S)-2-[(tert-butoxycarbonyl)(methyl)amino]-3-(5-chloro-2-isopropoxy-4-methylpyridin-3-yl)propanoate:



[0235] To a stirred mixture of methyl (2S)-2-[(tert-butoxycarbonyl)amino]-3-(5-chloro-2-isopropoxy-4-methylpyridin-3-yl)propanoate (20 g, 53.64 mmol, 1 eq) and Ag₂O (62.15 g, 268.21 mmol, 5 eq) in DMF (500 mL) was added MeI (77.66 g, 536.41 mmol, 10 eq) at 20 °C. The resulting mixture was stirred for 16 h at 60 °C. The resulting mixture was filtered, the filter cake was washed with EtOAc (3 x 500 mL). The filtrate was dissolved in H₂O (800 mL) and

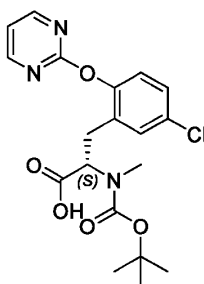
the mixture was extracted with EtOAc (3 x 1000 mL). The combined organic layers were washed with H₂O (4 x 1200 mL) and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure to afford methyl (2S)-2-[(tert-butoxycarbonyl)(methyl)amino]-3-(5-chloro-2-isopropoxy pyridin-3-yl)propanoate (20.5 g, 99 %) as a yellow oil. LCMS (ESI+): *m/z* 387.15 (M+H⁺).

Step 4: Int. 10:



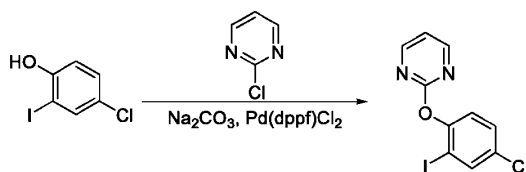
[0236] To a stirred mixture of methyl (2S)-2-[(tert-butoxycarbonyl)(methyl)amino]-3-(5-chloro-2-isopropoxy pyridin-3-yl)propanoate (20 g, 51.70 mmol, 1 eq) in EtOH (30 mL) and THF (60 mL) were added NaOH (6.20 g, 155.09 mmol, 3 eq) in H₂O (120 mL) dropwise at 0 °C. The resulting mixture was stirred for 16 h at 20 °C. The resulting mixture was extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with H₂O (1 x 150 mL). The combined water phase was acidified to pH=6 with diluted citric acid(1N). The resulting mixture was extracted with EtOAc (2 x 200 mL). The combined organic layers were washed with H₂O (1 x 100 mL) and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under vacuum to afford Int. 10 (14.2 g, 74%) as a yellow oil. LCMS (ESI+): *m/z* 373.15 (M+H⁺).

Int. 11: Preparation of (S)-2-((tert-butoxycarbonyl)(methyl)amino)-3-(5-chloro-2-(pyrimidin-2-yloxy)phenyl)propanoic acid



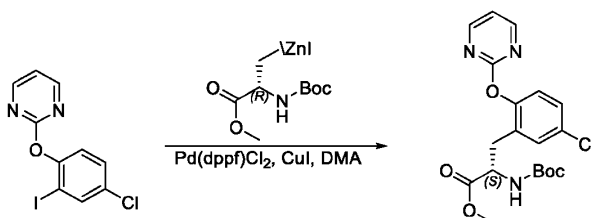
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Step 1: 5-(2-bromo-4-chlorophenyl) pyrimidine:



- [0237]** To a stirred solution of pyrimidin-5-ylboronic acid (10 g, 80.70 mmol, 1 eq) and 2-bromo-4-chloro-1-iodobenzene (25.61 g, 80.70 mmol, 1 eq) in 1,4-dioxane (80 mL) and H₂O (20 mL) were added Pd(dppf)Cl₂CH₂Cl₂ (6.57 g, 8.06 mmol, 0.10 eq) and Na₂CO₃ (25.66 g, 242.11 mmol, 3 eq) in portions at rt under nitrogen atmosphere. The resulting mixture was stirred for additional 4 h at 80 °C. Desired product could be detected by LCMS. The resulting mixture was filtered, and the filter cake was washed with EtOAc (3 x 10 mL). The resulting mixture was diluted with water and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water (0.1% TFA), 5% to 100% gradient in 30 min; detector, UV 220 nm. This resulted in 5-(2-bromo-4-chlorophenyl) pyrimidine (9.6 g, 44 %) as a brown oil. **LCMS** (ESI⁺): *m/z* 270.90 (M+H⁺).

- Step 2: Methyl (2S)-2-[(tert-butoxycarbonyl) amino]-3-[5-chloro-2-(pyrimidin-5-yl) phenyl] propanoate:**

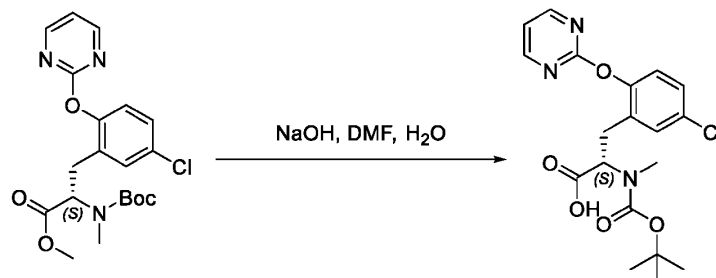


- [0238]** Into a stirred solution of Zn (6.31 g, 96.46 mmol, 2 eq) in DMA (30 mL) were added 1,2-dibromoethane (0.91 g, 4.82 mmol, 0.1 eq) and TMSCl (0.35 g, 3.23 mmol, 0.067 eq) dropwise at rt under nitrogen atmosphere. To the above mixture was added methyl (2R)-2-[(tert-butoxycarbonyl) amino]-3-iodopropanoate (15.87 g, 48.23 mmol, 1 eq) in DMA (30 mL) dropwise. The resulting mixture was stirred for additional 3 h at rt. To a stirred solution of 5-(2-bromo-4-chlorophenyl) pyrimidine (13 g, 48.23 mmol, 1 eq) in DMA (40 mL) were added Pd(dppf)Cl₂CH₂Cl₂ (3.93 g, 4.82 mmol, 0.1 eq) and CuI (1.84 g, 9.65 mmol, 0.2 eq) in portions at rt under nitrogen atmosphere. Then, the two mixtures were added together. The

- resulting mixture was stirred for additional 3 h at 80 °C. Desired product could be detected by LCMS. The reaction was quenched by the addition of water (100 mL) at rt. The resulting mixture was filtered, and the filter cake was washed with EA (3 x 100 mL). The residue was diluted with water and EA. The organic phase was washed with brine (100 mL x 3), dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water (0.1% FA), 5% to 100% gradient in 30 min; detector, UV 220 nm. This resulted in methyl (2S)-2-[(tert-butoxycarbonyl) amino]-3-[5-chloro-2-(pyrimidin-5-yl) phenyl] propanoate (8 g, 42 %) as a yellow solid. LCMS (ESI+): m/z 392.05 ($M+H^+$).
- 10 **Step 3: Methyl (S)-2-((tert-butoxycarbonyl)(methyl)amino)-3-(5-chloro-2-(pyrimidin-2-yloxy)phenyl)propanoate:**

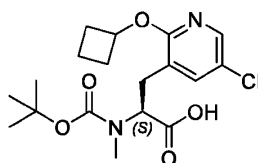


- [0239]** A solution of methyl (2S)-2-[(tert-butoxycarbonyl)amino]-3-[5-chloro-2-(pyrimidin-2-yloxy)phenyl]propanoate (1.3 g, 3.19 mmol, 1 eq) in DMF (15 mL) was treated with Ag_2O (3.69 g, 15.94 mmol, 5 eq) at rt under nitrogen atmosphere followed by the addition of CH_3I (6.79 g, 47.81 mmol, 15 eq) dropwise at rt. The resulting mixture was stirred for additional 3 h at rt. Desired product could be detected by LCMS. The resulting mixture was filtered, the filter cake was washed with DMF (30 mL). The filtrate was used in the next step directly without further purification. LCMS (ESI+): m/z 378.0 ($M+H^+$).
- 20 **Step 4: Int. 11:**

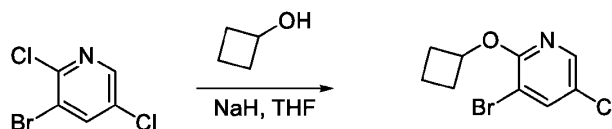


[0240] A solution of methyl (2S)-2-[(tert-butoxycarbonyl) (methyl)amino]-3-[5-chloro-2-(pyrimidin-2-yloxy) phenyl] propanoate (3 g, 7.111 mmol, 1 eq) in DMF (45 mL) and H₂O (10 mL) was treated with NaOH (0.85 g, 21.333 mmol, 3 eq) at rt. The resulting mixture was stirred for additional 16 h at rt. Desired product could be detected by LCMS. The resulting mixture was diluted with water (40 mL). The resulting mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (3 x 50 mL) and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water (0.1% FA), 5% to 100% gradient in 10 min; detector, UV 220 nm. This resulted in **Int. 11** (1.86 g, 62 %) as a yellow solid. LCMS (ESI+): *m/z* 408.05 (M+H⁺).

Int. 12: Preparation of (S)-2-((tert-butoxycarbonyl)(methyl)amino)-3-(5-chloro-2-cyclobutoxypyridin-3-yl)propanoic acid



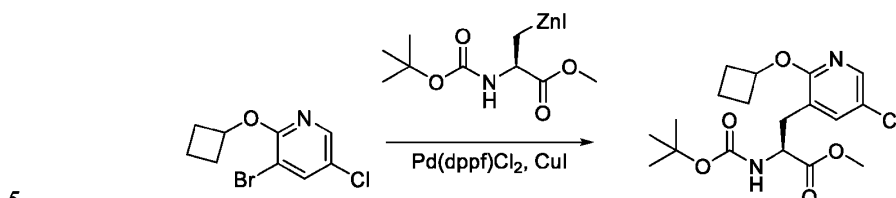
Step 1: 3-Bromo-5-chloro-2-cyclobutoxypyridine:



[0241] To a suspension of NaH (6.35 g, 158.67 mmol, 1.2 eq, 60 % in oil) in THF (250 mL) was added cyclobutanol (10.49 g, 145.45 mmol, 1.1 eq) in THF (20 mL) at 0 °C dropwise. The resulting mixture was stirred for 1 h at 0 °C under nitrogen atmosphere. 3-bromo-2,5-dichloropyridine (30.0 g, 132.23 mmol, 1.0 eq) in THF (30 mL) was added and the mixture was stirred for 16 h at 60 °C under nitrogen atmosphere. The reaction was quenched by the addition of sat. NH₄Cl (aq.) (100 mL) at 0 °C. The resulting mixture was diluted with water (500 mL) and then extracted with EtOAc (3 x 150 mL). The combined organic layers were washed with brine (1 x 300 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by

silica gel column chromatography, eluted with PE / EA (40:1) to afford 3-bromo-5-chloro-2-cyclobutoxypyridine (31.0 g, 89 %) as a colorless oil. LCMS (ESI⁺): *m/z* 262 (M+H⁺).

Step 2: Methyl (2S)-2-[(tert-butoxycarbonyl) amino]-3-(5-chloro-2-cyclobutoxypyridin-3-yl) propanoate:



[0242] To a stirred mixture of 3-bromo-5-chloro-2-cyclobutoxypyridine (15 g, 57.14 mmol, 1.0 eq), Pd(dppf)Cl₂.CH₂Cl₂ (2.33 g, 2.86 mmol, 0.05 eq) and CuI (1.09 g, 5.71 mmol, 0.1 eq) in N, N-dimethylacetamide (300 mL) was added methyl (2R)-2-[(tert-butoxycarbonyl) amino]-3-(iodozincio) propanoate (171.41 mL, 171.41 mmol, 3.00 eq) in one portion at rt under nitrogen atmosphere. The resulting mixture was stirred for 16 h at 80 °C under nitrogen atmosphere. The resulting mixture was diluted with water (600 mL) and EtOAc (200 mL), and then filtered. The filter cake was washed with EtOAc (1 x 20 mL). The filtrate was separated, and the aqueous layer was extracted with EtOAc (2 x 200 mL). The combined organic layers were washed with sat. NH₄Cl(aq.) (2 x 300 mL), brine (1 x 300 mL) and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water, 10% to 80% gradient in 20 min; detector, UV 220 nm. This resulted in methyl (2S)-2-[(tert-butoxycarbonyl) amino]-3-(5-chloro-2-cyclobutoxypyridin-3-yl) propanoate (16.4 g, 75 %) as a colorless oil. LCMS (ESI⁺): *m/z* 385 (M+H⁺).

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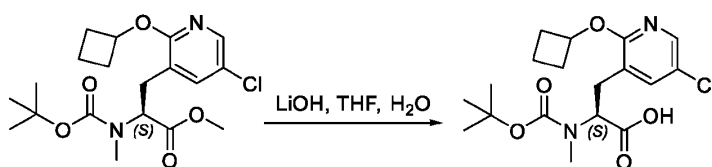
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Step 3: Methyl (2S)-2-[(tert-butoxycarbonyl) (methyl)amino]-3-(5-chloro-2-cyclobutoxypyridin-3-yl) propanoate:



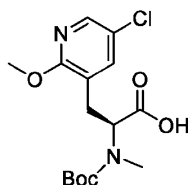
[0243] To a stirred mixture of methyl (2S)-2-[(tert-butoxycarbonyl) amino]-3-(5-chloro-2-cyclobutoxypyridin-3-yl) propanoate (16.4 g, 42.61 mmol, 1 eq) and Ag₂O (39.50 g, 170.45 mmol, 4.0 eq) in DMF (200 mL) was added CH₃I (96.8 g, 681.81 mmol, 16.0 eq) in one portion at rt under nitrogen atmosphere. The resulting mixture was stirred for 16 h at 50 °C under nitrogen atmosphere. The starting material was transformed completely. The resulting mixture was diluted with water (500 mL) and EtOAc (200 mL) and was then filtered. The filter cake was washed with EtOAc (1 x 20 mL). The resulting mixture was separated, and the aqueous layer was extracted with EtOAc (2 x 150 mL). The combined organic layers were washed with sat. NH₄Cl(aq.) (2 x 300 mL), brine (1 x 300 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (20:1) to afford methyl (2S)-2-[(tert-butoxycarbonyl) (methyl)amino]-3-(5-chloro-2-cyclobutoxypyridin-3-yl) propanoate (17.0 g, 95 %) as a colorless oil.

Step 4: Int. 12:

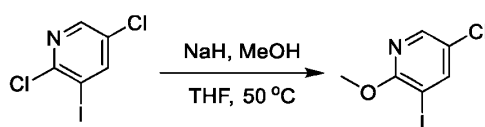


[0244] To a stirred solution of methyl (2S)-2-[(tert-butoxycarbonyl) (methyl)amino]-3-(5-chloro-2-cyclobutoxypyridin-3-yl) propanoate (17 g, 42.62 mmol, 1 eq) in THF (300 mL) and H₂O (100 mL) was added LiOH (3.06 g, 127.86 mmol, 3.00 eq) in H₂O (100 mL) dropwise at 0 °C. The resulting mixture was stirred for 16 h at rt. The resulting mixture was diluted with water (300 mL) and then acidified to pH 2 with HCl (2 M aq.). The resulting mixture was extracted with EtOAc (3 x 150 mL). The combined organic layers were washed with brine (1 x 300 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water, 10% to 60% gradient in 25 min; detector, UV 220 nm. This resulted in **Int. 12** (15.7 g, 95 %) as a white solid. **LCMS** (ESI+): *m/z* 385 (M+H⁺). **¹H NMR** (300 MHz, DMSO-*d*₆) δ 1.23 (d, J = 21.1 Hz, 9H), 1.54 – 1.88 (m, 2H), 1.93 – 2.20 (m, 2H), 2.28 – 2.47 (m, 2H), 2.68 (d, J = 1.4 Hz, 3H), 2.86 – 3.03 (m, 1H), 3.04 – 3.19 (m, 1H), 4.66 – 5.03 (m, 1H), 5.05 – 5.21 (m, 1H), 7.49 – 7.81 (m, 1H), 7.88 – 8.23 (m, 1H), 12.95 (s, 1H).

Int. 13: Preparation of (S)-2-((tert-butoxycarbonyl)(methyl)amino)-3-(5-chloro-2-methoxypyridin-3-yl)propanoic acid



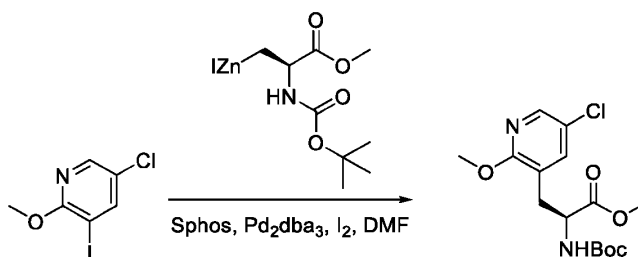
Step 1: 5-Chloro-2-methoxy-3-iodopyridine:



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[0245] 2,5-dichloro-3-iodopyridine (5.0 g, 1 eq, 18 mmol) solution in THF (26 mL) was brought to 0 °C and added NaH (1.5 g, 60% Wt, 2 eq, 37 mmol) as a solid. Then MeOH was added dropwise and stirred for 1 hour at 0 °C. Then the mixture was stirred at 50 °C until LCMS analysis showed the complete consumption of starting material. The reaction was added into ice water 100 mL, then extracted with EtOAc (150 mL × 2), the combined organic layers were washed with brine, dried over MgSO₄, and filtered. The filtrate was concentrated under reduced pressure to give crude product which was purified by column chromatography (SiO₂, EtOAc:Hexanes; 0-60%) to yield 5-chloro-2-methoxy-3-iodopyridine (4.3 g, 16 mmol, 87 % yield) as yellow solid.

Step 2: Methyl (S)-2-((tert-butoxycarbonyl)amino)-3-(5-chloro-2-methoxypyridin-3-yl)propanoate:

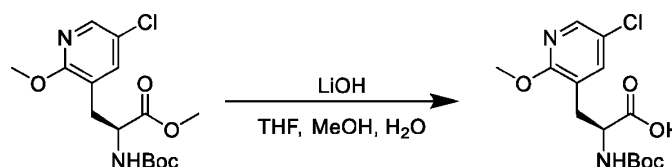


[0246] Zinc (2.4 g, 3 eq, 37 mmol) and DMF (15 mL) were added to a dry flask and degas with Ar. Then Boc-beta-iodo-Ala-OMe (4.0 g, 1 eq, 12 mmol) and iodine (0.47 g, 0.15 eq, 1.8 mmol) were added as solids. In a separate vial, 5-chloro-3-iodo-2-methoxypyridine (4.3

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g, 1.3 eq, 16 mmol) and 2-Dicyclohexylphosphino-2,6-Dimethoxy-1,1-Biphenyl (0.13 g, 0.025 eq, 0.31 mmol) were dissolved in DMF (15 mL) and degassed by Ar. Then Pd₂dba₃ (0.14 g, 0.013 eq, 0.15 mmol) was added. Transfer the first solution into the second solution and stir at rt until LCMS analysis showed the complete consumption of starting material. The reaction was added into ice water 50 mL, then extracted with EtOAc (100 mL × 2), the combined organic layers were washed with brine, dried over MgSO₄, and filtered. The filtrate was concentrated under reduced pressure to give crude product which was purified by column chromatography (SiO₂, EtOAc:Hexanes; 0-60%) to yield methyl (S)-2-((tert-butoxycarbonyl)amino)-3-(5-chloro-2-methoxypyridin-3-yl)propanoate (1.8 g, 8.1 mmol, 66 % yield) as white solid. LCMS (ESI⁺): *m/z* 345.3 (M+H⁺)

Step 3: (S)-2-((tert-butoxycarbonyl)amino)-3-(5-chloro-2-methoxypyridin-3-yl)propanoic acid:



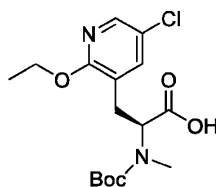
[0247] Methyl (S)-2-((tert-butoxycarbonyl)amino)-3-(5-chloro-2-methoxypyridin-3-yl)propanoate (2.8 g, 1 eq, 8.1 mmol) was dissolved into THF (20 mL), H₂O (14 mL) and MeOH (6.8 mL), then bring to 0 °C. Lithium hydroxide monohydrate (1.0 g, 0.68 mL, 3 eq, 24 mmol) was added and the mixture was stirred at 25 °C until LCMS analysis showed the complete consumption of starting material. Then the 10% citric acid was added to the mixture at 0 °C until pH was acidic. The reaction mixture was concentrated via rotavapor and extracted with EtOAc (80 mL × 2), the combined organic layers were washed with brine, dried over MgSO₄ and filtered. The filtrate was concentrated under reduced pressure to give crude product which was purified by column chromatography to give (S)-2-((tert-butoxycarbonyl)amino)-3-(5-chloro-2-methoxypyridin-3-yl)propanoic acid (2.3 g, 7.0 mmol, 86 % yield). LCMS (ESI⁺): *m/z* 331.4 (M+H⁺)

Step 4: Int. 13:



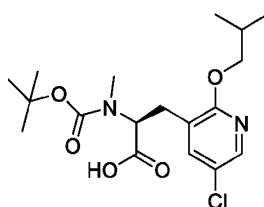
[0248] (S)-2-((tert-butoxycarbonyl)amino)-3-(5-chloro-2-methoxypyridin-3-yl)propanoic acid (2.3 g, 1 eq, 7.0 mmol) solid was dissolved in THF (35 mL) and brought to 0 °C under Ar. Then NaH (0.56 g, 60% Wt, 2 eq, 14 mmol) was added as solid, and MeI (5.9 g, 2.6 mL, 6 eq, 42 mmol) was added dropwise. The mixture was stirred for 1 hour at 0 °C. Then the mixture was stirred at 25 °C until LCMS analysis showed the complete consumption of starting material. The reaction was quenched with ice water 100 mL and 10% citric acid was added to the mixture at 0 °C until pH was acidic. The reaction mixture was concentrated via rotavapor and extracted with EtOAc (80 mL × 2), the combined organic layers were washed with brine, dried over MgSO₄, and filtered. The filtrate was concentrated under reduced pressure to give crude product which was purified by column chromatography to give **Int. 13** (2.3 g, 6.7 mmol, 96 % yield) as white solid. LCMS (ESI⁺): *m/z* 345.3 (M+H⁺).

Int. 14: (S)-2-((tert-butoxycarbonyl)(methyl)amino)-3-(5-chloro-2-ethoxypyridin-3-yl)propanoic acid:



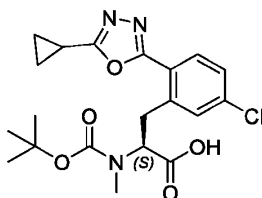
[0249] This material was synthesized by following the procedure for **Int. 13** with ethanol as the starting alcohol. LCMS (ESI⁺): *m/z* 359.3 (M+H⁺)

Int. 15: (S)-2-((tert-butoxycarbonyl)(methyl)amino)-3-(5-chloro-2-isobutoxypyridin-3-yl)propanoic acid:



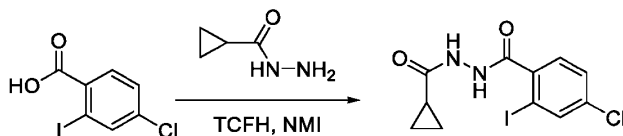
[0250] This material was synthesized by following the procedure for **Int. 13** with 2-methylpropan-1-ol as the starting alcohol. LCMS (ESI+): m/z 387.3 ($M+H^+$)

Int. 16: Preparation of (S)-2-((tert-butoxycarbonyl)(methyl)amino)-3-(5-chloro-2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)phenyl)propanoic acid



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Step 1: 4-Chloro-N'-cyclopropanecarbonyl-2-iodobenzohydrazide:

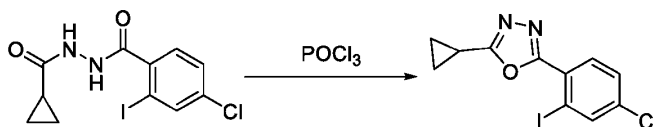


[0251] To a stirred solution of 4-chloro-2-iodobenzoic acid (1 g, 3.54 mmol, 1 eq) and NMI (0.87 g, 10.62 mmol, 3 eq) in ACN (40 mL) were added cyclopropanecarbohydrazide (354.45 mg, 3.540 mmol, 1 eq) and TCFH (1.19 g, 4.25 mmol, 1.2 eq) in portions at 0 °C. The resulting mixture was stirred for 16 h at rt. The resulting mixture was diluted with water (20 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (1 x 50 mL) and dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under vacuum. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, Acetonitrile in Water (0.1% FA), 0% to 60% gradient in 30 min; detector, UV 254 nm. This resulted in 4-chloro-N'-cyclopropanecarbonyl-2-iodobenzohydrazide (815 mg, 62%) as an off-white solid. LCMS (ESI+): m/z 364.80 ($M+H^+$).

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Step 2: 2-(4-chloro-2-iodophenyl)-5-cyclopropyl-1,3,4-oxadiazole:

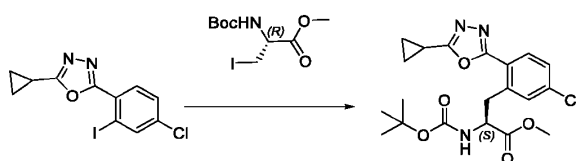


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[0252] A solution of 4-chloro-N'-cyclopropanecarbonyl-2-iodobenzohydrazide (5 g, 13.72 mmol, 1 eq) in $POCl_3$ (100 mL) was stirred for 2 h at 85 °C. The resulting mixture was

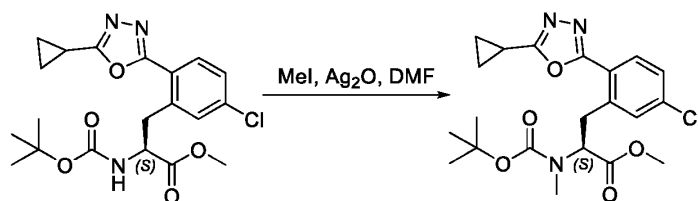
concentrated under vacuum and extracted with CH_2Cl_2 (3 x 200 mL). The combined organic layers were washed with $\text{NaHCO}_3(\text{aq.})$ (1 x 200 mL) and dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under vacuum to afford 2-(4-chloro-2-iodophenyl)-5-cyclopropyl-1,3,4-oxadiazole (4.5 g, 82 %) as a brown solid. The crude product was used in the next step directly without further purification. LCMS (ESI⁺): m/z 347.00 ($\text{M}+\text{H}^+$).

Step 3: Methyl (2S)-2-[(tert-butoxycarbonyl)amino]-3-[5-chloro-2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)phenyl]propanoate:



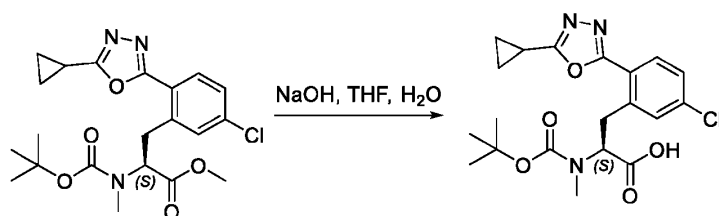
[0253] To a stirred solution of Zn (4.98 g, 76.18 mmol, 2.4 eq), 1,2-Dibromoethane (609.07 mg, 3.17 mmol, 0.1 eq) in DMA (20 mL) was added TMSCl (231.04 mg, 2.13 mmol, 0.067 eq) dropwise at 25 °C under nitrogen atmosphere. The resulting mixture was stirred for 30 min and methyl (2R)-2-[(tert-butoxycarbonyl)amino]-3-iodopropanoate (20.89 g, 63.48 mmol, 2.00 eq) in DMA (20 mL) was added to the above solution. The temperature risen and kept it under 50 °C. After 30 min, the mixture was added to a solution of 2-(4-chloro-2-iodophenyl)-5-cyclopropyl-1,3,4-oxadiazole (11 g, 31.74 mmol, 1 eq), CuI (1.21 g, 6.35 mmol, 0.2 eq) and Pd(dppf) Cl_2 (2.32 g, 3.174mmol, 0.1equiv.) in DMA (200 mL) dropwise and stirred for 2 h at 80 °C. The reaction was quenched with sat. NH_4Cl (aq.) at 0 °C. The resulting mixture was filtered, the filter cake was washed with CH_2Cl_2 (500 mL) and the filtrate was extracted with CH_2Cl_2 (1000 mL). The combined organic layers were washed with brine (3 x 200 mL) and dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under vacuum. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, Acetonitrile in Water (0.1% FA), 0% to 100% gradient in 40 min; detector, UV 254 nm. This resulted in methyl (2S)-2-[(tert-butoxycarbonyl)amino]-3-[5-chloro-2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)phenyl]propanoate (7.2 g, 197 %) as a brown solid. LCMS (ESI⁺): m/z 422.20 ($\text{M}+\text{H}^+$).

Step 4: Methyl (2S)-2-[(tert-butoxycarbonyl)(methyl)amino]-3-[5-chloro-2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)phenyl]propanoate:



- [0254]** To a stirred solution of methyl (2S)-2-[(tert-butoxycarbonyl)amino]-3-[5-chloro-2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)phenyl]propanoate (7 g, 16.59 mmol, 1 eq) and Ag₂O (15.38 g, 66.37 mmol, 4 eq) in DMF (140 mL) was added CH₃I (23.55 g, 165.9 mmol, 10 eq) dropwise at 0 °C. The resulting mixture was stirred for 72 h at rt. The resulting mixture was filtered, the filter cake was washed with EtOAc (3 x 100 mL) and the filtrate was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (3 x 200 mL) and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under vacuum. The crude product (7 g) was purified by Prep-HPLC with the following conditions (Column: XBridge C18 OBD Prep Column, 100Å 10 µm, 19 mm X 250 mm; Mobile Phase A: Water(10 mmol/L NH₄HCO₃), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 60% B to 60% B in 24 min; Wave Length: 220 nm; RT1(min): 18; Number Of Runs: 0) to afford methyl (2S)-2-[(tert-butoxycarbonyl)(methyl)amino]-3-[5-chloro-2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)phenyl]propanoate (3.6 g, 50 %) as a brown oil. LCMS (ESI+): *m/z* 565.60 (M+H⁺).

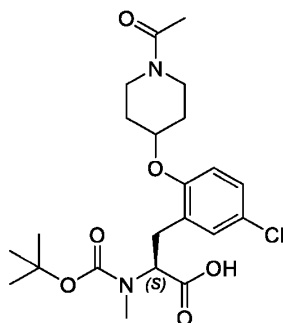
Step 5: Int. 16:



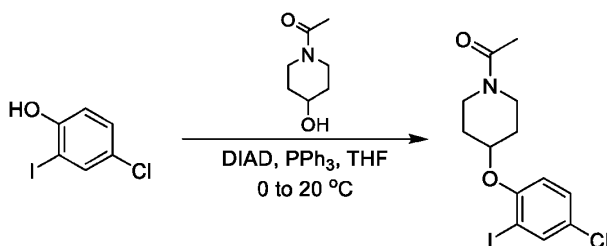
- [0255]** To a stirred solution of methyl (2S)-2-[(tert-butoxycarbonyl)(methyl)amino]-3-[5-chloro-2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)phenyl]propanoate (2.6 g, 5.97 mmol, 1 eq) in THF (24 mL)/H₂O (8 mL) was added NaOH (715.69 mg, 17.90 mmol, 3.00 eq) in water (10 mL) dropwise at 0 °C. The mixture was acidified to pH=5 with HCl (1N). The resulting mixture was extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine (1 x 50 mL) and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under vacuum. The residue was purified by reversed-phase flash

chromatography with the following conditions: column, C18 silica gel; mobile phase, Acetonitrile in Water (0.1% FA), 5% to 100% gradient in 30 min; detector, UV 254 nm. This resulted in **Int. 16** (2.73 g, 108 %) as an off-white solid. **LCMS** (ESI+): m/z 421.95 ($M+H^+$).

Int. 17: Preparation of (S)-3-(2-((1-acetyl-4-(4-chlorophenoxy)piperidin-1-yl)oxy)-5-chlorophenyl)-2-((tert-butoxycarbonyl)(methyl)amino)propanoic acid:

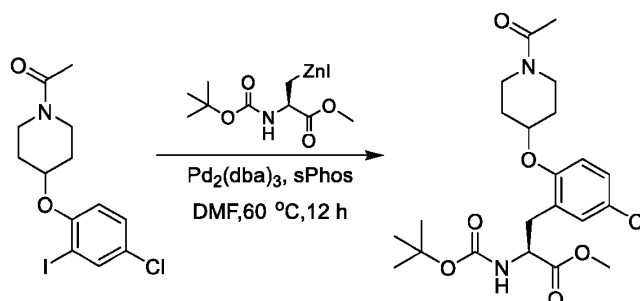


Step 1: 1-(4-(4-chloro-2-iodophenoxy)piperidin-1-yl)ethan-1-one:



[0256] To a solution of 4-chloro-2-iodophenol (20 g, 78.60 mmol, 1 eq), 1-(4-hydroxy-1-piperidinyl)ethanone (12.38 g, 86.46 mmol, 1.1 eq) and PPh_3 (24.74 g, 94.32 mmol, 1.2 eq) in THF (200 mL) was added DIAD (19.07 g, 94.32 mmol, 18.34 mL, 1.2 eq) dropwise at 0 °C under N_2 atmosphere. Then the reaction mixture was allowed to warm to 20 °C slowly and stirred at 20 °C for 12 h. LCMS showed starting material was consumed completely and desired mass was detected. The reaction mixture was quenched by water (200 mL), extracted with EtOAc (150 mL x 2). The combined organics were washed with brine (150 mL), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 330 g SepaFlash® Silica Flash Column, Eluent of 0~55% EtOAc/PE gradient @ 200 mL/min) to give 1-(4-(4-chloro-2-iodophenoxy)piperidin-1-yl)ethan-1-one (21.49 g, 39.55 mmol, 50 % yield, 70 % purity) as a light-yellow solid.

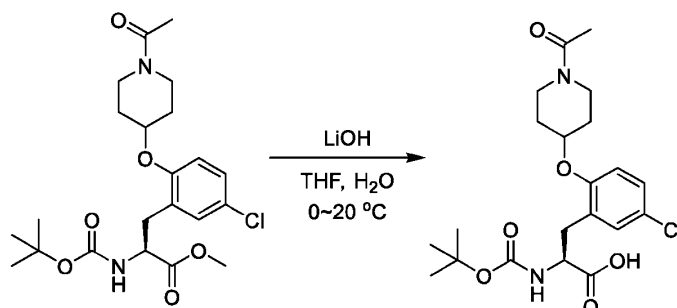
Step 2: methyl (S)-3-(2-((1-acetylpiperidin-4-yl)oxy)-5-chlorophenyl)-2-((tert-butoxycarbonyl)amino)propanoate



[0257] A mixture of Zn (6.95 g, 106.34 mmol, 3.5 eq) in DMF (50 mL) was degassed and
 5 purged with N₂ for 3 times, and the mixture was stirred at 120 °C for 10 min under N₂
 atmosphere. Then I₂ (2.31 g, 9.11 mmol, 1.84 mL, 0.3 eq) in DMF (10 mL) was added
 dropwise at 20 °C, methyl (R)-2-((tert-butoxycarbonyl)amino)-3-iodopropanoate (10 g, 30.38
 mmol, 1 eq) in DMF (30 mL) was added dropwise, I₂ (2.31 g, 9.11 mmol, 1.84 mL, 0.3 eq) in
 DMF (10 mL) was added dropwise, the reaction mixture was stirred at 20 °C for 1 hr. TLC
 10 (PE:EtOAc = 5:1, R_f = 0.5) showed starting material was consumed completely and a new
 major spot was detected. The (R)-2-((tert-butoxycarbonyl)amino)-3-methoxy-3-
 oxopropyl)zinc(II) iodide (11.99 g, crude) as a gray liquid was obtained, which was used into
 the next step without further purification.

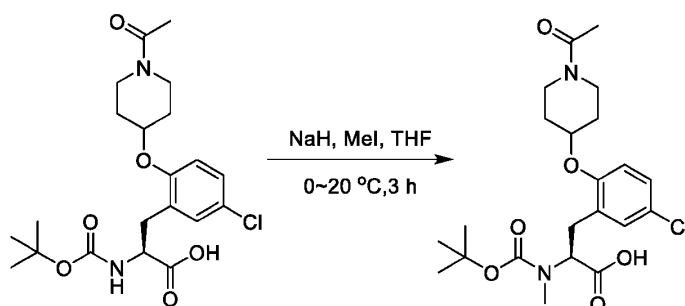
[0258] To a solution of 1-(4-(4-chloro-2-iodophenoxy)piperidin-1-yl)ethan-1-one (5.58 g,
 15 14.70 mmol, 1 eq), sPhos (603.43 mg, 1.47 mmol, 0.1 eq) and Pd₂(dba)₃ (673.00 mg, 734.95
 μmol, 0.05 eq) in DMF (50 mL) was degassed and purged with N₂ 3 times. Then (R)-2-
 ((tert-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)zinc(II) iodide (11.99 g, 30.39 mmol,
 2.07 eq) in DMF was added dropwise. Then, the reaction mixture was stirred at 65 °C for 12
 h. LCMS showed starting material was consumed completely and desired mass was detected.
 20 The reaction mixture was cooled to rt and quenched by water (150 mL), extracted with
 EtOAc (100 mL x 2). The combined organics were washed with brine (150 mL), dried over
 Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The residue was
 purified by prep-HPLC (column: 800g Agela C18; mobile phase: [water-ACN]; B%: 20-50%
 30min; 50% 20min) to give methyl (S)-3-(2-((1-acetylpiperidin-4-yl)oxy)-5-chlorophenyl)-2-
 25 ((tert-butoxycarbonyl)amino)propanoate (3.62 g, 7.66 mmol, 52 % yield, 96 % purity) as a
 white solid.

Step 3: (S)-3-(2-((1-acetylpiperidin-4-yl)oxy)-5-chlorophenyl)-2-((tert-butoxycarbonyl)amino)propanoic acid:



[0259] To a solution of methyl (S)-3-(2-((1-acetylpiperidin-4-yl)oxy)-5-chlorophenyl)-2-((tert-butoxycarbonyl)amino)propanoate (3.62 g, 7.96 mmol, 1 eq) in THF (40 mL) was added a solution of LiOH.H₂O (400.69 mg, 9.55 mmol, 1.2 eq) in H₂O (20 mL). Then the reaction mixture was stirred at 25 °C for 1 hr. LCMS showed starting material was consumed completely and desired mass was detected. The reaction mixture was concentrated under reduced pressure to remove THF. Then the mixture was acidified by 1N HCl to pH=2~3 at 0 °C and extracted with EtOAc (15 mL x 2). The combined organics were washed with brine (20 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give compound (S)-3-(2-((1-acetylpiperidin-4-yl)oxy)-5-chlorophenyl)-2-((tert-butoxycarbonyl)amino)propanoic acid (3.35 g, 7.60 mmol, 95 % yield, 100% purity) as a white solid.

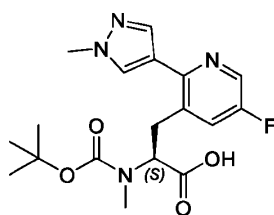
Step 4: Int. 17:



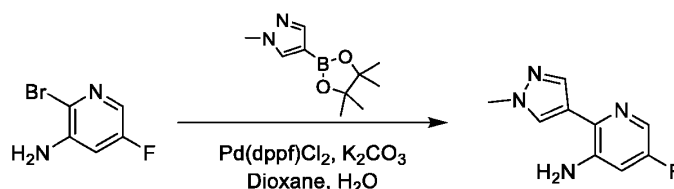
[0260] To a solution of (S)-3-(2-((1-acetylpiperidin-4-yl)oxy)-5-chlorophenyl)-2-((tert-butoxycarbonyl)amino)propanoic acid (3.35 g, 7.60 mmol, 1 eq) in THF (40 mL) was added NaH (759.71 mg, 18.99 mmol, 60% purity, 2.5 eq) at 0 °C under N₂ atmosphere. The mixture

was stirred at 20 °C for 30 min. Then MeI (14.02 g, 98.77 mmol, 6.15 mL, 13 eq) was added at 0 °C and the reaction mixture was stirred at 20 °C for 12 hr. LCMS showed 38% of starting material remained and 26% of desired mass was detected. The reaction mixture was cooled to 0 °C and quenched by NH₄Cl (40 mL), extracted with EtOAc (30 mL x 2). The combined organics were washed with brine (30 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The crude product was purified by reversed-phase HPLC (column: 800g Agela C18; mobile phase: [water (FA)-ACN]; B%: 25-55% 30min; 55% 20min) to **Int. 17** (3.02 g, 6.41 mmol, 97 % purity) was obtained as a light-yellow solid. Spectrum: ¹H NMR (400 MHz, DMSO-*d*₆) δ = 12.80 (br s, 1H), 7.28 - 6.99 (m, 3H), 4.90 - 4.60 (m, 2H), 3.73 - 3.54 (m, 2H), 3.39 (td, *J* = 3.8, 13.3 Hz, 2H), 3.18 (br dd, *J* = 3.8, 13.8 Hz, 1H), 2.95 - 2.82 (m, 1H), 2.66 (s, 3H), 2.01 (s, 3H), 1.97 - 1.80 (m, 2H), 1.74 - 1.50 (m, 2H), 1.30 - 1.15 (m, 9H)

Int. 18: Preparation of (S)-2-((tert-butoxycarbonyl)(methyl)amino)-3-(5-fluoro-2-(1-methyl-1H-pyrazol-4-yl)pyridine-3-yl)propanoic acid



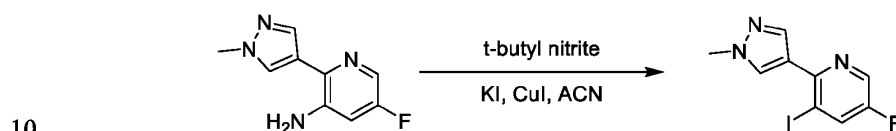
Step 1: 5-Fluoro-2-(1-methyl-1H-pyrazol-4-yl)pyridine-3-amine:



[0261] To a solution of 2-bromo-5-fluoropyridin-3-amine (12 g, 62.83 mmol, 1 eq) in dioxane (96 mL) and H₂O (18 mL) was added, 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole, Pd(dppf)Cl₂ (2.30 g, 3.14 mmol, 0.05 eq) and K₂CO₃ (17.37 g, 125.65 mmol, 2 eq), the mixture was stirred at 90 °C for 12 h under N₂. The reaction was monitored by LCMS, which showed 2-bromo-5-fluoropyridin-3-amine was consumed and one of peak with desired mass was detected. Five other reactions of the same size were set up and all six reactions were combined to work up. After cooling to rt, the mixture was filtered.

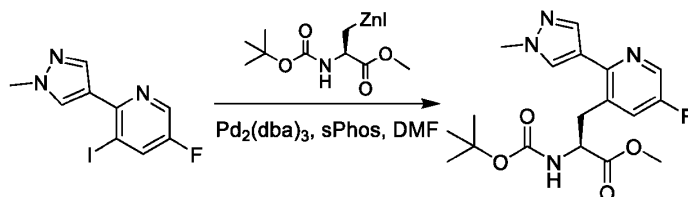
The filtrate was diluted with water (500 mL), extracted with EtOAc (200 mL x 3). The combined organics were washed with brine (300 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The residue was dissolved in DCM (200 mL), and 250 g of silica gel was added. The resulting mixture was evaporated under reduced pressure to give a dry flowing solid, and then it was loaded to Biotage® using a 400 g Agela flash silica gel column, eluted with 0 % to 50 % EtOAc in PE with the flow rate of 75 mL/min. The product fraction was combined and concentrated to give 5-fluoro-2-(1-methyl-1H-pyrazol-4-yl)pyridine-3-amine (63 g, crude) as a yellow solid.

Step 2: 5-Fluoro-3-iodo-2-(1-methyl-1H-pyrazol-4-yl)pyridine:



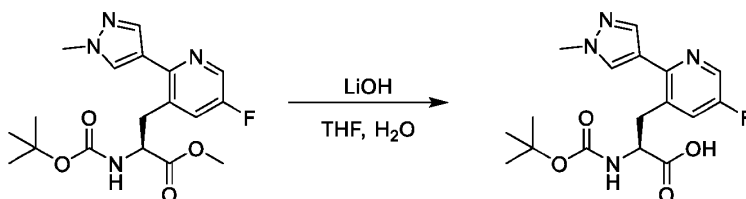
[0262] To a solution of 5-fluoro-2-(1-methyl-1H-pyrazol-4-yl)pyridine-3-amine (15.75 g, 81.95 mmol, 1 eq) in MeCN (450 mL) was added CuI (18.73 g, 98.34 mmol, 1.2 eq), KI (68.02 g, 409.75 mmol, 5 eq) and tert-butyl nitrite (42.25 g, 409.75 mmol, 48.73 mL, 5 eq), the mixture was stirred at 60 °C for 12 h under N₂. The reaction was monitored by LCMS, which showed 5-fluoro-2-(1-methyl-1H-pyrazol-4-yl)pyridine-3-amine as consumed and one of peak with desired mass was detected. Three other reactions of the same size were set up and all four reactions were combined and filtered, and the filter cake was rinsed with EtOAc (100 mL x 3). The combined filtrate were concentrated under reduced pressure to give a residue. The filtrate was diluted with water (200 mL), extracted with dichloromethane (80 mL x 3). The combined organics were washed with brine (100 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The residue was dissolved in DCM (100 mL), and 200 g of silica gel was added. The resulting mixture was evaporated under reduced pressure to give a dry flowing solid, and then it was loaded to Biotage® using a 300 g Agela flash silica gel column, eluted with 0 % to 20 % EtOAc in PE with the flow rate of 75 mL/min. The product fraction was combined and concentrated to give 5-fluoro-3-iodo-2-(1-methyl-1H-pyrazol-4-yl)pyridine (30 g, 98.99 mmol, 60 % yield, 100% purity) as a yellow solid.

Step 3: Methyl (S)-2-((tert-butoxycarbonyl)amino)-3-(5-fluoro-2-(1-methyl-1H-pyrazol-4-yl)pyridine-3-yl)propanoate:



- [0263]** To a solution of 5-fluoro-3-iodo-2-(1-methyl-1H-pyrazol-4-yl)pyridine (30 g, 98.99 mmol, 1 eq), SPhos (4.06 g, 9.90 mmol, 0.1 eq) and $\text{Pd}_2(\text{dba})_3$ (4.83 g, 5.28 mmol, 0.05 eq) in DMF (330 mL) was degassed and purged with N_2 3 times. Then (R)-2-((tert-butoxycarbonyl)amino)-3-methoxy-3-oxopropylzinc(II) iodide (78.10 g, 197.97 mmol, 2 eq) in DMF (200 mL) was added dropwise. Then the reaction mixture was stirred at 20 °C for 12 h. The reaction was monitored by LCMS, which showed 5-fluoro-3-iodo-2-(1-methyl-1H-pyrazol-4-yl)pyridine was consumed and one of peak with desired mass was detected. The mixture was filtered. The filtrate was diluted with water (200 mL), extracted with EtOAc (100 mL x 3). The combined organics were washed with brine (200 mL), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure to give a residue. The residue was purified by preparative HPLC (column: Welch Xtimate C18 250 x 100 mm#10 μm ; mobile phase: [water (NH_4HCO_3)-ACN]; B%: 30%-60%, 36 min) the HPLC fractions were combined, lyophilized. The product fraction was combined and concentrated to give methyl (S)-2-((tert-butoxycarbonyl)amino)-3-(5-fluoro-2-(1-methyl-1H-pyrazol-4-yl)pyridine-3-yl)propanoate (4.2 g, 11.10 mmol, 11 % yield, 100% purity) as a yellow solid.

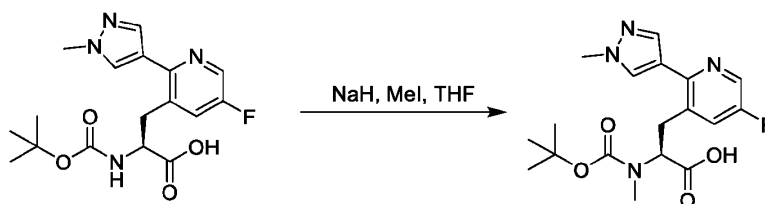
Step 4: (S)-2-((tert-butoxycarbonyl)amino)-3-(5-fluoro-2-(1-methyl-1H-pyrazol-4-yl)pyridine-3-yl)propanoic acid:



- [0264]** To a solution of methyl (S)-2-((tert-butoxycarbonyl)amino)-3-(5-fluoro-2-(1-methyl-1H-pyrazol-4-yl)pyridine-3-yl)propanoate (4.2 g, 11.10 mmol, 1 eq) in THF (60 mL) was added a solution of $\text{LiOH} \cdot \text{H}_2\text{O}$ (558.93 mg, 13.32 mmol, 1.2 eq) in H_2O (30 mL), the mixture was stirred at 20 °C for 1 h. The mixture was acidified by adding hydrochloric acid (0.1 M, 10 mL) dropwise at 20 °C to pH = 5. The filtrate was diluted with water (30 mL),

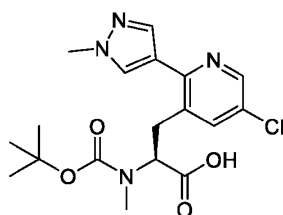
extracted with EtOAc (20 mL x 3). The combined organics were washed with brine (20 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give (S)-2-((tert-butoxycarbonyl)amino)-3-(5-fluoro-2-(1-methyl-1H-pyrazol-4-yl)pyridine-3-yl)propanoic acid (3.7 g, 10.15 mmol, 91 % yield, 100 % purity) as a yellow solid.

5 **Step 5: Int. 18:**

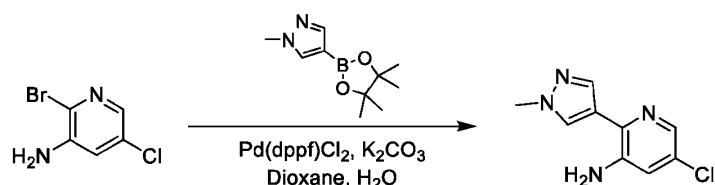


[0265] To a solution of (S)-2-((tert-butoxycarbonyl)amino)-3-(5-fluoro-2-(1-methyl-1H-pyrazol-4-yl)pyridine-3-yl)propanoic acid (1.85 g, 5.08 mmol, 1 eq) in THF (76 mL) was added NaH (1.02 g, 25.39 mmol, 60% purity, 5 eq) at 0 °C, the mixture was stirred at 0 °C for 1 h under N₂. MeI (7.21 g, 50.77 mmol, 3.16 mL, 10 eq) was added to the reaction mixture, the mixture was stirred at 20 °C for 12 h under N₂. LCMS showed the (S)-2-((tert-butoxycarbonyl)(methyl)amino)-3-(5-fluoro-2-(1-methyl-1H-pyrazol-4-yl)pyridine-3-yl)propanoic acid was consumed and desired mass was detected. One other reaction of the same size was set up and all two reactions were combined to work up. The reaction was quenched by addition of saturated ammonium chloride aqueous solution (20 mL), acidified by adding hydrochloric acid (0.1 M, 10 mL) dropwise at 0 °C to pH = 5, extracted with EtOAc (20 mL x 3). The combined organics were washed with brine (30 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give **Int. 18** (2.5 g, 6.53 mmol, 64.3% yield, 99 % purity) as a yellow solid. ¹H NMR (400 MHz, MeOD -d₄) δ = 8.34 (dd, J = 2.4, 15.3 Hz, 1H), 8.02 (d, J = 7.0 Hz, 1H), 7.84 (d, J = 3.1 Hz, 1H), 7.52 (dt, J = 2.6, 9.2 Hz, 1H), 4.74 - 4.62 (m, 1H), 4.02 - 3.92 (m, 3H), 3.64 - 3.54 (m, 1H), 3.28 - 3.12 (m, 1H), 2.66 (d, J = 6.9 Hz, 3H), 1.42 - 1.18 (m, 9H).

Int. 19: Preparation of (S)-2-((tert-butoxycarbonyl)(methyl)amino)-3-(5-chloro-2-(1-methyl-1H-pyrazol-4-yl)pyridine-3-yl)propanoic acid

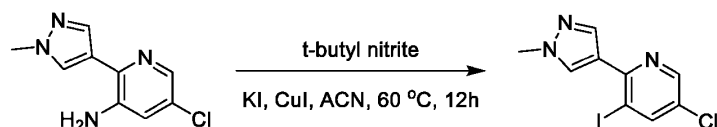


Step 1: 5-chloro-2-(1-methyl-1H-pyrazol-4-yl)pyridine-3-amine:



[0266] To a solution of 2-bromo-5-chloropyridin-3-amine (30 g, 144.61 mmol, 1 eq) and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (36.11 g, 173.53 mmol, 1.2 eq) in dioxane (720 mL) and H₂O (120 mL) was added K₂CO₃ (39.97 g, 289.22 mmol, 2 eq) and Pd(dppf)Cl₂ (3.17 g, 4.34 mmol, 0.03 eq), the mixture was stirred at 90 °C for 12 h under N₂. The reaction was monitored by LCMS, which showed 2-bromo-5-chloropyridin-3-amine was consumed and one of peak with desired mass was detected. The reaction mixture was filtered, and the filter cake was washed with EtOAc (50 mL x 3) and diluted with water (10 mL), extracted with EtOAc (200 mL x 3). The combined organics were washed with brine (50 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The residue was dissolved in DCM (80 mL), and 40 g of silica gel was added. The resulting mixture was evaporated under reduced pressure to give a dry flowing solid, and then it was loaded to Biotage® using a 180 g Agela flash silica gel column, eluted with 0 % to 40 % EtOAc in PE with the flow rate of 75 mL/min. The product fraction was combined and concentrated to give 5-chloro-2-(1-methyl-1H-pyrazol-4-yl)pyridine-3-amine (30 g, 142.35 mmol, 98 % yield, 99% purity) as a brown solid.

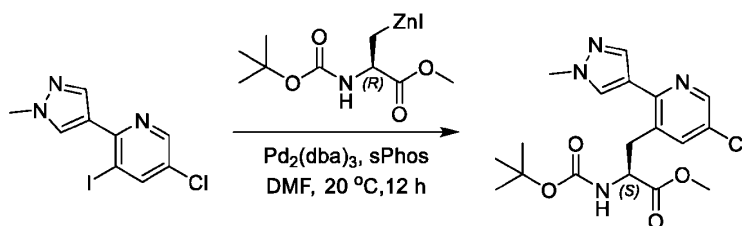
Step 2: 5-chloro-3-iodo-2-(1-methyl-1H-pyrazol-4-yl)pyridine:



20

[0267] To a solution of 5-chloro-2-(1-methyl-1H-pyrazol-4-yl)pyridine-3-amine (9 g, 43.14 mmol, 1 eq) in MeCN (300 mL) was added CuI (9.86 g, 51.76 mmol, 1.2 eq), KI (35.80 g, 215.68 mmol, 5 eq) and tert-butyl nitrite (22.24 g, 215.68 mmol, 25.65 mL, 5 eq), the mixture was stirred at 60 °C for 12 h under N₂. The reaction was monitored by LCMS, which showed 5-chloro-2-(1-methyl-1H-pyrazol-4-yl)pyridine-3-amine was consumed and one of peak with desired mass was detected. After cooling to rt, the solid was collected by filtration, washed with EtOAc (100 mL x 3) and dried under reduced pressure to give a brown solid. The solid was triturated with EtOAc at 20 °C for 30 min. Then the crude product was triturated with ammonia water at 20 °C for 30 min and filtered, the filter cake was concentrated to give 5-chloro-3-iodo-2-(1-methyl-1H-pyrazol-4-yl)pyridine (20.5 g, 50.04 mmol, 58 % yield, 78% purity) brown solid.

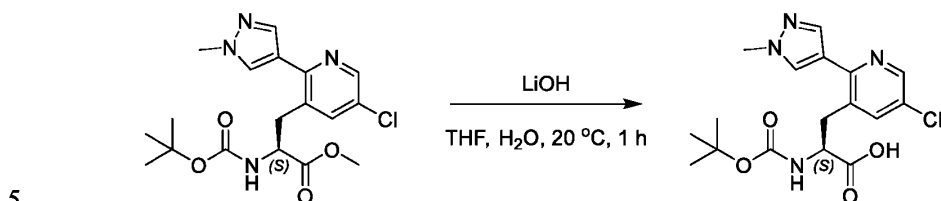
Step 3: Methyl (S)-2-((tert-butoxycarbonyl)amino)-3-(5-chloro-2-(1-methyl-1H-pyrazol-4-yl)pyridine-3-yl)propanoate:



[0268] To a solution of 5-chloro-3-iodo-2-(1-methyl-1H-pyrazol-4-yl)pyridine (20.5 g, 64.16 mmol, 1 eq) in DMF (200 mL) was added (R)-2-((tert-butoxycarbonyl)amino)-3-methoxy-3-oxopropylzinc(II) iodide (50.62 g, 128.31 mmol, 2 eq), Pd₂(dba)₃ (2.94 g, 3.21 mmol, 0.05 eq) and sPhos (2.63 g, 6.42 mmol, 0.1 eq), the mixture was stirred at 20 °C for 12 h under N₂. The reaction was monitored by LCMS, which showed 5-chloro-3-iodo-2-(1-methyl-1H-pyrazol-4-yl)pyridine was consumed and one of peak with desired mass was detected. The reaction was quenched by addition of saturated ammonium chloride aqueous solution (200 mL) and extracted with EtOAc (100 mL x 3). The combined organics were washed with brine (100 mL x 2), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The residue was dissolved in DCM (50 mL), and 40 g of silica gel was added. The resulting mixture was evaporated under reduced pressure to give a dry flowing solid, and then it was loaded to Biotage® using a 120 g Agela flash silica gel column, eluted with 0 % to 55 % EtOAc in PE with the flow rate of 75 mL/min. The product fraction was combined and concentrated to give methyl (S)-2-((tert-

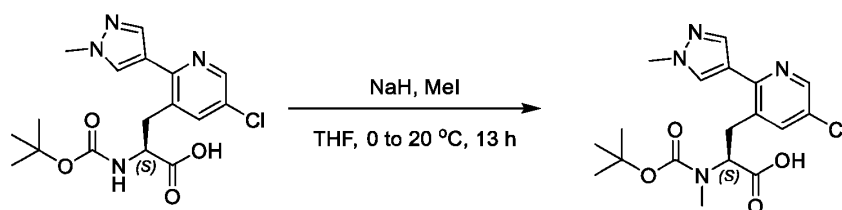
butoxycarbonyl)amino)-3-(5-chloro-2-(1-methyl-1H-pyrazol-4-yl)pyridine-3-yl)propanoate (8 g, 19.86 mmol, 31 % yield, 98% purity) as a yellow solid.

Step 4: (S)-2-((tert-butoxycarbonyl)amino)-3-(5-chloro-2-(1-methyl-1H-pyrazol-4-yl)pyridine-3-yl)propanoic acid:



[0269] To a solution of methyl (S)-2-((tert-butoxycarbonyl)amino)-3-(5-chloro-2-(1-methyl-1H-pyrazol-4-yl)pyridine-3-yl)propanoate (8 g, 20.26 mmol, 1 eq) in THF (100 mL) was added a solution of LiOH.H₂O (1.02 g, 24.31 mmol, 1.2 eq) in H₂O (50 mL), the mixture was stirred at 20 °C for 1 h. The reaction was monitored by LCMS, which showed methyl (S)-2-((tert-butoxycarbonyl)amino)-3-(5-chloro-2-(1-methyl-1H-pyrazol-4-yl)pyridine-3-yl)propanoate was consumed and one of peak with desired mass was detected. The mixture was extracted with EtOAc (100 mL). The aqueous phase was acidified by added hydrochloric acid (1 M, 50 mL) dropwise at 0 °C to pH = 4 and extracted with EtOAc (200 mL x 3). The combined organics were washed with brine (50 mL), dried over Na₂SO₄, filtered, and concentrated to give (S)-2-((tert-butoxycarbonyl)amino)-3-(5-chloro-2-(1-methyl-1H-pyrazol-4-yl)pyridine-3-yl)propanoic acid (7 g, 18.01 mmol, 89 % yield, 98% purity) as a yellow solid.

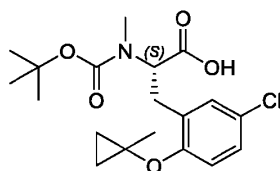
Step 5: Int. 19:



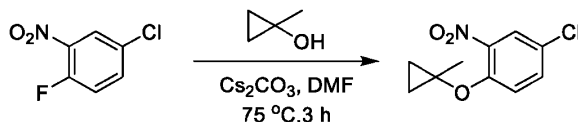
[0270] To a solution of (S)-2-((tert-butoxycarbonyl)amino)-3-(5-chloro-2-(1-methyl-1H-pyrazol-4-yl)pyridine-3-yl)propanoic acid (3.7 g, 9.72 mmol, 1 eq) in THF (100 mL) was added NaH (1.94 g, 48.58 mmol, 60% purity, 5 eq) at 0 °C, the mixture was stirred at 0 °C for 1 h under N₂. MeI (13.79 g, 97.16 mmol, 6.05 mL, 10 eq) was added to the reaction

mixture, the mixture was stirred at 20 °C for 12 h under N₂. The reaction was monitored by LCMS, which showed (S)-2-((tert-butoxycarbonyl)amino)-3-(5-chloro-2-(1-methyl-1H-pyrazol-4-yl)pyridine-3-yl)propanoic acid was consumed and one of peak with desired mass was detected. The reaction mixture was cooled to 0 °C and quenched by NH₄Cl (30 mL),
 5 extracted with EtOAc (50 mL x 2). The combined organics were washed with brine (30 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give **Int. 19** (3 g, 7.51 mmol, 77 % yield, 98 % purity) as a yellow solid. ¹H NMR (400 MHz, MeOD-d₄) ¹H NMR (400 MHz, METHANOL-d₄) δ = 8.48 - 8.32 (m, 1H), 8.08 (d, J = 6.8 Hz, 1H), 7.92 (s, 1H), 7.76 - 7.64 (m, 1H), 4.80 - 4.66 (m, 1H), 3.98 (s, 3H), 3.64 - 3.56 (m, 1H), 3.28 - 3.16
 10 (m, 1H), 2.66 (d, J = 9.8 Hz, 3H), 1.24 (s, 9H)

Int. 20: Preparation of (S)-2-((tert-butoxycarbonyl)(methyl)amino)-3-(5-chloro-2-(1-methylcyclopropoxy)phenyl)propanoic acid



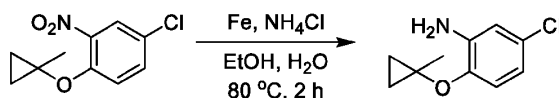
Step 1: 4-chloro-1-(1-methylcyclopropoxy)-2-nitrobenzene:



15

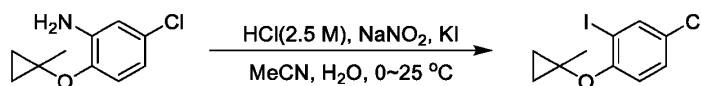
[0271] To a solution of 4-chloro-1-fluoro-2-nitrobenzene (21 g, 119.63 mmol, 1 eq) and 1-methylcyclopropanol (11.16 g, 131.59 mmol, 85% purity, 1.1 eq) in DMF (150 mL) was added Cs₂CO₃ (58.47 g, 179.44 mmol, 1.5 eq). Then, the reaction mixture was stirred at 75 °C for 3 h. HPLC showed starting material was consumed completely and a new major peak
 20 was detected. The reaction mixture was cooled to rt and quenched by water (200 mL), extracted with EtOAc (150 mL x 2). The combined organics were washed with water (100 mL x 3) and brine (150 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give 4-chloro-1-(1-methylcyclopropoxy)-2-nitrobenzene (25 g, 104.54 mmol, 87 % yield, 95.2 % purity) as a brown oil.

25 Step 2: 5-chloro-2-(1-methylcyclopropoxy)aniline:



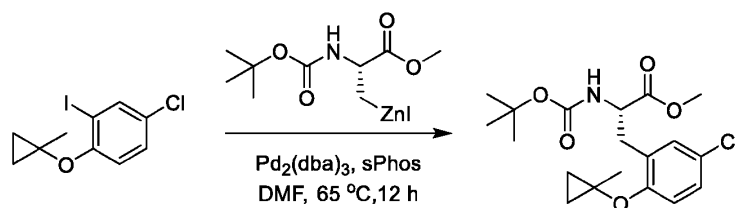
[0272] To a solution of 4-chloro-1-(1-methylcyclopropoxy)-2-nitrobenzene (25 g, 109.82 mmol, 1 eq) in EtOH (200 mL) and H₂O (100 mL) was added NH₄Cl (5.87 g, 109.82 mmol, 1 eq) and Fe (18.40 g, 329.46 mmol, 3 eq). Then, the reaction mixture was stirred at 80 °C for 2 h. LCMS showed starting material was consumed completely and desired mass was detected. The resultant mixture was filtered, and the filter cake was rinsed with EtOH (100 mL x 3). Then the combined filtrates were concentrated under reduced pressure to remove EtOH. Then the aqueous phase was extracted with EtOAc (150 mL x 2). The combined organics were washed with brine (100 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give 5-chloro-2-(1-methylcyclopropoxy)aniline (20.9 g, 104.54 mmol, 95 % yield, 99 % purity) as a black, brown oil.

Step 3: 4-chloro-2-iodo-1-(1-methylcyclopropoxy)benzene:



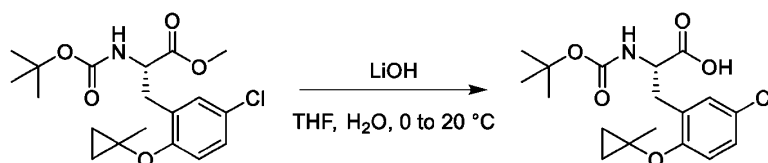
[0273] To a solution of 5-chloro-2-(1-methylcyclopropoxy)aniline (20.9 g, 105.74 mmol, 1 eq) in HCl (2.5 M, 209.00 mL, 4.94 eq) and ACN (100 mL) was added a solution of NaNO₂ (8.02 g, 116.31 mmol, 1.1 eq) in H₂O (100 mL) slowly at 0 °C. Then, a solution of KI (43.88 g, 264.34 mmol, 2.5 eq) in H₂O (100 mL) was added slowly. Then the reaction mixture was allowed to warm to 25 °C and stirred at 25 °C for 12 h. LCMS showed starting material was consumed completely and a new major spot was detected. The reaction mixture was adjusted pH = 7 by adding saturated NaHCO₃ aqueous solution slowly at 0 °C, extracted with EtOAc (60 mL x 2). The combined organics were washed with brine (80 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 220 g SepaFlash® Silica Flash Column, Eluent of 0~0% EtOAc/PE gradient @ 150 mL/min) to give 4-chloro-2-iodo-1-(1-methylcyclopropoxy)benzene (23 g, 73.84 mmol, 70 % yield, 99.1% purity) as a light-yellow oil.

Step 4: Methyl (S)-2-((tert-butoxycarbonylamino)-3-(5-chloro-2-(1-methylcyclopropoxy)phenyl)propanoate:



- [0274]** A mixture of 4-chloro-2-iodo-1-(1-methylcyclopropoxy)benzene (15 g, 48.62 mmol, 1 eq), sPhos (2.00 g, 4.86 mmol, 0.1 eq) and $\text{Pd}_2(\text{dba})_3$ (2.23 g, 2.43 mmol, 0.05 eq) in DMF (50 mL) was degassed and purged with N_2 3 times, then [(2R)-2-(tert-butoxycarbonylamino)-3-methoxy-3-oxo-propyl]-iodo-zinc (41.95 g, 106.34 mmol, 2.19 eq) was added to the mixture and then the mixture was stirred at 65 °C for 12 h under N_2 atmosphere. LCMS showed starting material was consumed completely and desired mass was detected. The reaction mixture was cooled to rt and quenched by water (300 mL), extracted with EtOAc (150 mL x 2). The combined organics were washed with water (200 mL x 2) and brine (200 mL), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Welch Xtimate C18 250*70mm#10um; mobile phase: [water (NH_4HCO_3)-ACN]; B%: 50%-80%, 20min) to give methyl (S)-2-((tert-butoxycarbonylamino)-3-(5-chloro-2-(1-methylcyclopropoxy)phenyl)propanoate (15 g, 36.75 mmol, 76 % yield, 94.0 % purity) as a light-yellow solid.

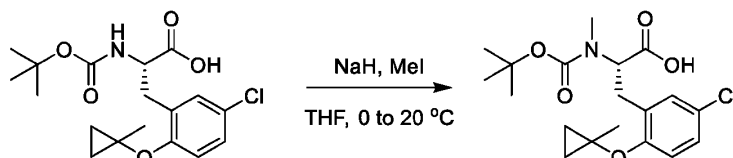
Step 5: (S)-2-((tert-butoxycarbonylamino)-3-(5-chloro-2-(1-methylcyclopropoxy)phenyl) propanoic acid:



- [0275]** To a solution of methyl(S)-2-((tert-butoxycarbonylamino)-3-(5-chloro-2-(1-methylcyclopropoxy)phenyl)propanoate (15 g, 39.08 mmol, 1 eq) in THF (200 mL) was added a solution of $\text{LiOH}\cdot\text{H}_2\text{O}$ (2.46 g, 58.61 mmol, 1.5 eq) in H_2O (100 mL) at 0~10 °C. Then the reaction mixture was stirred at 20 °C for 0.5 hr. LCMS showed starting material was consumed completely and desired mass was detected. The reaction mixture was concentrated under reduced pressure to remove THF and extracted with EtOAc (80 mL x 2). The aqueous phase was acidified by adding hydrochloric acid (1N) dropwise at 0 °C to pH = 2~3. The

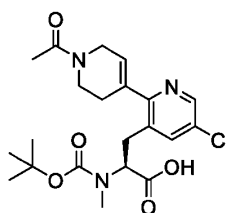
aqueous phase was extracted with EtOAc (100 mL x 2). The combined organics were washed with brine (150 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give (S)-2-((tert-butoxycarbonyl)amino)-3-(5-chloro-2-(1-methylcyclopropoxy)phenyl) propanoic acid (12.7 g, 33.65 mmol, 86 % yield, 98.1 % purity) as a light-yellow oil.

5 **Step 6: Int. 20:**

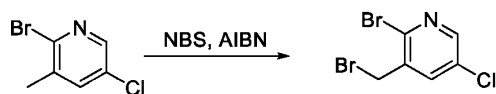


[0276] To a solution of (S)-2-((tert-butoxycarbonyl)amino)-3-(5-chloro-2-(1-methylcyclopropoxy)phenyl) propanoic acid (12.7 g, 34.34 mmol, 1 eq) in THF (400 mL) was added NaH (6.87 g, 171.70 mmol, 60% purity, 5 eq) at 0 °C under N₂ atmosphere. The mixture was stirred at 20 °C for 0.5 hr. Then MeI (48.74 g, 343.39 mmol, 21.38 mL, 10 eq) was added and the reaction mixture was stirred at 20 °C for 12 h. LCMS showed starting material was consumed completely and desired mass was detected. The reaction mixture was cooled to 0 °C and quenched by NH₄Cl (150 mL), acidified by adding hydrochloric acid (1 N) dropwise at 0 °C to pH = 2~3 and extracted with EtOAc (200 mL x 2). The combined organics were washed with brine (200 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give **Int. 20** (9.98 g, 26.00 mmol, 76 % yield, 100% purity) as a light-yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 7.28 - 7.04 (m, 3H), 4.83 - 4.39 (m, 1H), 3.15 - 2.97 (m, 1H), 2.89 - 2.71 (m, 1H), 2.61 (br d, *J* = 3.3 Hz, 3H), 1.49 (d, *J* = 11.1 Hz, 3H), 1.30 - 1.12 (m, 9H), 0.95 - 0.81 (m, 2H), 0.81 - 0.69 (m, 2H)

20 **Int. 22: Preparation of (S)-3-(1'-acetyl-5-chloro-1',2',3',6'-tetrahydro-[2,4'-bipyridin]-3-yl)-2-((tert-butoxycarbonyl)(methyl)amino)propanoic acid**

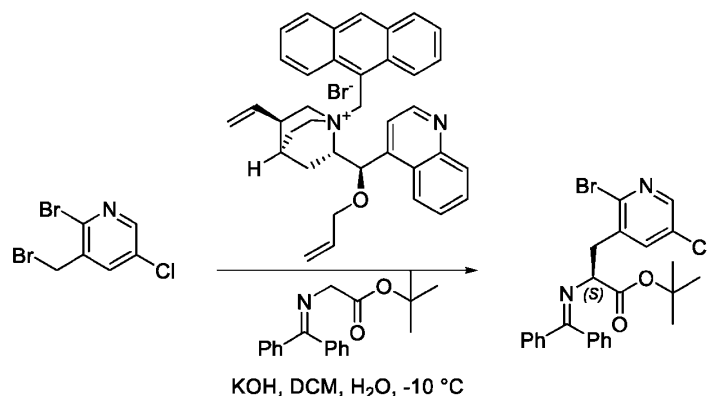


Step 1: 2-bromo-3-(bromomethyl)-5-chloropyridine:



- [0277]** To a stirred mixture of 2-bromo-5-chloro-3-methylpyridine (25 g, 121.08 mmol, 1 eq.) and NBS (23706.05 mg, 133.19 mmol, 1.1 eq) in ACN (200 mL) was added AIBN (1988.33 mg, 12.11 mmol, 0.1 eq.) at rt under nitrogen atmosphere. The resulting mixture was stirred overnight at 80 °C. The resulting mixture was concentrated in vacuo and diluted with water. The mixture was extracted with EtOAc (2 x 200 mL) and the combined organic layers were dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated under vacuum. This resulted in 2-bromo-3-(bromomethyl)-5-chloropyridine (30 g, 87 %) as a yellow oil. The crude product was used in the next step directly without further purification.
- LCMS (ESI+):** *m/z* 282.4.

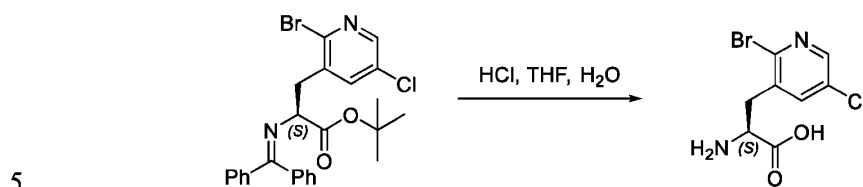
Step 2: Tert-butyl (2S)-3-(2-bromo-5-chloropyridin-3-yl)-2-[(diphenylmethylidene)amino]propanoate:



- [0278]** To a stirred mixture of 2-bromo-3-(bromomethyl)-5-chloropyridine (15 g, 52.57 mmol, 1 eq.), (2S,4S,5R)-1-[(anthracen-9-yl)methyl]-5-ethenyl-2-[(R)-(prop-2-en-1-yloxy)(quinolin-4-yl)methyl]-1-azabicyclo[2.2.2]octan-1-ium bromide (1591.69 mg, 2.63 mmol, 0.05 eq.) and isopropyl 2-[(diphenylmethylidene)amino]acetate (29578.95 mg, 105.13 mmol, 2 eq.) in DCM (100 mL) was added KOH (29.49 g, 525.65 mmol, 10 eq.) in H₂O (30 mL) in portions at -10 °C under air atmosphere. The resulting mixture was stirred for an additional 4 h at -10 °C. The resulting mixture was extracted with EtOAc (2 x 200 mL), and the combined organic layers were dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography,

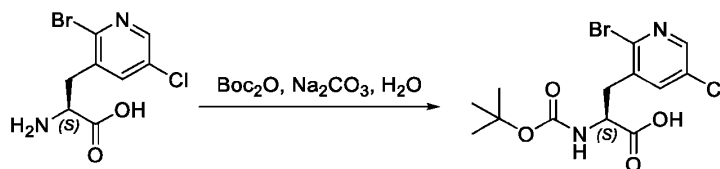
eluted with PE / EA (10:1) to afford tert-butyl (2S)-3-(2-bromo-5-chloropyridin-3-yl)-2-[(diphenylmethylidene)amino]propanoate (25 g, 95 %) as a yellow oil. LCMS (ESI+): m/z 501.1.

Step 3: (S)-2-amino-3-(2-bromo-5-chloropyridin-3-yl)propanoic acid:



[0279] A mixture of tert-butyl (2S)-3-(2-bromo-5-chloropyridin-3-yl)-2-[(diphenylmethylidene)amino]propanoate (5 g, 10.0 mmol, 1 eq.) and HCl (6M) (30 mL) in THF (10 mL) was stirred overnight at 55 °C. The resulting mixture was concentrated under vacuum. This resulted in (2S)-2-amino-3-(2-bromo-5-chloropyridin-3-yl)propanoic acid (2.6 g, 93 %) as a yellow oil. The crude product was used in the next step directly without further purification. LCMS (ESI+): m/z 278.9.

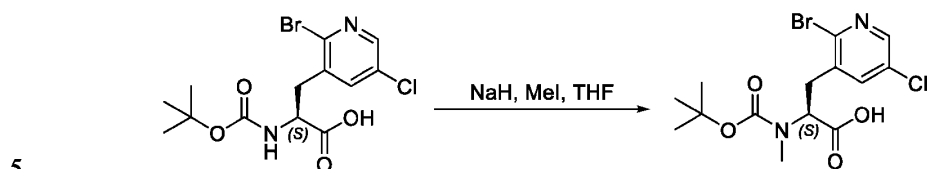
Step 4: (2S)-3-(2-bromo-5-chloropyridin-3-yl)-2-[(tert-butoxycarbonyl)amino]propanoic acid:



[0280] To a stirred mixture of (2S)-2-amino-3-(2-bromo-5-chloropyridin-3-yl)propanoic acid (9 g, 32.20 mmol, 1 eq.) and Na₂CO₃ (10.24 g, 96.59 mmol, 3 eq.) in H₂O (60 mL) was added Boc₂O (14.05 g, 64.40 mmol, 2 eq.) in portions at rt under air atmosphere. The resulting mixture was stirred overnight at rt. The mixture was acidified to pH=6 with diluted HCl (aq. 1N). The resulting mixture was extracted with EtOAc (2 x 100 mL), and the combined organic layers were dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated under vacuum. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (0.1% FA), 10% to 100% gradient in 30 min; detector, UV 210 nm. This resulted in (2S)-3-(2-bromo-5-chloropyridin-3-yl)-2-[(tert-

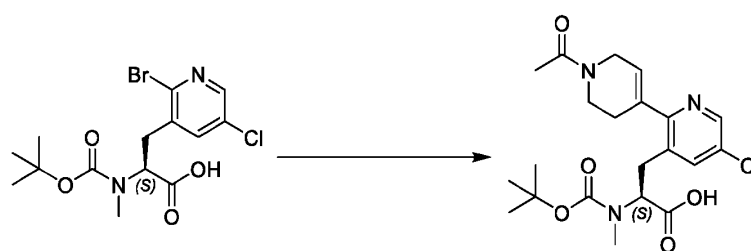
butoxycarbonyl)amino]propanoic acid (12 g, 98 %) as a white solid. LCMS (ESI+): m/z 380.90.

Step 5: (2S)-3-(2-bromo-5-chloropyridin-3-yl)-2-[(tert-butoxycarbonyl)(methyl)amino]propanoic acid:



[0281] NaH (6.32 g, 263.41 mmol, 10 eq.) was added into a stirred mixture of (2S)-3-(2-bromo-5-chloropyridin-3-yl)-2-[(tert-butoxycarbonyl)amino]propanoic acid (10 g, 26.34 mmol, 1 eq.) in THF (100 mL) portion wise at 0 °C under nitrogen and the resulting mixture was stirred for 1 h at 0 °C. MeI (56.08 g, 395.12 mmol, 15 eq.) was added dropwise at 0 °C under nitrogen atmosphere. The resulting mixture was stirred overnight at rt. The reaction was quenched with water at 0 °C. The mixture was acidified to pH= 6 with HCl (aq.). The resulting mixture was extracted with EtOAc (2 x 120 mL) and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (0.1% FA), 10% to 100% gradient in 30 min; detector, UV 220 nm. This resulted in (2S)-3-(2-bromo-5-chloropyridin-3-yl)-2-[(tert-butoxycarbonyl)(methyl)amino]propanoic acid (7.3 g, 70 %) as a yellow oil.

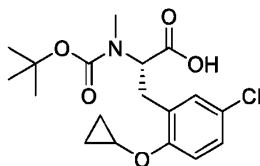
Step 6: Int. 22:



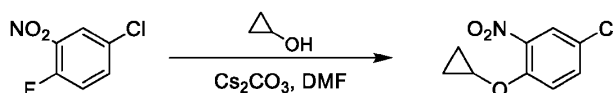
20 [0282] To a stirred mixture of (2S)-3-(2-bromo-5-chloropyridin-3-yl)-2-[(tert-butoxycarbonyl)(methyl)amino]propanoic acid (2.5 g, 6.35 mmol, 1 eq.) and 1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyridin-1-yl]ethanone (2392.26 mg, 9.53 mmol, 1.5 eq.) in dioxane (20 mL) was added Na₂CO₃ (2019.28 mg, 19.05 mmol, 3 eq.)

and Pd(dppf)Cl₂.DCM Adduct (517.34 mg, 0.635 mmol, 0.1 eq) in portions at rt under nitrogen atmosphere. The resulting mixture was stirred for an additional 3 h at 80 °C. The mixture was acidified to pH=6 with HCl (aq. 1N). The resulting mixture was extracted with EtOAc (2 x 60 mL), and the combined organic layers were dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated under vacuum. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (0.1% FA), 10% to 100% gradient in 30 min; detector, UV 254 nm. This resulted in **Int. 22** (1.94 g, 66 %) as a brown solid. LCMS (ESI+): *m/z* 438.2. ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.99 (s, 1H), 8.45 (dd, *J* = 15.5, 2.4 Hz, 1H), 7.81 (dd, *J* = 53.7, 2.4 Hz, 1H), 5.86 (d, *J* = 33.1 Hz, 1H), 4.85 – 4.50 (m, 1H), 4.09 (tt, *J* = 30.1, 13.7 Hz, 2H), 3.90 – 3.47 (m, 2H), 3.42 – 3.24 (m, 2H), 3.11 (dt, *J* = 26.2, 13.1 Hz, 1H), 2.58 – 2.37 (m, 4H), 2.41 – 2.15 (m, 1H), 2.05 (dd, *J* = 12.3, 2.5 Hz, 3H), 1.23 (dd, *J* = 31.0, 3.0 Hz, 9H).

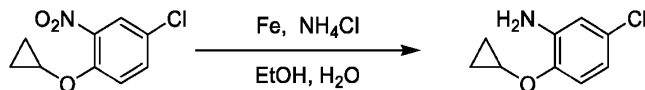
Int. 23: Preparation of (S)-2-((tert-butoxycarbonyl)(methyl)amino)-3-(5-chloro-2-cyclopropoxyphenyl)propanoic acid



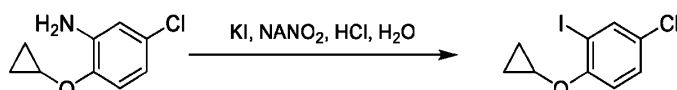
Step 1: 4-chloro-1-cyclopropoxy-2-nitrobenzene:



[0283] To a solution of 4-chloro-1-fluoro-2-nitrobenzene (40 g, 227.86 mmol, 1 eq) in DMF (400 mL) was added cyclopropanol (19.85 g, 341.79 mmol, 1.5 eq) and Cs₂CO₃ (111.36 g, 341.79 mmol, 1.5 eq), the mixture was stirred at 75 °C for 12 h under N₂. The reaction was monitored by LCMS, which showed 4-chloro-1-fluoro-2-nitrobenzene was consumed and one of peak with desired mass was detected. After cooling to rt, the filtrate was diluted with water (400 mL), extracted with EtOAc (200 mL x 3). The combined organics were washed with brine (400 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. 4-chloro-1-cyclopropoxy-2-nitrobenzene (35 g, crude) was obtained as a black, brown oil.

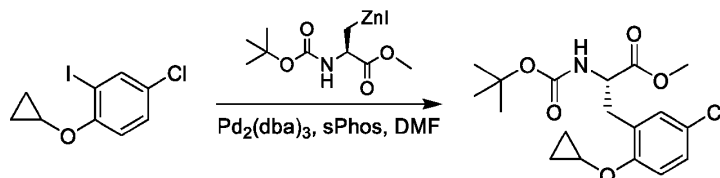
Step 2: 5-chloro-2-cyclopropoxyaniline:

[0284] To a solution of 4-chloro-1-cyclopropoxy-2-nitrobenzene (35 g, 163.84 mmol, 1 eq) in H₂O (280 mL) and ethanol (280 mL) was added Fe (45.75 g, 819.22 mmol, 5 eq) and
 5 NH₄Cl (4.38 g, 81.92 mmol, 0.5 eq), the mixture was stirred at 80 °C for 1 h. The reaction was monitored by LCMS, which showed 4-chloro-1-cyclopropoxy-2-nitrobenzene was consumed and one of peak with desired mass was detected. After cooling to rt, the reaction mixture was filtered, and the filter cake was rinsed with EtOAc (100 mL x 3). Then the combined filtrates were concentrated under reduced pressure to give a residue, 5-chloro-2-
 10 cyclopropoxyaniline (26 g, 115.93 mmol, 71 % yield, 82% purity) was obtained as a yellow oil.

Step 3: 4-chloro-1-cyclopropoxy-2-iodobenzene:

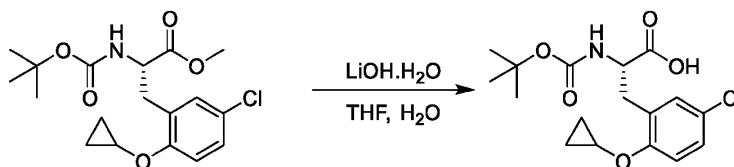
[0285] To a solution of 5-chloro-2-cyclopropoxyaniline (20 g, 108.91 mmol, 1 eq) in H₂O (216 mL) was added hydrogen chloride (12 M, 27.23 mL, 3 eq) dropwise at 0 °C adjusted pH to 2, the mixture was stirred at 0 °C for 0.5 hr, a solution of NaNO₂ (8.27 g, 119.80 mmol, 1.1 eq) in H₂O (36 mL) was added to the mixture dropwise at 0 °C and stirred for 1 hr. Then the reaction mixture was added to a solution of KI (54.24 g, 326.74 mmol, 3 eq) in H₂O (200 mL), the mixture was stirred at 20 °C for 12 hr. The reaction was monitored by LCMS, which
 20 showed 5-chloro-2-cyclopropoxyaniline was consumed and one of peak with desired mass was detected. The mixture was filtered, and filtrate was diluted with water (300 mL), extracted with EtOAc (150 mL x 3). The combined organics were washed with brine (150 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give residue. The residue was dissolved in DCM (100 mL), and 60 g of silica gel was added. The resulting
 25 mixture was evaporated under reduced pressure to give a dry flowing solid, and then it was loaded to Biotage® using a 120 g agela flash silica gel column, eluted with 0 % to 12 % EtOAc in PE with the flow rate of 75 mL/min. The product fraction was combined and evaporated. 4-chloro-1-cyclopropoxy-2-iodobenzene (20 g, 65.46 mmol, 60 % yield, 96.4% purity) was obtained as a black, brown oil.

Step 4: Methyl (S)-2-((tert-butoxycarbonyl)amino)-3-(5-chloro-2-cyclopropoxyphenyl)propanoate:



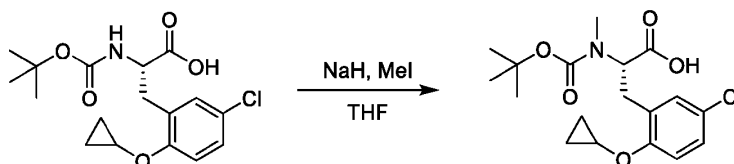
- [0286]** A mixture of Zn (34.77 g, 531.70 mmol, 3.5 eq) in DMF (210 mL) was degassed and purged with N₂ for 3 times, and the mixture was stirred at 120 °C for 10 min under N₂ atmosphere. Then I₂ (11.57 g, 45.57 mmol, 9.18 mL, 0.3 eq) in DMF (120 mL) was added dropwise at 20 °C, methyl (R)-2-((tert-butoxycarbonyl)amino)-3-iodopropanoate (50 g, 151.92 mmol, 1 eq) in DMF (40 mL) was added dropwise, I₂ (11.57 g, 45.57 mmol, 9.18 mL, 0.3 eq) in DMF (40 mL) was added dropwise, the reaction mixture was stirred at 20 °C for 1 hr. The reaction was monitored by TLC (PE: EtOAc = 5:1, R_f = 0.5) showed starting material was consumed completely and a new major spot was detected. The crude product was used into the next step without further purification. (R)-2-((tert-butoxycarbonyl)amino)-3-methoxy-3-oxopropylzinc(II) iodide (59.93 g, crude) was obtained as a grey liquid. The zincate was used without further purification.
- [0287]** To a solution of 4-chloro-1-cyclopropoxy-2-iodobenzene (20 g, 67.91 mmol, 1 eq), sPhos (4.18 g, 10.19 mmol, 0.15 eq) and Pd₂(dba)₃ (6.22 g, 6.79 mmol, 0.1 eq) in DMF (400 mL) was degassed and purged with N₂ for 3 times. Then (R)-2-((tert-butoxycarbonyl)amino)-3-methoxy-3-oxopropylzinc(II) iodide (53.58 g, 135.82 mmol, 2 eq) in DMF was added dropwise. Then the reaction mixture was stirred at 20 °C for 12 hr. The reaction was monitored by LCMS, which showed 4-chloro-1-cyclopropoxy-2-iodobenzene was consumed and one of peaks with desired mass was detected. The reaction was quenched by addition of saturated ammonium chloride aqueous solution (200 mL) and filtered, the filtrate was diluted with water (100 mL), extracted with EtOAc (100 mL x 3). The combined organics were washed with brine (50 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by preparative HPLC (column: Waters Xbridge BEH C18 250 x 70 mm x10 um; mobile phase: [water (NH₄HCO₃)-ACN]; B%:50%-80%,18 min) the HPLC fractions were combined, lyophilized. Methyl (S)-2-((tert-butoxycarbonyl)amino)-3-(5-chloro-2-cyclopropoxyphenyl)propanoate (8 g, 19.53 mmol, 29 % yield, 98% purity) was obtained as a yellow oil.

Step 5: (S)-2-((tert-butoxycarbonyl)amino)-3-(5-chloro-2-cyclopropoxyphenyl)propanoic acid:



[0288] To a solution of methyl (S)-2-((tert-butoxycarbonyl)amino)-3-(5-chloro-2-cyclopropoxyphenyl)propanoate (8 g, 21.63 mmol, 1 eq) in THF (112 mL) was added LiOH.H₂O (1.09 g, 25.96 mmol, 1.2 eq) in H₂O (56 mL), the mixture was stirred at 20 °C for 1 hr. The reaction was monitored by LCMS, which showed methyl (S)-2-((tert-butoxycarbonyl)amino)-3-(5-chloro-2-cyclopropoxyphenyl)propanoate was consumed and one of peak with desired mass was detected. The mixture was acidified pH = 5 by adding hydrochloric acid (0.1 M, 15 mL) dropwise at 0 °C. The residue was diluted with water (100 mL), extracted with EtOAc (40 mL x 3). The combined organics were washed with brine (50 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. (S)-2-((tert-butoxycarbonyl)amino)-3-(5-chloro-2-cyclopropoxyphenyl)propanoic acid (5 g, 13.77 mmol, 64 % yield, 98% purity) was obtained as a yellow solid.

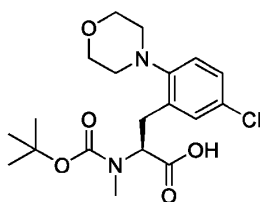
Step 6: Int. 23:



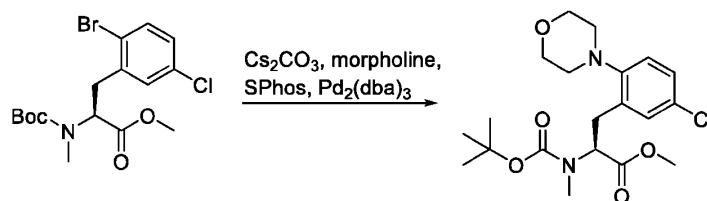
[0289] To a solution of (S)-2-((tert-butoxycarbonyl)amino)-3-(5-chloro-2-cyclopropoxyphenyl)propanoic acid (5 g, 14.05 mmol, 1 eq) in THF (50 mL) was added NaH (2.81 g, 70.26 mmol, 60% purity, 5 eq) at 0 °C, the mixture was stirred at 0 °C for 1 h under N₂, MeI (19.95 g, 140.52 mmol, 8.75 mL, 10 eq) was added to the reaction mixture, the mixture was stirred at 20 °C for 12 h. The reaction was monitored by LCMS, which showed (S)-2-((tert-butoxycarbonyl)amino)-3-(5-chloro-2-cyclopropoxyphenyl)propanoic acid was consumed and one of peak with desired mass was detected. The reaction was quenched by addition of saturated ammonium chloride aqueous solution (20 mL), the mixture was acidified pH = 5 by adding hydrochloric acid (0.1 M, 10 mL) dropwise at 0 °C. The residue

was extracted with EtOAc (20 mL x 3). The combined organics were washed with brine (20 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue **Int. 23** (3 g, 7.71 mmol, 54 % yield, 95% purity) was obtained as a yellow oil. ¹H NMR (400 MHz, DMSO-d₆) ¹H NMR (400 MHz, DMSO-d₆) δ = 7.31 - 7.08 (m, 3H), 4.85 - 4.52 (m, 1H), 3.91 - 3.80 (m, 1H), 3.12 - 2.99 (m, 1H), 2.94 - 2.80 (m, 1H), 2.65 - 2.55 (m, 3H), 1.24 (br d, J = 19.6 Hz, 9H), 0.87 - 0.58 (m, 4H)

Int. 24: Preparation of (2S)-2-[(tert-butoxycarbonyl)(methyl)amino]-3-[5-chloro-2-(morpholin-4-yl)phenyl]propanoic acid

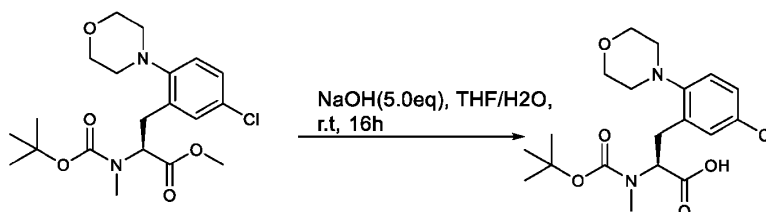


Step 1: (2S)-2-[(tert-butoxycarbonyl)(methyl)amino]-3-[5-chloro-2-(morpholin-4-yl)phenyl]propanoate



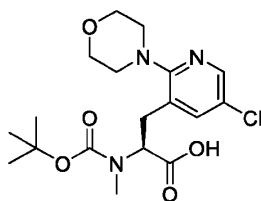
[0290] A solution of methyl (2S)-3-(2-bromo-5-chlorophenyl)-2-[(tert-butoxycarbonyl)(methyl)amino]propanoate (3 g, 7.376 mmol, 1 equiv.), Cs₂CO₃ (7232.46 mg, 22.128 mmol, 3 equiv.), morpholine (771.18 mg, 8.851 mmol, 1.2 equiv.), SPhos (605.66 mg, 1.475 mmol, 0.2 equiv.) and Pd₂(dba)₃ (675.48 mg, 0.738 mmol, 0.1 equiv.) in dioxane (50 mL) was stirred for 3 h at 80 °C under nitrogen atmosphere. The residual Cs₂CO₃ was removed by filtration. The residue was purified by silica gel column chromatography, eluted with PE / EA (5:1) to afford methyl (2S)-2-[(tert-butoxycarbonyl)(methyl)amino]-3-[5-chloro-2-(morpholin-4-yl)phenyl]propanoate (1.15 g, 38 %) as a brown oil. **LCMS** (ESI⁺): *m/z* 413 (M+H⁺).

Step 2: Int. 24:

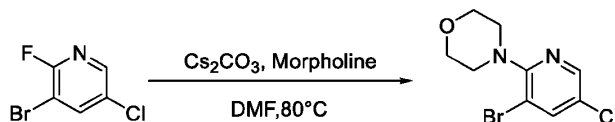


[0291] To a stirred solution of methyl (2S)-2-[(tert-butoxycarbonyl)(methyl)amino]-3-[5-chloro-2-(morpholin-4-yl)phenyl]propanoate (1.2 g, 2.906 mmol, 1 equiv.) in tetrahydrofuran (15 mL) was added caustic soda (0.58 g, 14.530 mmol, 5 equiv.) in water (5 mL) dropwise at 0 °C. The resulting mixture was stirred for 16 h at rt. The resulting mixture was concentrated under reduced pressure and then diluted with water (20 mL). The resulting mixture was acidified to pH=3 with diluted citric acid (1N) and then extracted with EtOAc (3x100 mL). The combined organic layers were washed with brine (1x100 mL) and dried over anhydrous Na₂SO₄. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (0.1% FA), 10% to 50% gradient in 10 min; detector, UV 220 nm. After filtration, the filtrate was concentrated under reduced pressure. This resulted in **Int. 24** (0.81 g, 70 %) as a Brown yellow solid. LCMS (ESI⁺): *m/z* 399 (M+H⁺).

Int. 25: Preparation of (S)-2-[(tert-butoxycarbonyl)(methyl)amino]-3-(5-chloro-2-morpholinopyridin-3-yl)propanoic acid



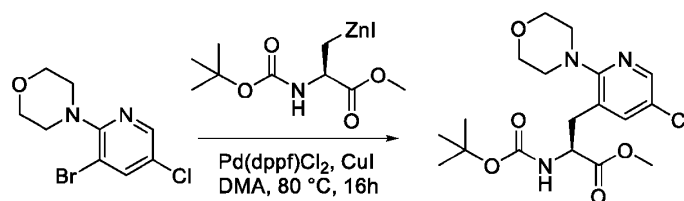
Step 1: 4-(3-bromo-5-chloropyridin-2-yl)morpholine:



[0292] A solution of 3-bromo-5-chloro-2-fluoropyridine (10 g, 47.52 mmol, 1 eq) in DMF (600 mL) was treated with Cs₂CO₃ (46.45 g, 142.57 mmol, 3 eq) at rt under nitrogen atmosphere followed by the addition of morpholine (6.21 g, 71.28 mmol, 1.5 eq.) in portions

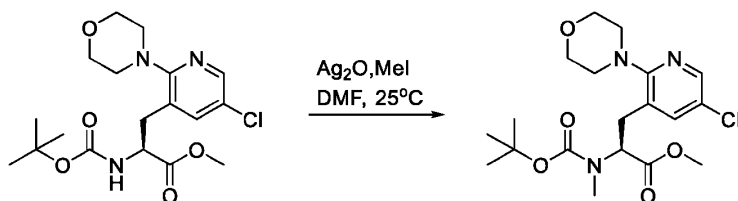
at rt. The resulting mixture was stirred for 16 h at rt under nitrogen atmosphere. Desired product could be detected by LCMS. The resulting mixture was diluted with ice water (1 L) and extracted with EtOAc (2 x 1L). The combined organic layers were washed with brine (500mL x 3) and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (0.1% FA), 10% to 100% gradient in 40 min; detector, UV 200.210 nm. This resulted in 4-(3-bromo-5-chloropyridin-2-yl)morpholine (3 g, 23 %) as a light-yellow solid. LCMS (ESI+): *m/z* 279.00.

Step 2: Methyl (2S)-2-[(tert-butoxycarbonyl)amino]-3-[5-chloro-2-(morpholin-4-yl)pyridin-3-yl]propanoate:



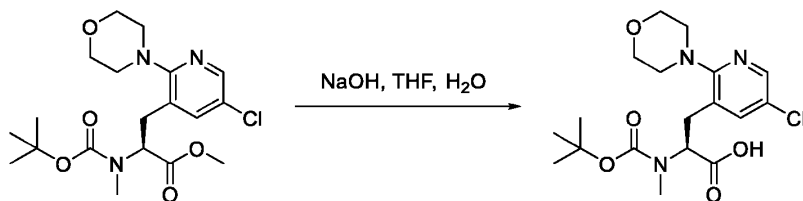
[0293] A solution of 4-(3-bromo-5-chloropyridin-2-yl)morpholine (3.3 g, 11.89 mmol, 1 eq.) in DMA (30 mL) was treated with CuI (0.45 g, 2.38 mmol, 0.2 eq.) and Pd(dppf)Cl₂.CH₂Cl₂ (0.87g, 1.19 mmol, 0.1 eq.) at rt under nitrogen atmosphere followed by the addition of methyl (2R)-2-[(tert-butoxycarbonyl)amino]-3-(iodozincio)propanoate (33 mL) at rt. The resulting mixture was stirred for 16 h at 80 °C under nitrogen atmosphere. Desired product could be detected by LCMS. The reaction was quenched with water (200 mL) and diluted with EA (200 mL). The precipitated solids were removed by filtration and washed with EtOAc (2 x 200 mL). The combined organic layers were dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (0.1% FA), 10% to 100% gradient in 40 min; detector, UV 200.210 nm. The residue was purified by Prep-TLC (PE / EA 2:1) to afford methyl (2S)-2-[(tert-butoxycarbonyl)amino]-3-[5-chloro-2-(morpholin-4-yl)pyridin-3-yl]propanoate (1 g, 21 %) as a light-yellow oil. LCMS (ESI+): *m/z* 400.15.

Step 3: Methyl (2S)-2-[(tert-butoxycarbonyl)(methyl)amino]-3-[5-chloro-2-(morpholin-4-yl)pyridin-3-yl]propanoate:



- [0294]** A solution of methyl (2S)-2-[(tert-butoxycarbonyl)amino]-3-[5-chloro-2-(morpholin-4-yl)pyridin-3-yl]propanoate (700 mg, 1.75 mmol, 1 eq.) in DMF (10 mL, 129.22 mmol) was treated with Ag_2O (2 g, 8.76 mmol, 5 eq.) at rt under nitrogen atmosphere followed by the addition of CH_3I (2.4 g, 17.51 mmol, 10 eq.) at rt. The resulting mixture was stirred for 16 h at rt under nitrogen atmosphere. Desired product could be detected by LCMS. The resulting mixture was extracted with EtOAc (2 x 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE / EA 2:1) to afford methyl (2S)-2-[(tert-butoxycarbonyl)(methyl)amino]-3-[5-chloro-2-(morpholin-4-yl)pyridin-3-yl]propanoate (500 mg, 69 %) as a light-yellow oil. **LCMS** (ESI+): m/z 414.15. **^1H NMR** (400 MHz, $\text{DMSO}-d_6$) : δ 1.15 – 1.34 (m, 8H), 2.61 (d, $J = 8.9$ Hz, 2H), 2.94 – 3.13 (m, 4H), 3.23 (dd, $J = 14.7, 4.5$ Hz, 1H), 3.66 – 3.75 (m, 5H), 7.69 (dd, $J = 34.4, 2.6$ Hz, 1H), 8.22 (dd, $J = 13.9, 2.6$ Hz, 1H).

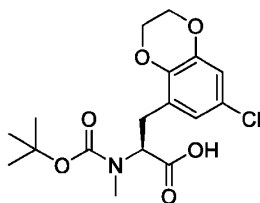
Step 4: Int. 25:



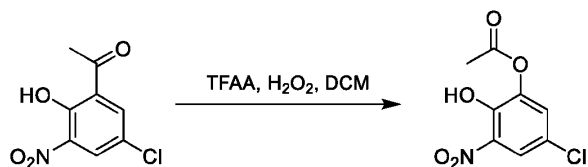
- [0295]** A solution of methyl (2S)-2-[(tert-butoxycarbonyl)(methyl)amino]-3-[5-chloro-2-(morpholin-4-yl)pyridin-3-yl]propanoate (660 mg, 1.60 mmol, 1 eq.) in THF (10 mL) was treated with NaOH (318.89 mg, 7.98 mmol, 5 eq.) in water (10 mL) at 0°C . The resulting mixture was stirred for 2 h at rt. Desired product could be detected by LCMS. The mixture neutralized to pH=2 with diluted HCl(1N). The resulting mixture was extracted with EtOAc (2 x 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica

gel; mobile phase, MeCN in Water (0.1% FA), 10% to 100% gradient in 40 min; detector, UV 200.210 nm. This resulted in **Int. 25** (423 mg, 66 %) as a white solid. LCMS (ESI⁺): m/z 400.15. ¹H NMR (400 MHz, DMSO-*d*₆): δ 1.26 (s, 9H), 2.61 (d, J = 8.7 Hz, 3H), 3.00 (tq, J = 13.5, 8.6, 7.2 Hz, 4H), 3.63 – 3.78 (m, 4H), 5.03 (ddd, J = 148.8, 11.4, 4.2 Hz, 1H), 7.67 (dd, J = 35.8, 2.6 Hz, 1H), 8.21 (dd, J = 14.5, 2.6 Hz, 1H), 12.91 (s, 1H).

Int. 26: Preparation of (S)-2-((tert-butoxycarbonyl)(methyl)amino)-3-(7-chloro-2,3-dihydrobenzo[b][1,4]dioxin-5-yl)propanoic acid



Step 1: 5-chloro-2-hydroxy-3-nitrophenyl acetate:



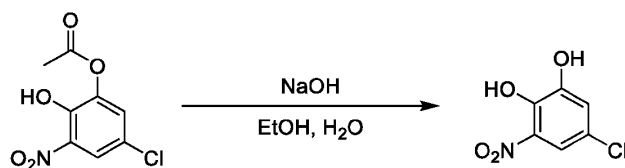
10

[0296] Add TFAA (409.17 g, 1.95 mol, 270.97 mL, 10 eq.) to a three-necked flask, add H₂O₂ (110.44 g, 974.07 mmol, 93.59 mL, 30% purity, 5 eq.) dropwise at -10 °C. After 10 min, add a solution of 1-(5-chloro-2-hydroxy-3-nitrophenyl)ethan-1-one (42 g, 194.81 mmol, 1 eq.) in DCM (250 mL) dropwise. The reaction mixture was stirred at 20 °C for 12 h. The reaction was monitored by LCMS, which showed starting material was consumed and one of peak with desired mass was detected. The reaction mixture was diluted with water (100 mL), extracted with DCM (300 mL x 3). The combined organics were washed with sodium sulfite aqueous solution (100 mL, 1M) and brine (100 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give 5-chloro-2-hydroxy-3-nitrophenyl acetate (30 g, 124.36 mmol, 64 % yield, 96% purity) as a yellow solid. LCMS (ESI⁺): m/z 230.0 (M+H⁺).

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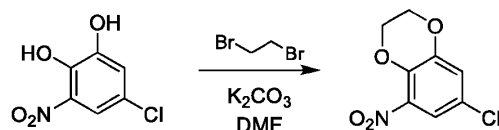
Step 2: 5-chloro-3-nitrobenzene-1,2-diol:



[0297] To a solution of 5-chloro-2-hydroxy-3-nitrophenyl acetate (30 g, 129.54 mmol, 1 eq) in EtOH (300 mL) was added NaOH (12.95 g, 129.54 mmol, 40 mL, 40% purity in H₂O, 1 eq), the mixture was stirred at 20 °C for 2 h. The reaction was monitored by LCMS, which showed starting material was consumed and one of peak with desired mass was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was acidified pH = 4 by adding hydrochloric acid (1 M, 50 mL) dropwise at 0 °C. The mixture was extracted with EtOAc (200 mL x 3). The combined organics were washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give 5-chloro-3-nitrobenzene-1,2-diol (22 g, 113.74 mmol, 87.80% yield, 98% purity) as a yellow solid.

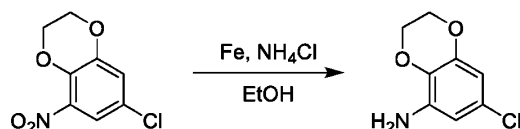
LCMS (ESI+): *m/z* 188.0 (M+H⁺).

Step 3: 7-chloro-5-nitro-2,3,-dihydrobenzo[b][1,4]dioxine:



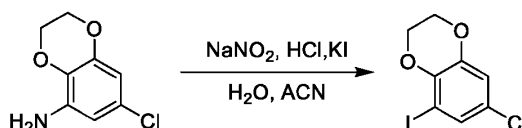
[0298] To a solution of 5-chloro-3-nitrobenzene-1,2-diol (10 g, 52.76 mmol, 1 eq) in DMF (100 mL) was added 1,2-dibromoethane (9.91 g, 52.76 mmol, 3.98 mL, 1 eq) and K₂CO₃ (14.58 g, 105.51 mmol, 2 eq) at 20 °C. Then the mixture was stirred at 80 °C for 12 h. The reaction was monitored by LCMS, which showed starting material was consumed and one of main peak was detected. The reaction mixture was cooled to rt and diluted by water (100 mL), extracted with EtOAc (60 mL x 3). The combined organics were washed with water (100 mL x 2). Then the combined organics were washed with brine (200 mL), dried over Na₂SO₄, filtered and the reaction mixture was concentrated under reduced pressure to give 7-chloro-5-nitro-2,3,-dihydrobenzo[b][1,4]dioxine (11 g, 51.0 mmol, 97 % yield) as a black, brown oil.

Step 4: 7-chloro-2,3-dihydrobenzo[b][1,4]dioxin-5-amine:



- [0299]** To a solution of 7-chloro-5-nitro-2,3-dihydrobenzo[b][1,4]dioxine (16 g, 74.21 mmol, 1 eq) in EtOH (80 mL) and H₂O (80 mL) were added Fe (20.72 g, 371.07 mmol, 5 eq) and NH₄Cl (19.85 g, 371.07 mmol, 5 eq) at 20 °C. The reaction was stirred at 80 °C for 2 h.
- 5 The reaction was monitored by LCMS, which showed starting material was consumed and one of main peak with desired mass was detected. The reaction mixture was filtered through a pad of celite and the celite was rinsed with EtOAc (100 mL). The filtrate was diluted with water (100 mL), extracted with EtOAc (120 mL x 3). The combined organics were washed with brine (200 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to
- 10 give a residue. The residue was dissolved in DCM (200 mL), and 50 g of silica gel was added. The resulting mixture was evaporated under reduced pressure to give a dry flowing solid, and then it was loaded to Biotage® using an 80 g Agela flash silica gel column, eluted with 30 % to 40 % EtOAc in PE with the flow rate of 75 mL/min. The product fraction was combined and evaporated to give 7-chloro-2,3-dihydrobenzo[b][1,4]dioxin-5-amine (8.6 g,
- 15 43.84 mmol, 30 % yield, 94 % purity) as a brown oil. LCMS (ESI⁺): *m/z* 186.3 (M+H⁺).

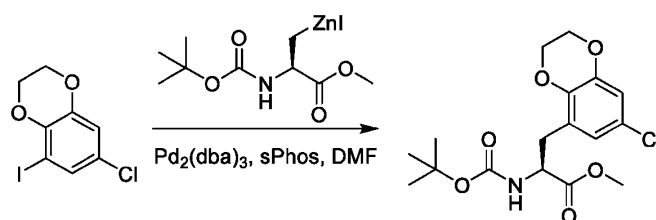
Step 5: 7-chloro-5-iodo-2,3-dihydrobenzo[b][1,4]dioxine:



- [0300]** To a solution of 7-chloro-2,3-dihydrobenzo[b][1,4]dioxin-5-amine (4.6 g, 24.78 mmol, 1 eq) in MeCN (24 mL) was added hydrogen chloride (2.5 M, 49.57 mL, 5 eq) at 0 °C.
- 20 The mixture was stirred at 0 °C for 0.5 h. Then a solution of NaNO₂ (1.88 g, 27.26 mmol, 1.1 eq) in H₂O (20 mL) was added to the reaction mixture, the mixture was stirred at 0 °C for 0.5 h. Then a solution of KI (12.34 g, 74.35 mmol, 3 eq) in H₂O (100 mL) was added to the reaction mixture, the reaction mixture was stirred at 0 °C for 2 h. The reaction was monitored by LCMS, which showed starting material was consumed and one of main peak with desired
- 25 mass was detected. The mixture was adjusted pH = 7-8 by adding saturated NaHCO₃ aqueous solution slowly at 0 °C. Then the mixture was extracted with EtOAc (50 mL x 3). The combined organics were washed with brine (100 mL), dried over Na₂SO₄, filtered, and

concentrated under reduced pressure to give a residue. The residue was dissolved in DCM (50 mL), and 20 g of silica gel was added. The resulting mixture was evaporated under reduced pressure to give a dry flowing solid, and then it was loaded to Biotage® using a 40 g Agela flash silica gel column, eluted with 15 % to 20 % EtOAc in PE with the flow rate of 75 mL/min. The product fraction was combined and evaporated to give 7-chloro-5-iodo-2,3-dihydrobenzo[b][1,4]dioxine (6.5 g, 21.71 mmol, 88 % yield, 99 % purity) as a black, purple solid. LCMS (ESI⁺): *m/z* 298.1(M+H⁺).

Step 6: methyl (S)-2-((tert-butoxycarbonyl)amino)-3-(7-chloro-2,3-dihydrobenzo[b][1,4]dioxin-5-yl)propanoate:



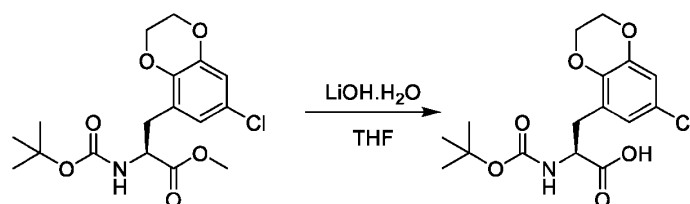
10

[0301] A mixture of Zn (13.91 g, 212.68 mmol, 3.5 eq) in DMF (100 mL) was degassed and purged with N₂ for 3 times, and the mixture was stirred at 120 °C for 10 min under N₂ atmosphere. Then I₂ (4.63 g, 18.23 mmol, 3.7 mL, 0.3 eq) in DMF (40 mL) was added dropwise at 20 °C, methyl (2R)-2-(tert-butoxycarbonylamino)-3-iodo-propanoate (20 g, 60.77 mmol, 1 eq) in DMF (30 mL) was added dropwise, I₂ (4.63 g, 18.23 mmol, 3.67 mL, 0.3 eq) in DMF (30 mL) was added dropwise, the reaction mixture was stirred at 20 °C for 1 hr. The zincate was used into the next step without further purification. [(2R)-2-(tert-butoxycarbonylamino)-3-methoxy-3-oxo-propyl]-iodo-zinc (23.95 g, 60.71 mmol, 99.9% yield) was obtained as a gray liquid. To a solution of 7-chloro-5-iodo-2,3-dihydrobenzo[b][1,4]dioxine (9 g, 30.36 mmol, 1 eq) in DMF (90 mL) was added [(2R)-2-(tert-butoxycarbonylamino)-3-methoxy-3-oxo-propyl]-iodo-zinc (23.95 g, 60.71 mmol, 2 eq), Pd₂(dba)₃ (1.39 g, 1.52 mmol, 0.05 eq) and SPhos (1.25 g, 3.04 mmol, 0.1 eq) at 20 °C. Then the mixture was stirred at 20 °C for 12 h. The reaction was monitored by LCMS, which showed starting material was consumed and one of main peak with desired mass was detected. The reaction mixture was diluted by water (90 mL), extracted with EtOAc (100 mL x 3). The combined organics were washed with water (150 mL x 2). Then the combined organics were washed with brine (200 mL), dried over Na₂SO₄, filtered and the reaction mixture was concentrated under reduced pressure to give a residue. The residue was

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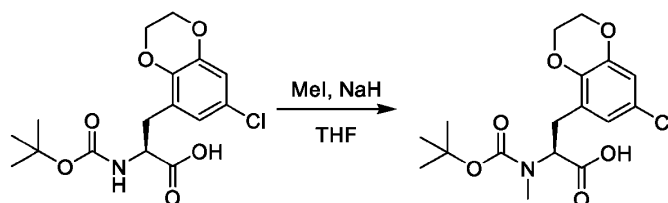
dissolved in DCM (30 mL), and 18 g of silica gel was added. The resulting mixture was evaporated under reduced pressure to give a dry flowing solid, and then it was loaded to Biotage® using a 40 g Agela flash silica gel column, eluted with 0 % to 20 % EtOAc in PE with the flow rate of 75 mL/min. The product fraction was combined and evaporated to give methyl (S)-2-((tert-butoxycarbonyl)amino)-3-(7-chloro-2,3-dihydrobenzo[b][1,4]dioxin-5-yl)propanoate (6 g, 15.55 mmol, 51% yield, 96 % purity) a yellow oil.

Step 7: (S)-2-((tert-butoxycarbonyl)amino)-3-(7-chloro-2,3-dihydrobenzo[b][1,4]dioxin-5-yl)propanoic acid:



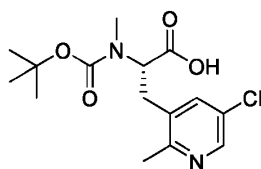
[0302] To a solution of methyl (S)-2-((tert-butoxycarbonyl)amino)-3-(7-chloro-2,3-dihydrobenzo[b][1,4]dioxin-5-yl)propanoate (5.5 g, 14.79 mmol, 1 eq) in THF (36 mL) was added a solution of LiOH.H₂O (744.89 mg, 17.75 mmol, 1.2 eq) in H₂O (18 mL) at 0 °C. The mixture was stirred at 20 °C for 2 h. The reaction was monitored by LCMS, which showed starting material was consumed and one of main peak with desired mass was detected. The mixture was acidified by adding hydrochloric acid (1 M) dropwise at 0 °C to pH = 3. The mixture was extracted with EtOAc (50 mL x 3). The combined organics were washed with brine (80 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The residue was dissolved in DCM (30 mL), and 10 g of silica gel was added. The resulting mixture was evaporated under reduced pressure to give a dry flowing solid, and then it was loaded to Biotage® using a 40 g Agela flash silica gel column, eluted with 0 % to 35 % EtOAc in PE with the flow rate of 75 mL/min. The product fraction was combined and evaporated to give (S)-2-((tert-butoxycarbonyl)amino)-3-(7-chloro-2,3-dihydrobenzo[b][1,4]dioxin-5-yl)propanoic acid (5.2 g, 14.53 mmol, 98 % yield, 100% purity) as a yellow oil. LCMS (ESI⁺): *m/z* 380.2 (M+Na⁺).

Step 8: Int. 26:

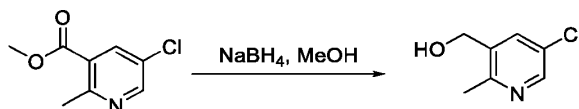


- [0303]** To a solution of (S)-2-((tert-butoxycarbonyl)amino)-3-(7-chloro-2,3-dihydrobenzo[b][1,4]dioxin-5-yl)propanoic acid (2.6 g, 7.27 mmol, 1 eq.) in THF (60 mL) was added NaH (1.45 g, 36.33 mmol, 60% purity, 5 eq) at 0 °C, the mixture was stirred at 0 °C for 1 h under N₂. MeI (10.31 g, 72.67 mmol, 4.52 mL, 10 eq.) was added to the reaction mixture, the mixture was stirred at 20 °C for 12 h under N₂. (Batch 2) The reaction was monitored by LCMS, which showed starting material was consumed and one of main peaks with desired mass was detected. The reaction was quenched by saturated ammonium chloride (30 mL) at 0 °C, extracted with EtOAc (60 mL x 2). The combined organics were washed with brine (50 mL), dried over Na₂SO₄, filtered and the reaction mixture was concentrated under reduced pressure to give **Int. 26** (3.9 g, 10.0 mmol, 69 % yield, 96 % purity) as a pale-yellow solid.). **LCMS** (ESI+): *m/z* 394.1 (M+Na⁺). **¹H NMR** (400 MHz, CHLOROFORM-d). δ ppm 1.40 (d, J=10.8 Hz, 9 H) 2.67 - 2.82 (m, 3 H) 3.00 - 3.13 (m, 1 H) 3.15 - 3.35 (m, 1 H) 4.18 - 4.34 (m, 4 H) 4.61 - 4.91 (m, 1 H) 6.68 (d, J=11.6 Hz, 1 H) 6.79 (d, J=2.0 Hz, 1 H).

15 Int. 27: Preparation of (S)-2-((tert-butoxycarbonyl)(methyl)amino)-3-(5-chloro-2-methylpyridin-3-yl)propanoic acid



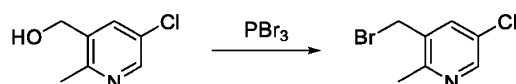
Step 1: (5-chloro-2-methylpyridin-3-yl)methanol:



- 20 [0304]** NaBH₄ (6.11 g, 161.63 mmol, 3 eq.) was added into a mixture of methyl 5-chloro-2-methylpyridine-3-carboxylate (10 g, 53.88 mmol, 1 eq.) in MeOH (200 mL) at 0 °C under air atmosphere. The mixture was stirred overnight at rt. Then the reaction was

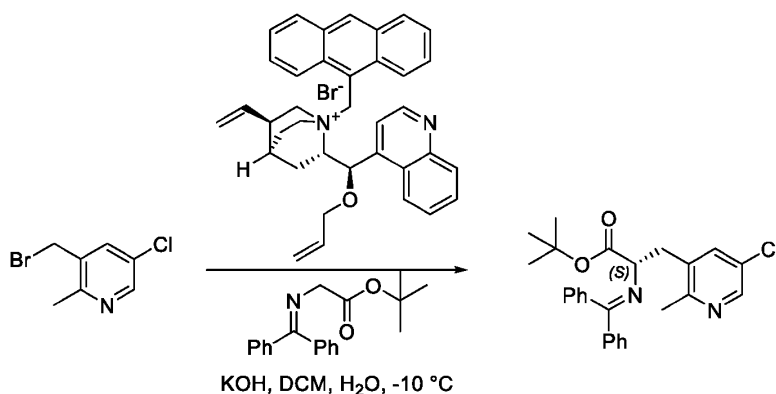
quenched with water (100 mL) and concentrated in vacuo. The residual water phase was extracted with EtOAc (2 x 200 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE / EA (10:1) to afford (5-chloro-2-methylpyridin-3-yl)methanol (6.1 g, 72 %) as a yellow oil. **LCMS** (ESI⁺): *m/z* 158.0.

Step 2: 3-(bromomethyl)-5-chloro-2-methylpyridine:



[0305] PBr₃ (31431.18 mg, 116.12 mmol, 3 eq.) was added into a mixture of (5-chloro-2-methylpyridin-3-yl)methanol (6.1 g, 38.71 mmol, 1 eq.) in DCM (50 mL) dropwise at 0 °C under nitrogen atmosphere. The mixture was stirred for 3 h at 0 °C. The resulting mixture was quenched with water (50 mL) at 0 °C and extracted with EtOAc (2 x 100 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated under vacuum. This resulted in 3-(bromomethyl)-5-chloro-2-methylpyridine (7 g, 82 %) as a yellow oil. The crude product was used in the next step directly without further purification. **LCMS** (ESI⁺): *m/z* 222.1.

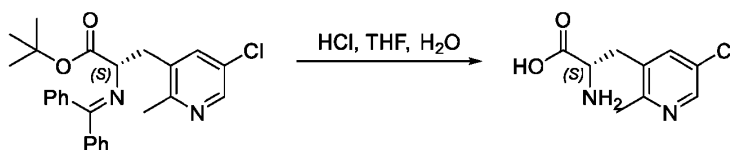
Step 3: Tert-butyl (2S)-3-(5-chloro-2-methylpyridin-3-yl)-2-[(diphenylmethylidene)amino]propanoate:



[0306] To a stirred mixture of 3-(bromomethyl)-5-chloro-2-methylpyridine (6.1 g, 27.67 mmol, 1 eq.) and tert-butyl 2-[(diphenylmethylidene)amino]acetate (12257.90 mg, 41.50 mmol, 1.5 eq.) in DCM (60 mL) was added KOH (15521.82 mg, 276.66 mmol, 10 eq.) in H₂O (15 mL) in portions at -10 °C under air atmosphere. The resulting mixture was

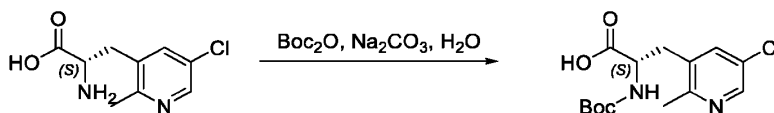
stirred overnight at -10 °C. The resulting mixture was extracted with DCM (2 x 100 mL) and the combined organic layers were dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE / EA (10:1) to afford tert-butyl (2S)-3-(5-chloro-2-methylpyridin-3-yl)-2-[(diphenylmethylidene)amino]propanoate (6.4 g, 53 %) as a yellow oil. LCMS (ESI+): *m/z* 435.0.

Step 4: (S)-2-amino-3-(5-chloro-2-methylpyridin-3-yl)propanoic acid:



[0307] A mixture of tert-butyl (2S)-3-(5-chloro-2-methylpyridin-3-yl)-2-[(diphenylmethylidene)amino] propanoate (300 mg, 0.69 mmol, 1 eq.) and HCl (6M) (100.00 mL, 3291.28 mmol, 119.30 eq.) in THF (10 mL) was stirred overnight at 55 °C under air atmosphere. The resulting mixture was concentrated under vacuum. This resulted in (2S)-2-amino-3-(5-chloro-2-methylpyridin-3-yl) propanoic acid (5 g, 84.43%) as a yellow oil. The crude product was used in the next step directly without further purification. LCMS (ESI+): *m/z* 215.0.

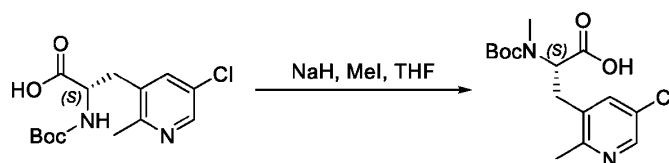
Step 5: (2S)-2-[(tert-butoxycarbonyl)amino]-3-(5-chloro-2-methylpyridin-3-yl)propanoic acid:



[0308] To a stirred mixture of (2S)-2-amino-3-(5-chloro-2-methylpyridin-3-yl)propanoic acid (4 g, 18.64 mmol, 1 eq.) and Boc₂O (12.20 g, 55.91 mmol, 3.00 eq.) in H₂O (100 mL) was added Na₂CO₃ (5.93 g, 55.91 mmol, 3 eq.) in portions at rt under air atmosphere. The resulting mixture was stirred overnight at rt. The mixture was acidified to pH=6 with diluted HCl (aq. 1N). The resulting mixture was stirred overnight at 0 °C. The resulting mixture was extracted with EtOAc (2 x 100 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (0.1% TFA), 10% to 100% gradient in 35 min; detector,

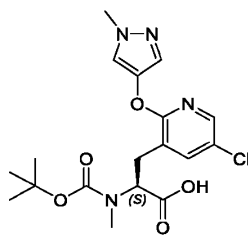
UV 220 nm. This resulted in (2S)-2-[(tert-butoxycarbonyl)amino]-3-(5-chloro-2-methylpyridin-3-yl)propanoic acid (5.6 g, 95 %) as a white solid. LCMS (ESI+): m/z 315.10. ¹H NMR (400 MHz, DMSO-*d*₆): δ 12.82 (s, 1H), 8.33 (d, J = 2.4 Hz, 1H), 7.65 (d, J = 2.5 Hz, 1H), 7.21 (d, J = 8.8 Hz, 1H), 4.28 – 4.10 (m, 1H), 3.11 (dd, J = 14.3, 4.4 Hz, 1H), 2.81 (dd, J = 14.4, 11.0 Hz, 1H), 2.47 (s, 3H), 1.30 (s, 9H).

Step 6: Int. 27:

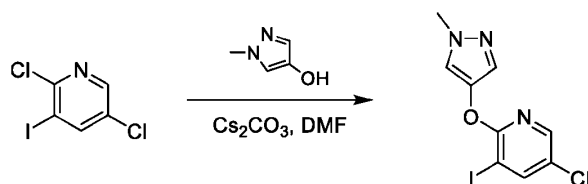


[0309] NaH (1.19 g, 49.56 mmol, 6 eq.) was added into a stirred mixture of (2S)-2-[(tert-butoxycarbonyl)amino]-3-(5-chloro-2-methylpyridin-3-yl)propanoic acid (2.6 g, 8.26 mmol, 1 eq.) in THF (25 mL) portion wise at 0 °C under nitrogen. Then the mixture was stirred for 1 h at 0 °C. MeI (11.72 g, 82.60 mmol, 10 eq.) was added into the above solution at 0 °C under nitrogen atmosphere. The resulting mixture was stirred overnight at rt. The reaction was quenched by the addition of sat. NH₄Cl (aq.) (20 mL) at 0 °C. The mixture was acidified to pH=6 with diluted HCl (aq. 1N). The resulting mixture was extracted with EtOAc (2 x 50mL), and the combined organic layers were dried over anhydrous Na₂SO₄ and filtered. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (0.1% FA), 10% to 100% gradient in 35 min; detector, UV 210 nm. This resulted in **Int. 27** (3.71 g, 133 % mass recovery) as a yellow solid. LCMS (ESI+): m/z 329.10. ¹H NMR (400 MHz, DMSO-*d*₆): δ 12.98 (s, 1H), 8.34 (dd, J = 16.6, 2.4 Hz, 1H), 7.59 (dd, J = 21.9, 2.4 Hz, 1H), 4.72 (ddd, J = 53.9, 11.2, 4.4 Hz, 1H), 3.27 – 2.92 (m, 2H), 2.65 (d, J = 2.0 Hz, 3H), 2.50 (s, 3H), 1.25 (d, J = 34.2 Hz, 9H).

Int. 28: Preparation of (S)-2-[(tert-butoxycarbonyl)(methyl)amino]-3-(5-chloro-2-[(1-methyl-1H-pyrazol-4-yl)oxy]pyridine-3-yl)propanoic acid

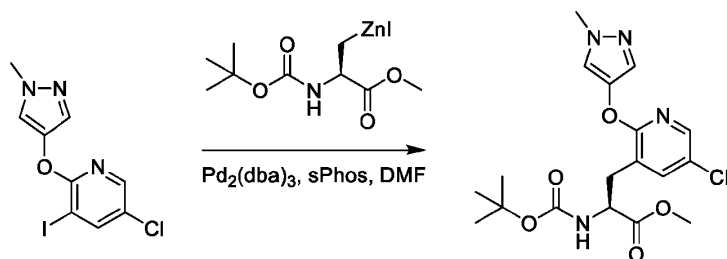


Step 1: 5-chloro-3-iodo-2-((1-methyl-1H-pyrazol-4-yl)oxy)pyridine:



[0310] To a solution of 2,5-dichloro-3-iodopyridine (10 g, 36.51 mmol, 1 eq) in DMF (140 mL) was added Cs₂CO₃ (23.79 g, 73.02 mmol, 2 eq) and 1-methylpyrazol-4-ol (4.30 g, 43.81 mmol, 1.2 eq). The mixture was stirred at 80 °C for 1 hr. LCMS showed 2,5-dichloro-3-iodopyridine was consumed completely and desired mass was detected. After cooling to rt, the reaction mixture was diluted with water (200 mL), extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The resulting crude product was purified by flash chromatography on silica gel (0 – 22 % EtOAc in PE). 5-chloro-3-iodo-2-((1-methyl-1H-pyrazol-4-yl)oxy)pyridine (10.9 g, 29.59 mmol, 81 % yield, 91 % purity) was obtained as a yellow solid.

Step 2: methyl (S)-2-((tert-butoxycarbonyl)amino)-3-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)oxy)pyridine-3-yl)propanoate

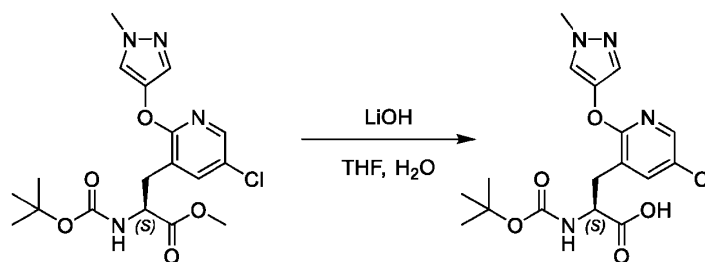


[0311] A mixture of Zn (18.08 g, 276.49 mmol, 3.5 eq) in DMF (150 mL) was degassed and purged with N₂ for 3 times, and the mixture was stirred at 120 °C for 10 min under N₂

atmosphere. Then I₂ (6.01 g, 23.70 mmol, 4.77 mL, 0.3 eq) in DMF (20 mL) was added dropwise at 20 °C, methyl (R)-2-((tert-butoxycarbonyl)amino)-3-iodopropanoate (26 g, 79.00 mmol, 1 eq) in DMF (70 mL) was added dropwise, I₂ (6.01 g, 23.70 mmol, 4.77 mL, 0.3 eq) in DMF (20 mL) was added dropwise, the reaction mixture was stirred at 20 °C for 1 hr. The zincate was used directly.

[0312] To a solution of 5-chloro-3-iodo-2-((1-methyl-1H-pyrazol-4-yl)oxy)pyridine (9.9 g, 29.51 mmol, 1 eq) in DMF (260 mL) was added Pd₂(dba)₃ (1.35 g, 1.48 mmol, 0.05 eq) and sPhos (1.21 g, 2.95 mmol, 0.1 eq) under N₂ atmosphere, and then was added dropwise, (R)-2-((tert-butoxycarbonyl)amino)-3-methoxy-3-oxopropylzinc(II) iodide (24.33 g in DMF, 61.67 mmol, 2.09 eq), under N₂ atmosphere and the reaction was stirred at 65 °C for 12 hr under N₂. LCMS showed 5-chloro-3-iodo-2-((1-methyl-1H-pyrazol-4-yl)oxy)pyridine was consumed completely and desired mass was detected. The mixture was quenched by NH₄Cl (200 mL) and extracted with EtOAc (200 mL x 3). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The resulting crude product was purified by flash chromatography on silica gel (0 – 21 % EtOAc in PE) to give methyl (S)-2-((tert-butoxycarbonyl)amino)-3-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)oxy)pyridine-3-yl)propanoate (5.6 g, 11.97 mmol, 41 % yield, 87.8% purity) as a pale-yellow gum.

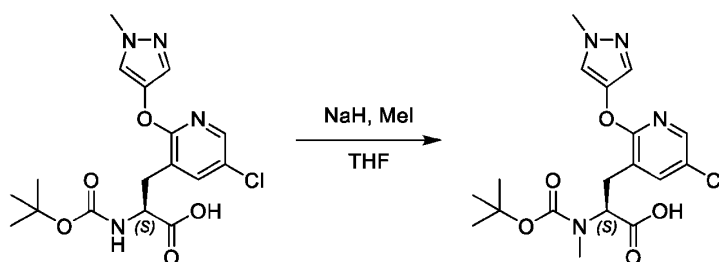
Step 3: (S)-2-((tert-butoxycarbonyl)amino)-3-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)oxy)pyridine-3-yl)propanoic acid:



[0313] To a solution of methyl (S)-2-((tert-butoxycarbonyl)amino)-3-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)oxy)pyridine-3-yl)propanoate (4.6 g, 11.20 mmol, 1 eq) in THF (40 mL) was added LiOH.H₂O (704.75, 16.79 mol, 1499.99 eq) in H₂O (20 mL) at 0 °C and the reaction was stirred at 25 °C for 0.5 hr. LCMS showed methyl (S)-2-((tert-butoxycarbonyl)amino)-3-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)oxy)pyridine-3-yl)propanoate was consumed completely and desired mass was detected. The reaction

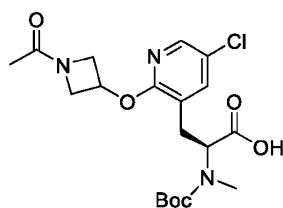
mixture was washed with MTBE (10 mL x 2), then the aqueous phase was adjusted pH to 3-4 with 1M HCl, extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue, (S)-2-((tert-butoxycarbonyl)amino)-3-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)oxy)pyridine-3-yl)propanoic acid (4 g, 9.37 mmol, 84 % yield, 93% purity) was obtained as a pale yellow gum without purification.

Step 4: Int. 28:



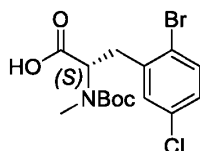
[0314] To a solution of (S)-2-((tert-butoxycarbonyl)amino)-3-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)oxy)pyridine-3-yl)propanoic acid (3 g, 7.56 mmol, 1 eq) in THF (90 mL) was added NaH (1.51 g, 37.80 mmol, 60% purity, 5 eq) at 0 °C under N₂ atmosphere, the mixture was stirred at 0 °C for 30 min then was added MeI (10.73 g, 75.60 mmol, 4.71 mL, 10 eq). The mixture was warmed to 25 °C and stirred at 25 °C for 12 hr. LCMS showed (S)-2-((tert-butoxycarbonyl)amino)-3-(5-chloro-2-((1-methyl-1H-pyrazol-4-yl)oxy)pyridine-3-yl)propanoic acid was consumed completely and desired mass was detected. The reaction mixture was quenched with NH₄Cl (100 mL), adjusted pH to 3-4 with 1M HCl, extracted with EtOAc (30 mL x 4). The combined organics were washed with brine (50 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The residue was diluted with MeOH (50 mL) and washed with PE (20 mL x 4). The residue was concentrated under reduced pressure to give pale yellow solid. **Int. 28** (2.6 g, 6.10 mmol, 81 % yield, 92.8 % purity) was obtained as a pale-yellow solid without purification.

Int. 29: (S)-3-(2-((1-acetylazetidin-3-yl)oxy)-5-chloropyridin-3-yl)-2-((tert-butoxycarbonyl)(methyl)amino)propanoic acid:

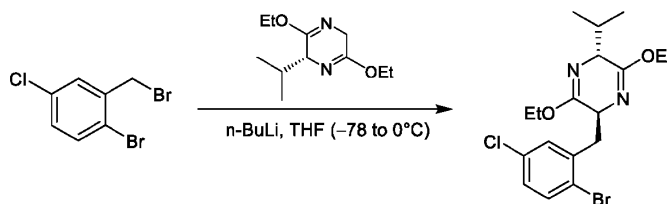


[0315] This material was synthesized by following the procedure for **Int. 13** with 1-(3-hydroxyazetidin-1-yl)ethan-1-one as the starting alcohol. LCMS (ESI⁺): *m/z* 428.1 (M+H⁺)

Int. 30: Preparation of (S)-3-(2-bromo-5-chlorophenyl)-2-((tert-butoxycarbonyl)(methyl)amino)propanoic acid



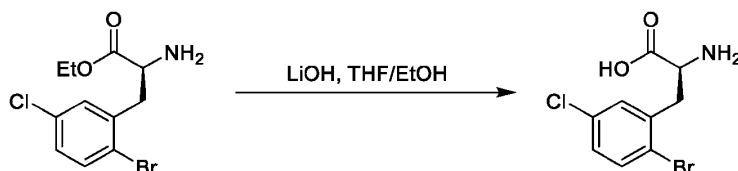
Step 1: (2S,5R)-2-(2-bromo-5-chlorobenzyl)-3,6-diethoxy-5-isopropyl-2,5-dihydropyrazine:



- [0316] To a solution of (R)-3,6-diethoxy-2-isopropyl-2,5-dihydropyrazine (151 g, 711 mmol, 1.00 eq) in THF (1500 mL) was added n-BuLi (2.5 M, 285 mL, 1.00 eq) at -70 °C under N₂, then to the above solution was added 1-bromo-2-(bromomethyl)-4-chlorobenzene (222.5 g, 782 mmol, 1.10 eq) in THF (220 mL) at -70 °C. The mixture was stirred at 25 °C for 12 hours. TLC indicated 1-bromo-2-(bromomethyl)-4-chlorobenzene was remained, and some new spots was detected. The reaction was poured into sat. NH₄Cl (aq.) 6000 mL, the reaction mixture was partitioned between water phase 6000 mL and THF 6000 mL. The organic phase was separated and dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, PE/EtOAc=100/0 to 1/1) to give desired (2S,5R)-2-(2-bromo-5-chlorobenzyl)-3,6-diethoxy-5-isopropyl-2,5-dihydropyrazine (620 g, 1.48 mol, 104 % yield, 99.3% purity) as a yellow gum. LCMS (ESI⁺): *m/z* 415/417 (M+H⁺)

Step 2: Ethyl (S)-2-amino-3-(2-bromo-5-chlorophenyl)propanoate:

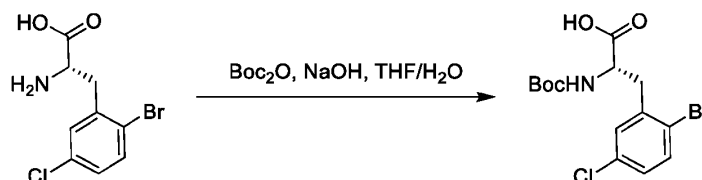
[0317] To a solution of (2S,5R)-2-(2-bromo-5-chlorobenzyl)-3,6-diethoxy-5-isopropyl-2,5-dihydropyrazine (100 g, 240 mmol, 1.00 eq) in ACN (1500 mL) was added HCl (0.20 M, 1.40 L, 1.16 eq) at 0 °C, then was stirred at 25 °C for 48 hours. TLC indicated (2S,5R)-2-(2-bromo-5-chlorobenzyl)-3,6-diethoxy-5-isopropyl-2,5-dihydropyrazine was consumed completely. The reaction mixture was concentrated under reduced pressure to remove ACN and extracted with DCM 4000 mL (2000 mL x 2), the organic layers was concentrated under reduced pressure to give a residue. Then the water phase was basified with sat.aq. NaHCO₃ to pH=7 and extracted with DCM 4.00 L (2.00 L x 2). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give desired ethyl (S)-2-amino-3-(2-bromo-5-chlorophenyl)propanoate (143 g, 466 mmol, 49 % yield) as a white solid and to give (2S,5R)-2-(2-bromo-5-chlorobenzyl)-3,6-diethoxy-5-isopropyl-2,5-dihydropyrazine (200 g, crude) was obtained as a yellow gum.

Step 3: (S)-2-amino-3-(2-bromo-5-chlorophenyl)propanoic acid:

[0318] To a solution of ethyl (S)-2-amino-3-(2-bromo-5-chlorophenyl)propanoate (143 g, 466 mmol, 1.00 eq) in THF (715 mL) and EtOH (715 mL) was added LiOH·H₂O (58.7 g, 1.40 mol, 3.00 eq) at 0 °C, then the reaction was stirred at 25 °C for 12 hours. TLC indicated ethyl (S)-2-amino-3-(2-bromo-5-chlorophenyl)propanoate was consumed completely. The reaction mixture was concentrated under reduced pressure at 30 °C to remove half of solvent. It was added into a saturated solution of citric acid (1.50 L) at 5-10 °C, to keep all the progress worked under acid condition. Some solid precipitated, then the suspension was filtered, the filter cake was washed with MTBE (1.00 L). The filter cake was collected and dried in vacuum to give desired (S)-2-amino-3-(2-bromo-5-chlorophenyl)propanoic acid (130

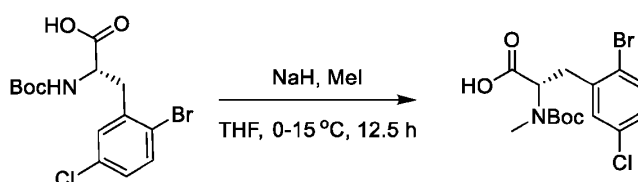
g, crude) as yellow solid which was confirmed by LCMS and SFC, then was used to the next step without further purification.

Step 4: (S)-3-(2-bromo-5-chlorophenyl)-2-((tert-butoxycarbonyl)amino)propanoic acid:



- 5 **[0319]** To a mixture of (2S)-2-amino-3-(2-bromo-5-chloro-phenyl)propanoic acid (70.00 g, 251.32 mmol, 1 eq) in THF (750 mL) and NaOH (1 N, 750 mL) was added Boc₂O (109.70 g, 502.64 mmol, 115.47 mL, 2 eq) at 0 °C, the mixture was stirred at 20 °C for 12 h. The LCMS showed that the reactant 1 was consumed completely, and the desired product was detected. The mixture was poured into sat. Citric acid (4 L) and extracted with EtOAc (1 L x 3). The organic layer was washed with water (2 L) and brine (2 L), dried over Na₂SO₄, filtered, and concentrated. The mixture was suspended in PE (1 L) and stirred at 20 °C for 0.5 h. Then the mixture was filtered, and the white solid was collected and dried to dryness to give compound 2 (2S)-3-(2-bromo-5-chloro-phenyl)-2-(tert-butoxycarbonylamino)propanoic acid (124 g, 320.9 mmol, 64 % yield, 98% purity) as a white solid. ¹H NMR: ET53616-98-P1Z (400
- 10
- 15 MHz, MeOD) δ 7.54 (d, *J* = 8.4 Hz, 1H), 7.33 (d, *J* = 2.4 Hz, 1H), 7.17-7.15 (m, 1H), 4.49 (dd, *J* = 4.4, 10.4 Hz, 1H), 3.39 (br dd, *J* = 4.4, 9.6 Hz, 1H), 2.94 - 2.88 (m, 1H), 1.36 - 1.28 (m, 9H). LCMS (ESI+): *m/z* 277.9 / 279.9 (M+H⁺)

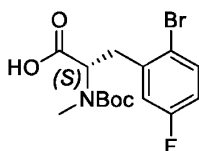
Step 5: Int. 30:



- 20 **[0320]** To a mixture of (2S)-3-(2-bromo-5-chloro-phenyl)-2-(tert-butoxycarbonylamino)propanoic acid (3.00 g x 10, 7.92 mmol, 1 eq) in THF (90 mL x 10) was added NaH (1.58 g x 10, 39.61 mmol, 60% purity, 5 eq) at 0 °C, the mixture was stirred at 0 °C for 0.5 h. Then MeI (11.25 g x 10, 79.23 mmol, 4.93 mL, 10 eq) was added at 0 °C, the mixture was stirred at 15 °C for 12 h. The LCMS showed that the (2S)-3-(2-bromo-5-

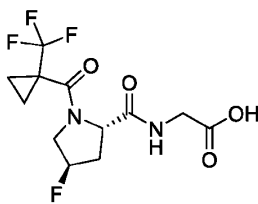
- chloro-phenyl)-2-(tert-butoxycarbonylamino)propanoic acid was consumed completely, and the desired product was detected. The mixture was quenched by sat. Citric acid (1.5 L), extracted with EtOAc (1.5 Lx2). The organic layer was washed with brine (1.5 L), dried over Na₂SO₄, filtered, and concentrated. The residue was purified by column chromatography (SiO₂, PE/EtOAc/THF=20/1/0 to 6/1/1) to give crude product. The mixture was combined with ET53616-100,104. The residue was dissolved in DCM (1 L) and concentrated under reduced pressure to give the desired product **Int. 30** (114.0 g, 285.70 mmol, 98 % purity) as a yellow solid. ¹H NMR: ET53616-105-P1Z2 (400 MHz, CHLOROFORM-d) δ 11.44 (brs, 1H), 7.50 - 7.47 (m, 1H), 7.20 - 7.19 (m, 1H), 7.13 - 7.11 (m, 1H), 4.83 - 4.71 (m, 1H), 3.48- 3.43 (m, 1H), 3.31 - 3.06 (m, 1H), 2.81 - 2.70 (m, 3H), 1.44 - 1.37 (m, 9H). LCMS (ESI⁺): *m/z* 291.9/293.9 (M+H⁺).

Int. 31: (S)-3-(2-bromo-5-fluorophenyl)-2-((tert-butoxycarbonyl)(methyl)amino)propanoic acid:



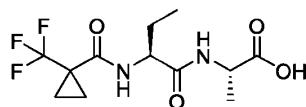
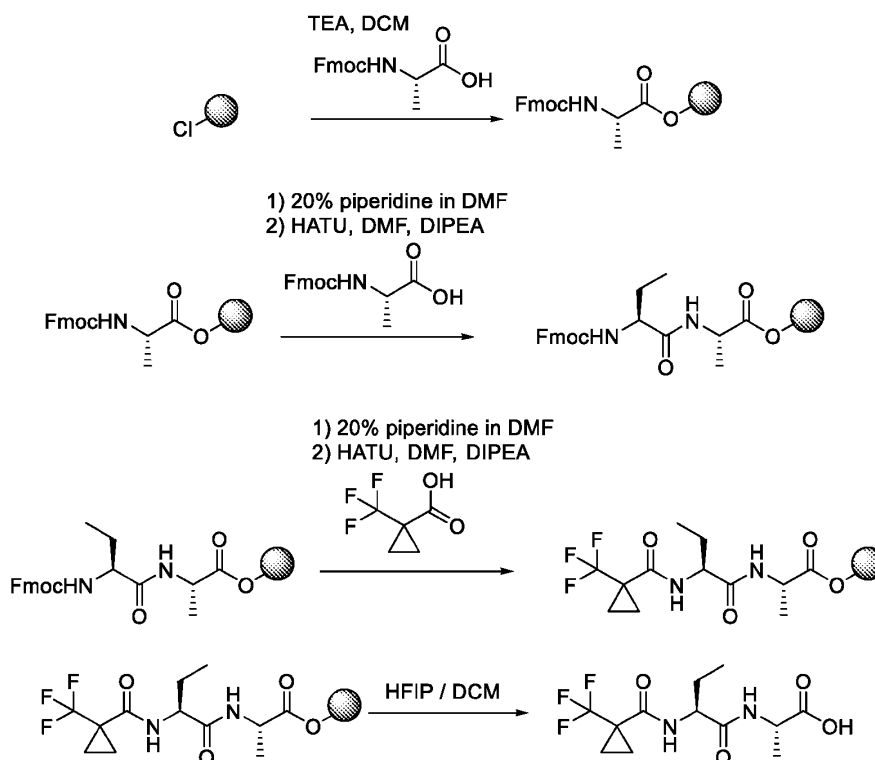
- 15 [0321] This material was synthesized by following the procedure for **Int. 30** acid using 1-bromo-2-(bromomethyl)-4-fluorobenzene as the starting material.

Int. 33: ((2S,4R)-4-fluoro-1-(1-(trifluoromethyl)cyclopropane-1-carbonyl)pyrrolidine-2-carbonyl)glycine:



- 20 [0322] This material was synthesized in an identical way to **Int. 34** using commercially available Fmoc protected amino acids. LCMS (ESI⁺): *m/z* 327.1 (M+H⁺).

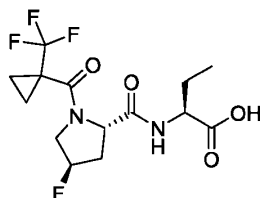
Int. 34: Preparation of ((S)-2-(1-(trifluoromethyl)cyclopropane-1-carboxamido)butanoyl)-L-alanine

**Steps 1-4: Int. 34:**

- [0323]** A mix of TEA (7.61 g, 10.5 mL, 6 Eq, 75.2 mmol) and (((9H-fluoren-9-yl)methoxy)carbonyl)-L-alanine (3.90 g, 1 Eq, 12.5 mmol) in DCM (50 mL) was added to a pre-swelled 2-Chlorotrityl chloride resin (5 g). The reaction was agitated for 1 h, then
- 10 filtered. The loaded resin was washed with DMF (3 x 50 mL). Next, piperidine 20% in DMF (50 mL) was added to the resin and stirred for 1 h, then washed with DMF (3 x 50 mL). The freshly deprotected resin was next subjected to a pre-activated solution of Fmoc-protected amino acid consisting of (S)-2-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)butanoic acid (4.08 g, 1 eq, 12.5 mmol), HATU (5.24 g, 1.1 Eq, 13.8 mmol) DIPEA (13.0 g, 17.5 mL, 8 Eq,
- 15 100 mmol) in DMF (50 mL). The Resin was agitated for 1 h, then washed with DMF (3 x 50 mL). The deprotection was repeated with the addition of piperidine 20% in DMF (50 mL). The resin was agitated for 1 h, then washed with DMF (3 x 50 mL). The final coupling was

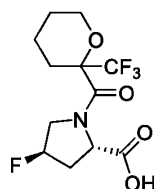
- performed by adding another preactivated carboxylic acid solution, consisting of 1-(trifluoromethyl)cyclopropane-1-carboxylic acid (1.93 g, 1 Eq, 12.5 mmol), HATU (5.24 g, 1.1 Eq, 13.8 mmol), and DIPEA (13.0 g, 17.5 mL, 8 Eq, 100 mmol) in DMF (50 mL), to the resin. This was agitated for 1 h, then washed with DMF (3 x 50 mL), Methanol (3 x 50 mL), then DCM (3 x 50 mL). The tripeptide was then cleaved by agitating the resin with a HFIP/DCM mixture (1:1, 2 x 50 mL). The combined cleavage filtrate was concentrated and the crude residue was purified by FCC (SiO₂, MeOH in DCM 0 to 20% over 10 min.). **Int. 34** (500 mg, 80% based on 0.5 mmol/ resin loading) was isolated as a white solid. **LCMS** (ESI⁺): *m/z* 311.1 (M+H⁺).

- 10 **Int. 35: (S)-2-((2S,4R)-4-fluoro-1-(1-trifluoromethyl)cyclopropane-1-carbonyl)pyrrolidine-2-carboxamido)butanoic acid:**



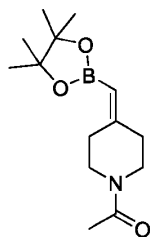
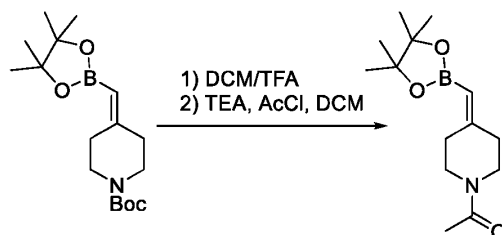
[0324] This material was synthesized in an identical way to **Int. 34** using commercially available Fmoc protected amino acids. **LCMS** (ESI⁺): *m/z* 355.4 (M+H⁺).

- 15 **Int. 39: preparation of (2S,4R)-4-fluoro-1-(2-(trifluoromethyl)tetrahydro-2H-pyran-2-carbonyl)pyrrolidine-2-carboxylic acid:**



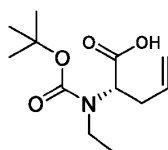
[0325] **Int. 39** was synthesized in accordance with **Int. 148** and **149**, but without separating the diastereomers.

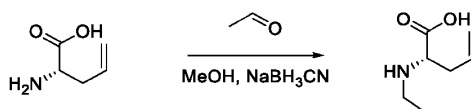
- 20 **Int. 40: Preparation of 1-(4-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methylene)piperidin-1-yl)ethan-1-one**

**Step 1: Int. 40:**

- [0326]** tert-butyl 4-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methylene)piperidine-1-carboxylate (1.0 g, 1 Eq, 3.1 mmol) was dissolved in 10 mL of DCM/TFA (3:1) and was stirred until the consumption of starting material (monitored by LCMS). The volatile solvent was completely removed and residual TFA was removed via co-evaporation with toluene. The deprotected amine was used directly without further purification. The crude material from above was dissolved in DCM (20 mL) and cooled to 0 °C and TEA (0.94 g, 1.3 mL, 3 eq, 9.3 mmol) and AcCl (0.29 g, 0.26 mL, 1.2 eq, 3.7 mmol) were added subsequently and stirred at 0 °C. Upon completion, the volatile solvent was removed, and the resulting solid was placed under high vacuum overnight. The resulting solid **Int. 40** (750 mg, 2.83 mmol, 91 %) was used in subsequent reactions with no additional purification. LCMS (ESI+): m/z 266.1 ($M+H^+$).

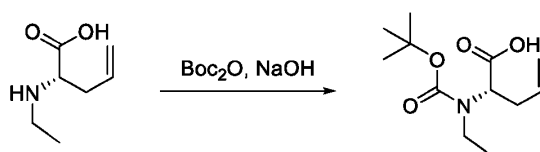
15 **Int. 41: Preparation of (S)-2-((tert-butoxycarbonyl)(ethyl)amino)pent-4-enoic acid**

**Step 1: (2S)-2-(ethylamino) pent-4-enoic acid:**



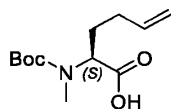
[0327] Into a stirred solution of (2S)-2-aminopent-4-enoic acid (5 g, 43.43 mmol, 1 eq) in MeOH (50 mL) was added NaBH₃CN (3.41 g, 54.29 mmol, 1.25 eq) at 0 °C under nitrogen atmosphere. The resulting solution was stirred for 10 min at 0 °C. Acetaldehyde (10.97 mL, 195.43 mmol, 1.5 eq) was added and the resulting solution was stirred for 1 h at 0 °C. After warming to rt, the mixture was stirred for 16 h at rt. The resulting mixture was quenched with water at 0 °C and extracted with EtOAc (2 x 10 mL). This resulted in (2S)-2-(ethylamino)pent-4-enoic acid (15 g, 76 %) and the crude resulting mixture was used in the next step directly without further purification. LCMS (ESI+): *m/z* 144.09 (M+H⁺).

10 Step 2: Int. 41:

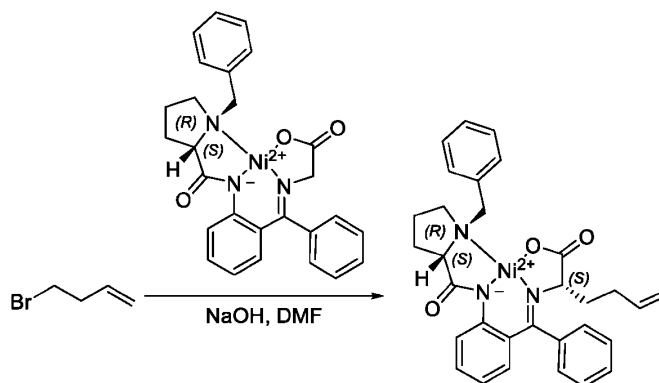


[0328] Into a stirred solution of (2S)-2-(ethylamino)pent-4-enoic acid (15 g, 104.76 mmol, 1 eq) and NaOH (29.33 g, 733.31 mmol, 7 eq) in dioxane (150 mL)/ H₂O (150 mL) was added Boc₂O (45.73 g, 209.52 mmol, 2 eq) at 0 °C under nitrogen atmosphere. The resulting solution was stirred for 16 h at rt. The reaction mixture was concentrated in vacuo to remove dioxane. The aqueous layer was acidified with 1 N HCl to pH=5. The aqueous layer was extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine, dried over Na₂SO₄ and filtered. The filtrate was concentrated in vacuo and the residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water (0.1% FA), 0% to 100% gradient in 40 min; detector, UV 210 nm. This resulted in Int. 41 (11.9 g, 46 %) as a white solid. LCMS (ESI+): *m/z* 244.15 (M+H⁺). ¹H NMR (400 MHz, DMSO-d₆): δ 1.05 (dt, *J* = 7.0, 7.0, 14.3 Hz, 3H), 1.38 (d, *J* = 14.8 Hz, 9H), 2.51 – 2.69 (m, 2H), 3.03 (dq, *J* = 6.8, 6.8, 6.8, 18.6 Hz, 1H), 3.26 (ddq, *J* = 6.9, 7.0, 7.0, 14.0, 28.9 Hz, 1H), 4.18 (ddd, *J* = 5.1, 9.9, 114.9 Hz, 1H), 4.97 – 5.18 (m, 2H), 5.64 – 5.90 (m, 1H), 12.52 (s, 1H).

Int. 42: Preparation of (S)-2-((tert-butoxycarbonyl)(methyl)amino)hex-5-enoic acid

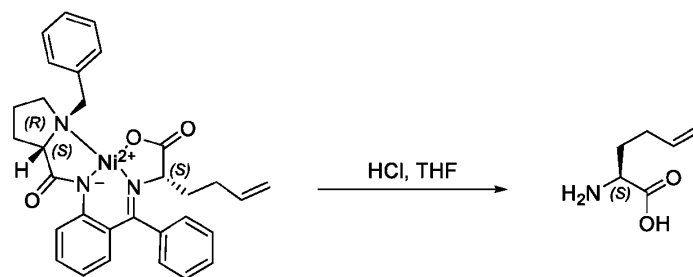


Step 1: (S)-1-[(2R)-1-benzylpyrrolidine-2-carbonyl]-5-(but-3-en-1-yl)-7-phenyl-5H-benzo[d]1-oxa-3,7-diaza-2-nickelacyclononan-4-one:



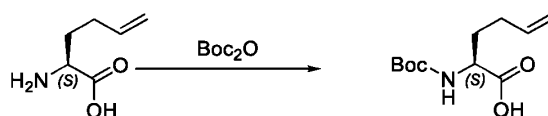
- 5 **[0329]** A solution of 1-[(2R)-1-benzylpyrrolidine-2-carbonyl]-7-phenyl-5H-benzo[d]1-oxa-3,7-diaza-2-nickelacyclononan-4-one (75.31 g, 151.17 mmol, 1 eq) and NaOH (60.46 g, 1511.67 mmol, 10 eq) in DMF (600 mL) was stirred for 15 min at rt under nitrogen atmosphere. 4-bromo-1-butene (20 g, 148.14 mmol, 0.98 eq) was added to the solution dropwise and stirred for 1.5 h at rt. The mixture was acidified to pH=6 with HOAc (5%) and
- 10 extracted with EtOAc (3 x 1 L). The combined organic layers were washed with NH₄Cl (aq.) (3 x 1 L) and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under vacuum and purified by silica gel column chromatography, eluted with CH₂Cl₂ /MeOH (20:1) to afford crude product (5S)-1-[(2R)-1-benzylpyrrolidine-2-carbonyl]-5-(but-3-en-1-yl)-7-phenyl-5H-benzo[d]1-oxa-3,7-diaza-2-nickelacyclononan-4-one (80 g, 86 %) as a red
- 15 solid. LCMS (ESI+): *m/z* 552.3 (M+H⁺). ¹H NMR (400 MHz, DMSO-*d*₆): δ 1.19 (t, *J* = 7.1 Hz, 7H), 1.59 (dtd, *J* = 13.3, 6.6, 3.3 Hz, 1H), 1.99 (s, 5H), 2.07 (s, 6H), 2.02 – 2.25 (m, 3H), 2.48 (s, 1H), 3.33 (s, 4H), 3.34 – 3.48 (m, 1H), 3.48 – 3.62 (m, 2H), 3.64 (td, *J* = 10.6, 9.7, 3.7 Hz, 1H), 3.99 – 4.13 (m, 5H), 4.82 (dd, *J* = 10.2, 1.9 Hz, 1H), 4.85 – 4.97 (m, 1H), 5.49 (s, 1H), 5.95 (s, 1H), 6.55 (dd, *J* = 8.2, 1.7 Hz, 1H), 6.61 – 6.74 (m, 1H), 7.03 – 7.16 (m, 2H),
- 20 7.13 – 7.27 (m, 1H), 7.36 (t, *J* = 7.7 Hz, 2H), 7.39 – 7.49 (m, 1H), 7.45 – 7.53 (m, 1H), 7.50 – 7.64 (m, 3H), 7.98 (dd, *J* = 8.7, 1.2 Hz, 1H), 8.32 – 8.43 (m, 2H).

Step 2: (2S)-2-aminohex-5-enoic acid:



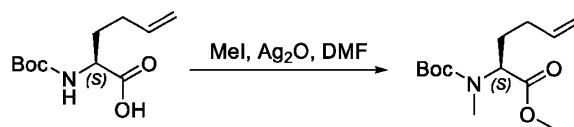
- [0330]** A solution of (5S)-1-[(2R)-1-benzylpyrrolidine-2-carbonyl]-5-(but-3-en-1-yl)-7-phenyl-5H-benzo[d]1-oxa-3,7-diaza-2-nickelacyclononan-4-one (100 g, 181.06 mmol, 1eq) and HCl (600 mL, 3N) in THF (600 mL) was stirred for 2 h at 80 °C. The mixture was
- 5 basified to pH=7 with NaOH/Na₂CO₃. The resulting mixture was extracted with CH₂Cl₂ (3 x 500 mL). (2S)-2-amino-5-hexenoic acid (25 g, 427 %) was in water layer was used in the next step directly without further purification. LCMS (ESI+): *m/z* 130.15 (M+H⁺).

Step 3: (2S)-2-[(tert-butoxycarbonyl)amino]hex-5-enoic acid:



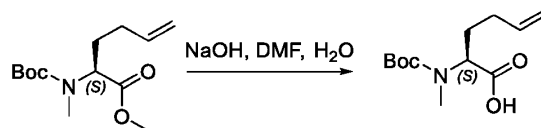
- 10 **[0331]** To the above water solution (1.5 L) including (2S)-2-amino-5-hexenoic acid (25 g, 193.56 mmol, 1eq) was added Boc₂O (84.50 g, 387.12 mmol, 2 eq) was stirred for 16 h at rt. The mixture was acidified to pH =6 with citric acid and extracted with CH₂Cl₂ (3 x 500 mL). The combined organic layers were washed with brine (1 x 200 mL) and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under vacuum. The residue was
- 15 purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, Acetonitrile in Water, 5% to 100% gradient in 30 min; detector, UV 210 nm. This resulted in (2S)-2-[(tert-butoxycarbonyl)amino]hex-5-enoic acid (12 g, 135 %) as a light-yellow oil. LCMS (ESI+): *m/z* 130.15 (M+H⁺). ¹H NMR (400 MHz, DMSO-*d*₆): δ 1.18 (t, *J* = 7.1 Hz, 1H), 1.35 (s, 1H), 1.39 (s, 8H), 1.57 – 1.69 (m, 1H), 1.66 – 1.78 (m, 1H),
- 20 1.91 (s, 2H), 1.99 (s, 1H), 2.06 (dq, *J* = 13.9, 7.2 Hz, 2H), 3.88 (ddd, *J* = 9.5, 8.1, 4.7 Hz, 1H), 4.03 (q, *J* = 7.1 Hz, 1H), 4.94 – 5.06 (m, 2H), 5.78 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 7.08 (d, *J* = 8.1 Hz, 1H), 12.26 (s, 2H).

Step 4: methyl (S)-2-((tert-butoxycarbonyl)(methyl)amino)hex-5-enoate:



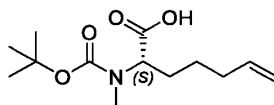
- [0332] To a stirred solution of (2S)-2-[(tert-butoxycarbonyl)amino]hex-5-enoic acid (6 g, 26.17 mmol, 1 eq) and Ag₂O (24.26 g, 104.68 mmol, 4 eq) in DMF (90 mL) was added CH₃I (55.72 g, 392.54 mmol, 15 eq) dropwise at 0 °C. The resulting mixture was stirred overnight at rt. The resulting mixture was filtered, the filter cake was washed with DMF (3 x 50 mL). The filtrate was used in the next step directly without further purification. LCMS (ESI+): *m/z* 258.20 (M+H⁺).

Step 5: Int. 42:

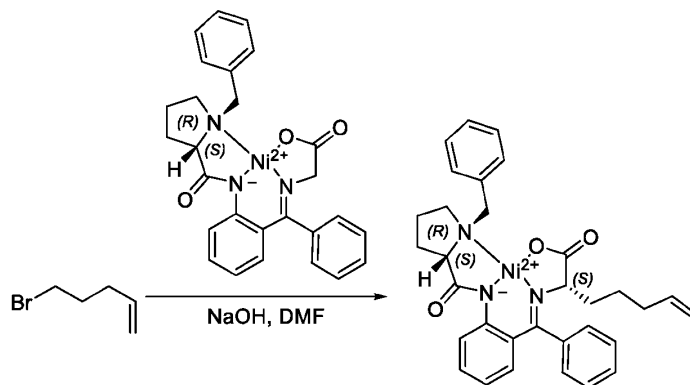


- [0333] To a stirred solution of methyl (2S)-2-[(tert-butoxycarbonyl)(methyl)amino]hex-5-enoate (20 g, 77.72 mmol, 1 eq) in H₂O (500 mL) /DMF (500 mL) was added and NaOH (18.65 g, 466.33 mmol, 6 eq) in portions at 0 °C. The resulting mixture was stirred for 16 h at rt and acidified to pH 6 with HCl (3N). The mixture was extracted with CH₂Cl₂ (3 x 0.5 L). The combined organic layers were washed with brine (3 x 300 mL) and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under vacuum and purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, Acetonitrile in Water, 5% to 50% gradient in 30 min; detector, UV 200 nm. This resulted in racemic product (20 g) which was purified by Prep-CHIRAL-HPLC with the following conditions (Column: CHIRALPAK IC-3, 4.6 x 50mm, 3μm; Mobile Phase A: Hex(0.1%TFA): IPA=98: 2; Flow rate: 1 mL/min; Gradient: 0% B to 0% B; Injection Volume: 5ul mL) to afford **Int. 42** (15.78 g, 83 %) as a light yellow oil. LCMS (ESI+): *m/z* 242.10 (M+H⁺). ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.38 (d, *J* = 13.4 Hz, 1H), 1.71 – 1.86 (m, 1H), 1.89 (s, 1H), 1.94 (d, *J* = 4.9 Hz, 1H), 1.94 – 2.12 (m, 3H), 2.72 (s, 6H), 4.26 (dd, *J* = 10.4, 4.6 Hz, 1H), 4.50 (dd, *J* = 10.8, 4.4 Hz, 1H), 4.93 – 5.05 (m, 3H), 5.02 – 5.10 (m, 1H), 5.81 (ddd, *J* = 16.9, 10.2, 3.6 Hz, 1H), 12.73 (s, 2H).

Int. 43: Preparation of (S)-2-((tert-butoxycarbonyl)(methyl)amino)hept-6-enoic acid

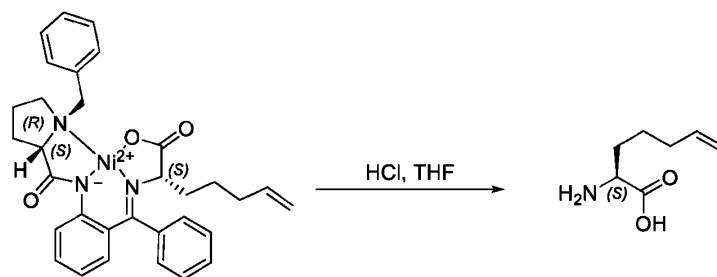


Step 1: (5S)-1-[(2S)-1-benzylpyrrolidine-2-carbonyl]-5-(pent-4-en-1-yl)-7-phenyl-5H-benzo[d]1-oxa-3,7-diaza-2-nickelacyclononan-4-one:



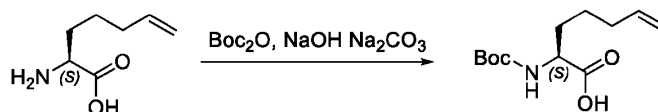
- 5 **[0334]** To a solution of NaOH (80.51 g, 2013.0 mmol, 10 eq.) in DMF (270 mL), 1-[(2S)-1-benzylpyrrolidine-2-carbonyl]-7-phenyl-1H,4H,5H-benzo[d]1-oxa-3,7-diaza-2-nickelacyclononan-4-one (102.29 g, 205.33 mmol, 1.02 eq) was added in at 25 °C under nitrogen atmosphere. The reaction was stirred for 15 min at 25 °C. 5-bromopent-1-ene (30 g, 201.30 mmol, 1 eq) was dropwise below 25 °C. The reaction was stirred for 5 hours at 25 °C.
- 10 The reaction was purified together with Page EB2141275-183 and EB2141275-184. The mixture was acidified to pH=3 with acetic acid (5%), The resulting mixture was extracted with EtOAc (2 x 250 mL). The combined organic layers were dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH₂Cl₂ / MeOH (20:1) to afford (5S)-1-[(2S)-1-benzylpyrrolidine-2-carbonyl]-5-(pent-4-en-1-yl)-7-phenyl-5H-benzo[d]1-oxa-3,7-diaza-2-nickelacyclononan-4-one (88 g, 77 %) as a yellow oil. LCMS (ESI⁺): *m/z* 566 (M+H⁺). ¹H NMR (400 MHz, DMSO-*d*₆): δ 1.54 (dddd, 2H), 1.76 – 2.04 (m, 3H), 2.12 – 2.34 (m, 3H), 2.45 (t, 2H), 3.32 (d, 2H), 3.50 – 3.71 (m, 3H), 4.07 (d, 1H), 4.85 – 5.09 (m, 2H), 5.76 (ddt, 1H), 6.53 (dd, 1H), 6.66 (ddd, 1H), 7.01 – 7.24 (m, 3H), 7.36 (t, 2H), 7.45 – 7.66 (m, 4H), 7.91 – 8.09 (m, 1H), 8.27 – 8.46 (m, 2H).
- 20

Step 2: (S)-2-aminohept-6-enoic acid:



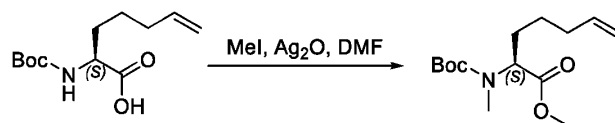
[0335] To a solution of (5S)-1-[(2S)-1-benzylpyrrolidine-2-carbonyl]-5-(pent-4-en-1-yl)-7-phenyl-5H-benzo[d]1-oxa-3,7-diaza-2-nickelacyclopentadecan-4-one (88 g, 155.39 mmol, 1 eq.) in THF (880.0 g, 12204.1 mmol, 78.54 eq) was added HCl (517.96 mL, 1553.87 mmol, 10 eq) at 25 °C. The reaction was stirred for 2 hours at 60 °C. The resulting mixture was diluted with water (1500 mL). The mixture was basified to pH= 8 with NaOH (aq., 2N). The resulting mixture was extracted with EtOAc (2 x 500 mL). The aqueous phase(including about 22g product) was used in next step without further purification. **LCMS** (ESI+): *m/z* 144 (*M*+*H*⁺).

Step 3: (2S)-2-[(tert-butoxycarbonyl)amino]hept-6-enoic acid:



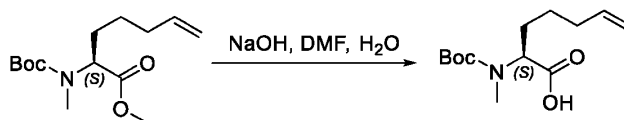
[0336] To a solution of (2S)-2-aminohept-6-enoic acid (22 g, 153.65 mmol, 1 eq), Na₂CO₃ (97.71 g, 921.88 mmol, 6 eq) in water (2000 mL) was added Boc₂O (100.60 g, 460.94 mmol, 3 eq) at 25 °C. The reaction was stirred for 6 hours at 25 °C. The mixture was acidified to pH=6 with diluted citric acid. The resulting mixture was extracted with EtOAc (3 x 150 mL). The combined organic layers were dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH₂Cl₂ / MeOH (20:1) to afford (2S)-2-[(tert-butoxycarbonyl)amino]hept-6-enoic acid (30 g, 80 %) as a yellow oil. **LCMS** (ESI+): *m/z* 266 (*M*+*Na*⁺). **¹H NMR** (400 MHz, DMSO-*d*₆): δ 1.38 (s, 11H), 1.50 – 1.59 (m, 1H), 1.66 (dddd, 1H), 2.74 (s, 1H), 2.90 (s, 1H), 3.86 (ddd, 1H), 4.95 (ddt, 1H), 5.00 (dt, 1H), 5.68 – 5.88 (m, 1H), 7.07 (d, 1H), 12.38 (s, 1H).

Step 4: Methyl (S)-2-((tert-butoxycarbonyl)(methyl)amino)hept-6-enoate:



- [0337] MeI (175.02 g, 1233.03 mmol, 10 eq) was added into a solution of (2S)-2-[(tert-butoxycarbonyl)amino]hept-6-enoic acid (30 g, 123.30 mmol, 1 eq) and Ag₂O (142.87 g, 616.52 mmol, 5 eq) in DMF (200 mL). The reaction was stirred for 6 hours at 25 °C. Desired product could be detected by LCMS. The resulting mixture was filtered, the filter cake was washed with DMF (2 x 5 mL). The filtrate was used in next step without further purification (about 35 g). LCMS (ESI⁺): *m/z* 172 (M+H-Boc⁺).

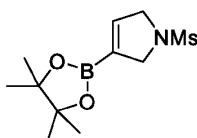
Step 5: Int. 43:



- [0338] NaOH (25.79 g, 644.91 mmol, 5 eq) in water (350.00 mL, 19428.41 mmol, 150.63 eq) was added into a solution of methyl (2S)-2-[(tert-butoxycarbonyl)(methyl)amino]hept-6-enoate (35 g, 128.98 mmol, 1 eq) in DMF (20 mL) at 25 °C. The reaction was stirred for 5 hours at 25 °C. Desired product could be detected by LCMS. The reaction was purified with Page EB2206983-001 and EB2206983-002 and EB2206983-003 and EB2206983-004. The resulting mixture was diluted with water (500 mL). The mixture was acidified to pH=6 with HCl (aq.2N). The resulting mixture was extracted with EtOAc (3 x 1000 mL). The combined organic layers were washed with saturated ammonium chloride (2 x 500 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in Water, 10% to 60% gradient in 20 min; detector, UV 254 nm to afford (2S)-2-[(tert-butoxycarbonyl)(methyl)amino]hept-6-enoic acid (31 g, 93.40%) as a light yellow oil. The compound was further purified by PREP_CHIRAL_HPLC with the following conditions: Column: CHIRAL ART Cellulose-SC, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.1% FA)--HPLC, Mobile Phase B: IPA--HPLC; Flow rate: 20 mL/min; Gradient: 2% B to 2% B in 17 min; Wave Length: 220/254 nm; RT1(min): 6.939; RT2(min): 12.248; Sample Solvent: EtOH—HPLC to afford **Int. 43** (21.4 g, 66 %) as a light yellow oil. LCMS (ESI⁺): *m/z* 280 (M+Na⁺). ¹H NMR (400 MHz,

DMSO-*d*₆: δ 1.39 (d, 11H), 1.56 – 1.88 (m, 2H), 2.05 (qp, 2H), 2.70 (s, 3H), 4.41 (ddd, 1H), 4.92 – 5.09 (m, 2H), 5.71 – 5.88 (m, 1H), 12.65 (s, 1H).

Int. 44: 1-(methylsulfonyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,5-dihydro-1H-pyrrole:

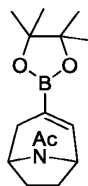


5

[0339] This material was synthesized according to the procedure for **Int. 40** with tert-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,5-dihydro-1H-pyrrole-1-carboxylate and methanesulfonyl chloride as starting materials. LCMS (ESI+): m/z 274.2 ($M+H^+$).

Int. 45: 1-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-8-azabicyclo[3.2.1]oct-2-en-8-yl)ethan-1-one:

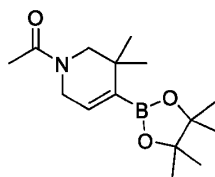
10



[0340] This material was synthesized according to the procedure for **Int. 40** with tert-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate as the starting material LCMS (ESI+): m/z 278.2 ($M+H^+$).

Int. 122: 1-(3,3-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridin-1(2H)-yl)ethan-1-one:

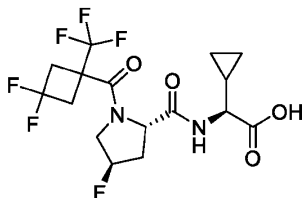
15



[0341] Int. 122 was synthesized according to the procedure **Int. 40** with tert-butyl 3,3-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate as starting material. LCMS (ESI+): m/z 280.5 ($M+H^+$).

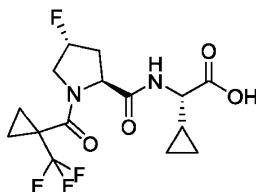
20

Int. 127: (S)-2-cyclopropyl-2-((2S,4R)-1-(3,3-difluoro-1-(trifluoromethyl)cyclobutene-1-carbonyl)-4-fluoropyrrolidine-2-carboxamido)acetic acid:



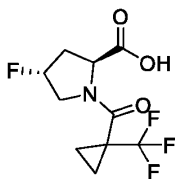
[0342] This material was synthesized in an identical way to **Int. 34** using commercially available Fmoc protected amino acids. LCMS (ESI+): m/z 417.1 ($M+H^+$).

Int. 129: (S)-2-cyclopropyl-2-((2S,4R)-4-fluoro-1-(1-(trifluoromethyl)cyclopropane-1-carbonyl)pyrrolidine-2-carboxamido)acetic acid:



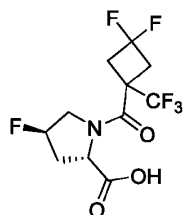
[0343] This material was synthesized in an identical way to **Int. 34** using commercially available Fmoc protected amino acids. LCMS (ESI+): m/z 367.4 ($M+H^+$).

Int. 140: Preparation of (2S,4R)-4-fluoro-1-(1-(trifluoromethyl)cyclopropane-1-carbonyl)pyrrolidine-2-carboxylic acid

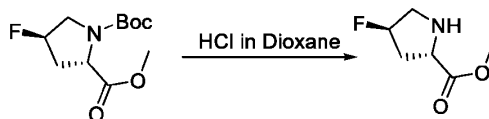


[0344] This compound was prepared following the general synthetic sequence described for the preparation of **Int. 141** With 1-(trifluoromethyl)cyclopropane-1-carboxylic acid as the starting material. LCMS (ESI+): m/z 417.99 ($M+H^+$).

Int. 141: Preparation of (2S,4R)-1-(3,3-difluoro-1-(trifluoromethyl)cyclobutane-1-carbonyl)-4-fluoropyrrolidine-2-carboxylic acid

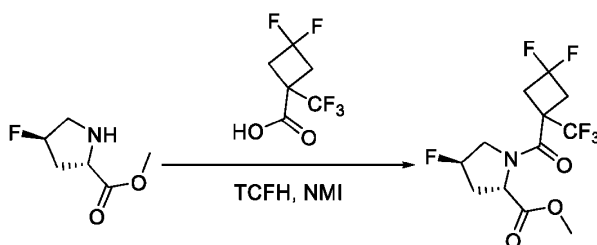


Step 1: Methyl (2S,4R)-4-fluoropyrrolidine-2-carboxylate:



[0345] A solution of 1-tert-butyl 2-methyl (2S,4R)-4-fluoropyrrolidine-1,2-dicarboxylate (150 g, 101.1 mmol, 1 eq) and HCl_(gas) in 1,4-dioxane (758.29 mL, 505.53 mmol, 5 eq) was stirred for 0.5 h at rt and then concentrated under vacuum to afford methyl (2S,4R)-4-fluoropyrrolidine-2-carboxylate (110 g, yield, 99%, purity 80%) as a white solid. The crude product was used in the next step directly without further purification. LCMS (ESI+): *m/z* 148.15 (M+H⁺).

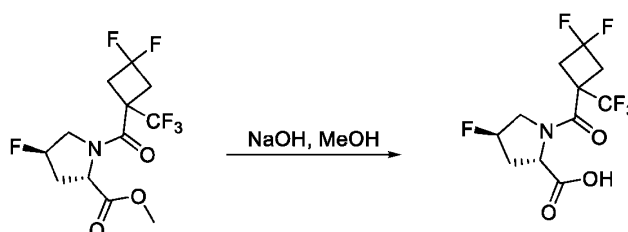
Step 2: Methyl (2S,4R)-1-[3,3-difluoro-1-(trifluoromethyl)cyclobutanecarbonyl]-4-fluoropyrrolidine-2-carboxylate:



[0346] To a stirred solution of methyl (2S,4R)-4-fluoropyrrolidine-2-carboxylate (110 g, 103.3 mmol, 1 eq, 80%), 3,3-difluoro-1-(trifluoromethyl)cyclobutanecarboxylic acid (122.06 g, 103.3 mmol, 1 eq) and TCFH (251.69 g, 154.95 mmol, 1.5 eq) in ACN (1100 mL) was added NMI (245.51 g, 516.49 mmol, 5 eq) dropwise in 45 min at 0 °C. The mixture was slowly warmed up to rt and stirred overnight at rt. The mixture was concentrated under vacuum at 28 °C and diluted with EtOAc (900 mL) and washed with HCl (0.5N, 1400 mL x 1). The aqueous layer was extracted again with EtOAc (1x500 mL). The combined organic layers were washed with saturated NaHCO₃ (1000 mL x1). The aqueous layer was extracted

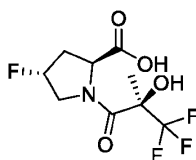
with EtOAc (300mL x1) again. The combined organic layers were washed with brine and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under vacuum to afford methyl (2S,4R)-1-[3,3-difluoro-1-(trifluoromethyl)cyclobutanecarbonyl]-4-fluoropyrrolidine-2-carboxylate 180 g, 81 %) as a light-yellow solid. The crude product was used in the next step directly without further purification. LCMS (ESI+): *m/z* 334.15 (M+H⁺).

Step 3: Int. 141:



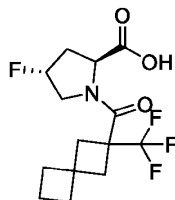
[0347] To a stirred solution of methyl (2S,4R)-1-[3,3-difluoro-1-(trifluoromethyl)cyclobutanecarbonyl]-4-fluoropyrrolidine-2-carboxylate (180 g, 82.15 mmol, 1 eq, 90%) in MeOH (1400 mL) was added dropwise NaOH (58.33 g, 246.45 mmol, 3 eq) in H₂O (400 mL) in 30 min at 0-20 °C. The mixture was stirred for 2 h at rt. MeOH was evaporated out under vacuum. The residue was diluted with water (2500 mL) and acidified with HCl (3N, 400 mL) at 0-20 °C. Then the precipitated solids were collected by filtration and washed with water (3x200 mL). The filtrate was added HCl (3N, 100 mL). The precipitated solids were collected by filtration and washed with water (3x100 mL). The combined solids were dried in an oven for 16 h at 40 °C. This resulted in afford **Int. 40** (150.7 g, 97 %) as a white solid. LCMS (ESI+): *m/z* 319.95 (M+H⁺).

Int. 142: Preparation of (2S,4R)-4-fluoro-1-((R)-3,3,3-trifluoro-2-hydroxy-2-methylpropanoyl)pyrrolidine-2-carboxylic acid



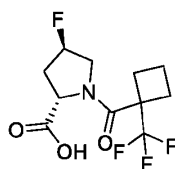
[0348] This compound was prepared following the general synthetic sequence described for the preparation of **Int. 141**. With (R)-3,3,3-trifluoro-2-hydroxy-2-methylpropanoic acid as the starting material. LCMS (ESI+): *m/z* 421.08

Int. 143: Preparation of (2S,4R)-4-fluoro-1-(2-(trifluoromethyl)spiro[3.3]heptane-2-carbonyl)pyrrolidine-2-carboxylic acid



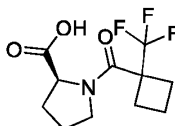
- 5 [0349] This compound was prepared following the general synthetic sequence described for the preparation of **Int. 141** with 2-(trifluoromethyl)spiro[3.3]heptane-2-carboxylic acid as the starting material. LCMS (ESI+): m/z 323.11 ($M+H^+$).

Int. 144: Preparation of (2S,4R)-4-fluoro-1-(1-(trifluoromethyl)cyclobutane-1-carbonyl)pyrrolidine-2-carboxylic acid



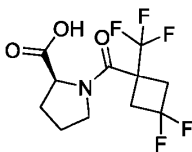
- 10 [0350] This compound was prepared following the general synthetic sequence described for the preparation of **Int. 141** with 1-(trifluoromethyl)cyclobutane-1-carboxylic acid as the starting material. LCMS (ESI+): m/z 283.08 ($M+H^+$).

Int. 145: Preparation of (1-(trifluoromethyl)cyclobutane-1-carbonyl)-L-proline:



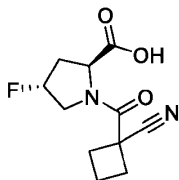
- 15 [0351] This compound was prepared following the general synthetic sequence described for the preparation of **Int. 141** with (tert-butoxycarbonyl)-L-proline and 1-(trifluoromethyl)cyclobutane-1-carboxylic acid as the starting materials. LCMS (ESI+): m/z 266.1 ($M+H^+$).

Int. 146: (3,3-difluoro-1-(trifluoromethyl)cyclobutane-1-carbonyl)-L-proline:



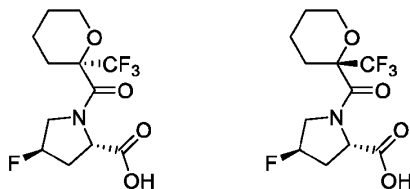
[0352] This compound was prepared following the general synthetic sequence described for the preparation of **Int. 141** with (tert-butoxycarbonyl)-L-proline as the starting material. LCMS (ESI+): m/z 302.2 ($M+H^+$).

5 **Int. 147: Preparation of (2S,4R)-1-(1-cyanocyclobutane-1-carbonyl)-4-fluoropyrrolidine-2-carboxylic acid**

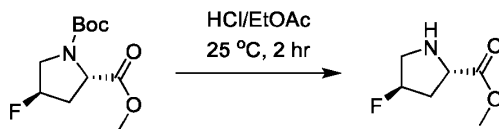


[0353] This compound was prepared following the general synthetic sequence described for the preparation of **Int. 141** with 1-cyanocyclobutane-1-carboxylic acid as the starting material. LCMS (ESI+): m/z 240.09 ($M+H^+$).

Int. 148 and 149: Preparation of (2S,4R)-4-fluoro-1-((R)-2-(trifluoromethyl)tetrahydro-2H-pyran-2-carbonyl)pyrrolidine-2-carboxylic acid and (2S,4R)-4-fluoro-1-((S)-2-(trifluoromethyl)tetrahydro-2H-pyran-2-carbonyl)pyrrolidine-2-carboxylic acid



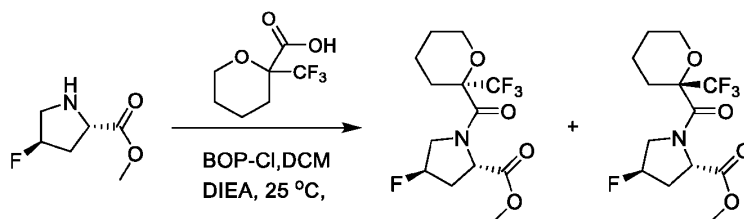
15 **Step 1: Methyl (2S,4R)-4-fluoropyrrolidine-2-carboxylate:**



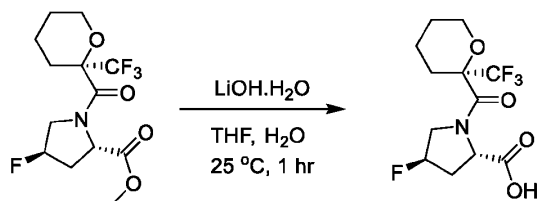
[0354] A mixture of 1-(tert-butyl) 2-methyl (2S,4R)-4-fluoropyrrolidine-1,2-dicarboxylate (20 g, 80.9 mmol, 1 eq) in HCl/EtOAc (200 mL) (4 M) was stirred at 25 °C for 2 h. LC-MS

showed starting material was consumed and one main peak with desired mass was detected. The reaction mixture was concentrated to give methyl (2S,4R)-4-fluoropyrrolidine-2-carboxylate (15 g, crude, HCl) as a light-yellow solid. This was taken on to the next reaction without further purification.

5 Step 2: (2S,4R)-4-fluoro-1-((R)-2-(trifluoromethyl)tetrahydro-2H-pyran-2-carbonyl)pyrrolidine-2-carboxylate and (2S,4R)-4-fluoro-1-((S)-2-(trifluoromethyl)tetrahydro-2H-pyran-2-carbonyl)pyrrolidine-2-carboxylate:

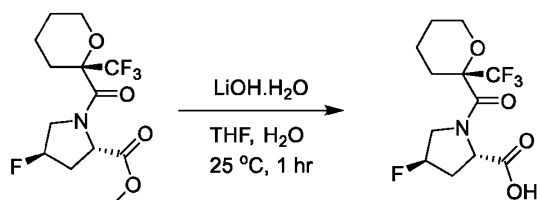


- [0355]** To a solution of 2-(trifluoromethyl)tetrahydro-2H-pyran-2-carboxylic acid (13 g, 65.61 mmol, 1 eq) in DCM (200 mL) was added DIEA (8.48 g, 65.61 mmol, 11.43 mL, 1 eq), and the mixture was stirred for 10 min, then BOP-Cl (18.37 g, 72.17 mmol, 1.1 eq), methyl (2S,4R)-4-fluoropyrrolidine-2-carboxylate, and DIEA (16.96 g, 131.22 mmol, 22.86 mL, 2 eq) were added. The mixture was stirred at 25 °C for 12 h. LC-MS showed one main peak with desired mass was detected. The reaction mixture was concentrated under reduced pressure to remove DCM, and then EtOAc (30 mL) was added. The solution was washed three times with 5% NaHCO₃ solution (15 mL) and once consecutively with water (15 mL), 2M HCl solution (15 mL), water (15 mL) and saturated brine (15 mL). The organic layer was dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, PE:EtOAc = 10:1 to 2:1) to give methyl (2S,4R)-4-fluoro-1-((R)-2-(trifluoromethyl)tetrahydro-2H-pyran-2-carbonyl)pyrrolidine-2-carboxylate (10.7 g, 31.7 mmol, 48 % yield, 96.8% purity) as a light yellow oil and to give methyl (2S,4R)-4-fluoro-1-((S)-2-(trifluoromethyl)tetrahydro-2H-pyran-2-carbonyl)pyrrolidine-2-carboxylate (11 g, 32.0 mmol, 49 % yield, 95.2% purity) as a light yellow oil.
- 25 Step 3: (2S,4R)-4-fluoro-1-((R)-2-(trifluoromethyl)tetrahydro-2H-pyran-2-carbonyl)pyrrolidine-2-carboxylic acid:**



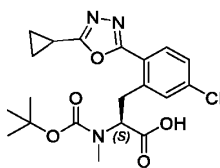
- [0356]** To a solution of methyl (2S,4R)-4-fluoro-1-((R)-2-(trifluoromethyl)tetrahydro-2H-pyran-2-carbonyl)pyrrolidine-2-carboxylate (10.7 g, 31.66 mmol, 96.83% purity, 1 eq) in THF (100 mL) and H₂O (100 mL) was added LiOH.H₂O (2.66 g, 63.32 mmol, 2 eq). Then the mixture was stirred at 25 °C for 1 hr. LC-MS showed methyl (2S,4R)-4-fluoro-1-((R)-2-(trifluoromethyl)tetrahydro-2H-pyran-2-carbonyl)pyrrolidine-2-carboxylate was consumed and one main peak with desired mass was detected. The mixture was acidified at 0 °C with HCl (1 N) until pH = 2~3. Then the mixture was extracted with EtOAc 300 mL (100 mL × 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, PE:EtOAc = 10:1 to 2:1) to give (2S,4R)-4-fluoro-1-((R)-2-(trifluoromethyl)tetrahydro-2H-pyran-2-carbonyl)pyrrolidine-2-carboxylic acid (8.9 g, 28.33 mmol, 89 % yield, 99 % purity) as a white solid. LCMS (ESI+): *m/z* 314.0 (M+H⁺).

Step 4: Int. 149:



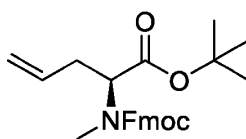
- [0357]** The same hydrolysis procedure was performed on methyl (2S,4R)-4-fluoro-1-((S)-2-(trifluoromethyl)tetrahydro-2H-pyran-2-carbonyl)pyrrolidine-2-carboxylate to provide the desired product **Int. 149** (9.1 g, 28.97 mmol, 90.5 % yield, 99.7% purity) as a white solid. LCMS (ESI+): *m/z* 314.0 (M+H⁺).

- 20** **Int. 150: Preparation of (2S,4R)-4-fluoro-1-(3,3,3-trifluoro-2,2-dimethylpropanoyl)pyrrolidine-2-carboxylic acid**

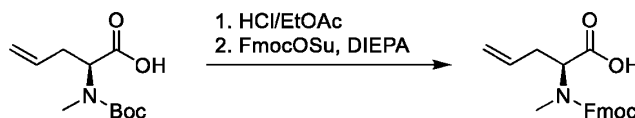


[0358] Int. 150 was prepared following the general synthetic sequence described for the preparation of Int. 141. LCMS (ESI+): m/z 271.08 ($M+H^+$).

5 **Int. 154: Preparation of tert-butyl (S)-2-(((9H-fluoren-9-yl)methoxy)carbonyl)(methyl)amino)pent-4-enoate**



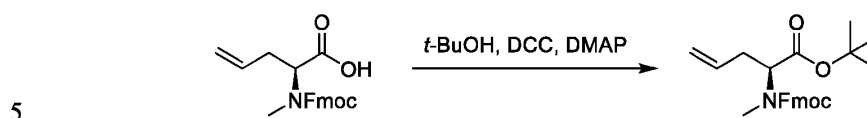
Step 1: Int. 154:



- [0359] To a solution of Int. 152 (250 g, 1.09 mol, 1 eq) in HCl/EtOAc (2500 mL). The mixture was stirred at 25 °C for 12 hour. The reaction mixture was concentrated under reduced pressure to remove solvent to give the deprotected HCl salt (180.5 g, crude, HCl) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.33-13.58 (m, 1H), 10.10-8.94 (m, 2H), 5.84-5.69 (m, 1H), 5.31-5.11 (m, 2H), 3.99 (br t, *J* = 5.2 Hz, 1H), 2.68 (br t, *J* = 6.4 Hz, 2H), 2.60-2.52 (m, 3H).
- 15 [0360] To a solution of the crude HCl salt (170 g, 1.03 mol, 1 eq) in H₂O (860 mL) and dioxane (1140 mL) was added FmocOSu (346 g, 1.03 mol, 1 eq) and DIEA (398 g, 3.08 mol, 536 mL, 3 eq). The mixture was stirred until the LCMS showed consumption of starting material. The reaction was quenched with citric acid solution (800 mL) at 25 °C, and then extracted with EtOAc (500 mL x 4). The combined organic layers were washed with brine
- 20 (500 mL x 2), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (Eluent of 0~40% EtOAc/PE) to give (S)-2-(((9H-fluoren-9-yl)methoxy)carbonyl)(methyl)amino)pent-4-enoic acid (290 g, 815 mmol, 80 % yield, 99% purity) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.13-12.72 (m, 1H), 7.89 (dd, *J*

= 3.7, 7.2 Hz, 2H), 7.63 (br d, $J = 7.6$ Hz, 2H), 7.45-7.27 (m, 4H), 5.73-5.46 (m, 1H), 5.17-4.95 (m, 2H), 4.67-4.44 (m, 1H), 4.40-4.21 (m, 3H), 2.80-2.70 (m, 3H), 2.53 (br s, 1H), 2.48-2.32 (m, 1H).

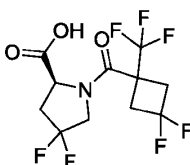
Step 2: Int. 154:



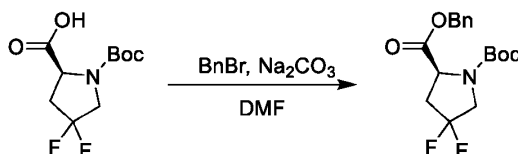
[0361] Dissolve (S)-2-(((9H-fluoren-9-yl)methoxy)carbonyl)(methyl)amino)pent-4-enoic acid (10 g, 1 Eq, 28 mmol) in DCM (20 mL), bring to 0 °C under argon. Add DCC (6.5 g, 1.1 Eq, 31 mmol) and DMAP (0.35 g, 0.1 Eq, 2.8 mmol) as solids. Add tert-butanol (8.4 g, 11 mL, 4 Eq, 0.11 mol) by syringe. Stir at rt overnight. Dilute in water and DCM, extract 3X DCM. Wash combined organic layers with water and brine, dry over MgSO_4 , filter, concentrate. Purify by normal phase chromatography (0 to 100% EtOAc in hexanes) to yield **Int. 154** (9.8 g, 24 mmol, 85 %) as a pale oil.

Int. 162: Preparation of (S)-1-(3, 3-difluoro-1-(trifluoromethyl) cyclobutane-1-carbonyl)-4, 4-difluoropyrrolidine-2-carboxylic acid

15



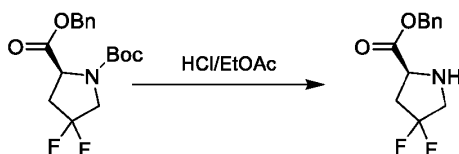
Step 1: 2-benzyl 1-(tert-butyl) (S)-4, 4-difluoropyrrolidine-1, 2-dicarboxylate:



[0362] To a solution of (S)-1-(tert-butoxycarbonyl)-4, 4-difluoropyrrolidine-2-carboxylic acid (2.50 g, 9.95 mmol, 1.0 Equiv.) in DMF (50 mL) was added Na_2CO_3 (2.11 g, 19.9 mmol, 2.0 Equiv.) and stirred at room temperature for 0.5 hrs. The reaction mixture was then cooled to 0°C and BnBr (1.87 g, 10.9 mmol, 1.30 mL, 1.1 Equiv.) was added. The mixture was stirred at 0°C for another 2.5 hrs. Water (80 mL) was added, and the aqueous phase was extracted with EtOAc (30 mL×3), the combined organic layer was washed by brine (30 mL),

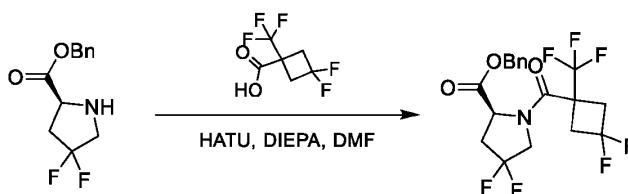
dried over Na_2SO_4 , filtered and the filtrate was concentrated to give a residue. The residue was purified by silica gel column chromatography (Pet. Ether / EtOAc, 30:1) to afford 2-benzyl 1-(tert-butyl) (S)-4, 4-difluoropyrrolidine-1, 2-dicarboxylate (2.80 g, 8.20 mmol, 82.4% yield) as a clear oil. $^1\text{H NMR}$ (400 MHz, DMSO-d_6): δ 7.37 (d, $J = 4.8$ Hz, 5H), 5.23-5.10 (m, 2H), 4.59-4.50 (m, 1H), 3.83-3.70 (m, 2H), 3.02-2.87 (m, 1H), 2.59-2.50 (m, 1H), 1.41-1.25 (m, 9H).

Step 2: benzyl (S)-4, 4-difluoropyrrolidine-2-carboxylate:



[0363] To a solution of 2-benzyl 1-(tert-butyl) (S)-4, 4-difluoropyrrolidine-1, 2-dicarboxylate (2.00 g, 5.86 mmol, 1.0 Equiv.) in EtOAc (10 mL) was added HCl / EtOAc (4 M, 40 mL, 27.3 Equiv.) and stirred at 20°C for 1 hr. The reaction mixture was concentrated to afford benzyl (S)-4, 4-difluoropyrrolidine-2-carboxylate (2.14 g, crude) as a white solid. $^1\text{H NMR}$ (400 MHz, DMSO-d_6): δ 10.78-10.59 (m, 1H), 7.48-7.33 (m, 5H), 5.30-5.22 (m, 2H), 4.86 (t, $J = 8.8$ Hz, 1H), 3.83-3.64 (m, 2H), 2.97-2.85 (m, 1H), 2.75 (dq, $J = 8.8, 14.8$ Hz, 1H).

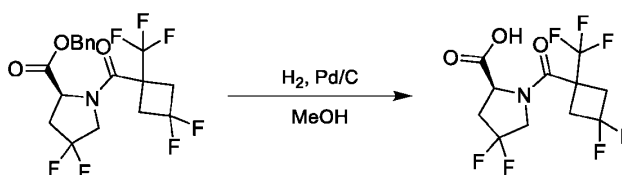
Step 3: benzyl (S)-1-(3, 3-difluoro-1-(trifluoromethyl) cyclobutane-1-carbonyl)-4, 4-difluoropyrrolidine-2-carboxylate



[0364] To a solution of benzyl (S)-4,4-difluoropyrrolidine-2-carboxylate (1.90 g, 7.88 mmol, 1.0 Equiv.) in DMF (30 mL) was added DIPEA (3.05 g, 23.6 mmol, 4.12 mL, 3.0 Equiv.), 3, 3-difluoro-1-(trifluoromethyl)cyclobutanecarboxylic acid (2.41 g, 11.8 mmol, 1.5 Equiv.) and HATU (4.49 g, 11.8 mmol, 1.5 Equiv.), the mixture was stirred at 20°C for 2 hrs. Water (60 mL) was added and the aqueous phase was extracted with EtOAc (20 mL $\times$ 3). Then the organic layers was washed with brine (30 mL), dried over Na_2SO_4 , filtered and the filtrate was concentrated to give a residue. The residue was purified by silica gel column

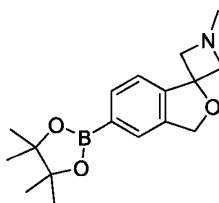
chromatography, eluted with Pet. Ether / EtOAc (10:1 to 3:1) to afford benzyl (S)-1-(3, 3-difluoro-1-(trifluoromethyl) cyclobutane-1-carbonyl)-4, 4-difluoropyrrolidine-2-carboxylate (2.30 g, 5.38 mmol, 68.3% yield) as a yellow oil. ¹H NMR (400 MHz, DMSO-d₆): δ 7.41-7.32 (m, 5H), 5.15 (s, 2H), 4.83 (dd, J = 4.4, 10.0 Hz, 1H), 4.13-4.00 (m, 2H), 3.34-3.20 (m, 4H), 2.99-2.83 (m, 1H), 2.59-2.51 (m, 1H).

Step 4: Int. 162

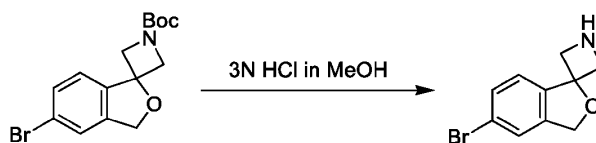


[0365] To a solution of benzyl (S)-1-(3,3-difluoro-1-(trifluoromethyl)cyclobutane-1-carbonyl)-4,4-difluoropyrrolidine-2-carboxylate (2.30 g, 5.38 mmol, 1.0 Equiv.) in MeOH (30 mL) was added 10% Pd/C (572 mg, 538 μmol, 0.1 Equiv.) under Ar atmosphere. The suspension was degassed and purged with H₂. The mixture was stirred under H₂ (15 Psi) at 20°C for 2 hrs. The reaction is filtered with diatomaceous earth and the filter cake was rinsed with MeOH (10 mL x 3). Then the combined filtrates were concentrated under reduced pressure. The resulting residue was purified by reversed-phase flash chromatography (C18, MeCN in Water (0.2% formic acid), 35%-65% gradient over 10 min) to give **Int. 162** (1.08 g, 3.03 mmol, 56.2% yield, 94.5% purity) as a white solid after lyophilization. LCMS: m/z 336.0 (M-H⁺). ¹H NMR (400 MHz, DMSO-d₆): δ 13.03 (s, 1H), 4.68-4.61 (m, 1H), 3.99 (t, J = 11.6 Hz, 2H), 3.33-3.23 (m, 4H), 2.94-2.80 (m, 1H), 2.50-2.40 (m, 1H). 17 (s, 12H), 1.12 (s, 6H).

20 **Int. 172: Preparation of 1-methyl-5'-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3'H-spiro[azetidine-3,1'-isobenzofuran]:**

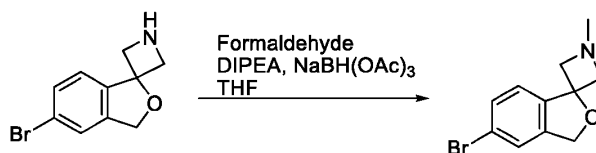


Step 1: 5'-bromo-3'H-spiro[azetidine-3,1'-isobenzofuran]:



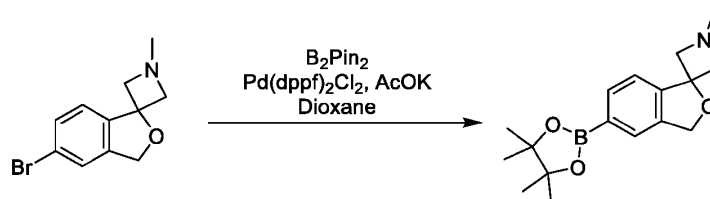
- [0366]** Tert-butyl 5'-bromo-3'-H-spiro[azetidine-3,1'-isobenzofuran]-1-carboxylate (300 mg, 1 Equiv., 882 μmol) was dissolved in 3 mL 3N HCl in MeOH and stirred at 50 °C until the deprotection was complete (monitored via LCMS). The volatile solvent was completely removed to afford the crude deprotection product as the HCl salt. The material can be used without any further purification in the next reaction. **LCMS** (ESI+): m/z 240.37 (M+H).

Step 2: 5'-bromo-1-methyl-3'-H-spiro[azetidine-3,1'-isobenzofuran]:



- [0367]** Crude 5'-bromo-3'-H-spiro[azetidine-3,1'-isobenzofuran] hydrochloride, formaldehyde (98.2 mg, 90.1 μL , 37% Wt, 1.5 Equiv., 1.21 mmol) and DIPEA (313 mg, 421 μL , 3 Equiv., 2.42 mmol) were dissolved in THF (8.67 mL) stirred at 25 °C for 15 mins. Then, $\text{NaBH}(\text{OAc})_3$ (305 mg, 2 Equiv., 1.61 mmol) was added portion-wise to the reaction mixture. The reaction was stirred at room temperature until the starting material was completely consumed (monitored by LCMS). The reaction mixture was diluted with water (20 mL) and extracted with EtOAc (2 x 20 mL). The combined organic layer was washed with brine, dried over MgSO_4 , filtered, and concentrated. The crude mixture was purified by silica gel column chromatography, eluted with DCM / MeOH (95:5). The solvent was removed to afford 5'-bromo-1-methyl-3'-H-spiro[azetidine-3,1'-isobenzofuran] (185 mg, 728 μmol , 90.3 %) as white solid. **LCMS** (ESI+): m/z 253.96 (M+H).

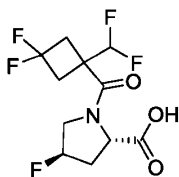
Step 3: Int. 172:



- [0368] In a sealed tube were placed 5'-bromo-1-methyl-3'H-spiro[azetidine-3,1'-isobenzofuran] (185 mg, 1 Equiv., 544 μ mol), Potassium acetate (213 mg, 136 μ L, 4 Equiv., 2.18 mmol) and Bis(pinacolato)diborane (414 mg, 3 Equiv., 1.63 mmol) in Dioxane (2.72 mL). The reaction was degassed for 15 min with Ar and then [1,1'-
- 5 Bis(diphenylphosphino)ferrocene]dichloropalladium(II) Dichloro (22.2 mg, 0.05 Equiv., 27.2 μ mol) was added. The reaction was sealed and heated to 80 °C until the complete consumption of starting material (monitored by LCMS). Then the reaction was cooled to room temperature, quenched with water, and the organic layers were extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with water (2 x 10 mL) and brine (10
- 10 mL), dried (Na_2SO_4), concentrated, and purified by flash column chromatography, (DCM:MeOH, 95:5) and concentrated. This resulted in **Int. 172** (149 mg, 495 μ mol, 68.0 %) as brown solid. LCMS (ESI+): m/z 387.52 (M+H).

Int. 174: (2S,4R)-1-(1-(difluoromethyl)-3,3-difluorocyclobutane-1-carbonyl)-4-fluoropyrrolidine-2-carboxylic acid

15



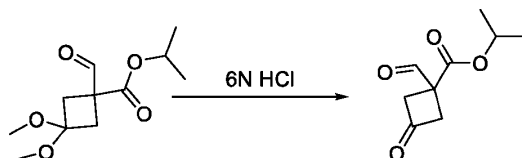
Step 1: Isopropyl 1-formyl-3,3-dimethoxycyclobutane-1-carboxylate:



- [0369] To a stirred solution of 1,1-diisopropyl 3,3-dimethoxycyclobutane-1,1-dicarboxylate (10 g, 34.681 mmol, 1 Equiv.) in DCM (100 mL) was added DIBAL (69.36 mL, 69.362 mmol, 2 Equiv., 1M in DCM) dropwise at -78°C under argon atmosphere. The resulting mixture was stirred for 4hr at -78°C under argon atmosphere. The desired product could be detected by GCMS. The reaction was quenched with 2 N HCl (aq.) at 0°C. The aqueous layer was extracted with CH_2Cl_2 (50 mL x2). The combined organics were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified
- 20
- 25 by silica gel column chromatography, eluted with Pet. Ether / EtOAc (5:1) to afford isopropyl

1-formyl-3,3-dimethoxycyclobutane-1-carboxylate (2.1 g, 25.0%) as a colorless oil. **GCMS**: (EIC): m/z 230.00 (M).

Step 2: Isopropyl 1-formyl-3-oxocyclobutane-1-carboxylate:



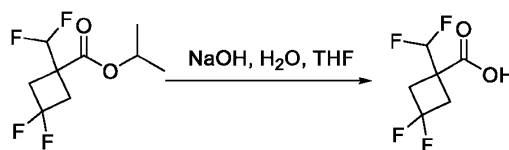
- 5 **[0370]** A mixture of isopropyl 1-formyl-3,3-dimethoxycyclobutane-1-carboxylate (2.1 g, 9.120 mmol, 1 Equiv.) in 6N HCl (25 mL) was stirred overnight at room temperature. Desired product could be detected by GCMS. The aqueous layer was extracted with CH_2Cl_2 (50 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. This resulted in isopropyl 1-formyl-3-oxocyclobutane-1-carboxylate (1.0 g, 53.6%) as a colorless oil which was used in the next reaction without further purification. **GCMS** (EIC): m/z 184.00 (M).

Step 3: Isopropyl 1-(difluoromethyl)-3,3-difluorocyclobutane-1-carboxylate:



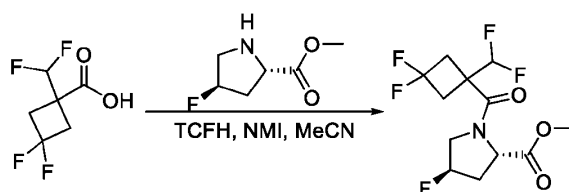
- 15 **[0371]** To a stirred solution of isopropyl 1-formyl-3-oxocyclobutane-1-carboxylate (1 g, 5.429 mmol, 1 Equiv.) in DCM (20 mL) was added DAST (4.81 g, 29.860 mmol, 5.5 Equiv.) dropwise at 0°C under atmosphere of argon. The resulting mixture was stirred overnight at room temperature. Desired product could be detected by GCMS. The reaction was quenched by the addition of sat. NaHCO_3 (aq.) (100 mL) at 0°C . The organics were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 to afford isopropyl 1-(difluoromethyl)-3,3-difluorocyclobutane-1-carboxylate (1 g, 72.65%) as a colorless oil. **GCMS** (EIC): m/z 228.00 (M).

Step 4: 1-(difluoromethyl)-3,3-difluorocyclobutane-1-carboxylic acid:



- [0372]** To a stirred solution of isopropyl 1-(difluoromethyl)-3,3-difluorocyclobutane-1-carboxylate (1.5 g, 6.574 mmol, 1 Equiv.) in THF (20 mL) was added dropwise NaOH (0.79 g, 19.722 mmol, 3 Equiv.) in H₂O (20 mL) at 0°C. The resulting mixture was stirred overnight at room temperature. Desired product could be detected by LCMS. The resulting mixture was diluted with water (20mL) and acidified with HCl (aq.) to pH ~4. The aqueous layer was extracted with EtOAc (2x30 mL). The combined organics were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. This resulted in 1-(difluoromethyl)-3,3-difluorocyclobutane-1-carboxylic acid (730 mg, 56.69%) as a colorless oil. The material was used directly in the next step without further purification. **LCMS (ESI):** *m/z* 185.00 (M-H⁺).

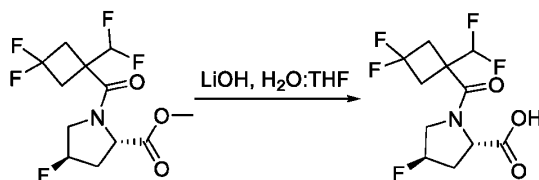
Step 5: Methyl (2S,4R)-1-(1-(difluoromethyl)-3,3-difluorocyclobutane-1-carbonyl)-4-fluoropyrrolidine-2-carboxylate:



- [0373]** Into a solution of 1-(difluoromethyl)-3,3-difluorocyclobutane-1-carboxylic acid (1 g, 5.373 mmol, 1 Equiv.), TCFH (2.26 g, 8.06 mmol, 1.5 Equiv.) and methyl (2S,4R)-4-fluoropyrrolidine-2-carboxylate (0.87 g, 5.910 mmol, 1.1 Equiv.) in MeCN (20 mL) was added NMI (3.31 g, 40.297 mmol, 7.5 Equiv.) dropwise at 0 °C under nitrogen atmosphere. The mixture was stirred for 16 h at room temperature. The reaction solution was concentrated in vacuo. The residue was purified by reverse chromatography (20 g C18; MeCN in Water +0.1% formic acid; 10% to 50% gradient in 40 min). This resulted in methyl (2S,4R)-1-[1-(difluoromethyl)-3,3-difluorocyclobutanecarbonyl]-4-fluoropyrrolidine-2-carboxylate (300 mg, 15.94%) as a brown solid upon removal of solvents. **LCMS (ESI):** *m/z* 315.24 (M+H⁺). **¹H NMR** (400 MHz, DMSO-*d*₆): δ 2.11 (dddd, J = 4.0, 8.9, 14.7, 39.8 Hz, 1H), 2.51 – 2.67

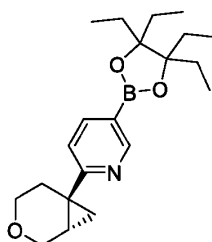
(m, 2H), 2.85 – 3.24 (m, 4H), 3.31 – 3.46 (m, 1H), 3.66 – 3.99 (m, 3H), 4.55 (t, J = 8.7, 8.7 Hz, 1H), 5.41 (dt, J = 3.3, 3.3, 52.6 Hz, 1H), 6.47 (t, J = 55.2, 55.2 Hz, 1H).

Step 6: Int 174:

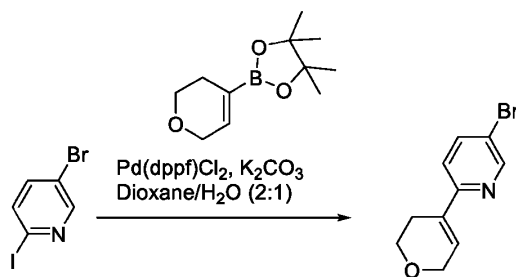


- 5 **[0374]** Into a solution of methyl (2S,4R)-1-[1-(difluoromethyl)-3,3-difluorocyclobutanecarbonyl]-4-fluoropyrrolidine-2-carboxylate (600 mg, 1.903 mmol, 1 Equiv.) in THF (10 mL) was added LiOH (136.75 mg, 5.709 mmol, 3 Equiv.) in H₂O (10 mL) at 0 °C. The resulting solution was stirred for 16hr at room temperature. The reaction mixture was concentrated in vacuo to remove THF. The aqueous layer was acidified with 1 N
- 10 HCl to pH ~4 and extracted with EtOAc (3x20 mL). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated in vacuo. This resulted in **Int. 174** (0.496 g, 84.8%) as a white solid. LCMS (ESI): *m/z* 302.21 (M+H⁺). ¹H NMR (400 MHz, CD₃OD): δ 2.07 – 2.27 (m, 1H), 2.59 – 2.75 (m, 1H), 2.91 – 3.16 (m, 3H), 3.20 – 3.31 (m, 1H), 3.73 (ddd, J = 2.7, 12.6, 36.6 Hz, 1H), 3.95 (ddd, J = 2.3, 12.6, 17.7 Hz, 1H), 4.63 (t, J =
- 15 8.8, 8.8 Hz, 1H), 5.35 (dd, J = 3.4, 52.1 Hz, 1H), 6.24 (t, J = 55.6, 55.6 Hz, 1H).

Int. 176: 2-((1S,6R)-3-oxabicyclo[4.1.0]heptan-6-yl)-5-(4,4,5,5-tetraethyl-1,3,2-dioxaborolan-2-yl)pyridine

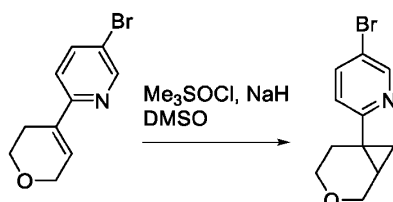


Step 1: 5-bromo-2-(3,6-dihydro-2H-pyran-4-yl)pyridine:



[0375] To a stirred solution of 5-bromo-2-iodopyridine (5 g, 17.612 mmol, 1 Equiv.) and 2-(3,6-dihydro-2H-pyran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.44 g, 21.134 mmol, 1.2 Equiv.) in dioxane (100 mL) and H₂O (50 mL) were added PdCl₂(Dppf)•CH₂Cl₂ (1.43 g, 1.761 mmol, 0.1 Equiv.) and K₂CO₃ (4.87 g, 35.224 mmol, 2 Equiv.) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 6hr at 80°C under nitrogen atmosphere. The resulting mixture was diluted with water (50mL). The aqueous layer was extracted with EtOAc (3x100 mL). The combined organics were dried over anhydrous Na₂SO₄ and concentrated under vacuum. The residue was purified by flash chromatography (PE / EtOAc 3:1) to afford 5-bromo-2-(3,6-dihydro-2H-pyran-4-yl)pyridine (2.8 g, 66.2%) as a light yellow solid. LCMS: (ESI): *m/z* 240.10 (M+H⁺). ¹H NMR (400 MHz, DMSO-*d*₆): δ 2.61 (dddq, *J* = 5.6, 3.9, 2.8, 1.4 Hz, 2H), 3.94 (t, *J* = 5.5 Hz, 2H), 4.36 (q, *J* = 2.8 Hz, 2H), 6.70 (tt, *J* = 3.1, 1.6 Hz, 1H), 7.28 (d, *J* = 8.4 Hz, 1H), 7.78 (dd, *J* = 8.5, 2.4 Hz, 1H), 8.61 (d, *J* = 2.4 Hz, 1H).

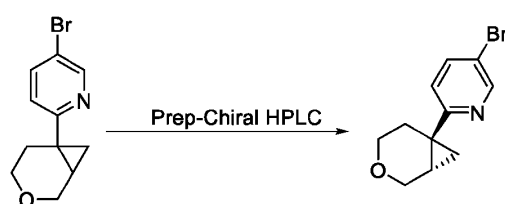
15 Step 2: 2-(3-oxabicyclo[4.1.0]heptan-6-yl)-5-bromopyridine:



[0376] To a stirred mixture of trimethylsulfoxonium chloride Th(3.00 g, 23.324 mmol, 2.00 Equiv.) and NaH (0.93 g, 23.324 mmol, 2.00 Equiv., 60%) in DMSO (30 mL) was added 5-bromo-2-(3,6-dihydro-2H-pyran-4-yl)pyridine (2.8 g, 11.662 mmol, 1 Equiv.) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for overnight at 65°C under nitrogen atmosphere. The reaction was quenched with sat. NH₄Cl (aq.) at 0°C and extracted with EtOAc (3x100 mL). The combined organics were dried over anhydrous Na₂SO₄ and concentrated in vacuo. The residue was purified by reversed-phase flash

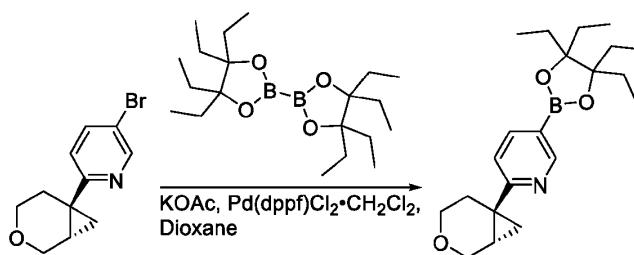
chromatography (C18 silica gel; mobile phase, MeCN in Water with 10mmol/L NH_4HCO_3 , 5% to 95) This resulted in 2-(3-oxabicyclo[4.1.0]heptan-6-yl)-5-bromopyridine (1.1 g, 37.12%) as a light yellow oil. LCMS (ESI): m/z 254.0 ($\text{M}+\text{H}^+$). ^1H NMR (400 MHz, Chloroform- d): δ 1.08 (dd, $J = 6.3, 4.2$ Hz, 1H), 1.27 (dd, $J = 9.1, 4.2$ Hz, 1H), 1.69 (dddd, $J = 9.1, 6.1, 4.3, 1.5$ Hz, 1H), 2.11 (ddd, $J = 14.2, 8.9, 5.6$ Hz, 1H), 2.44 (dt, $J = 13.9, 4.9$ Hz, 1H), 3.46 (ddd, $J = 11.6, 8.9, 5.1$ Hz, 1H), 3.64 (dt, $J = 11.6, 5.2$ Hz, 1H), 3.91 – 4.09 (m, 2H), 7.12 (d, $J = 8.3$ Hz, 1H), 7.71 (dd, $J = 8.5, 2.4$ Hz, 1H), 8.53 (d, $J = 2.4$ Hz, 1H).

Step 3: 2-((1S,6R)-3-oxabicyclo[4.1.0]heptan-6-yl)-5-bromopyridine:



[0377] The 2-(3-oxabicyclo[4.1.0]heptan-6-yl)-5-bromopyridine (800 mg, 3.148 mmol, 1 Equiv.) was purified by Prep-Chiral-HPLC with the following conditions (Column: CHIRALPAK IG, 2x25 cm, 5 μm ; Mobile Phase A: Hex(0.5% 2M $\text{NH}_3\text{-MeOH}$), Mobile Phase B: MeOH: DCM=1: 1--HPLC; Flow rate: 20 mL/min; Gradient: 10% B) to afford 2-((1S,6R)-3-oxabicyclo[4.1.0]heptan-6-yl)-5-bromopyridine (250 mg, 31.25%) as a colorless oil. LCMS (ESI): m/z 254.00 ($\text{M}+\text{H}^+$).

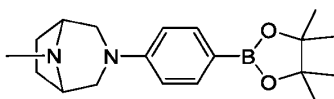
Step 4: Int.176:



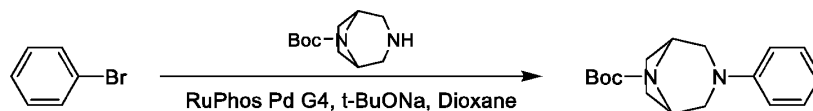
[0378] To a stirred solution of 2-((1S,6R)-3-oxabicyclo[4.1.0]heptan-6-yl)-5-bromopyridine (240 mg, 0.944 mmol, 1 Equiv.), KOAc (278.06 mg, 2.83 mmol, 3 Equiv.) and 4,4,5,5-tetraethyl-2-(4,4,5,5-tetraethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (414.97 mg, 1.133 mmol, 1.2 Equiv.) in dioxane (10 mL) was added $\text{Pd}(\text{dppf})\text{Cl}_2\cdot\text{CH}_2\text{Cl}_2$ (76.93 mg, 0.094 mmol, 0.1 Equiv.) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2h at 80°C under nitrogen atmosphere. The resulting mixture

was concentrated under vacuum. The residue was purified by Prep-TLC (Pet. Ether / EtOAc 7:1) to afford **Int. 176** as a colorless oil. LCMS (ESI): m/z 358.15 ($M+H^+$). 1H NMR (400 MHz, DMSO- d_6): δ 0.91 (t, $J = 7.4$ Hz, 12H), 1.03 (dd, $J = 6.3, 3.9$ Hz, 1H), 1.27 (dd, $J = 9.0, 3.8$ Hz, 1H), 1.58 (q, $J = 7.5$ Hz, 2H), 1.63 – 1.78 (m, 9H), 1.98 (ddd, $J = 13.8, 8.6, 5.4$ Hz, 1H), 2.53 – 2.62 (m, 1H), 3.35 – 3.44 (m, 1H), 3.53 (dt, $J = 11.1, 5.3$ Hz, 1H), 3.81 (d, $J = 11.3$ Hz, 1H), 3.92 (dd, $J = 11.3, 4.6$ Hz, 1H), 7.35 (d, $J = 8.0$ Hz, 1H), 7.92 (dd, $J = 8.1, 1.8$ Hz, 1H), 8.66 (s, 1H).

Int. 178: Preparation of 8-methyl-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-3,8-diazabicyclo[3.2.1]octane

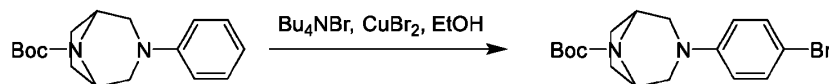


Step 1: tert-butyl 3-phenyl-3,8-diazabicyclo[3.2.1]octane-8-carboxylate:



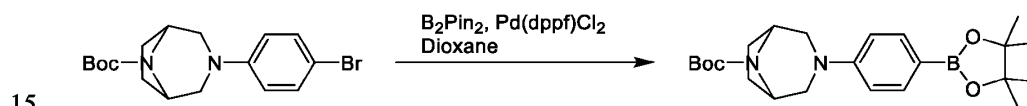
[0379] To a solution of bromobenzene (5 g, 31.85 mmol, 3.35 mL, 1 Equiv.) in dioxane (25 mL) was added *t*-BuONa in dioxane (2 M, 31.85 mL, 2), tert-butyl 3,8-diazabicyclo[3.2.1]octane-8-carboxylate (7.44 g, 35.03 mmol, 1.1 Equiv.) and RuPhos Pd G4 (2.71 g, 3.18 mmol, 0.1 Equiv.) under N_2 . The mixture was stirred at 90 °C for 12 hr under N_2 . LCMS showed starting material was consumed desired mass was detected. The reaction mixture was cooled to room temperature and diluted with water (50 mL), extracted with EtOAc (2 x 50 mL). The combined organics were washed with brine (50 mL), dried over Na_2SO_4 , filtered, and concentrated under reduced. The resulting residue was purified by flash silica gel chromatography (Pet. Ether / EtOAc, 5:1) to afford tert-butyl 3-phenyl-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (9 g, 31.2 mmol, 97%) as a white solid. LCMS (ESI+): m/z 289.3 ($M+H^+$). 1H NMR (400 MHz, $CDCl_3$): δ 7.32 - 7.28 (m, 2H), 6.90 - 6.81 (m, 3H), 4.49 - 4.30 (m, 2H), 3.44 (dd, $J = 1.9, 11.1$ Hz, 2H), 3.02 (br s, 2H), 2.02 - 1.85 (m, 4H), 1.51 (s, 9H).

Step 2: tert-butyl 3-(4-bromophenyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate:



[0380] To a solution of tert-butyl 3-phenyl-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (9 g, 31.21 mmol, 1 Equiv.) ethanol (540 mL) was added tetrabutylammonium bromide (10.06 g, 31.21 mmol, 1 Equiv.) and dibromocopper (10.46 g, 46.81 mmol, 2.19 mL, 1.5 Equiv.) under N₂. The mixture was stirred at 25 °C for 12 hrs. LCMS showed starting material was consumed and desired mass was detected. The reaction mixture was filtered, and the filter cake was rinsed with EtOAc (3 x 20 mL). Then the combined filtrates were concentrated under reduced pressure. The resulting residue was purified by flash silica gel chromatography (Pet. Ether / EtOAc, 5:1) to afford tert-butyl 3-(4-bromophenyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (5.0 g, 13.6 mmol, 44%) as a white solid. LCMS (ESI+): *m/z* 367.1 (M+H⁺). ¹H NMR (400 MHz, CDCl₃): δ 7.33 (d, J = 9.0 Hz, 2H), 6.70 (br d, J = 9.0 Hz, 2H), 4.36 (br s, 2H), 3.40 - 3.30 (m, 2H), 2.97 (br s, 2H), 2.02 - 1.79 (m, 4H), 1.48 (s, 9H).

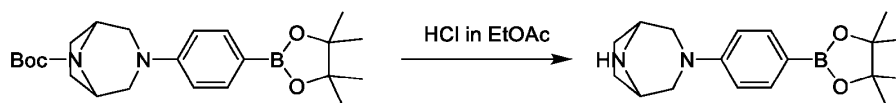
Step 3: tert-butyl 3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate:



[0381] To a solution of tert-butyl 3-(4-bromophenyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (4 g, 10.89 mmol, 1 Equiv.) dioxane (40 mL) was added bis(pinacolato)diboron (4.15 g, 16.34 mmol, 1.5 Equiv.), potassium acetate (3.21 g, 32.67 mmol, 3 Equiv.) and Pd(dppf)Cl₂ (796.89 mg, 1.09 mmol, 0.1 Equiv.) under N₂. The mixture was stirred at 80 °C for 12 hrs under N₂. LCMS showed starting material was consumed and desired mass was detected. The reaction mixture was filtered, and the filter cake was rinsed with EtOAc (45 mL). Then the combined filtrates were concentrated under reduced pressure. The resulting residue was purified by flash silica gel chromatography, eluted with Pet. Ether / EtOAc (4:1) to afford a yellow solid. The yellow solid was triturated with Pet. Ether (30 mL) at 25 °C for 30 min, filtered. The filter cake was concentrated to give tert-butyl 3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (3.4 g, 8.21 mmol, 75%) as a white solid. LCMS (ESI+): *m/z* 415.2 (M+H⁺). ¹H NMR (400 MHz, CDCl₃): δ 7.71 (d, J = 8.5 Hz, 2H), 6.82 (d, J = 8.5 Hz, 2H), 4.48 - 4.27 (m, 2H), 3.49 (dd, J = 1.8, 11.3 Hz, 2H), 3.04 (s, 2H), 2.00 - 1.80 (m, 4H), 1.48 (s, 9H), 1.38 - 1.30 (m, 12H).

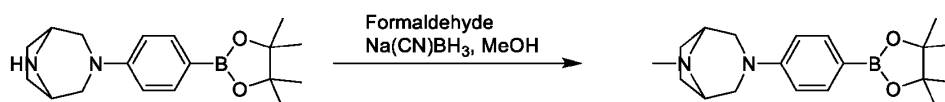
30 **Step 4: 3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-3,8-diazabicyclo[3.2.1]**

octane:



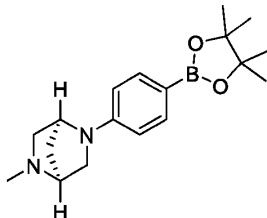
- [0382]** To a solution of tert-butyl 3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (4.1 g, 9.90 mmol, 1 Equiv.) in EtOAc (20 mL) was added HCl / EtOAc (4 M, 40 mL, 16.17 Equiv.) dropwise. The mixture was stirred at 25 °C until LCMS showed the consumption of starting material. The mixture was filtered with EtOAc (30 mL) and the filter cake was concentrated under reduced pressure to give 3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-3,8-diazabicyclo[3.2.1]octane (2.6 g, 7.4 mmol, 75%, HCl Salt) as a white solid. LCMS (ESI+): m/z 315.2 (M+H⁺). ¹H NMR (400 MHz, MeOD-*d*₆): δ 7.65 (d, J = 8.8 Hz, 2H), 6.93 (d, J = 8.8 Hz, 2H), 4.19 (s, 2H), 3.80 (dd, J = 2.4, 13.1 Hz, 2H), 3.13 (d, J = 12.1 Hz, 2H), 2.13 (s, 4H), 1.33 (s, 12H)

Step 5: Int. 178:

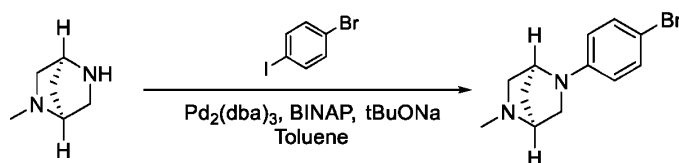


- [0383]** To a solution of 3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-3,8-diazabicyclo[3.2.1]octane (2.4 g, 6.84 mmol, 1 Equiv., HCl) in methanol (24 mL) was added formaldehyde (2.78 g, 34.22 mmol, 2.55 mL, 37% purity, 5 Equiv.). The mixture was stirred for 30 min under N₂. Then Na(CN)BH₃ (860.14 mg, 13.69 mmol, 2 Equiv.) was added to the reaction. The mixture was stirred at 25 °C until the consumption of starting material was observed (LCMS). The reaction mixture was diluted by water (50 mL), extracted with EtOAc (2 x 50 mL). The combined organics were washed with brine (50 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting residue was triturated with methyl tert-butyl ether (20 mL), then filtered. The filter cake was collected to give **Int. 178** (1.07 g, 3.26 mmol, 48%) as a white solid. LCMS (ESI+): m/z 329.2 (M+H⁺). ¹H NMR (400 MHz, MeOD-*d*₆): δ 7.58 (d, J = 8.6 Hz, 2H), 6.80 (d, J = 8.6 Hz, 2H), 3.53 - 3.48 (m, 2H), 3.35 - 3.32 (m, 2H), 2.99 (br d, J = 10.0 Hz, 2H), 2.36 (s, 3H), 2.14 - 2.06 (m, 2H), 1.81 - 1.74 (m, 2H), 1.32 (s, 12H)

Int. 179: Preparation of (1S,4S)-2-methyl-5-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-2,5-diazabicyclo[2.2.1]heptane



Step 1: (1S, 4S)-2-(4-bromophenyl)-5-methyl-2, 5-diazabicyclo [2.2.1] heptane:



5

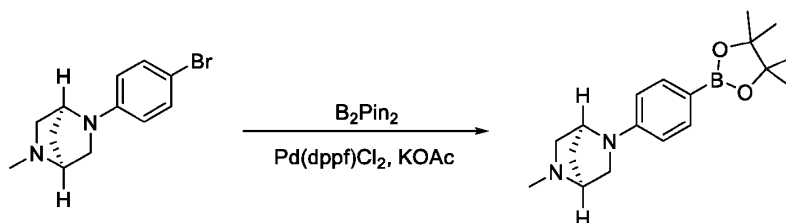
[0384] A mixture of (1S,4S)-2-methyl-2,5-diazabicyclo[2.2.1]heptane; dihydrobromide (3.90 g, 14.2 mmol, 1.0 Equiv.), 1-bromo-4-iodo-benzene (4.03 g, 14.2 mmol, 1.0 Equiv.), $\text{Pd}_2(\text{dba})_3$ (391 mg, 427 μmol , 0.03 Equiv.), *t*-BuONa (3.42 g, 35.6 mmol, 2.5 Equiv.) and [1-(2-diphenylphosphanyl-1-naphthyl)-2-naphthyl]-diphenyl-phosphane (88.63 mg, 142.34 μmol , 0.01 Equiv.) in toluene (160 mL) was degassed and purged with N_2 , then the mixture was stirred at 110°C for 12hr under N_2 atmosphere. After cooling to room temperature, the reaction mixture was concentrated to remove solvent. Water (50 mL) was added and the aqueous phase was extracted with EtOAc (30 mL $\times$ 3), the combined organic phase was washed with brine (30 mL $\times$ 3), dried over Na_2SO_4 , filtered, and concentrated. The resulting residue was dissolved in water (50 mL) and acidified to pH of 5-6 with HCl (1 M), the aqueous phase was extracted with MTBE (30mL $\times$ 3). Then the aqueous phase was alkalized to pH of 7-8 with saturated NaHCO_3 and extracted with ethyl acetate (50 mL $\times$ 3), the combined organic layers were dried over Na_2SO_4 , filtered and the filtrate was concentrated to give (1S,4S)-2-(4-bromophenyl)-5-methyl-2,5-diazabicyclo[2.2.1]heptane (1.70 g, 6.12 mmol, 43.01% yield) as a yellow oil. LCMS (ESI $^+$): m/z 267.2 ($\text{M}^+ \text{H}^+$).

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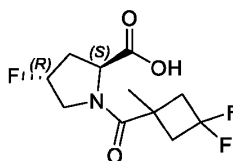
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Step 2: Int. 179:



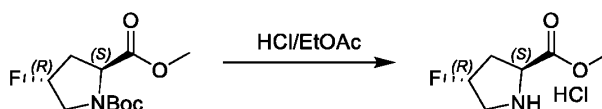
[0385] A mixture of (1S, 4S)-2-(4-bromophenyl)-5-methyl-2,5-diazabicyclo[2.2.1]heptane (1.70 g, 6.36 mmol, 1.0 Equiv.), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (2.75 g, 10.8 mmol, 1.7 Equiv.), KOAc (1.56 g, 15.9 mmol, 2.5 Equiv.), Pd(dppf)Cl₂ (232 mg, 318 μmol, 0.05 Equiv.) in dioxane (20 mL) was degassed and purged with N₂. The mixture was stirred at 100 °C for 12hr under N₂ atmosphere. After cooling to room temperature, the reaction mixture was concentrated. The resulting residue was diluted with water (30 mL) and EtOAc (20 mL), the resultant mixture was filtered, and the filter cake was rinsed with EtOAc (20 mL x3), the resulting biphasic solution was separated, then the aqueous phase was extracted with EtOAc (30 mL x3), the combined organic layers were dried over Na₂SO₄, filtered and the filtrate was concentrated. The resulting residue was purified by silica gel column chromatography (Pet. Ether / EtOAc, 1:0 to 20:1) to afford **Int. 179** (650 mg, 2.02 mmol, 31.74% yield) as a brown solid. **LCMS** (ESI+): m/z 315.2 (M+H⁺). **¹H NMR** (400 MHz, DMSO-d₆): δ 7.44 (d, J = 8.0 Hz, 2H), 6.53 (d, J = 8.0 Hz, 2H), 4.32 (s, 1H), 3.30 (d, J = 9.2 Hz, 2H), 3.17 (d, J = 9.2 Hz, 1H), 2.78 (d, J = 8.8 Hz, 1H), 2.42 (d, J = 9.2 Hz, 1H), 2.24 (s, 3H), 1.84-1.91 (m, 1H), 1.75 (d, J = 8.8 Hz, 1H), 1.25 (s, 12H).

Int. 180: (2S,4R)-1-(3,3-difluoro-1-methylcyclobutane-1-carbonyl)-4-fluoropyrrolidine-2-carboxylic acid



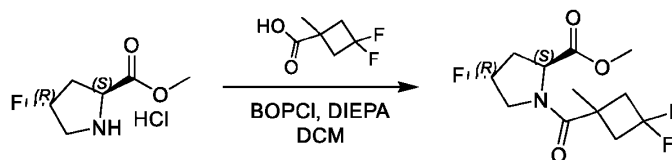
20

Step 1: methyl (2S,4R)-4-fluoropyrrolidine-2-carboxylate hydrochloride:



[0386] To a solution of 1-(tert-butyl) 2-methyl (2S,4R)-4-fluoropyrrolidine-1,2-dicarboxylate (5 g, 20.22 mmol, 1 Equiv.) in EtOAc (10 mL) was added dropwise HCl / EtOAc (4 M, 200 mL, 39.56 Equiv.). The mixture was stirred until the complete consumption of starting material (LCMS). The reaction was concentrated under reduced pressure to afford methyl (2S,4R)-4-fluoropyrrolidine-2-carboxylate hydrochloride (3.5 g, 17.16 mmol, 84.84% yield, HCl salt) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.25 (br d, J = 1.1 Hz, 1H), 5.57 - 5.32 (m, 1H), 4.55 (dd, J = 7.3, 11.3 Hz, 1H), 3.66 - 3.34 (m, 3H), 2.79 - 2.51 (m, 3H), 2.43 - 2.21 (m, 1H).

Step 2: methyl (2S,4R)-4-fluoropyrrolidine-2-carboxylate hydrochloride:



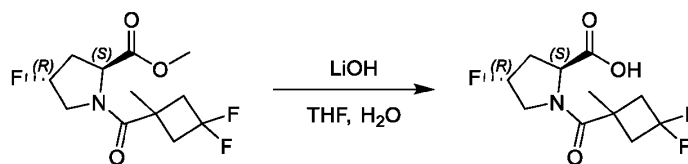
10

[0387] To a solution of 3,3-difluoro-1-methyl-cyclobutanecarboxylic acid (2.70 g, 17.97 mmol, 1.1 Equiv.) in DCM (30 mL) was added DIEPA (2.11 g, 16.34 mmol, 2.85 mL, 1 Equiv.). The mixture was stirred at 20 °C for 10 min. 3-[chloro-(2-oxooxazolidin-3-yl)phosphoryl]oxazolidin-2-one (4.58 g, 17.97 mmol, 1.1 Equiv.) was added to the mixture. Methyl (2S,4R)-4-fluoropyrrolidine-2-carboxylate (3 g, 16.34 mmol, 1 Equiv., HCl) and DIEPA (4.22 g, 32.68 mmol, 5.69 mL, 2 Equiv.) were added to the mixture. The mixture was stirred at room temperature until the complete consumption of starting material (LCMS). The reaction mixture was quenched by water (30 mL), extracted with DCM (2 x 30 mL). The combined organics were washed with NaHCO₃ (2 x 20 mL), brine (20 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to afford methyl(2S,4R)-1-(3,3-difluoro-1-methyl-cyclobutanecarbonyl)-4-fluoro-pyrrolidine-2-carboxylate (4.5 g, 14.82 mmol, 90.69%) as a yellow gum. LCMS (ESI⁺): *m/z* 280.2 (M+H⁺).

15

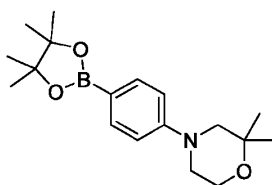
20

Step 3: Int. 180:

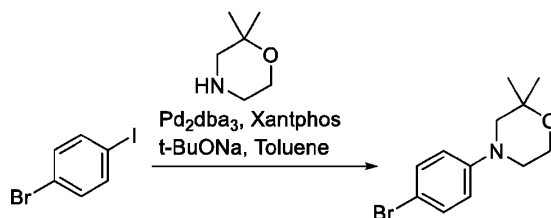


- [0388] To a solution of methyl (2S,4R)-1-(3,3-difluoro-1-methyl-cyclobutanecarbonyl)-4-fluoro-pyrrolidine-2-carboxylate (4.5 g, 16.11 mmol, 1 Equiv.) in THF (20 mL) was added LiOH•H₂O (2 M, 12.09 mL, 1.5 Equiv.). The reaction was stirred at 20 °C until the complete consumption of starting material was observed (LCMS). The reaction mixture was
- 5 concentrated under reduced pressure to remove THF, extracted with MTBE (2 x 20 mL) and acidified by 1N HCl to pH=1~2 at 0 °C. The aqueous phase was extracted with EtOAc (2 x 20 mL). The combined organics were washed with brine (20 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to afford **Int. 180** (3.85 g, 13.58 mmol, 84.28%) as a white solid. **LCMS** (ESI+): *m/z* 266.00 (M+H⁺). **¹H NMR** (400 MHz, CDCl₃):
- 10 5.40 - 5.20 (m, 1H), 4.79 (t, J = 8.6 Hz, 1H), 3.77 (ddd, J = 1.9, 12.6, 17.9 Hz, 1H), 3.66 - 3.47 (m, 1H), 3.23 - 2.95 (m, 2H), 2.70 - 2.37 (m, 4H), 1.55 (s, 3H).

Int. 181: 2,2-dimethyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)morpholine



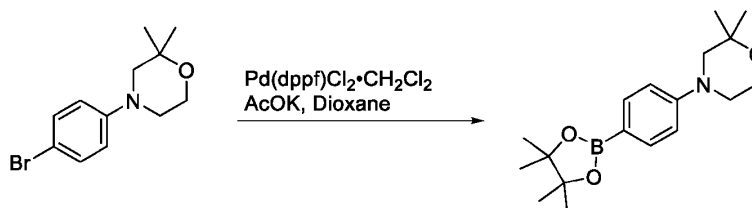
- 15 **Step 1: 4-(4-bromophenyl)-2,2-dimethylmorpholine:**



- [0389] A solution of 4-bromoiodobenzene (2 g, 7.069 mmol, 1 Equiv.), 2,2-dimethylmorpholine (1.63 g, 14.14 mmol, 2 Equiv.), XantPhos (409.06 mg, 0.707 mmol, 0.1 Equiv.), t-BuONa (4.24 mL, 8.483 mmol, 1.20 Equiv.) and Pd₂dba₃ (323.69 mg, 0.353 mmol, 0.05 Equiv.) in Toluene (20 mL) was stirred for 16hr at 100°C under N₂ atmosphere. The resulting mixture was diluted with water (50mL) and then extracted with EtOAc (3 x 50mL). The combined organic layers were washed with brine (2 x 20mL) and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under vacuum. The residue was
- 20 purified by reversed-phase flash chromatography with the following conditions: C18; mobile

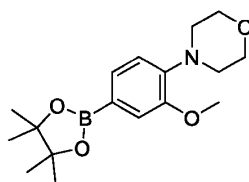
phase, MeCN in Water (0.1% FA), 0% to 100% gradient in 20 min. This resulted in 4-(4-bromophenyl)-2,2-dimethylmorpholine (1.4 g, 73.3%) as a brown oil. **LCMS**: (ESI): m/z 270.01 ($M+H^+$). **1H NMR** (400 MHz, DMSO- d_6): δ 1.21 (s, 6H), 2.93 (s, 2H), 2.98 – 3.08 (m, 2H), 3.67 – 3.77 (m, 2H), 6.84 – 6.94 (m, 2H), 7.29 – 7.38 (m, 2H).

5 **Step 2: Int. 181:**

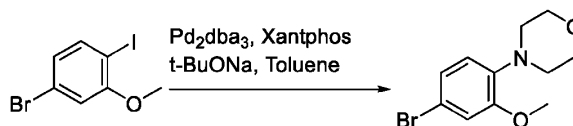


[0390] A solution of 4-(4-bromophenyl)-2,2-dimethylmorpholine (1.41 g, 5.219 mmol, 1 Equiv.), bis(pinacolato)diboron (1.46 g, 5.741 mmol, 1.1 Equiv.), AcOK (1.54 g, 15.657 mmol, 3 Equiv.) and Pd(dppf)Cl₂CH₂Cl₂ (425.14 mg, 0.522 mmol, 0.1 Equiv.) in 1,4-dioxane
 10 (15 mL) was stirred for 16h at 80°C under N₂ atmosphere. The resulting mixture was diluted with EtOAc (100mL) and then filtered. The filter cake was washed with EtOAc (2 x 50mL). The combined filtrates were concentrated under vacuum. The residue was purified FCC (PE / EtOAc 4:1) to afford **Int. 181** (1.45 g, 87.3%) as an off-white solid. **LCMS** (ESI): m/z 318.20 ($M+H^+$). **1H NMR** (400 MHz, DMSO- d_6): δ 1.23 (d, J = 20.8 Hz, 18H), 3.03 (s, 2H), 3.08 –
 15 3.16 (m, 2H), 3.68 – 3.76 (m, 2H), 6.85 – 6.92 (m, 2H), 7.47 – 7.53 (m, 2H).

Int. 182: 4-(2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)morpholine



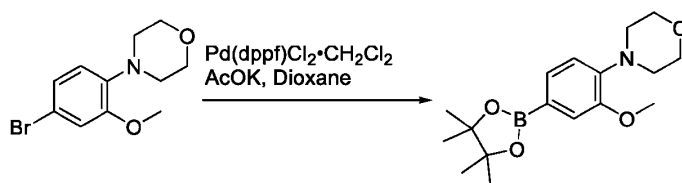
Step 1: 4-(4-bromo-2-methoxyphenyl)morpholine:



20

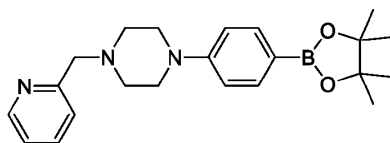
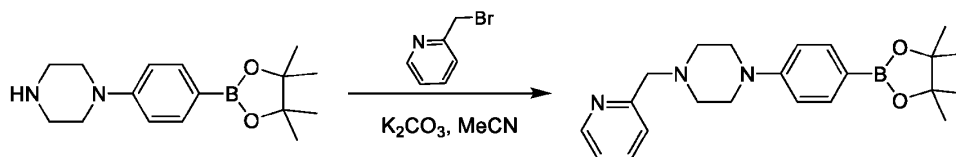
- [0391] A solution of morpholine (1.11 g, 12.8 mmol, 2 Equiv.), 4-bromo-1-iodo-2-methoxybenzene (2 g, 6.391 mmol, 1 Equiv.), XantPhos (369.81 mg, 0.639 mmol, 0.1 Equiv.), t-BuONa (3.83 mL, 7.669 mmol, 1.2 Equiv.) and Pd₂dba₃ (292.63 mg, 0.32 mmol, 0.05 Equiv.) in toluene (20 mL) was stirred for 16hr at 100°C under N₂ atmosphere. The resulting mixture was diluted with water (50mL) and then extracted with EtOAc (3 x 50mL). The combined organic layers were washed with brine (3x50mL) and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under vacuum. The residue was purified by reversed-phase flash chromatography with the following conditions: C18; mobile phase, MeCN in Water (0.1% FA), 0% to 100%. This resulted in 4-(4-bromo-2-methoxyphenyl)morpholine (1.1 g, 63.2%) as a light yellow solid upon the removal of solvent. LCMS: (ESI): *m/z* 271.95 (M+H⁺). ¹H NMR (400 MHz, DMSO-*d*₆): δ 2.88 – 2.96 (m, 4H), 3.70 (d, *J* = 9.3 Hz, 4H), 3.80 (s, 3H), 6.82 (d, *J* = 8.4 Hz, 1H), 7.03 – 7.10 (m, 2H).

Step 2: Int. 182:



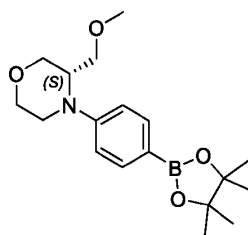
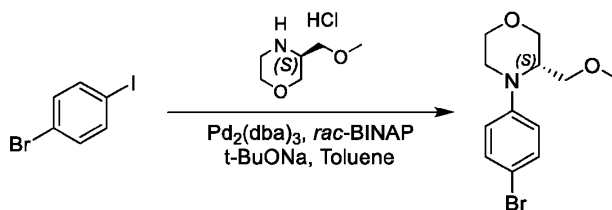
- [0392] A solution of 4-(4-bromo-2-methoxyphenyl)morpholine (1.4 g, 5.1 mmol, 1 Equiv.), bis(pinacolato)diboron (1.44 g, 5.7 mmol, 1.1 Equiv.), AcOK (1.51 g, 15.4 mmol, 3 Equiv.) and Pd(dppf)Cl₂·CH₂Cl₂ (419.07 mg, 0.514 mmol, 0.1 Equiv.) in 1,4-dioxane (20 mL) was stirred for 16hr at 80°C under N₂ atmosphere. The resulting mixture was diluted with water (50mL) and then extracted with EtOAc (3 x 50mL). The combined organic layers were washed with brine (50mL) and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under vacuum. The residue was purified by FCC (PE / EtOAc 3:1) to afford Int. 182 (1.28 g, 78.1%) as an off-white solid. LCMS (ESI): *m/z* 320.20 (M+H⁺). ¹H NMR (400 MHz, DMSO-*d*₆): δ 1.28 (s, 12H), 2.95 – 3.03 (m, 4H), 3.72 (t, *J* = 4.6 Hz, 4H), 3.79 (s, 3H), 6.87 (d, *J* = 7.8 Hz, 1H), 7.12 (d, *J* = 1.3 Hz, 1H), 7.24 (dd, *J* = 7.8, 1.3 Hz, 1H).

Int. 183: 1-(pyridin-2-ylmethyl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazine

**Step 1: Int. 183:**

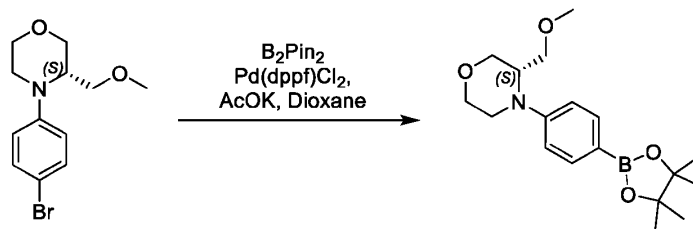
- [0393]** To a solution of 1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine (8.7 g, 30.19 mmol, 1 Equiv.) in MeCN (200 mL) was added 2-(bromomethyl)pyridine (5.71 g, 33.21 mmol, 1.1 Equiv.) and K_2CO_3 (16.69 g, 120.75 mmol, 4 eq). The mixture was stirred at 60 °C for 12 hrs. LCMS showed starting material was consumed and desired mass was detected. The reaction mixture was concentrated under reduced pressure to afford a crude residue. The residue was triturated with Pet. Ether (20 mL), then filtered, the filter cake was dried and collected to afford **Int. 183** (8.3 g, 21.9 mmol, 73%) as a yellow solid. LCMS (ESI⁺): m/z 380.20 ($M+H^+$). ¹H NMR (400 MHz, $CDCl_3$): δ 8.65 - 8.55 (m, 1H), 7.78 - 7.62 (m, 3H), 7.46 (br d, 1H), 7.19 (dd, 1H), 6.89 (d, 2H), 3.74 (s, 2H), 3.31 (br d, 4H), 2.69 (br s, 4H), 1.33 (s, 12H).

Int. 184: Preparation of (S)-3-(methoxymethyl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl) morpholine

**Step 1: (S)-4-(4-bromophenyl)-3-(methoxymethyl) morpholine:**

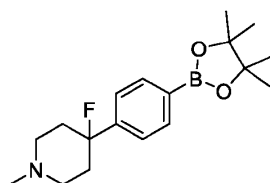
[0394] A mixture of 1-bromo-4-iodo-benzene (3.80 g, 13.4 mmol, 1.0 Equiv.), (3S)-3-(methoxymethyl) morpholine (2.03 g, 12.1 mmol, 0.9 Equiv., HCl), Pd₂(dba)₃ (123 mg, 134 μmol, 0.01 Equiv.), BINAP (83.6 mg, 134 μmol, 0.01 Equiv.) and *t*-BuONa (3.87 g, 40.3 mmol, 3.0 Equiv.) in toluene (50 mL) was degassed and purged with N₂. The mixture was stirred at 80°C for 10 hr under N₂ atmosphere. The toluene was removed in vacuum, then water (50 mL) and saturated NH₄Cl (20 mL) were added, and the aqueous phase was extracted with EtOAc (50 mL x 3), the combined organic phase was dried with anhydrous Na₂SO₄, filtered, and concentrated in vacuum. The resulting residue was purified by silica gel column chromatography (Pet. Ether / EtOAc, 1:0 to 10:1) to afford (S)-4-(4-bromophenyl)-3-(methoxymethyl) morpholine (2.80 g, 9.78 mmol, 72.8%) as brown oil. LCMS (ESI+): m/z 286.3/288.3 (M+H⁺).

Step 2: Int. 184:

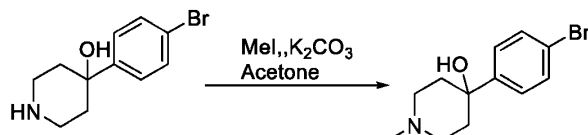


[0395] A mixture of (3S)-4-(4-bromophenyl)-3-(methoxymethyl)morpholine (2.60 g, 9.09 mmol, 1.0 Equiv.), Pd(dppf)Cl₂ (332 mg, 454 μmol, 0.05 Equiv.), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (2.54 g, 9.99 mmol, 1.1 Equiv.) and KOAc (2.23 g, 22.7 mmol, 2.5 Equiv.) in dioxane (30 mL) was degassed and purged with N₂. The reaction mixture was stirred at 100 °C for 5hr under N₂ atmosphere. The dioxane was removed in vacuum, water (30 mL) was added and the aqueous phase was extracted with EtOAc (30 mL x 3), the combined organic phase was dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was subsequently purified by silica gel column chromatography (Pet. Ether / EtOAc, 1:0 to 10:1) to afford **Int. 18** (1.30 g, 3.90 mmol, 42.9%) as white solid. LCMS (ESI+): m/z 334.2 (M+H⁺). ¹H NMR (400 MHz, CDCl₃): δ 7.79-7.68 (m, 2H), 6.85 (d, J = 8.4 Hz, 2H), 4.15 (d, J = 11.6 Hz, 1H), 4.05-3.96 (m, 1H), 3.84 (d, J = 10.0 Hz, 1H), 3.77-3.68 (m, 3H), 3.32 (s, 3H), 3.30 (s, 2H), 3.19-3.09 (m, 1H), 1.34 (s, 12H).

Int. 186: 4-fluoro-1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidine

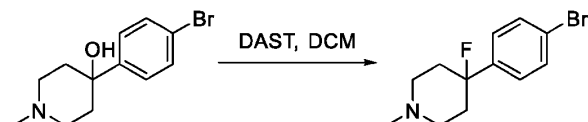


Step 1: 4-(4-bromophenyl)-1-methylpiperidin-4-ol:



[0396] To a solution of 4-(4-bromophenyl)piperidin-4-ol (5 g, 19.520 mmol, 1
5 Equiv.) in acetone (20 mL) was added MeI (3.05 g, 21.5 mmol, 1.1 Equiv.) and K₂CO₃ (4.05
g, 29.3 mmol, 1.5 Equiv.). The resulting mixture was stirred for 1h at room
temperature under nitrogen atmosphere. The product was detected by LCMS. The reaction
was filtered, and the filter cake was washed with EtOAc. The combined organics were dried
over anhydrous Na₂SO₄ and concentrated in vacuo. The residue was purified by reversed-
10 phase flash chromatography (MeCN in Water with 0.1% FA 5% to 100%) to afford 4-(4-
bromophenyl)-1-methylpiperidin-4-ol (1 g, 18.96%) as a white solid after removal of
solvents. **LCMS:** (ESI): *m/z* 270.00 (M+H⁺).

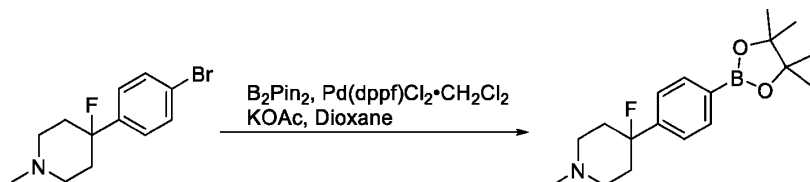
Step 2: 4-(4-bromophenyl)-4-fluoro-1-methylpiperidine:



15 **[0397]** To a solution of 4-(4-bromophenyl)-1-methylpiperidin-4-ol (2 g, 7.403 mmol, 1
Equiv.) in DCM (30 mL) was added dropwise DAST (2.39 g, 14.806 mmol, 2 Equiv.) in
DCM (30 mL) at -78°C under nitrogen atmosphere. The resulting mixture was stirred
warmed to RT and stirred overnight. The desired product could be detected by LCMS. The
reaction mixture was quenched by the addition of saturated NaHCO₃ at -10°C and extracted
20 with DCM. The combined organics were dried over anhydrous Na₂SO₄ and concentrated in
vacuo. The resulting crude product was purified by Prep-HPLC (Water with 10mmol/L
NH₄HCO₃ + 0.05% NH₃H₂O and MeOH/t 58% to 80% over 10 min) to afford 4-(4-

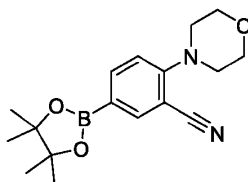
bromophenyl)-4-fluoro-1-methylpiperidine (700 mg, 34.74%) as a white solid. LCMS (ESI): m/z 272.00 ($M+H^+$).

Step 3: Int. 186:



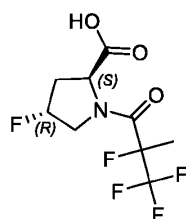
- 5 **[0398]** To a mixture of 4-(4-bromophenyl)-4-fluoro-1-methylpiperidine (700 mg, 2.57 mmol, 1 Equiv.) and bis(pinacolato)diboron (979.70 mg, 3.86 mmol, 1.5 Equiv.) in dioxane (20 mL) were added Pd(dppf)Cl₂·CH₂Cl₂ (209.52 mg, 0.257 mmol, 0.1 Equiv.) and KOAc (757.27 mg, 7.72 mmol, 3 Equiv.) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at 80°C under nitrogen atmosphere. The reaction
- 10 mixture was diluted with water and extracted with EtOAc. The organic layer was dried over anhydrous Na₂SO₄ and concentrated in vacuo. The residue was purified FCC (DCM / MeOH 10:1) to afford **Int. 186** (211 mg, 25.70%) as a light yellow solid after the removal of solvent. LCMS (ESI): m/z 320.25 ($M+H^+$). ¹H NMR (400 MHz, DMSO-*d*₆): δ 1.29 (s, 11H), 1.88 – 2.01 (m, 3H), 2.09 – 2.32 (m, 2H), 2.42 (s, 3H), 2.51 (s, 2H), 2.93 (s, 2H), 7.40 (dd, J = 21.2,
- 15 7.9 Hz, 2H), 7.76 (dd, J = 42.1, 7.8 Hz, 2H).

Int. 187: Preparation of 2-morpholino-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile:

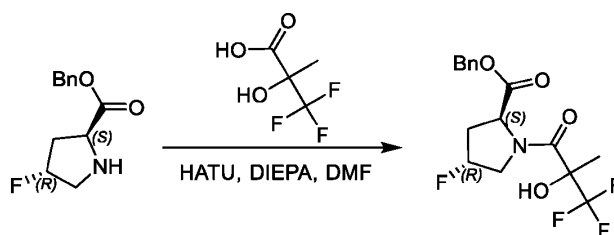


- [0399]** 2-morpholino-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile (Int. 187): Int. 187 was prepared according to the procedure for step 3 of Int. 172 using 5-Bromo-2-morpholinobenzonitrile as starting material. LCMS (ESI+): m/z 313.85 ($M+H$).
- 20

Int. 189: Preparation of (2S, 4R)-4-fluoro-1-(2, 3, 3, 3-tetrafluoro-2-methylpropanoyl)pyrrolidine-2-carboxylic acid

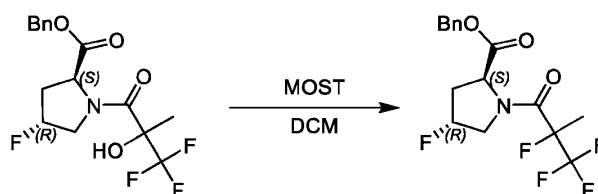


Step 1: benzyl (2S, 4R)-4-fluoro-1-(3, 3, 3-trifluoro-2-hydroxy-2-methylpropanoyl) pyrrolidine-2-carboxylate:



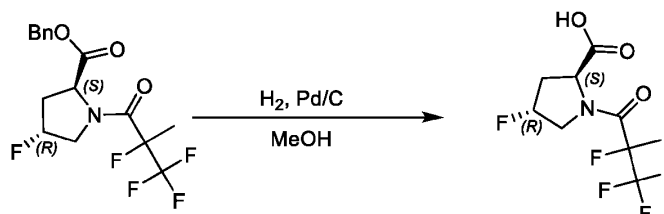
- 5 **[0400]** To a solution of benzyl (2S,4R)-4-fluoropyrrolidine-2-carboxylate (4.24 g, 18.9 mmol, 1.0 Equiv.) in DMF (70 mL) was added DIEPA (7.36 g, 56.9 mmol, 9.92 mL, 3.0 Equiv.), then 3,3,3-trifluoro-2-hydroxy-2-methyl-propanoic acid (3.00 g, 18.9 mmol, 1.0 Equiv.) and HATU (10.8 g, 28.4 mmol, 1.5 Equiv.) were added at 0°C and stirred at 25°C for 2h. The reaction mixture was quenched with water (50 mL) and the aqueous phase was
- 10 extracted with EtOAc (80 ml x 3), the combined organic phase was washed with brine (30 mL x 2), dried with anhydrous Na₂SO₄, filtered, and concentrated in vacuum. The residue was purified by silica gel column chromatography (Pet. Ether / EtOAc, 1:0 to 3:2) to afford benzyl (2S, 4R)-4-fluoro-1-(3, 3, 3-trifluoro-2-hydroxy-2-methyl-propanoyl) pyrrolidine-2-carboxylate (6.14 g, 16.9 mmol, 89.0%) as a yellow oil. **LCMS** (ESI⁺): m/z 364.3 (M+H⁺).
- 15 **¹H NMR** (400 MHz, CDCl₃-d): 87.39-7.30 (m, 5H), 5.39-5.22 (m, 1H), 5.21-5.10 (m, 2H), 4.76 (dt, J = 2.4, 8.8 Hz, 1H), 4.54-4.30 (m, 1H), 3.92-3.70 (m, 1H), 2.84-2.49 (m, 1H), 2.00-1.75 (m, 1H), 1.65 (d, J = 5.2 Hz, 3H).

Step 2: benzyl (2S, 4R)-4-fluoro-1-(2, 3, 3, 3-tetrafluoro-2-methylpropanoyl) pyrrolidine-2-carboxylate:



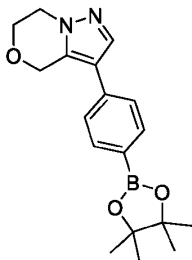
- [0401]** To a solution of benzyl (2S, 4R)-4-fluoro-1-(3, 3, 3-trifluoro-2-hydroxy-2-methylpropanoyl) pyrrolidine-2-carboxylate (2.57 g, 7.07 mmol, 1.0 Equiv.) in DCM (25 mL) was added trifluoro- (morpholino)-sulfane (4.96 g, 28.3 mmol, 3.45 mL, 4.0 Equiv.) and stirred at 50°C for 12hr under N₂. The reaction mixture was poured into ice (50 ml) and the aqueous phase was extracted with DCM (30 ml x 3), the combined organic phase was washed with brine (20 mL x 2), dried with anhydrous Na₂SO₄, filtered, and concentrated in vacuum. The residue was purified by silica gel column chromatography (Pet. Ether / EtOAc, 1:0 to 3:2) to afford benzyl (2S, 4R)-4-fluoro-1-(2, 3, 3, 3-tetrafluoro-2-methylpropanoyl) pyrrolidine-2-carboxylate (2.40 g, 6.57 mmol, 46.4%) as a white solid. **LCMS** (ESI+): m/z 366.3 (M+H⁺). **¹H NMR** (400 MHz, CDCl₃): δ 7.41-7.32 (m, 5H), 5.37-5.26 (m, 1H), 5.23-5.10 (m, 2H), 4.83-4.71 (m, 1H), 4.37-4.22 (m, 1H), 3.99-3.79 (m, 1H), 2.88-2.54 (m, 1H), 2.28-2.06 (m, 1H), 2.04-1.92 (m, 1H), 1.89-1.72 (m, 3H).

Step 3: Int. 189

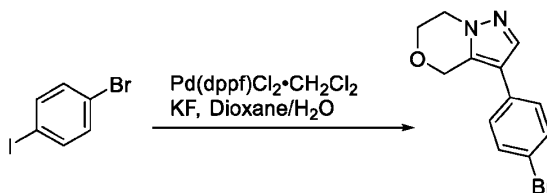


- [0402]** To a solution of benzyl (2S, 4R)-4-fluoro-1-(2, 3, 3, 3-tetrafluoro-2-methylpropanoyl) pyrrolidine-2-carboxylate (2.40 g, 6.57 mmol, 1.0 Equiv.) in MeOH (25 mL) was added 10% Pd/C (500 mg, 469 μmol) and purged with H₂. The mixture was stirred at 25°C for 2h under H₂ (25 psi) atmosphere. The reaction solution was filtered over Diatomaceous earth, and the filtrate was concentrated under reduced pressure to afford **Int. 189** (1.60 g, 5.81 mmol, 88.5%) as a colorless oil. **LCMS** (ESI+): m/z 276.3 (M+H⁺). **¹H NMR** (400 MHz, CDCl₃): δ 8.25 (d, J = 1.2 Hz, 1H), 5.45-5.14 (m, 1H), 4.79-4.62 (m, 1H), 4.30 (ddd, J = 6.4, 13.2, 20.0 Hz, 1H), 4.00-3.79 (m, 1H), 2.94-2.57 (m, 1H), 2.32-2.04 (m, 1H), 1.90-1.73 (m, 3H).

Int. 190: 3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-6,7-dihydro-4H-pyrazolo[5,1-c][1,4]oxazine



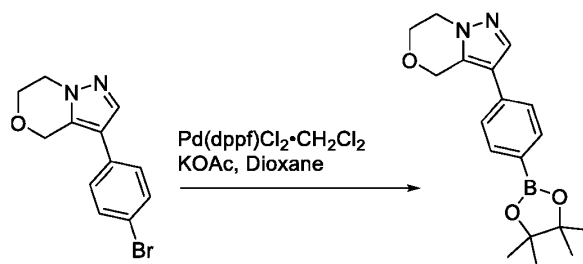
Step 1: 3-(4-bromophenyl)-6,7-dihydro-4H-pyrazolo[5,1-c][1,4]oxazine:



5

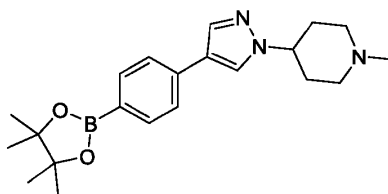
[0403] A solution of 4-bromoiodobenzene (1 g, 3.535 mmol, 1 Equiv.), 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4H,6H,7H-pyrazolo[3,2-c][1,4]oxazine (0.97 g, 3.889 mmol, 1.1 Equiv.), KF (0.41 g, 7.07 mmol, 2 Equiv.) and Pd(dppf)Cl₂·CH₂Cl₂ (0.23 g, 0.283 mmol, 0.08 Equiv.) in dioxane (10 mL) and water (4 mL) was stirred overnight at 80°C under nitrogen atmosphere. The residue was diluted with water (20 mL) and extracted with EtOAc (3x50 mL). The combined organics were dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by silica gel column chromatography, eluted with Pet. Ether / EtOAc (50%) to afford 3-(4-bromophenyl)-4H,6H,7H-pyrazolo[3,2-c][1,4]oxazine (750 mg, 76.01%) as a yellow solid. LCMS: (ESI): *m/z* 279.05 (M+H⁺).

Step 2: Int. 190:

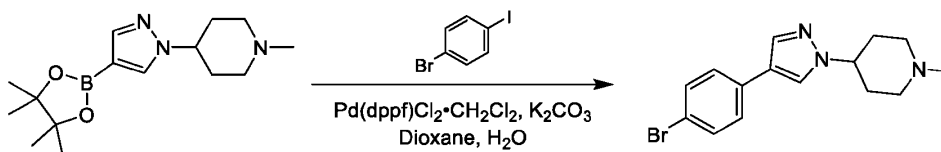


[0404] A solution of 3-(4-bromophenyl)-4H,6H,7H-pyrazolo[3,2-c][1,4]oxazine (750 mg, 2.687 mmol, 1 Equiv.), bis(pinacolato)diboron (750.53 mg, 2.96 mmol, 1.1 Equiv.), KOAc (527.39 mg, 5.37 mmol, 2 Equiv.) and Pd(dppf)Cl₂•CH₂Cl₂ (175.10 mg, 0.215 mmol, 0.08 Equiv.) in dioxane (10 mL) was stirred for 3h at 100°C under nitrogen atmosphere. The residue was purified by Prep-TLC (PE / EtOAc, 50%) to afford **Int. 190** (0.7230 g, 82.49%) as a yellow solid. LCMS (ESI): *m/z* 327.20 (M+H⁺). ¹H NMR (400 MHz, DMSO-*d*₆): δ 1.07 (s, 3H), 1.16 (s, 4H), 1.30 (s, 10H), 4.21 – 4.08 (m, 4H), 4.21 – 4.08 (m, 4H), 7.41 – 7.33 (m, 2H), 5.03 (s, 2H), 7.71 – 7.63 (m, 2H), 7.93 (d, *J* = 20.4 Hz, 1H).

Int. 191: Preparation of 1-methyl-4-(4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1H-pyrazol-1-yl)piperidine



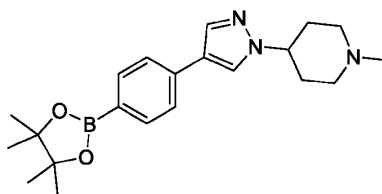
Step 1: 4-(4-(4-bromophenyl)-1H-pyrazol-1-yl)-1-methylpiperidine:



[0405] To a solution of 1-bromo-4-iodobenzene (5.13 g, 18.13 mmol, 1.1 Equiv.) in dioxane (60 mL) was added 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)piperidine (4.8 g, 16.48 mmol, 1 Equiv.), K₂CO₃ (4.56 g, 32.97 mmol, 2 Equiv.) in H₂O (15 mL) and Pd(dppf)Cl₂•CH₂Cl₂ (1.35 g, 1.65 mmol, 0.1 Equiv.) under N₂. The reaction stirred at 90 °C for 16 hrs under N₂. LCMS showed starting material was consumed completely and desired mass was detected. The reaction mixture was cooled to room temperature and quenched by water (100 mL), extracted with EtOAc (2 x 60 mL). The combined organics were washed with brine (100 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a crude residue. The residue was purified by column chromatography (DCM / methanol, 20:1) to afford crude product. The product was triturated with MTBE (50 mL) and filtered. The filter cake was dried and collected to give 4-(4-(4-bromophenyl)-1H-pyrazol-1-yl)-1-methylpiperidine (2.36 g, 4.79 mmol, 29.1%) as a

light yellow solid. LCMS (ESI⁺): m/z 320.2 ($M+H^+$). ¹H NMR (400 MHz, MeOD-*d*₄) δ = 8.09 (s, 1H), 7.83 (s, 1H), 7.48 (s, 4H), 4.19 (dt, J = 5.5, 10.6 Hz, 1H), 3.01 (br d, J = 11.9 Hz, 2H), 2.34 (s, 3H), 2.26 - 2.21 (m, 2H), 2.15 - 2.08 (m, 4H)

Step 2: Int.191:

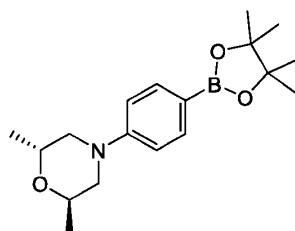


5

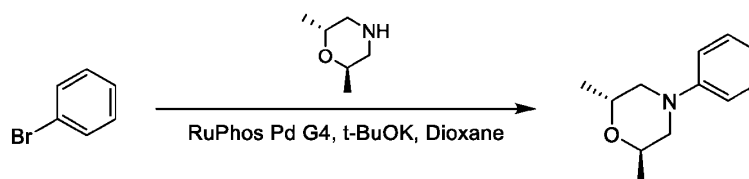
[0406] The boronic ester, **Int.191**, was synthesized using the procedure outlined in Step 2 of the synthesis of **Int. 179** using 4-(4-(4-bromophenyl)-1H-pyrazol-1-yl)-1-methylpiperidine as starting material. LCMS (ESI⁺): m/z 368.3 ($M+H^+$). ¹H NMR (400 MHz, CDCl₃) δ = 7.86 - 7.76 (m, 3H), 7.74 (s, 1H), 7.49 (d, J = 8.1 Hz, 2H), 4.26 - 4.13 (m, 1H), 3.08 (br d, J = 11.9 Hz, 2H), 2.39 (s, 3H), 2.32 - 2.10 (m, 6H), 1.36 (s, 12H)

10

Int. 192: Preparation of (2R,6R)-2,6-dimethyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)morpholine



Step 1: (2R,6R)-2,6-dimethyl-4-phenylmorpholine:



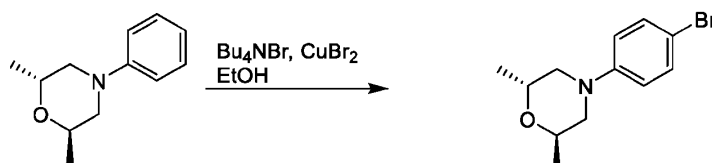
15

[0407] To a solution of bromobenzene (2 g, 12.74 mmol, 1.34 mL, 1 Equiv.) in dioxane (30 mL) was added (2R,6R)-2,6-dimethylmorpholine (1.61 g, 14.01 mmol, 1.1 Equiv.), *t*-BuONa (2.45 g, 25.48 mmol, 2 Equiv.) and RuPhos Pd G4 (1.08 g, 1.27 mmol, 0.1 Equiv.) under N₂. The mixture was stirred at 90 °C for 2 hrs under N₂. LCMS showed starting material was consumed and desired mass was detected. The residue was diluted with H₂O (50 mL) and

20

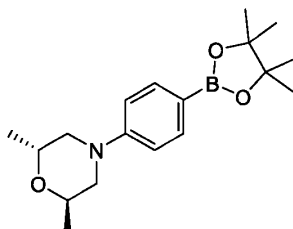
extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na₂SO₄, then filtered and concentrated under reduced pressure to give a crude residue. The residue was purified by column chromatography (Pet. Ether / EtOAc, 10:1) to afford (2R,6R)-2,6-dimethyl-4-phenyl-morpholine (1.7 g, 8.90 mmol, 64%) as a yellow oil. LCMS (ESI+): *m/z* 192.10 (M+H⁺). ¹H NMR (400 MHz, CDCl₃): δ 7.26 - 7.13 (m, 2H), 6.89 - 6.71 (m, 3H), 4.09 (d, 2H), 3.14 (dd, 2H), 2.82 (dd, 2H), 1.25 (d, 6H).

Step 2: (2R,6R)-4-(4-bromophenyl)-2,6-dimethylmorpholine:



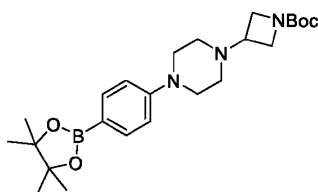
[0408] To a solution of (2R,6R)-2,6-dimethyl-4-phenyl-morpholine (1.5 g, 7.84 mmol, 1 Equiv.) in EtOH (30 mL) was added tetrabutylammoniumbromide (2.53 g, 7.84 mmol, 1 Equiv.) and CuBr₂ (2.63 g, 11.76 mmol, 1.5 Equiv.) under N₂. The mixture was stirred at 25 °C for 12 hr. LCMS showed starting material was consumed and desired mass was detected. The resulting mixture was filtered and washed with EtOAc (100 mL). The filtrate was concentrated under reduced pressure to remove EtOH, then diluted with H₂O (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (50mL), dried over anhydrous Na₂SO₄, then filtered and concentrated under reduced pressure to give a crude residue. The residue was purified by column chromatography (Pet. Ether / EtOAc, 10:1) to afford (2R,6R)-4-(4-bromophenyl)-2,6-dimethylmorpholine (1.5 g, 5.6 mmol, 71%) as a pale-yellow solid. LCMS (ESI+): *m/z* 270.0 (M+H⁺). ¹H NMR (400 MHz, CDCl₃): δ 7.45 - 7.29 (m, 2H), 6.87 - 6.62 (m, 2H), 4.16 (d, 2H), 3.18 (dd, 2H), 2.86 (dd, 2H), 1.31 (d, 6H).

Step 3: Int. 192:



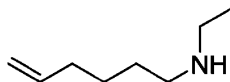
[0409] The boronic ester, **Int. 192**, was synthesized using the procedure outlined in Step 2 of the synthesis of **Int. 179** using (2R,6R)-4-(4-bromophenyl)-2,6-dimethylmorpholine as the starting material. LCMS (ESI+): m/z 318.20 ($M+H^+$). 1H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, 2H), 6.85 (d, 2H), 4.26 - 4.03 (m, 2H), 3.30 (dd, 2H), 2.98 (dd, 2H), 1.37 - 1.28 (m, 18H)

5 **Int. 193: Preparation of tert-butyl 3-(4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazin-1-yl)azetidine-1-carboxylate:**



[0410] **Int. 193** was synthesized following the procedure for **Int. 172** (step 2) using 1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazine and tert-butyl-3-oxoazetidine-1-carboxylate as starting materials. LCMS (ESI+): m/z 444.53 ($M+H$).

Int. 195: N-ethylhex-5-en-1-amine:

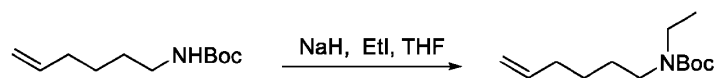


Step 1: Isopropyl 1-formyl-3,3-dimethoxycyclobutane-1-carboxylate:



15 [0411] Into a solution of hex-5-en-1-amine (500 mg, 5.041 mmol, 1 Equiv.) and TEA (1.53 g, 15.123 mmol, 3 Equiv.) in DCM (70 mL) was added Boc_2O (1.32 g, 6.049 mmol, 1.2 Equiv.) dropwise at 0 °C under nitrogen atmosphere. The resulting solution was stirred for 16hr at room temperature. The mixture was concentrated in vacuo. The residue was purified by silica gel column chromatography, eluted with Pet. Ether / EtOAc (50:1) to afford tert-butyl N-(hex-5-en-1-yl)carbamate (176.5 mg, 17.42%) as a colorless oil. LCMS: (ESI): m/z 200.16 ($M+H^+$). 1H NMR (400 MHz, $DMSO-d_6$): δ 1.37 (s, 13H), 1.94 - 2.17 (m, 2H), 2.90 (q, J = 6.4, 6.4, 6.5 Hz, 2H), 4.81 - 5.11 (m, 2H), 5.78 (ddt, J = 6.6, 6.6, 10.2, 16.9 Hz, 1H), 6.78 (t, J = 5.6, 5.6 Hz, 1H).

Step 2: Tert-butyl ethyl(hex-5-en-1-yl)carbamate:



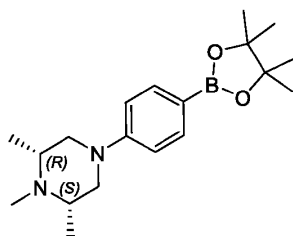
- [0412] Into a solution of tert-butyl N-(hex-5-en-1-yl)carbamate (4.2 g, 21.07 mmol, 1 Equiv.) in THF (40 mL) was added portion wise NaH (1.01 g, 25.29 mmol, 1.2 Equiv., 60%) at 0 °C under nitrogen atmosphere. The mixture was stirred for 30 min at 0 °C. Iodoethane (4.93 g, 31.61 mmol, 1.5 Equiv.) was added dropwise. The mixture was stirred for 16 hr at room temperature. The reaction was quenched by the addition of sat. NH₄Cl (aq.) (100mL) at 0 °C and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (2 x 50 mL) and dried over anhydrous MgSO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with Pet. Ether / EtOAc (50:1) to afford tert-butyl ethyl(hex-5-en-1-yl)carbamate (3.04 g, 11.35 mmol, 53.9%) as a yellow oil. LCMS (ESI): *m/z* 228.35 (M+H⁺). ¹H NMR (400 MHz, DMSO-*d*₆): δ 1.01 (t, *J* = 7.0, 7.0 Hz, 3H), 1.26 – 1.34 (m, 2H), 1.38 (s, 9H), 1.45 (t, *J* = 7.4, 7.4 Hz, 2H), 2.02 (p, *J* = 6.7, 6.7, 6.9, 6.9 Hz, 2H), 3.06 – 3.18 (m, 4H), 4.85 – 5.09 (m, 2H), 5.67 – 5.94 (m, 1H).

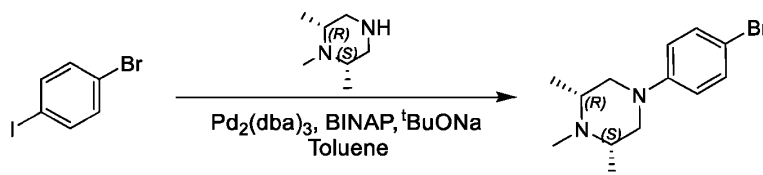
15 **Step 3: Int 195:**



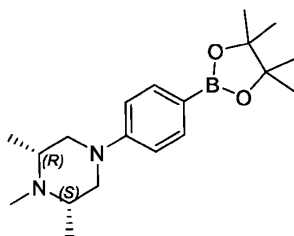
- [0413] Tert-butyl ethyl(hex-5-en-1-yl)carbamate was dissolved in TFA:DCM (1:1, 0.1M) and stirred at RT until the complete consumption of starting material was observed by LCMS. The solvent was removed and the residue was co-evaporated with DCE twice. The crude deprotected amine was used in the next reaction without further purification. LCMS (ESI): *m/z* 128.35 (M+H⁺).

Int. 196: Preparation of (2R,6S)-1,2,6-trimethyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazine.



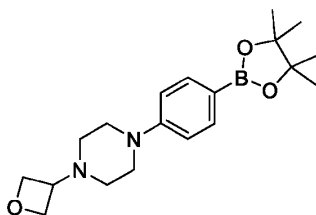
Step 1: (2R, 6S)-4-(4-bromophenyl)-1, 2, 6-trimethylpiperazine:

[0414] A mixture of 1-bromo-4-iodo-benzene (5.00 g, 17.6 mmol, 1.0 Equiv.), (2S, 6R)-1, 2, 6-trimethylpiperazine (2.27 g, 17.6 mmol, 1.0 Equiv.), ^tBuONa (5.10 g, 53.0 mmol, 3.0 Equiv.), BINAP (110 mg, 176 μmol, 0.01 Equiv.) and Pd₂(dba)₃ (161 mg, 176 μmol, 0.01 Equiv.) in toluene (50 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 110 °C for 6hr under N₂ atmosphere. The reaction mixture was concentrated to remove toluene, then water (50 mL) was added and the aqueous phase was extracted with EtOAc (50 mL × 3), the combined organic layers was washed with brine (50 mL), dried over Na₂SO₄, filtered and the filtrate was concentrated to give a residue. The residue was purified by prep-HPLC (TFA condition; column: Phenomenex luna C18 (250 x 70mm, 15 μm); mobile phase: [H₂O (0.1%TFA)-ACN]; gradient: 15%-45% B over 20.0 min) to give (2S, 6R)-4-(4-bromophenyl)-1,2,6-trimethyl-piperazine (1.8 g, 6.29 mmol, 35.6%) as a brown solid.. LCMS (ESI+): m/z 283.2/285.2 (M+H⁺).

Step 2: Int. 196:

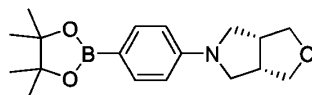
[0415] The boronic ester, **Int. 196**, was synthesized using the procedure outlined in Step 2 of the synthesis of **Int. 179** using (2S, 6R)-4-(4-bromophenyl)-1,2,6-trimethyl-piperazine as starting material LCMS (ESI+): m/z 331.4 (M+H⁺). ¹H NMR (400 MHz, DMSO): δ 7.50 (d, J = 8.0 Hz, 1H), 6.91 (d, J = 8.0 Hz, 1H), 3.71-3.69 (m, 1H), 2.34-2.32 (m, 4H), 2.27 (s, 1H), 1.17 (s, 12H), 1.12 (s, 6H).

Int. 199: Preparation of 1-(oxetan-3-yl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazine

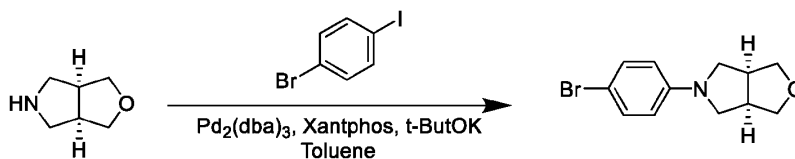


[0416] 1-(oxetan-3-yl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazine (Int. 199) was prepared according to the procedure for Int. 193 using Oxetan-3-on as starting material. LCMS (ESI⁺): *m/z* 344.39 (M+H).

5 **Int. 400: Preparation of (3aR,6aS)-5-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)hexahydro-1H-furo[3,4-c]pyrrole:**

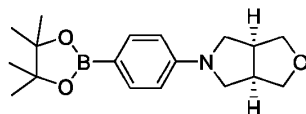


Step 1: (3aR,6aS)-5-(4-bromophenyl)hexahydro-1H-furo[3,4-c]pyrrole:



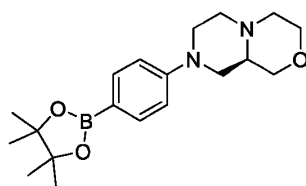
- 10 [0417] In a sealed tube were placed (3aR,6aS)-hexahydro-1H-furo[3,4-c]pyrrole (109 mg, 1 Equiv., 964 μ mol), 1-bromo-4-iodobenzene (300 mg, 1.1 Equiv., 1.06 mmol) and *t*-BuOK (216 mg, 2 Equiv., 1.93 mmol). Toluene (10.6 mL) was added, and the reaction was degassed for 15 min with Ar. Then, 4,5-Bis(diphenylphosphino)-9,9-dimethyl xanthene (83.7 mg, 0.15 Equiv., 145 μ mol) and Tris(dibenzylideneacetone)dipalladium (44.1 mg, 0.05 Equiv., 48.2
- 15 μ mol) were added. The reaction was heated to 45 °C until the complete consumption of starting material (monitored by LCMS). Then it was cooled to room temperature, quenched with water and the organic layers were extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with water (2 x 10 mL) and brine (10 mL), dried (Na₂SO₄), concentrated, and purified by flash column chromatography (Hexane:EtOAc 2:3) and
- 20 concentrated. This resulted in (3aR,6aS)-5-(4-bromophenyl)hexahydro-1H-furo[3,4-c]pyrrole (243 mg, 906 μ mol, 94.0 %) as yellow solid. LCMS (ESI⁺): *m/z* 269.35 (M+H).

Step 2: Int. 400:

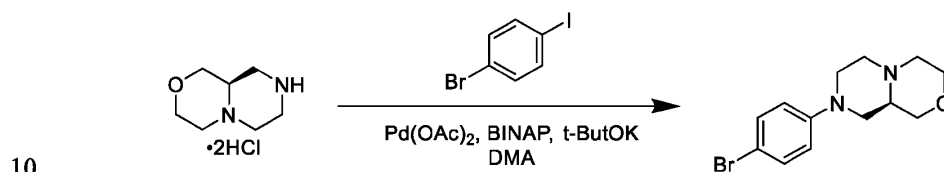


[0418] (3aR,6aS)-5-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)hexahydro-1H-furo[3,4-c]pyrrole (**Int. 400**) was prepared according to the procedure for step 3 of synthesis of Int. 172 using (3aR,6aS)-5-(4-bromophenyl)hexahydro-1H-furo[3,4-c]pyrrole as starting material. LCMS (ESI⁺): m/z 315.34 (M+H).

Int. 401: Preparation of (R)-8-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)octahydropyrazino[2,1-c][1,4]oxazine:

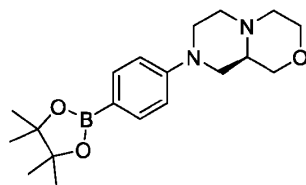


Step 1: (R)-8-(4-bromophenyl)octahydropyrazino[2,1-c][1,4]oxazine:



[0419] In a sealed tube were placed (R)-octahydropyrazino[2,1-c][1,4]oxazine dihydrochloride (351 mg, 1 Equiv., 1.63 mmol), 1-bromo-4-iodobenzene (600 mg, 1.3 Equiv., 2.12 mmol) *t*-BuOK (915 mg, 1.03 mL, 5 Equiv., 8.16 mmol) in DMA (10.6 mL). The reaction was degassed for 15 min with Ar and then Pd(OAc)₂ (18.3 mg, 0.05 Equiv., 81.6 μmol) and BINAP (102 mg, 0.1 Equiv., 163 μmol) were added. The reaction was heated to 70 °C and stirred until the complete consumption of starting material (monitored by LCMS). The reaction was cooled to room temperature, quenched with water and extracted with EtOAc (3 x 10 mL) The combined organic layers were washed with water (2 x 10 mL) and brine (10 mL), dried with Na₂SO₄, concentrated, and purified by flash column chromatography (DCM / MeOH, 9:1) and concentrated. This resulted in (R)-8-(4-bromophenyl)octahydropyrazino[2,1-c][1,4]oxazine (50 mg, 0.17 mmol, 10 %) as yellow solid. LCMS (ESI⁺): m/z 297.08 (M+H).

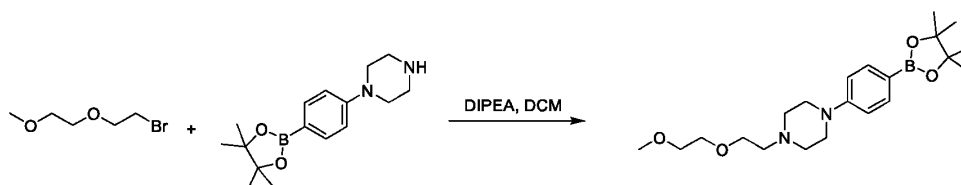
Step 2: Int. 401:



- [0420] (R)-8-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)octahydropyrazino[2,1-c][1,4]oxazine (**Int. 401**) was prepared according to the procedure for step 3 of Int. 172 using (R)-8-(4-bromophenyl)octahydropyrazino[2,1-c][1,4]oxazine as starting material. LCMS (ESI⁺): m/z 344.23 (M+H).

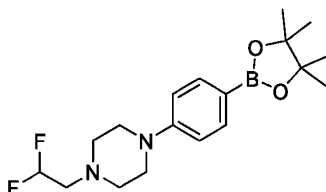
Int. 403: Preparation of tert-butyl 3-(4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazin-1-yl)azetidine-1-carboxylate:

Step 1: Int. 403:



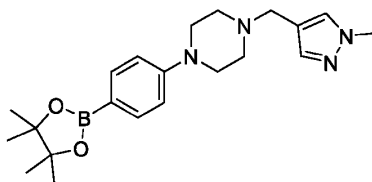
- [0421] 1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazine (200 mg, 1 Equiv., 694 μ mol), DIPEA (179 mg, 242 μ L, 2 Equiv., 1.39 mmol), and 2-(2-methoxyethoxy)ethylbromide (254 mg, 188 μ L, 2 Equiv., 1.39 mmol) were dissolved in DCM (2.0 mL) and stirred until the starting material was completely consumed (monitored by LCMS). The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (2 x 10 mL). The combined organic layer was washed with brine, dried over MgSO₄, filtered, and concentrated. The crude mixture was purified by silica gel column chromatography (DCM / MeOH, 95:5) and concentrated. This afforded **Int. 403** (230 mg, 589 μ mol, 84.9 %) as yellow solid. LCMS (ESI⁺): m/z 390.67 (M+H).

- [0422] **Int. 404: Preparation of 1-(2,2-difluoroethyl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazine:**



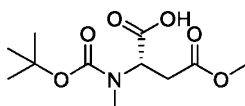
[0422] 1-(2,2-difluoroethyl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazine (Int. 402) was prepared according to the procedure for Int. 403 using 2,2-difluoroethyl trifluoromethanesulfonate as starting material. LCMS (ESI+): m/z 352.02 (M+H).

Int. 405: Preparation of 1-((1-methyl-1H-pyrazol-4-yl)methyl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazine



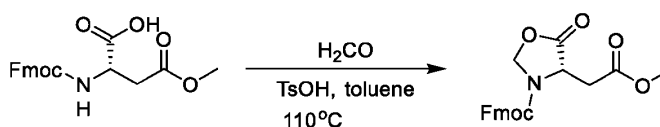
[0423] 1-((1-methyl-1H-pyrazol-4-yl)methyl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazine (Int. 405) was prepared according to the procedure for Int. 193 using 1-methyl-1H-pyrazole-4-carbaldehyde as starting material. LCMS (ESI+): m/z 383.16 (M+H).

Int. 406: Preparation of (S)-2-((tert-butoxycarbonyl)(methyl)amino)-4-methoxy-4-oxobutanoic acid



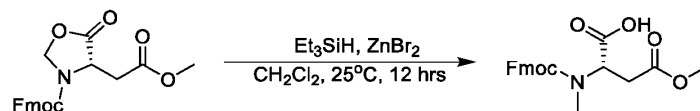
15

Step 1: (9H-fluoren-9-yl)methyl (S)-4-(2-methoxy-2-oxoethyl)-5-oxooxazolidine-3-carboxylate:



- [0424] A mixture of (S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-4-methoxy-4-oxobutanoic acid (100 g, 270.74 mmol, 1 eq), 37% formaldehyde (43 g, 1432.1 mmol, 39.44 mL, 5.29 eq), TsOH (2.34 g, 13.54 mmol, 0.05 eq) in toluene (1800 mL) was degassed for several minutes, and then the mixture was stirred at 110°C for 12 h under N₂ atmosphere.
- 5 The resultant mixture was filtered over a pad of diatomaceous earth and the filter cake was washed with EtOAc (200 mL x 3). The combined filtrates were concentrated under reduced pressure to give a crude residue. The residue was adjusted to pH ~9 with a saturated Na₂CO₃ solution. The aqueous phase was diluted with additional H₂O (600 mL) and extracted with EtOAc (300 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered and
- 10 concentrated to give (9H-fluoren-9-yl)methyl (S)-4-(2-methoxy-2-oxoethyl)-5-oxooxazolidine-3-carboxylate (90 g, 207.20 mmol, 76.53%) as a yellow oil. The product was used with no further purification. LCMS (ESI⁺): *m/z* 382.2 (M+H⁺), ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.89 (d, *J* = 7.2 Hz, 2H), 7.68 - 7.61 (m, 2H), 7.46 - 7.39 (m, 2H), 7.37 - 7.31 (m, 2H), 5.34 (br d, *J* = 2.0 Hz, 1H), 5.24 - 5.01 (m, 1H), 4.75 - 4.18 (m, 4H), 3.60 (s, 3H),
- 15 3.19 - 2.51 (m, 2H).

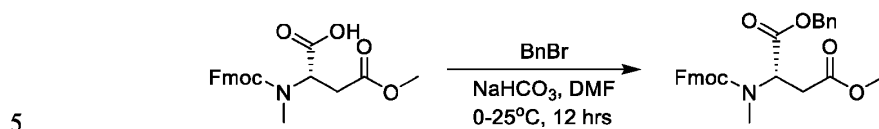
Step 2: (S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)(methyl)amino)-4-methoxy-4-oxobutanoic acid:



- [0425] To a solution of (9H-fluoren-9-yl)methyl (S)-4-(2-methoxy-2-oxoethyl)-5-oxooxazolidine-3-carboxylate (85 g, 195.68 mmol, 1 eq) in CH₂Cl₂ (1700 mL) was added ZnBr₂ (66.10 g, 293.52 mmol, 14.68 mL, 1.5 eq) and Et₃SiH (68.26 g, 587.06 mmol, 93.76 mL, 3 eq). The mixture was stirred at 25°C for 12 h. The resulting mixture was filtered over a pad of diatomaceous earth and the filter cake was washed with additional CH₂Cl₂ (2 x 200 mL). The filtrate was diluted with H₂O (500 mL) and extracted with EtOAc (200 mL x 3). The
- 20 combined organic layers were dried over Na₂SO₄, filtered and concentrated to give (S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)(methyl)amino)-4-methoxy-4-oxobutanoic acid (100 g, 194.58 mmol, 99.43%) as a yellow oil. The product was used with no further purification. LCMS (ESI⁺): *m/z* 384.1 (M+H⁺), ¹H NMR (400 MHz, DMSO-*d*₆): δ 13.42 (s, 1H), 7.93 - 7.85 (m, 2H), 7.69 - 7.60 (m, 2H), 7.45 - 7.38 (m, 2H), 7.37 - 7.28 (m, 2H), 4.93 - 4.70 (m,
- 25

1H), 4.39 - 4.21 (m, 3H), 3.65 - 3.55 (m, 3H), 3.00 - 2.88 (m, 1H), 2.85 - 2.76 (m, 3H), 2.76 - 2.57 (m, 1H).

Step 3: 1-benzyl 4-methyl N-(((9H-fluoren-9-yl)methoxy)carbonyl)-N-methyl-L-aspartate:

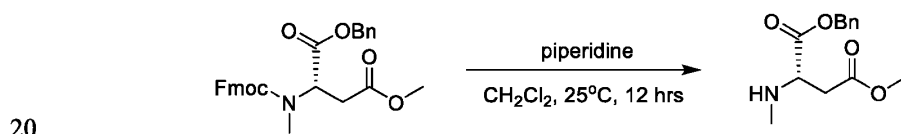


[0426] To a solution of (S)-2-(((9H-fluoren-9-yl)methoxy)carbonyl)(methylamino)-4-methoxy-4-oxobutanoic acid (80 g, 208.66 mmol, 1 eq) in DMF (700 mL) was added NaHCO₃ (35.06 g, 417.32 mmol, 16.24 mL, 2 eq) at 25°C for 30 min and BnBr (107.06 g, 625.98 mmol, 74.36 mL, 3 eq) was added at 0°C. The mixture was stirred at 0°C for 12 h.

10 Then, the mixture was quenched by the addition of H₂O (1500 mL) and extracted with EtOAc (500 mL x 3). The combined organic layers were washed with brine (200 mL x 3) and dried over Na₂SO₄ and filtered. The filtrate was concentrated and the crude product was purified by column chromatography (SiO₂, pet. ether/EtOAc, 7:1 to 3:1) to give 1-benzyl 4-methyl N-(((9H-fluoren-9-yl)methoxy)carbonyl)-N-methyl-L-aspartate (75 g, 142.55 mmol, 68.32%) as a yellow oil. **LCMS** (ESI⁺): *m/z* 474.4 (M+H⁺), **¹H NMR** (400 MHz, DMSO-*d*₆): δ 7.92 - 7.83 (m, 2H), 7.64 - 7.56 (m, 2H), 7.45 - 7.37 (m, 2H), 7.37 - 7.31 (m, 2H), 7.31 - 7.22 (m, 5H), 5.20 - 4.96 (m, 2H), 4.89 - 4.75 (m, 1H), 4.46 - 4.16 (m, 3H), 3.58 (s, 3H), 3.01 (dd, *J* = 6.8, 16.4 Hz, 1H), 2.87 - 2.73 (m, 4H)

15

Step 4: 1-benzyl 4-methyl methyl-L-aspartate:

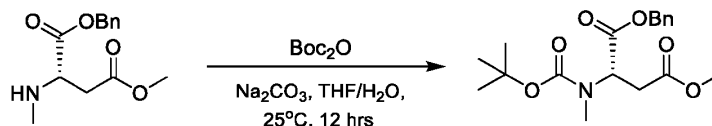


[0427] To a solution of 1-benzyl 4-methyl N-(((9H-fluoren-9-yl)methoxy)carbonyl)-N-methyl-L-aspartate (75 g, 158.38 mmol, 1 eq) in CH₂Cl₂ (750 mL) was added piperidine (40.46 g, 547.16 mmol, 46.92 mL, 3 eq) at 0°C. The mixture was stirred at 25°C for 12 h. The reaction mixture was concentrated. H₂O (1000 mL) was added to the crude product and

25 the aqueous layer was extracted with EtOAc (500 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and the solution was concentrated to give a crude residue.

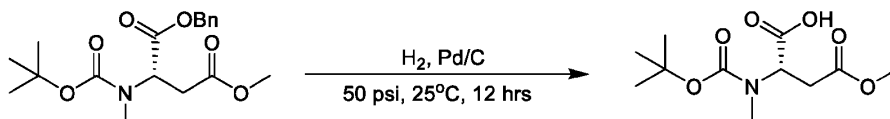
1-benzyl 4-methyl methyl-L-aspartate (32 g, 113.98 mmol, 71.96%) was isolated as a yellow oil after column chromatography (SiO₂, pet. ether/EtOAc, 20:1 to 3:1). LCMS (ESI⁺): *m/z* 252.3 (M+H⁺), ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.40 - 7.31 (m, 5H), 5.19 (s, 2H), 3.61 - 3.52 (s, 3H), 3.52 - 3.29 (m, 1H), 2.83 - 2.51 (m, 2H), 2.28 - 2.15 (s, 3H).

5 **Step 5: 1-benzyl 4-methyl N-(tert-butoxycarbonyl)-N-methyl-L-aspartate:**



- [0428] To a solution of 1-benzyl 4-methyl methyl-L-aspartate (32 g, 127.34 mmol, 1 eq) in THF (320 mL) and H₂O (320 mL) was added Na₂CO₃ (27 g, 254.7 mmol, 2 eq) and Boc₂O (111.18 g, 509.4 mmol, 117.02 mL, 4 eq). The mixture was stirred at 25°C for 12 h. The reaction mix was then extracted with EtOAc (300 mL x3). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered, and the filtrate was concentrated to give a crude residue. The residue was purified by column chromatography (SiO₂, Pet. ether/EtOAc, 20:1 to 3:1). The product was then purified by prep-HPLC to give 1-benzyl 4-methyl N-(tert-butoxycarbonyl)-N-methyl-L-aspartate (27 g, 74.92 mmol, 58.83%) as a yellow oil. LCMS (ESI⁺): *m/z* 374.3 (M+ Na⁺), ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.36 (d, *J* = 5.6 Hz, 5H), 5.18 - 5.07 (m, 2H), 4.82 - 4.59 (m, 1H), 3.59 (d, *J* = 6.0 Hz, 3H), 3.05 - 2.97 (m, 1H), 2.86 - 2.76 (m, 4H), 1.38 - 1.27 (m, 9H).

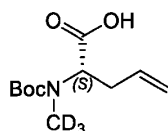
Step 6: Int. 406:



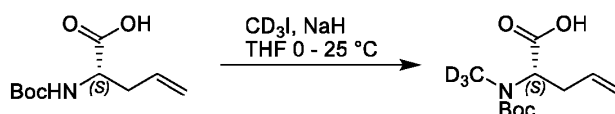
- [0429] To a solution of 1-benzyl 4-methyl N-(tert-butoxycarbonyl)-N-methyl-L-aspartate (27 g, 76.84 mmol, 1 eq) in MeOH (400 mL) was added Pd/C (8.18 g, 7.68 mmol, 10 Wt.%, 0.1 eq) under N₂ atmosphere. The suspension was degassed and purged with H₂ (x3). The mixture was stirred under H₂ (50 Psi) at 25°C for 12 h. Upon completion, the reaction was filtered over a pad of diatomaceous earth and the filter cake was washed with EtOAc (100 mL x 2). **Int. 406** (19.4 g, 67.50 mmol, 87.84%) was isolated as white solid after the removal of solvent. LCMS (ESI⁺): *m/z* 284 (M+ Na⁺). ¹H NMR (400 MHz, DMSO-*d*₆): δ 12.88 (br s,

1H), 4.75 - 4.39 (m, 1H), 3.60 (d, $J = 6.8$ Hz, 3H), 2.98 - 2.88 (m, 1H), 2.80 - 2.66 (m, 4H), 1.37 (d, $J = 15.2$ Hz, 9H).

Int. 408: Preparation of (S)-2-((tert-butoxycarbonyl)(methyl-d₃)amino)pent-4-enoic acid

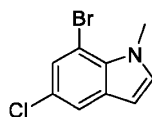


5 Step 1: Int. 408:

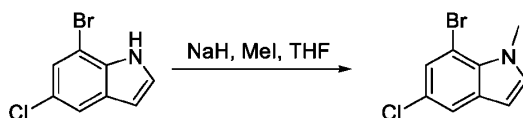


[0430] To a solution of (S)-2-((tert-butoxycarbonyl)amino)pent-4-enoic acid (17.5 g, 81.30 mmol, 1 eq) in THF (800 mL) was added 60% NaH (9.76 g, 243.91 mmol, 3 eq) in portions at 0 °C under a nitrogen atmosphere, and the mixture was stirred at 0 °C for 30 min. Then
 10 iodomethane-*d*₃ (82.50 g, 569.12 mmol, 35.42 mL, 7 eq) was added at 0 °C, then the reaction was warmed to 25 °C and stirred for 4 h. The reaction mixture was cooled to 0 °C, quenched with saturated NH₄Cl (300 mL). The reaction mixture was extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine (300 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a thick oil. The residue was purified
 15 by column chromatography (SiO₂, pet. ether/EtOAc, 10- 25%) to give a pale yellow solid. The pale-yellow solid was triturated with pet. ether (45 mL) for 30 min, and the mixture was filtered to give **Int. 408** (28 g, 117.22 mmol, 72.09%,) as a white solid. **LCMS** (ESI+): m/z 231.1 (M-H⁻). **¹H NMR** (400 MHz, DMSO-*d*₆): δ 12.73 (s, 1H), 5.81 - 5.62 (m, 1H), 5.20 - 4.93 (m, 2H), 4.62 - 4.30 (m, 1H), 2.63 - 2.53 (m, 1H), 2.48 - 2.39 (m, 1H), 1.37 (d, $J = 11.4$
 20 Hz, 9H).

Int. 411: Preparation of 7-bromo-5-chloro-1-methyl-1H-indole

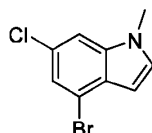


Step 1: Int. 411:



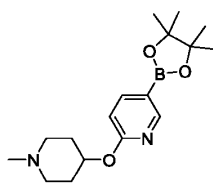
[0431] 7-bromo-5-chloro-1H-indole (500 mg, 1 Eq, 2.17 mmol) and THF (10 mL) were cooled to 0°C and 60% NaH in mineral oil (174 mg, 2 Eq, 4.34 mmol) was added in portions. MeI (924 mg, 407 μ L, 3 Eq, 6.51 mmol) was added after 15 min. The reaction was warmed to RT and continued until the complete consumption of starting material (monitored by LCMS). The reaction was carefully quenched with water and was partitioned between water (20 mL) and EtOAc (30 mL). the organic layer was washed with brine, dried with MgSO₄, concentrated, and purified by flash column chromatography (SiO₂, 0 to 30% EtOAc in Hexanes). 7-bromo-5-chloro-1-methyl-1H-indole (394 mg, 1.61 mmol, 74.3%) was isolated as a white solid. LCMS (ESI⁺): m/z 245.5 (M+H⁺).

Int. 412: Preparation 4-bromo-6-chloro-1-methyl-1H-indole

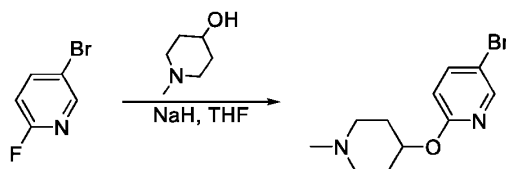


[0432] Int. 412 was synthesized using the procedure outlined in Int. 411 using 4-bromo-6-chloro-1-methyl-1H-indole as starting material. LCMS (ESI⁺): m/z 245.5 (M+H⁺).

Int. 414: Preparation of 2-((1-methylpiperidin-4-yl)oxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine

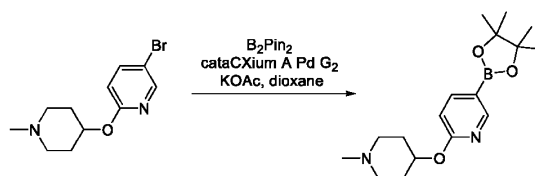


Step 1: 5-bromo-2-((1-methylpiperidin-4-yl)oxy)pyridine:



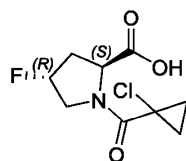
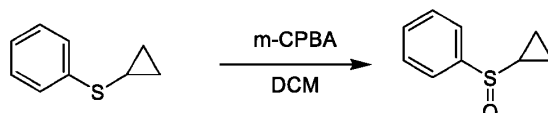
[0433] To a solution of 1-methylpiperidin-4-ol (3.31 g, 28.7 mmol, 3.36 mL, 1.1 eq) in THF (50 mL) was added 60% NaH (2.09 g, 52.2 mmol, 2.0 eq) at 0°C. The reaction was stirred at this temperature for 30 min, then 5-bromo-2-fluoropyridine (4.6 g, 26.1 mmol, 2.69 mL, 1.0 eq) was added and the reaction vessel was warmed to 25°C and stirred for 2.5 h. The reaction mixture was quenched with saturated NH₄Cl (50 mL), and the aqueous phase was extracted with EtOAc (80 mL × 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated to give 5-bromo-2-((1-methylpiperidin-4-yl)oxy)pyridine (7.8 g, crude) as a yellow oil. The product was used without further purification. LCMS: (ESI+): *m/z* 271.0 (M+H⁺).

10 Step Int. 414:

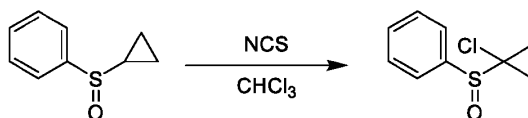


[0434] A mixture of 5-bromo-2-((1-methylpiperidin-4-yl)oxy)pyridine (7.4 g, 27.3 mmol, 1.0 eq), B₂Pin₂ (8.32 g, 32.7 mmol, 1.2 eq), KOAc (6.70 g, 68.23 mmol, 2.5 eq) and [2-(2-aminophenyl)phenyl]-chloro-palladium;bis(1-adamantyl)-butyl-phosphane (1.82 g, 2.73 mmol, 0.1 eq) in dioxane (74 mL) was degassed with N₂ for 15 min. The mixture was stirred at 120°C for 12 hrs under N₂ atmosphere. After cooling to ambient temperature, the reaction mixture was concentrated and the resultant mixture was dissolved in EtOAc (100 mL), filtered, and concentrated under reduced pressure. The crude residue was purified by flash silica gel chromatography (SiO₂, 0~2% Methanol /EtOAc) to give Int. 414 (1.8 g, 5.32 mmol, 19.49%) as a yellow solid. LCMS: (ESI+): *m/z* 319.1 (M+H⁺). ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.36 (s, 1H), 7.85 (dd, *J* = 8.4, 1.6 Hz, 1H), 6.75 (d, *J* = 8.4 Hz, 1H), 5.03 (dt, *J* = 8.4, 4.0 Hz, 1H), 2.58-2.64 (m, 2H), 2.17 (s, 3H), 2.13 (s, 2H), 1.94 (d, *J* = 9.2 Hz, 2H), 1.63-1.69 (m, 2H), 1.28 (s, 12H).

25 **Int. 415: Preparation of (2S,4R)-1-(1-chlorocyclopropane-1-carbonyl)-4-fluoropyrrolidine-2-carboxylic acid**

**Step 1: (cyclopropylsulfinyl)benzene:**

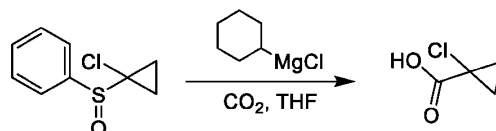
[0435] To a stirred mixture of cyclopropyl(phenyl)sulfane (4.8 g, 31.95 mmol, 4.59 mL, 1 eq) in DCM (50 mL) was added m-CPBA (7.13 g, 35.14 mmol, 1.1 eq, 85 wt.%) at 0 °C under N₂ atmosphere. The resulting mixture was stirred at 0 °C for 0.5 hr under nitrogen atmosphere until the complete consumption of starting material (monitored by LCMS). The reaction mixture was quenched with a Na₂SO₃ solution (10 %, 50 mL), extracted with DCM (2 x 100 mL). The combined organics were washed with NaOH (5 %, 50 mL) and brine (50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give (cyclopropylsulfinyl)benzene (5.2 g, crude) as a light-yellow oil. **LCMS** (ESI⁺): *m/z* 167.2 (M+H⁺). **¹H NMR** (400 MHz, CDCl₃-*d*): δ 7.61 - 7.59 (m, 2H), 7.45 - 7.44 (m, 3H), 2.22 - 2.18 (m, 1H), 1.18 - 0.99 (m, 1H), 0.97 - 0.87 (m, 3H)

Step 2: ((1-chlorocyclopropyl)sulfinyl)benzene:

[0436] To a stirred mixture of (cyclopropylsulfinyl)benzene (5.2 g, 31.28 mmol, 1 eq) in CHCl₃ (50 mL) was added 1-chloropyrrolidine-2,5-dione (5.01 g, 37.54 mmol, 1.2 eq) at 20 °C under nitrogen atmosphere until the complete consumption of starting material (monitored by LCMS). The residue was diluted with H₂O (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO₂, 0-50 % EtOAc in Pet. ether). ((1-chlorocyclopropyl)sulfinyl)benzene (5.4 g, 23.09 mmol, 73.8%) was isolated as a clear oil after concentration. **LCMS** (ESI⁺): *m/z* 201.1 (M+H⁺). **¹H NMR** (400 MHz, CDCl₃-*d*) δ 7.71

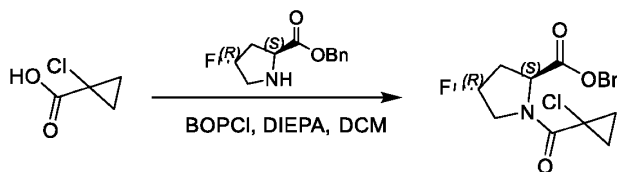
- 7.59 (m, 2H), 7.54 - 7.43 (m, 3H), 1.66 - 1.55 (m, 2H), 1.34 - 1.25 (m, 1H), 1.23 - 1.13 (m, 1H)

Step 3: 1-chlorocyclopropane-1-carboxylic acid:



- 5 **[0437]** To a stirred mixture of ((1-chlorocyclopropyl)sulfinyl)benzene in THF (60 mL) was added cyclohexylmagnesium chloride (1.3 M, 16.87 mL, 1 eq) and purged with Ar -78 °C. After 60 min, gaseous carbon dioxide was bubbled into the reaction for 2 h. Upon completion (monitored by TLC), the residue was diluted with a saturated solution of NH₄Cl (100 mL), and the reaction mixture was concentrated under reduced pressure to remove THF. Then, the
- 10 pH was adjusted with saturated NaHCO₃ (50 mL) and extracted with MTBE (3 x 100 mL). Next, the aqueous phase was acidified with 1N HCl (200 mL). When the pH was ~2-3 the aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to give 1-chlorocyclopropane-1-carboxylic acid (1.2 g, crude) as a white solid. The product was used
- 15 with no further purification. ¹H NMR (400 MHz, CDCl₃-d): δ 1.78 - 1.73 (m, 2H), 1.51 - 1.45 (m, 2H), 7.99 (s, 1H).

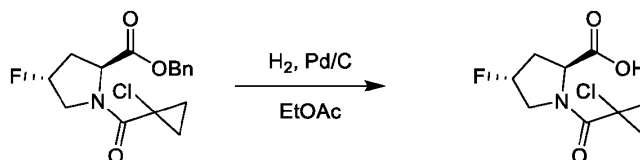
Step 4: benzyl (2S,4R)-1-(1-chlorocyclopropane-1-carbonyl)-4-fluoropyrrolidine-2-carboxylate:



- 20 **[0438]** To a stirred mixture of 1-chlorocyclopropane-1-carboxylic acid (1.2 g, 9.96 mmol, 1 eq) in DCM (30 mL) was added DIPEA (1.29 g, 9.96 mmol, 1.73 mL, 1 eq) and the reaction was stirred for 30 min at ambient temperature. Then, BOPCl (2.79 g, 10.95 mmol, 1.1 eq), benzyl (2S,4R)-4-fluoropyrrolidine-2-carboxylate (2.84 g, 10.95 mmol, 1.1 eq, HCl), DIPEA (2.57 g, 19.91 mmol, 3.47 mL, 2 eq) were added sequentially. The resulting mixture was
- 25 stirred at ambient temperature until the consumption of starting material was observed

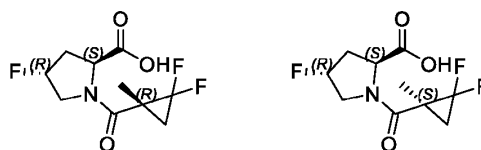
(monitored by LCMS), the reaction was diluted with H₂O (30 mL) and extracted with DCM (3 x 30 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na₂SO₄, then filtered and concentrated. The residue was purified by column chromatography (SiO₂, 0-50 % EtOAc in pet. ether). The resulting product was further purified by trituration with petroleum ether (15 mL) to give benzyl (2S,4R)-1-(1-chlorocyclopropane-1-carbonyl)-4-fluoropyrrolidine-2-carboxylate (2.1 g, 6.45 mmol, 64.75%) as a white solid. LCMS (ESI+): *m/z* 326.1 (M+H⁺). ¹H NMR (400 MHz, CDCl₃-*d*): δ 7.39 - 7.31 (m, 5H), 5.39 - 5.10 (m, 3H), 4.70 (t, *J* = 8.6 Hz, 1H), 4.41 - 4.21 (m, 1H), 4.09 - 3.85 (m, 1H), 2.75 - 2.51 (m, 1H), 2.25 - 1.96 (m, 1H), 1.70 - 1.49 (m, 2H), 1.39 - 1.26 (m, 2H)

Step 3: Int. 415:

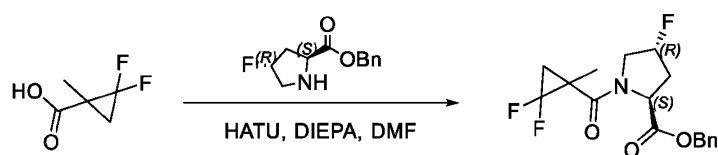


[0439] To a stirred mixture of 10% Pd/C (620.69 mg, 583.25 μmol, 0.1 eq) in EtOAc (50 mL) was added benzyl (2S,4R)-1-(1-chlorocyclopropane-1-carbonyl)-4-fluoropyrrolidine-2-carboxylate (1.9 g, 5.83 mmol, 1 eq) at 20 °C under N₂ atmosphere. The atmosphere was exchanged with H₂, and the resulting mixture was stirred under H₂ (50 Psi) at 20 °C until the complete consumption of starting material (monitored by LCMS). The reaction mixture was filtered over celite, and the filter cake rinsed with EtOAc (150 mL). The filtrate was concentrated under reduced pressure to give **Int. 415** (1.25 g, 5.27 mmol, 90.39%) as a pale yellow solid. LCMS (ESI+): *m/z* 236.0 (M+H⁺). ¹H NMR (400 MHz, CDCl₃-*d*): δ 8.84 (s, 1H), 5.40 - 5.27 (d, *J* = 52 Hz 1H), 4.69 (t, *J* = 8.6 Hz, 1H), 4.37 (ddd, *J* = 1.9, 13.1, 19.6 Hz, 1H), 4.04 - 3.82 (m, 1H), 2.74 - 2.53 (m, 1H), 2.48 - 2.19 (m, 1H), 1.70 - 1.55 (m, 1H), 1.39 - 1.18 (m, 3H)

Int. 416 and 417: Preparation of (2S,4R)-1-((R)-2,2-difluoro-1-methylcyclopropane-1-carbonyl)-4-fluoropyrrolidine-2-carboxylic acid and (2S,4R)-1-((S)-2,2-difluoro-1-methylcyclopropane-1-carbonyl)-4-fluoropyrrolidine-2-carboxylic acid:

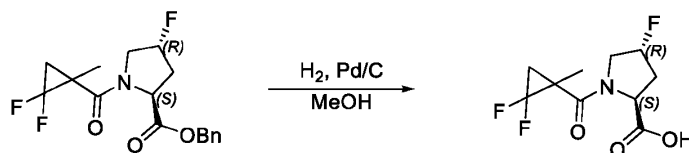


Step 1: benzyl (2S,4R)-1-(2,2-difluoro-1-methylcyclopropane-1-carbonyl)-4-fluoropyrrolidine-2-carboxylate:



- 5 **[0440]** To a solution of 2,2-difluoro-1-methylcyclopropane-1-carboxylic acid (3 g, 22.04 mmol, 1 eq) in DMF (80 mL) was added DIEPA (8.55 g, 66.13 mmol, 11.52 mL, 3 eq), benzyl (2S,4R)-4-fluoropyrrolidine-2-carboxylate (6.30 g, 24.25 mmol, 1.1 eq, HCl) and HATU (16.76 g, 44.09 mmol, 2 eq) sequentially at 0°C under a N₂ atmosphere. The mixture was stirred at 25°C for 12h. Water (30 mL) was added, and the aqueous phase was extracted with EtOAc (100 mL x 3). The combined organic layers were dried with anhydrous Na₂SO₄ and concentrated. The resulting residue was purified by flash chromatography (SiO₂, 0-30% EtOAc in Pet. ether). This resulted in benzyl (2S,4R)-1-(2,2-difluoro-1-methylcyclopropane-1-carbonyl)-4-fluoropyrrolidine-2-carboxylate (7 g, 20.51 mmol, 93.04%) as a yellow oil.
- 10 **LCMS** (ESI⁺): *m/z* 342.3 (M+H⁺). **¹H NMR** (400 MHz, CDCl₃-*d*): δ 7.40 - 7.29 (m, 5H), 5.37 - 5.09 (m, 3H), 4.78 - 4.64 (m, 1H), 4.06 - 3.73 (m, 2H), 2.73 - 2.56 (m, 1H), 2.22 - 2.05 (m, 1H), 2.02 - 1.77 (m, 1H), 1.52 - 1.41 (m, 3H), 1.47 - 1.45 (m, 1H).
- 15

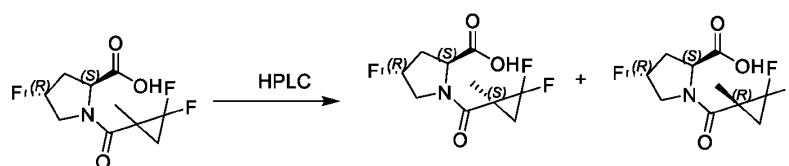
Step 2: (2S,4R)-1-(2,2-difluoro-1-methylcyclopropane-1-carbonyl)-4-fluoropyrrolidine-2-carboxylic acid:



- 20 **[0441]** To a solution of benzyl (2S,4R)-1-(2,2-difluoro-1-methylcyclopropane-1-carbonyl)-4-fluoropyrrolidine-2-carboxylate (3 g, 8.79 mmol, 1 eq) in MeOH (50 mL) was added Pd/C (1.8 g, 1.69 mmol, 10% wt.%, 0.19 eq). The mixture was stirred under H₂ (50 psi) for 2 h. The

reaction solution was filtered over celite and concentrated under reduced pressure. (2S,4R)-1-(2,2-difluoro-1-methylcyclopropane-1-carbonyl)-4-fluoropyrrolidine-2-carboxylic acid (2.2 g, 8.50 mmol, 96.65%) was obtained as a white solid. ¹H NMR (400 MHz, CDCl₃-d): δ 6.53 (s, 1H), 5.38 - 5.25 (d, *J* = 52 Hz, 1H), 4.69 (q, *J* = 8.8 Hz, 1H), 4.11 - 3.92 (m, 1H), 3.90 - 3.69 (m, 1H), 2.76 - 2.57 (m, 1H), 2.54 - 2.19 (m, 1H), 2.07 - 1.80 (m, 1H), 1.49 (d, *J* = 1.1 Hz, 3H), 1.39 - 1.24 (m, 1H).

Step 3: Int. 416, 417:

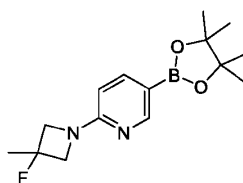


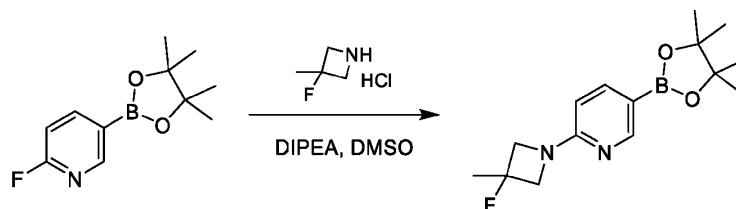
[0442] The (2S,4R)-1-(2,2-difluoro-1-methylcyclopropane-1-carbonyl)-4-fluoropyrrolidine-2-carboxylic acid was purified by prep-HPLC (Agela DuraShell C18 250 x 70mm x 10um; mobile phase: [H₂O (10mM NH₄HCO₃) / MeCN]; gradient:0%-10% B over 17.0 min to afford **Int. 416** and **Int. 417**.

[0443] **Int. 417** (1.5 g, 5.97 mmol, 50.95%) as a white solid. LCMS (ESI⁺): *m/z* 250.1 (M-H⁺). ¹H NMR (400 MHz, DMSO-*d*₆): δ 12.69 (br s, 1H), 5.52 - 5.31 (d, *J* = 52 Hz, 1H), 4.33 (t, *J* = 8.4 Hz, 1H), 4.02 - 3.88 (m, 1H), 3.78 - 3.60 (m, 1H), 2.64 - 2.53 (m, 1H), 2.25 - 2.04 (m, 1H), 1.70 - 1.57 (m, 2H), 1.37 (s, 3H).

[0444] **Int. 416** (1.3 g, 5.18 mmol, 44.16%) as a white solid. LCMS (ESI⁺): *m/z* 250.1 (M-H⁺). ¹H NMR (400 MHz, DMSO-*d*₆): δ 5.44 - 5.31 (d, *J* = 52 Hz, 1H), 4.34 (t, *J* = 8.4 Hz, 1H), 3.92 - 3.69 (m, 2H), 2.66 - 2.53 (m, 1H), 2.21 - 2.01 (m, 1H), 1.90 - 1.79 (m, 1H), 1.63 - 1.52 (m, 1H), 1.40 (s, 3H).

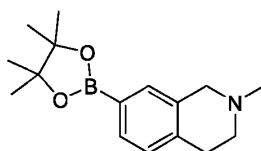
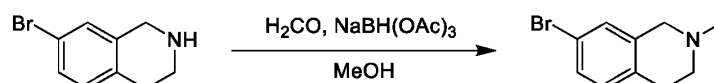
Int. 419: Preparation of 2-(3-fluoro-3-methylazetidin-1-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine:



Step 1: Int. 419:

- [0445] A mixture of 2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (3 g, 13.45 mmol, 1 eq), 3-fluoro-3-methylazetidine hydrochloride (1.69 g, 13.45 mmol, 1 eq),
 5 DIPEA (5.21 g, 40.35 mmol, 7.03 mL, 3 eq) in DMSO (50 mL), was heated to 100 °C under an atmosphere of nitrogen. The reaction continued until the complete consumption of starting material (monitored by LCMS). The reaction mixture was cooled to room temperature and diluted with water (50 mL), extracted with EtOAc (2 x 50 mL). The combined organics were washed with brine (50 mL), dried over Na₂SO₄, filtered, and concentrated. A second batch of
 10 this reaction (using the above conditions and scale) was added at this point. The combined residues were triturated with MTBE (40 mL) and filtered. The filter cake was dried to give **Int. 419** (2.29 g, 7.84 mmol, 29.14%) as a yellow solid. LCMS (ESI⁺): *m/z* 211.1 (M-80+H⁺). ¹H NMR (400 MHz, MeOD-*d*₄): δ 8.33 (s, 1H), 7.82 (dd, *J* = 1.7, 8.4 Hz, 1H), 6.43 (d, *J* = 8.4 Hz, 1H), 4.24 - 4.00 (m, 4H), 1.76 - 1.60 (d, *J* = 21 Hz, 3H), 1.33 (s, 12H)

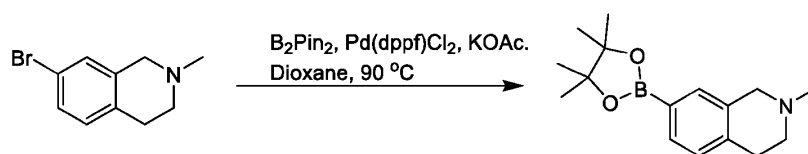
- 15 **Int. 421: Preparation of 2-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,4-tetrahydroisoquinoline**

**Step 1: 7-bromo-2-methyl-1,2,3,4-tetrahydroisoquinoline:**

- 20 [0446] To a solution of 7-bromo-1,2,3,4-tetrahydroisoquinoline (2.5 g, 11.79 mmol, 1 eq) in MeOH (50 mL) was added H₂CO (37% in H₂O, 4.78 g, 58.94 mmol, 4.39 mL, 5 eq) and the suspension was stirred at 25°C for 1 h. Then, the reaction was cooled to 0 °C and

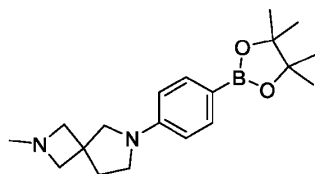
NaBH(OAc)₃ (3.00 g, 14.15 mmol, 1.2 eq) was added. The reaction was warmed to ambient temperature and continued until the complete consumption of starting material (monitored by LCMS). The reaction mixture was concentrated under reduced pressure to remove MeOH, and diluted with water (20 mL), extracted with MTBE (25 mL). The aqueous phase was then
 5 adjusted to pH 7 with saturated Na₂HCO₃, extracted with EtOAc (3 x 20 mL), the combined organic layers were washed with brine (50 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give 7-bromo-2-methyl-1,2,3,4-tetrahydroisoquinoline (4.5 g, 18.51 mmol, 78.51%) as a colorless liquid without purification. The product was used with no further purification. LCMS (ESI+): *m/z* 226.2 (M+H⁺). ¹H NMR (400 MHz, CDCl₃-*d*): δ
 10 7.30-7.32 (m, 1H), 7.20 (s, 1H), 7.01 (d, *J* = 8.2 Hz, 1H), 3.58 (s, 2H), 2.93 - 2.87 (t, 2H), 2.76 - 2.69 (t, 2H), 2.49 (s, 3H)

Step 2: Int. 421:

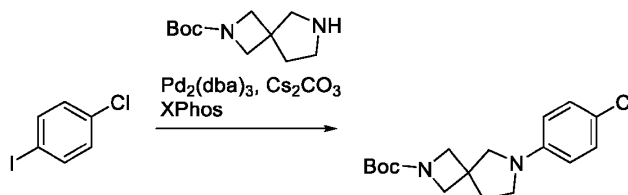


[0447] To a solution of 7-bromo-2-methyl-1,2,3,4-tetrahydroisoquinoline (4.5 g, 19.90
 15 mmol, 1 eq) in dioxane (50 mL) was added B₂Pin₂ (7.58 g, 29.85 mmol, 1.5 eq) and KOAc (4.88 g, 49.75 mmol, 2.5 eq) under nitrogen atmosphere. The suspension was degassed with N₂ (15 min) and Pd(dppf)Cl₂·CH₂Cl₂ (1.63 g, 1.99 mmol, 0.1 eq) was added. The reaction mixture was heated to 90 °C until the complete consumption of starting material (monitored by LCMS). The reaction mixture was cooled to ambient temperature and concentrated. The
 20 crude residue was diluted with sat. NaHCO₃ (30 mL), extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting crude product was purified by flash chromatography (SiO₂, 0 – 6 % MeOH in DCM) to give Int. 421 (2.1 g, 7.10 mmol, 35.69%) was obtained as a black solid. LCMS (ESI+): *m/z* 274.1 (M+H⁺). ¹H NMR (400 MHz, CDCl₃-*d*): δ 7.57 (d, *J* = 7.6 Hz, 1H), 7.48 (s, 1H), 7.12 (d, *J* = 7.5 Hz, 1H), 3.60 (s, 2H), 2.94
 25 (t, *J* = 5.8 Hz, 2H), 2.73 - 2.66 (m, 2H), 2.45 (d, *J* = 1.1 Hz, 3H), 1.34 (s, 12H).

Int. 424: Preparation of 2-methyl-6-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-2,6-diazaspiro[3.4]octane

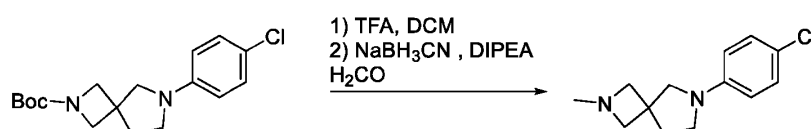


Step 1: tert-butyl 6-(4-chlorophenyl)-2,6-diazaspiro[3.4]octane-2-carboxylate:



[0448] To a stirred mixture of 4-chloriodobenzene (5 g, 20.969 mmol, 1 eq) and tert-butyl 2,6-diazaspiro[3.4]octane-2-carboxylate (6.68 g, 31.454 mmol, 1.5 eq) in dioxane (50 mL) were added $\text{Pd}_2(\text{dba})_3$ (2.17 g, 2.097 mmol, 0.1 eq), XPhos (2.00 g, 4.194 mmol, 0.2 eq) and Cs_2CO_3 (20.50 g, 62.907 mmol, 3 eq) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for additional overnight at 80°C. The resulting mixture was extracted with EtOAc (2 x 100mL). The combined organic layers were dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure. The residue was purified RP-HPLC (C18, 10-100% MeCN in water with 0.1% FA). Tert-butyl 6-(4-chlorophenyl)-2,6-diazaspiro[3.4]octane-2-carboxylate (4.6 g, 67.95%) was recovered as a brown solid. LCMS (ESI+): m/z 323.1 ($\text{M}+\text{H}^+$).

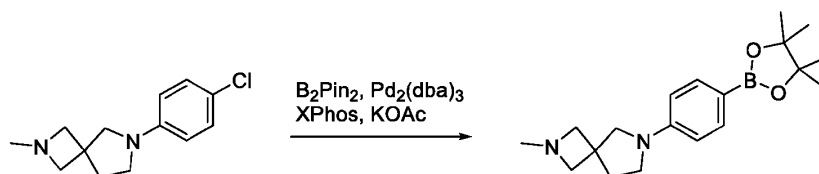
Step 2-3 6-(4-chlorophenyl)-2-methyl-2,6-diazaspiro[3.4]octane:



[0449] A mixture of tert-butyl 6-(4-chlorophenyl)-2,6-diazaspiro[3.4]octane-2-carboxylate (1 g, 3.098 mmol, 1 eq) and TFA (3 mL) in DCM (15 mL) was stirred overnight at room temperature. The resulting mixture was concentrated to afford resulted 6-(4-chlorophenyl)-2,6-diazaspiro[3.4]octane (530 mg, 76.82%) as a brown oil. The product was used in the next step without further purification. LCMS (ESI+): m/z 223.15 ($\text{M}+\text{H}^+$).

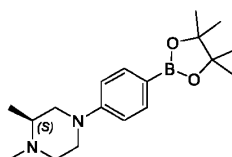
- [0450] To a stirred mixture of 6-(4-chlorophenyl)-2,6-diazaspiro[3.4]octane (700 mg, 3.143 mmol, 1 eq) and DIEA (812.44 mg, 6.29 mmol, 2 eq) in 1:1 MeOH:THF (4 mL) were added H₂CO (0.86 mL, 9.42 mmol, 3 eq, 40% in water) and NaBH₃CN (592.5 mg, 9.43 mmol, 3 eq) in portions at room temperature under an atmosphere of nitrogen. The resulting mixture was stirred for an additional 2 h at room temperature. The reaction was directly purified by RP-HPLC (C18, 10-100% MeCN in water with 0.1% FA) to afford 6-(4-chlorophenyl)-2-methyl-2,6-diazaspiro[3.4]octane (150 mg, 20.16%) an oil. LCMS (ESI⁺): *m/z* 237.15 (M+H⁺).

Step 4: Int. 424:

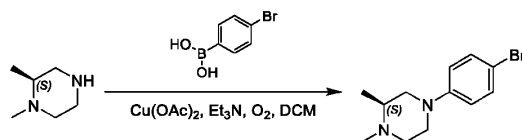


- [0451] To a stirred mixture of 6-(4-chlorophenyl)-2-methyl-2,6-diazaspiro[3.4]octane (1.2 g, 5.069 mmol, 1 eq) and bis(pinacolato)diboron (1.93 g, 7.604 mmol, 1.5 eq) in dioxane (20 mL) were added Pd₂(dba)₃ (0.52 g, 0.507 mmol, 0.1 eq), XPhos (0.48 g, 1.014 mmol, 0.2 eq) and KOAc (1.49 g, 15.207 mmol, 3 eq) under nitrogen. The reaction was heated to 100 °C until consumption of starting material was observed (LCMS). The resulting mixture was extracted with EtOAc (2 x 100mL). The combined organic layers were dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Preparative TLC (CH₂Cl₂ / MeOH 10:1) to afford **Int. 424** (0.2993 g, 15.00%) as a yellow green solid. LCMS (ESI⁺): *m/z* 329.15 (M+H⁺). ¹H NMR (400 MHz, DMSO-d₆) δ 7.46 (d, J = 8.1 Hz, 1H), 7.23 – 7.05 (m, 1H), 6.48 (t, J = 8.9 Hz, 2H), 3.35 (s, 2H), 3.28 – 3.09 (m, 6H), 2.27 (d, J = 2.5 Hz, 3H), 1.16 (d, J = 71.8 Hz, 12H).

Int. 425: Preparation of (S)-1,2-dimethyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazine

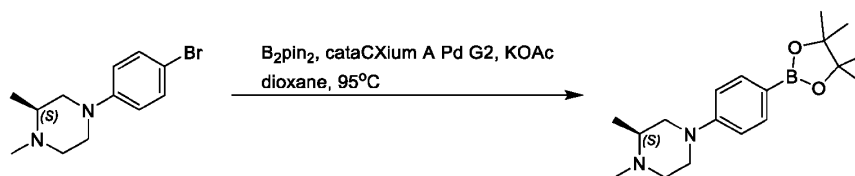


Step 1: (S)-4-(4-bromophenyl)-1,2-dimethylpiperazine:



- [0452]** To a solution of (S)-1,2-dimethylpiperazine (3 g, 26.27 mmol, 1 eq) and (4-bromophenyl)boronic acid (7.91 g, 39.41 mmol, 1.5 eq) in CH₂Cl₂ (100 mL) was added Cu(OAc)₂ (954.39 mg, 5.25 mmol, 0.2 eq), Et₃N (10.63 g, 105.09 mmol, 14.63 mL, 4 eq), and 4 Å molecular sieves (1 g). The mixture was (C18, 10-100% MeCN in water with 0,1% FA). SiO₂, 0-100% EtOAc in pet. ether (C18, 10-100% MeCN in water with 0,1% FA). SiO₂, 0-100% EtOAc in pet. ether (C18, 10-100% MeCN in water with 0,1% FA). stirred at ambient temperature under an atmosphere of oxygen (15 psi). The reaction continued until the consumption of starting materials (monitored by LCMS). The resulting suspension was filtered through a pad of silica gel and the filter cake was washed with EtOAc (20 mL x 3). The combined filtrates were concentrated to dryness and the residue was purified by flash silica gel chromatography (SiO₂, 0-100% EtOAc in pet. ether). (S)-4-(4-bromophenyl)-1,2-dimethylpiperazine (3 g, 11.14 mmol, 42.42%) was obtained as a gray solid. **LCMS:** (ESI+): *m/z* 269.3 (M+H⁺). **¹H NMR** (400 MHz, CDCl₃-*d*): δ 7.33 (d, *J* = 8.8 Hz, 2H), 6.77 (d, *J* = 8.8 Hz, 2H), 3.51 - 3.36 (m, 2H), 3.01 - 2.87 (m, 2H), 2.62 - 2.43 (m, 2H), 2.42 - 2.29 (m, 4H), 1.17 (d, *J* = 6.4 Hz, 3H).

Step 2: Int. 425:

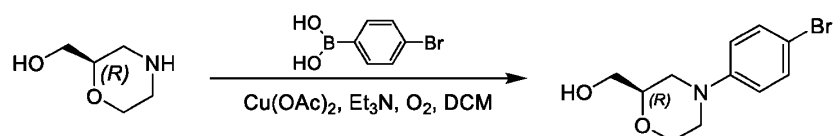


- [0453]** A mixture of (S)-4-(4-bromophenyl)-1,2-dimethylpiperazine (2.9 g, 10.77 mmol, 1 eq), B₂Pin₂ (3.28 g, 12.93 mmol, 1.2 eq), KOAc (2.64 g, 26.93 mmol, 2.5 eq) and [2-(2-aminophenyl)phenyl]-chloro-palladium;bis(1-adamantyl)-butyl-phosphane (720.34 mg, 1.08 mmol, 0.1 eq) in dioxane (50 mL) was degassed with N₂ for 20 min. The reaction was heated to 95 °C for 4 h. The suspension was filtered through a pad of silica gel and the filter cake was washed with EtOAc (20 mL x 3). The combined filtrates were concentrated to dryness and the residue was purified by flash silica gel chromatography (SiO₂, 0-100% EtOAc in Pet. ether). **Int. 425** (2 g, 6.32 mmol, 58.70%) was obtained as a gray solid. **LCMS:** (ESI+): *m/z*

317.2 ($M+H^+$), 1H NMR (400 MHz, $CDCl_3-d$) δ 7.71 (d, $J = 8.4$ Hz, 2H), 6.89 (d, $J = 8.4$ Hz, 2H), 3.69 - 3.50 (m, 2H), 3.02 - 2.87 (m, 2H), 2.65 - 2.55 (m, 1H), 2.41 (dt, $J = 3.2, 11.4$ Hz, 1H), 2.37 - 2.32 (m, 3H), 2.27 (ddd, $J = 3.2, 6.4, 9.7$ Hz, 1H), 1.33 (s, 12H), 1.15 (d, $J = 6.4$ Hz, 3H).

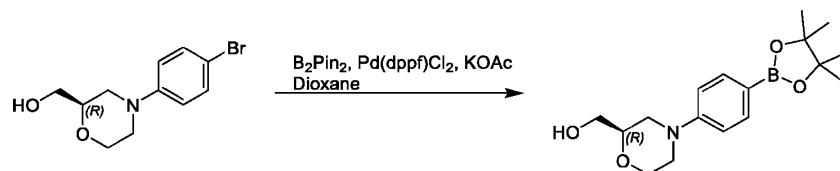
5 **Int. 426: Preparation of (S)-N,N-dimethyl-1-(4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)morpholin-2-yl)methanamine**

Step 1: (R)-(4-(4-bromophenyl)morpholin-2-yl)methanol:



[0454] Step 1 was performed using the procedure outline in step 1 for the synthesis of Int. 10 425 using (R)-morpholin-2-ylmethanol as starting material. LCMS (ESI+): m/z 272.0 ($M+H^+$). 1H NMR (400 MHz, $CDCl_3-d$): δ 7.42 - 7.34 (m, 2H), 6.83 (d, $J = 8.6$ Hz, 2H), 4.12 - 4.03 (m, 1H), 3.95 - 3.63 (m, 4H), 3.46 - 3.34 (m, 2H), 2.86 (dt, $J = 3.4, 11.9$ Hz, 1H), 2.69 (t, $J = 11.1$ Hz, 1H), 1.93 (s, 0.5H), 1.51 (s, 0.5H)

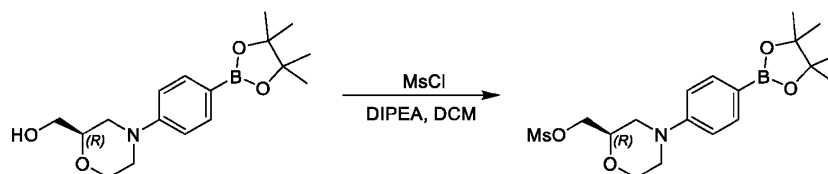
15 Step 2: (R)-(4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)morpholin-2-yl)methanol:



[0455] To a solution of (R)-(4-(4-bromophenyl)morpholin-2-yl)methanol (2.5 g, 9.19 mmol, 1 eq), bis(pinacolato)diboron (3.50 g, 13.78 mmol, 1.5 eq), KOAc (2.70 g, 27.56 mmol, 3 eq) in dioxane (25 mL) was degassed with N_2 for 10 min. $Pd(dppf)Cl_2$ (750.21 mg, 918.65 μ mol, 0.1 eq) was added to the reaction. The mixture was heated to 100 $^{\circ}C$ until the complete consumption of starting material (monitored by LCMS). The reaction mixture was diluted with water (50 mL), extracted with EtOAc (2 x 50 mL). The combined organics were washed with brine (50 mL), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (SiO_2 , 0-40% EtOAc in

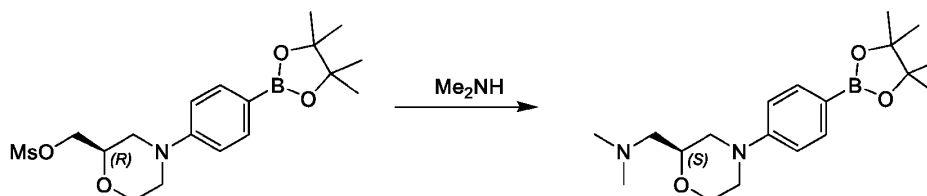
pet. ether) to give (R)-(4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)morpholin-2-yl)methanol (1.7 g, 5.06 mmol, 55.08%) as a yellow solid. LCMS (ESI+): m/z 320.2 (M+H⁺). ¹H NMR (400 MHz, CDCl₃-d): δ 7.74 (d, J = 8.6 Hz, 2H), 6.94 (d, J = 7.1 Hz, 2H), 4.11 - 4.04 (m, 1H), 3.95 - 3.65 (m, 4H), 3.60 - 3.50 (m, 2H), 2.99 - 2.69 (m, 2H), 2.04 - 1.91 (m, 1H), 1.34 (s, 12H).

Step 3: (R)-(4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)morpholin-2-yl)methyl methanesulfonate:



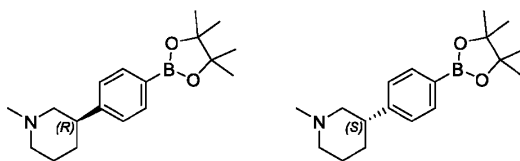
[0456] To a solution of (R)-(4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)morpholin-2-yl)methanol (1.6 g, 5.01 mmol, 1 eq) in dichloromethane (80 mL) was added DIPEA (3.24 g, 25.06 mmol, 4.37 mL, 5 eq) at 0 °C. Then MsCl (918.70 mg, 8.02 mmol, 620.74 μ L, 1.6 eq) was added to the reaction dropwise under a N₂ atmosphere at 0 °C. The reaction was warmed to ambient temperature and stirred until the consumption of starting material (monitored by LCMS). The reaction mixture was cooled, diluted with water (50 mL), and extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give (R)-(4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)morpholin-2-yl)methyl methanesulfonate (2 g, 4.53 mmol, 90.39%) as a yellow oil. LCMS (ESI+): m/z 398.2 (M+H⁺). ¹H NMR (400 MHz, CDCl₃-d): δ 7.74 (d, J = 8.6 Hz, 2H), 6.89 (d, J = 8.6 Hz, 2H), 4.37 - 4.30 (m, 2H), 4.10 - 4.04 (m, 1H), 4.01 - 3.91 (m, 1H), 3.81 (dt, J = 2.7, 11.5 Hz, 1H), 3.64 - 3.48 (m, 2H), 3.10 (s, 3H), 2.91 (dt, J = 3.4, 11.9 Hz, 1H), 2.77 - 2.68 (m, 1H), 1.34 (s, 12H).

Step 4: Int. 426:



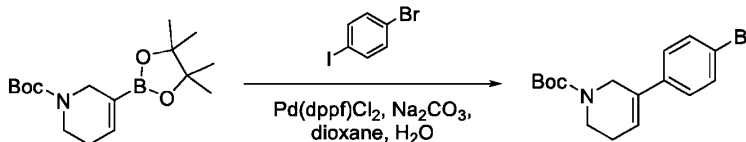
[0457] A solution of (R)-(4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)morpholin-2-yl)methyl methanesulfonate (2 g, 5.03 mmol, 1 eq) in dimethylamine (2 M in THF, 42.79 mL, 17 eq) was added to 100 mL Teflon tank. The reaction was stirred at 75 °C for 12 h. The reaction mixture was diluted with water (50 mL), extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (heptane / EtOH with 0.1% iso-propylamine) to give **Int. 426** (0.85 g, 2.30 mmol, 45.68%) as a white solid. LCMS (ESI+): *m/z* 347.2 (M+H⁺). ¹H NMR (400 MHz, MeOD-*d*₄): δ 7.62 (d, *J* = 8.6 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 4.01 (td, *J* = 1.8, 9.8 Hz, 1H), 3.81 - 3.68 (m, 2H), 3.67 - 3.52 (m, 2H), 2.79 (dt, *J* = 3.4, 11.9 Hz, 1H), 2.59 - 2.40 (m, 3H), 2.31 (s, 6H), 1.32 (s, 12H).

Int. 427 and Int. 428: Preparation of (R)-1-methyl-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidine and (S)-1-methyl-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidine



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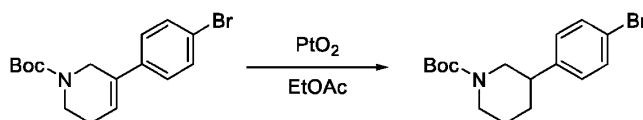
Step 1: tert-butyl 5-(4-bromophenyl)-3,6-dihydropyridine-1(2H)-carboxylate:



[0458] To a solution of tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (10.0 g, 32.34 mmol, 1 eq) in dioxane (200 mL) and H₂O (35 mL) was added Pd(dppf)Cl₂ (236.64 mg, 323.41 μmol, 0.01 eq) and Na₂CO₃ (6.86 g, 64.68 mmol, 2 eq) and 1-bromo-4-iodo-benzene (9.15 g, 32.34 mmol, 1 eq). The mixture was stirred at 80 °C for 1 h. The reaction mixture was diluted with water (100 mL) and extracted with EtOAc (80 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Pet. ether/EtOAc 0-15%). tert-butyl 5-(4-bromophenyl)-3,6-dihydropyridine-1(2H)-carboxylate (14 g, 41.39 mmol, 63.99%) was obtained as a clear

oil. LCMS (ESI+): m/z 338.1 ($M+H^+$). 1H NMR (400 MHz, $CDCl_3-d$): δ 7.46 (d, J = 8.4 Hz, 2H), 7.24 (d, J = 8.4 Hz, 2H), 6.20 (td, J = 2.0, 4.0 Hz, 1H), 4.23 (s, 2H), 3.55 (t, J = 6.0 Hz, 2H), 2.31 (d, J = 3.6 Hz, 2H), 1.50 (s, 9H).

Step 2: tert-butyl 3-(4-bromophenyl)piperidine-1-carboxylate:



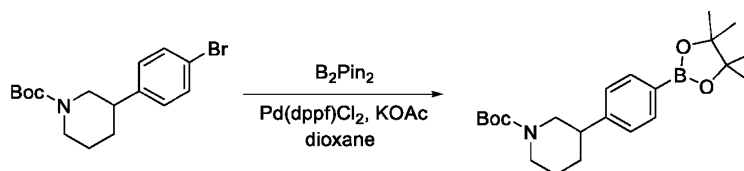
5

[0459] To a suspension of PtO_2 (0.5 g) of in EtOAc (80 mL) was added and tert-butyl 5-(4-bromophenyl)-3,6-dihydropyridine-1-carboxylate (5 g, 14.78 mmol, 1 eq) and the mixture was stirred at 20 °C for 2 h under H_2 atmosphere. The reaction mixture was filtered through a pad of silica gel and the filter cake was washed with EtOAc (50 mL x 3). The combined filtrates were concentrated to dryness and the residue was purified by column chromatography (SiO_2 , EtOAc:PE 0-50%) to afford tert-butyl 3-(4-bromophenyl)piperidine-1-carboxylate (5 g, 14.69 mmol, 99.41%) as a white oil. LCMS (ESI+): m/z 340.0 ($M+H^+$) 1H NMR (400 MHz, $CDCl_3-d$): δ 7.44 (d, J = 8.4 Hz, 2H), 7.11 (d, J = 8.4 Hz, 2H), 4.20-4.12 (m, 2H), 2.73 (d, J = 11.2 Hz, 2H), 2.00 (d, J = 9.2 Hz, 1H), 1.80-1.71 (m, 1H), 1.66-1.54 (m, 3H), 1.47 (s, 9H).

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Step 3: tert-butyl 3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidine-1-carboxylate:



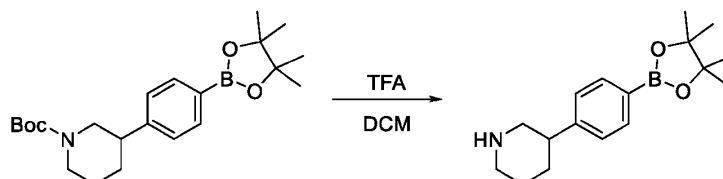
[0460] To a solution of tert-butyl 3-(4-bromophenyl)piperidine-1-carboxylate (2 g, 5.88 mmol, 1 eq) in dioxane (40 mL) was added B_2Pin_2 (2.24 g, 8.82 mmol, 1.5 eq), KOAc (1.15 g, 11.76 mmol, 2 eq) and $Pd(dppf)Cl_2$ (430.10 mg, 587.80 μ mol, 0.1 eq). The solution was degassed with a stream of N_2 and heated to 100 °C for 1h. Upon the consumption of the starting material (monitored by LCMS) the reaction mixture was diluted with water (30 mL) and extracted with EtOAc (30 mL x 3), the combined organic layers were dried over Na_2SO_4 , filtered, and concentrated. The resulting residue was purified by column chromatography (SiO_2 , 0 to 10% EtOAc in pet. ether) to afford tert-butyl 3-(4-(4,4,5,5-tetramethyl-1,3,2-

25

dioxaborolan-2-yl)phenyl)piperidine-1-carboxylate (2.2 g, 5.68 mmol, 96.63%) as a clear oil.

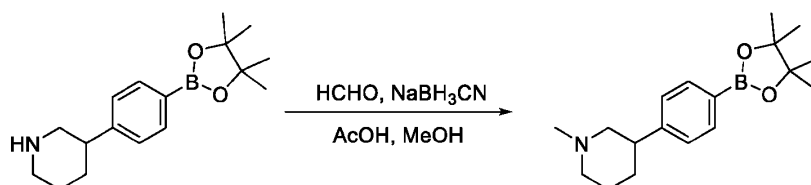
LCMS (ESI+): m/z 388.2 ($M+H^+$). **1H NMR** (400 MHz, $CDCl_3-d$): δ 7.77 (d, J = 7.6 Hz, 2H), 7.25 (d, J = 8.0 Hz, 2H), 4.24-4.09 (m, 2H), 2.81-2.64 (m, 3H), 1.79-1.55 (m, 4H), 1.34 (s, 9H), 1.27 (s, 12H).

5 Step 4: 3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidine:



[0461] To a solution of tert-butyl 3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidine-1-carboxylate (1.05 g, 2.71 mmol, 1 eq) in DCM (20 mL) was added TFA (4.2 mL). The mixture was stirred at 25 °C for 1 h. The solution was basified to pH = 7 with $NaHCO_3$ (1 mol/L), and extracted with EtOAc (10 mL x 3), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure to give 3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidine (1.7 g, crude) as a white solid. The material was used directly in the next reaction. **LCMS** (ESI+): m/z 288.2 ($M+H^+$). **1H NMR** (400 MHz, $CDCl_3-d$): δ 7.78 (d, J = 8.0 Hz, 2H), 7.20 (d, J = 8.0 Hz, 2H), 3.43 (d, J = 12.4 Hz, 2H), 3.16-3.04 (m, 1H), 2.96-2.82 (m, 2H), 2.14-1.95 (m, 3H), 1.76-1.62 (m, 1H), 1.34 (s, 12H).

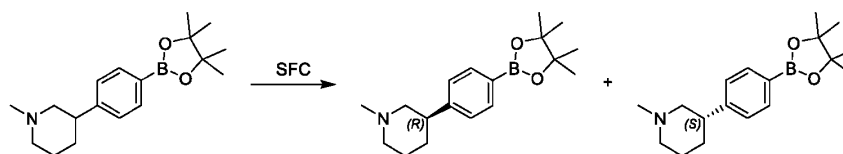
Step 5: 1-methyl-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidine:



[0462] To a solution of 3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidine (1 g, 3.48 mmol, 1 eq) in MeOH (10 mL) was added a 37% formaldehyde solution (1.41 g, 17.41 mmol, 1.30 mL, 5 eq) and AcOH (20.91 mg, 348.18 μ mol, 19.93 μ L, 0.1 eq) at 0°C. The reaction was stirred for 30 minutes, then, $NaBH_3CN$ (656.42 mg, 10.45 mmol, 3 eq) was added. The reaction continued for an additional 30 min. The reaction mixture was then diluted with water (20 mL) and extracted with EtOAc (15 mL x 3), the combined organic layers were dried over Na_2SO_4 , filtered, and concentrated. The

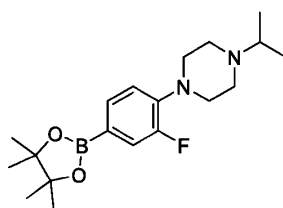
residue was triturated with MTBE (10 mL) to give 1-methyl-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidine (0.2 g, 663 μ mol, 19.0%) as a white solid. LCMS (ESI+): m/z 302.4 ($M+H^+$). 1H NMR (400 MHz, $CDCl_3-d$): δ 7.79 (d, J = 8.0 Hz, 2H), 7.25 (d, J = 8.0 Hz, 2H), 3.56-3.39 (m, 2H), 3.30-3.16 (m, 1H), 2.89 (t, J = 12.4 Hz, 2H), 2.84 (s, 3H), 2.20-2.02 (m, 3H), 1.78-1.64 (m, 1H), 1.33 (s, 12H).

Step 6: Int. 427, Int. 428:

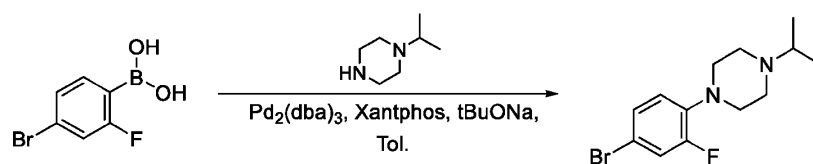


[0463] The 1-methyl-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidine was further separated by SFC (condition: column: Daicel Chiralcel OZ 250 x 50 mm; 10 μ m; mobile phase: $[CO_2-MeOH$ (0.1% IPAm)]; B%: 25%, isocratic elution) to afford (*R*)-stereochemistry **Int. 428** (0.5 g, 1.56 mmol, 23.50%), LCMS (ESI+): m/z 302.4 ($M+H^+$) 1H NMR (400 MHz, $CDCl_3-d$): δ 7.76 (d, J = 7.6 Hz, 2H), 7.25 (d, J = 7.6 Hz, 2H), 3.01-2.81 (m, 3H), 2.31 (s, 3H), 2.02-1.89 (m, 3H), 1.83-1.68 (m, 2H), 1.43 (dd, J = 4.4, 12.4 Hz, 1H), 1.34 (s, 12H), and (*S*)-stereochemistry **Int. 427** (0.46 g, 1.39 mmol, 20.93%) as white solid. LCMS (ESI+): m/z 302.4 ($M+H^+$) 1H NMR (400 MHz, $CDCl_3-d$): δ 7.77 (d, J = 7.6 Hz, 2H), 7.24 (d, J = 7.6 Hz, 2H), 3.15 (d, J = 11.6 Hz, 2H), 3.03 (tt, J = 3.4, 12.0 Hz, 1H), 2.49 (s, 3H), 2.32-2.20 (m, 2H), 2.02-1.87 (m, 3H), 1.57-1.48 (m, 1H), 1.34 (s, 12H).

Int. 429: Preparation of 1-(2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-4-isopropylpiperazine

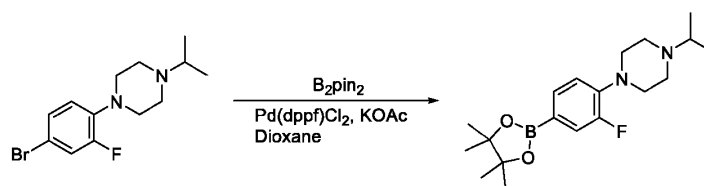


Step 1: 1-(4-bromo-2-fluorophenyl)-4-isopropylpiperazine:



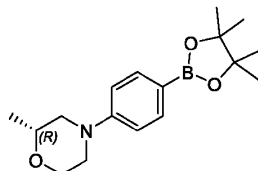
- [0464]** A mixture of (4-bromo-2-fluorophenyl)boronic acid (4 g, 13.29 mmol, 1 eq), 1-isopropylpiperazine (1.70 g, 13.29 mmol, 1.90 mL, 1 eq), $\text{Pd}_2(\text{dba})_3$ (304.33 mg, 332.34 μmol , 0.025 eq), Xantphos (769.20 mg, 1.33 mmol, 0.1 eq) and NaOt-Bu (2.56 g, 26.59 mmol, 2 eq) in Tol. (80 mL) was degassed and purged with N_2 (20 min). The mixture was stirred at 80 °C for 1 h. The reaction mixture was concentrated to give a residue and the residue was purified by flash chromatography (SiO_2 , 30-35% EtOAc in pet. ether) to give 1-(4-bromo-2-fluorophenyl)-4-isopropylpiperazine (2.8 g, 7.41 mmol, 55.74%) as a brown oil. **LCMS** (ESI+): m/z 301.0 ($\text{M}+\text{H}^+$), **^1H NMR** (CDCl_3 - d , 400 MHz): δ 7.15-7.22 (m, 2H), 6.82 (t, J = 8.8 Hz, 1H), 3.07-3.12 (m, 4H), 2.73-2.78 (m, 1H), 2.69-2.72 (m, 4H), 1.10 (d, J = 6.4 Hz, 6H).

Step 2: Int. 429:

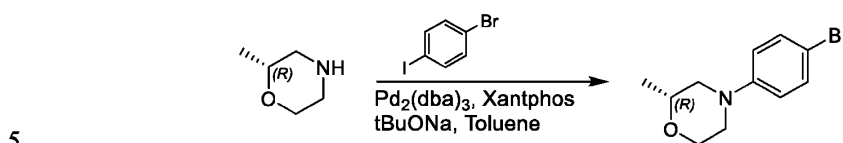


- [0465]** A mixture of 1-(4-bromo-2-fluorophenyl)-4-isopropylpiperazine (2.7 g, 8.96 mmol, 1 eq), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (3.41 g, 13.45 mmol, 1.5 eq), KOAc (2.20 g, 22.41 mmol, 2.5 eq), $\text{Pd}(\text{dppf})\text{Cl}_2$ (327.96 mg, 448.21 μmol , 0.05 eq) in dioxane (50 mL) was degassed with N_2 for 20 min. The mixture was heated to 100°C for 5 h. The reaction mixture was concentrated and the resulting residue was purified by flash chromatography (SiO_2 , 0~5% MeOH in EtOAc) to afford **Int. 429**. The product further purified by salt formation with HCl in EtOAc. **Int. 429** (2.3 g, 5.86 mmol, 65.32%, HCl) as a white solid. **LCMS**: (ESI+): m/z 349.2 ($\text{M}+\text{H}^+$), **^1H NMR** (400 MHz, $\text{DMSO}-d_6$): δ 7.44 (dd, J = 7.6, 1.2 Hz, 1H), 7.31 (dd, J = 13.6, 1.2 Hz, 1H), 7.09 (t, J = 8.4 Hz, 1H), 3.58 (br d, J = 12.8 Hz, 2H), 3.47 (d, J = 11.2 Hz, 3H), 3.32 (t, J = 11.6 Hz, 2H), 3.10-3.23 (m, 2H), 1.32 (d, J = 6.4 Hz, 6H), 1.27 (s, 12H).

Int. 430: Preparation of ((R)-2-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)morpholine:

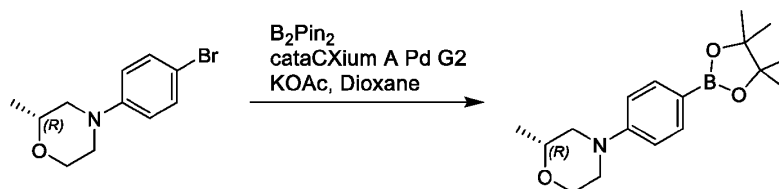


Step 1: (R)-4-(4-bromophenyl)-2-methylmorpholine:



- [0466] A mixture of (R)-2-methylmorpholine (3 g, 29.66 mmol, 1 eq), 1-bromo-4-iodobenzene (10.91 g, 38.56 mmol, 1.3 eq), NaOtBu (8.55 g, 88.98 mmol, 3 eq), Xantphos (2.15 g, 3.71 mmol, 0.125 eq) and Pd₂(dba)₃ (1.36 g, 1.48 mmol, 0.05 eq) in toluene (50 mL) was degassed with N₂ for 10 min, then heated to 85°C for 1h. After cooling to room temperature,
- 10 the reaction mixture was concentrated. The resulting residue was diluted with water (50 mL) and extracted with EtOAc (80 mL × 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated. The residue was purified by flash chromatography (SiO₂, 0-5% EtOAc in Pet. ether) to give (R)-4-(4-bromophenyl)-2-methylmorpholine (7 g, 23.27 mmol, 78.44%) as a yellow solid. LCMS: (ESI+): *m/z* 256.0 (M+H⁺), ¹H NMR (400 MHz,
- 15 DMSO-*d*₆): δ 7.35 (d, *J* = 9.2 Hz, 2H), 6.89 (d, *J* = 9.2 Hz, 2H), 3.89 (dd, *J* = 11.6, 2.4 Hz, 1H), 3.54-3.64 (m, 3H), 3.46 (br d, *J* = 11.6 Hz, 1H), 2.61 (td, *J* = 11.6, 3.6 Hz, 1H), 2.29 (t, *J* = 10.8 Hz, 1H), 1.14 (d, *J* = 6.4 Hz, 3H).

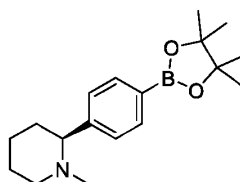
Step 2: Int. 430:



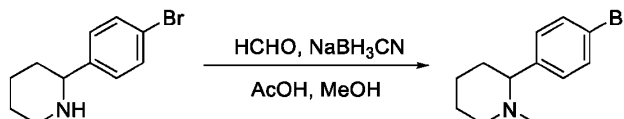
- 20 [0467] A mixture of (R)-4-(4-bromophenyl)-2-methylmorpholine (4 g, 15.62 mmol, 1 eq), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane

(7.93 g, 31.23 mmol, 2 eq), KOAc (3.83 g, 39.04 mmol, 2.5 eq), cataCXium A Pd G2 (1.04 g, 1.56 mmol, 0.1 eq) in dioxane (50 mL) was degassed with N₂ for 15 min. The reaction was heated to 90°C for 2h. After cooling to room temperature, the reaction mixture was concentrated. EtOAc (30 mL) was added, solids were filtered off, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (SiO₂, 0~5% EtOAc in Pet. ether) to give **Int. 430** (2.06 g, 6.20 mmol, 39.68%) as a gray solid. LCMS: (ESI+): *m/z* 304.2 (M+H⁺), ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.52 (d, *J* = 8.4 Hz, 2H), 6.90 (d, *J* = 8.4 Hz, 2H), 3.90 (d, *J* = 10.8 Hz, 1H), 3.54-3.69 (m, 4H), 2.66 (td, *J* = 12.0, 3.2 Hz, 1H), 2.34 (t, *J* = 10.8 Hz, 1H), 1.26 (s, 12H), 1.15 (d, *J* = 6.4 Hz, 3H).

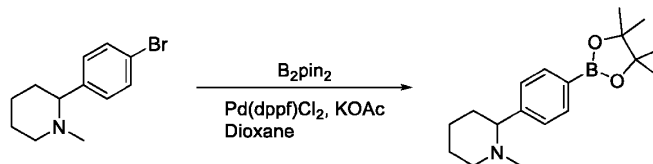
10 Int. 431: Preparation of (S)-1-methyl-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidine



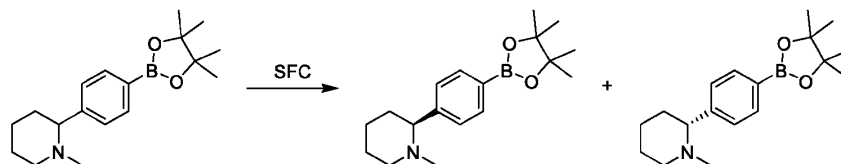
Step 1: 2-(4-bromophenyl)-1-methylpiperidine:



15 [0468] To a solution of 2-(4-bromophenyl)piperidine (2 g, 8.32 mmol, 1.0 eq) in MeOH (40 mL) was added 37% formaldehyde (3.38 g, 41.64 mmol, 3.10 mL, 5 eq) and AcOH (50.02 mg, 832.86 μmol, 47.68 μL, 0.1 eq) and stirred at 0°C for 30 min. Then, NaBH₃CN (1.57 g, 24.98 mmol, 3 eq) was added and stirred at 0 °C for 30 min. Upon the consumption of starting material, the reaction mixture was diluted with water (50 mL) and extracted with EtOAc (40 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give 2-(4-bromophenyl)-1-methylpiperidine (2.2 g, crude) as a yellow oil. The product was used without further purification. LCMS (ESI+): *m/z* 254.2 (M+H⁺). ¹H NMR (400 MHz, CDCl₃-*d*): δ 7.48 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 2H), 3.20-3.10 (m, 1H), 2.92 (dd, *J* = 2.8, 11.2 Hz, 1H), 2.32-2.22 (m, 1H), 2.08 (s, 3H), 1.91-1.84 (m, 1H), 1.80-1.76 (m, 2H), 1.75-1.70 (m, 1H), 1.70-1.60 (m, 1H), 1.48-1.35 (m, 1H).

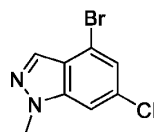
Step 2: 1-methyl-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidine:

- [0469]** To a solution of 2-(4-bromophenyl)-1-methylpiperidine (1.1 g, 4.33 mmol, 1 eq) in dioxane (40 mL) was added B₂Pin₂ (1.65 g, 6.49 mmol, 1.5 eq), Pd(dppf)Cl₂ (316.67 mg, 432.79 μmol, 0.1 eq) and KOAc (849.50 mg, 8.66 mmol, 2 eq). The mixture was degassed with N₂ then stirred at 100°C for 1h under N₂. Then, the reaction mixture was diluted with water (50 mL) and extracted with EtOAc (40 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by prep-HPLC (C18, H₂O +10mM NH₄HCO₃ and MeCN) to afford 1-methyl-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidine (117 mg, 388.41 μmol, 8.97%) as a white solid. **LCMS** (ESI+): *m/z* 302.1 (M+H⁺). **¹H NMR** (400 MHz, DMSO-*d*₆) δ 7.62 (d, *J* = 7.6 Hz, 2H), 7.31 (d, *J* = 7.6 Hz, 2H), 2.93 (d, *J* = 11.2 Hz, 1H), 2.76 (d, *J* = 9.2 Hz, 1H), 2.02 (t, *J* = 10.4 Hz, 1H), 1.87 (s, 3H), 1.72 (d, *J* = 12.4 Hz, 1H), 1.67-1.52 (m, 3H), 1.45-1.30 (m, 2H), 1.28 (s, 9H).

Step 3: Int. 431:

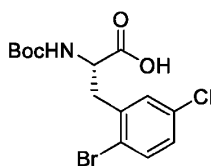
- [0470]** 1-methyl-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidine was further separated by SFC (DAICEL CHIRALPAK AD, CO₂/MeOH + 0.1% IPAm 10% isocratic) to afford **Int. 431** (0.1 g, 331.97). **LCMS** (ESI+): *m/z* 302.1 (M+H⁺). **¹H NMR** (400 MHz, CDCl₃-*d*) δ 7.77 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 7.6 Hz, 2H), 3.04 (br d, *J* = 11.6 Hz, 1H), 2.78 (dd, *J* = 2.4, 11.2 Hz, 1H), 2.17-2.06 (m, 1H), 2.00 (s, 3H), 1.83-1.68 (m, 4H), 1.64-1.52 (m, 1H), 1.38 (br d, *J* = 4.4 Hz, 1H), 1.34 (s, 12H).

Int. 433: Preparation of 4-bromo-6-chloro-1-methyl-1H-indazole

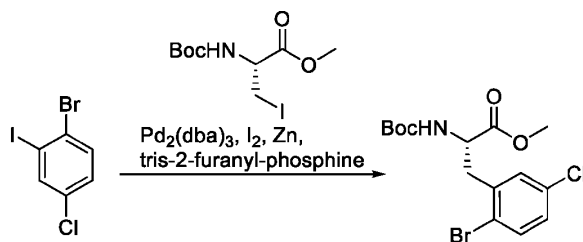


[0471] Int. 433 was synthesized using the procedure outlined in Int. 411. LCMS (ESI⁺): m/z 293.5 (M+H⁺).

5 **Int. 438: Preparation of (S)-3-(2-bromo-5-chlorophenyl)-2-((tert-butoxycarbonyl)amino)propanoic acid:**



Step 1: methyl (S)-3-(2-bromo-5-chlorophenyl)-2-((tert-butoxycarbonyl)amino)propanoate

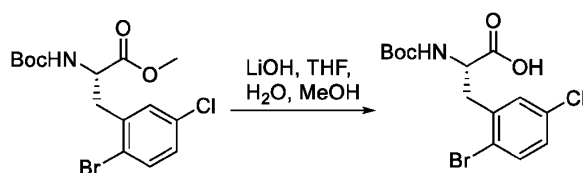


10 [0472] To a vial was added zinc (4.8 g, 3 Eq, 73 mmol). The vial was evacuated and backfilled with argon. DMA (10 mL) was added by syringe. Iodine (0.37 g, 0.06 Eq, 1.5 mmol) was added as a solid, and the mixture was stirred until exotherm and color change had subsided. Separately, methyl (R)-2-((tert-butoxycarbonyl)amino)-3-iodopropanoate (18 g, 2.3 Eq, 55 mmol) was dissolved in 10 mL DMA, and this solution was added by syringe to
15 zinc/iodine mixture while stirring, forming the zincate reagent *in situ*.

[0473] Separately, 1-bromo-4-chloro-2-iodobenzene (7.7 g, 1 Eq, 24 mmol) was added to a flask, and the flask was evacuated and backfilled with argon. DMA (10 mL) was added to this flask by syringe. To this solution was added Pd₂(dba)₃ (0.67 g, 0.03 Eq, 0.73 mmol) and tris-2-furanyl-phosphine (1.0 g, 0.18 Eq, 4.4 mmol) as solids, and the mixture was stirred to
20 dissolve. The zincate solution was added to the reaction flask by syringe while stirring. The reaction was heated to 55° C and stirred overnight. The reaction was allowed to cool to room

temperature, diluted with water, and extracted three times with EtOAc. The combined organics were washed with brine, dried over MgSO_4 , filtered, and concentrated by rotary evaporation. The crude product was purified by silica gel chromatography (0 to 100% EtOAc in hexanes) to yield methyl (S)-3-(2-bromo-5-chlorophenyl)-2-((tert-butoxycarbonyl)amino)propanoate (3.93 g, 10.02 mmol, 41%). **LCMS** (ESI+): m/z 338.1 ($\text{M}-55+\text{H}^+$).

Step 2: Int. 438



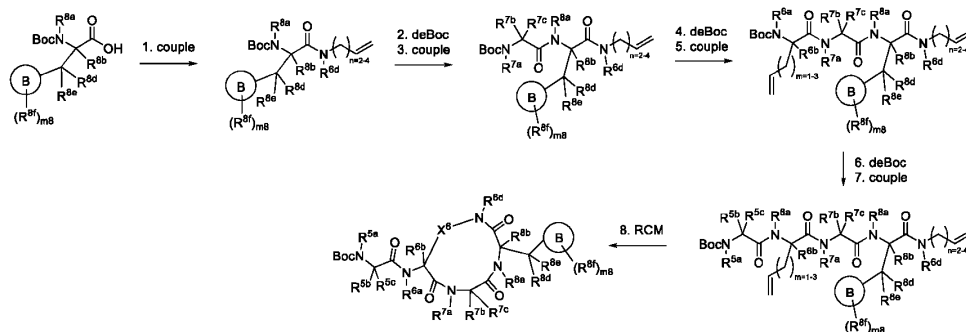
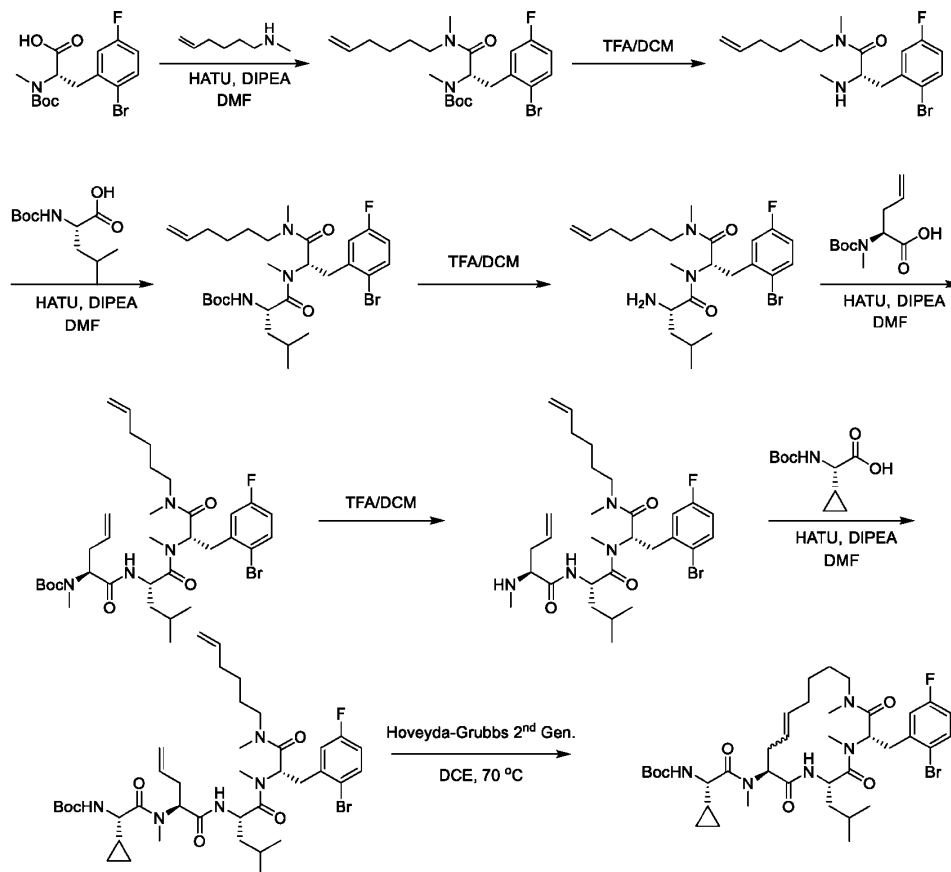
[0474] Methyl (S)-3-(2-bromo-5-chlorophenyl)-2-((tert-butoxycarbonyl)amino)propanoate (3.93 g, 1 Eq, 10 mmol) was dissolved in THF (4 mL), water (2 mL), and MeOH (1 mL). Lithium hydroxide monohydrate (480 mg, 2 Eq, 20 mmol) was added and the reaction mixture was stirred for 1 hour. The reaction was stirred for 1 hour, acidified with 1M HCl, and extracted three times with EtOAc. The combined organics were washed with brine, dried over MgSO_4 , filtered, and concentrated by rotary evaporation. **Int. 438** (3.78g, 10 mmol, quant.) was used without further purification. **LCMS** (ESI+): m/z 378.2 ($\text{M}-55+\text{H}^+$).

B. Representative Procedures for Preparing Compounds of Formula (I)

[0475] The following subsections describe procedures for preparing compounds of Formula (I). It is understood that compounds of Formula (I) can be prepared using variety of synthetic routes. The following procedures are meant to be illustrative, not limiting.

Generally, compounds of Formula (I) are prepared by synthesizing a macrocyclic portion of the compound and completing final synthetic steps to obtain compounds of Formula (I). The final synthetic steps include optional modifications (e.g., reduction, Phe Suzuki coupling, acylation) and tail addition (comprising the R^3 , $\text{R}^{4a/b/c}$, and sometimes $\text{R}^{5a/b/c}$ variable positions of Formula (I)). The macrocyclic synthesis procedures described herein include Methods A, B, C, and D. The final synthesis procedures described herein include Methods 1-14.

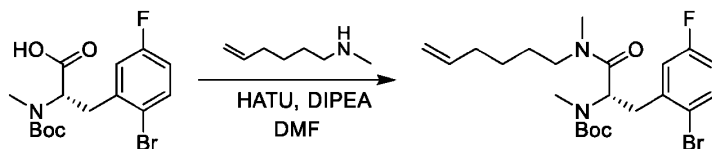
1. Macrocycle Synthesis Procedures

a. Method A**Generic Procedure for Method A:****Representative Procedure for Method A:**

5

Representative Experimental for Method A:

Step 1: (S)-3-(2-bromo-5-fluorophenyl)-2-((tert-butoxycarbonyl)(methyl)amino)propanoic acid (201):



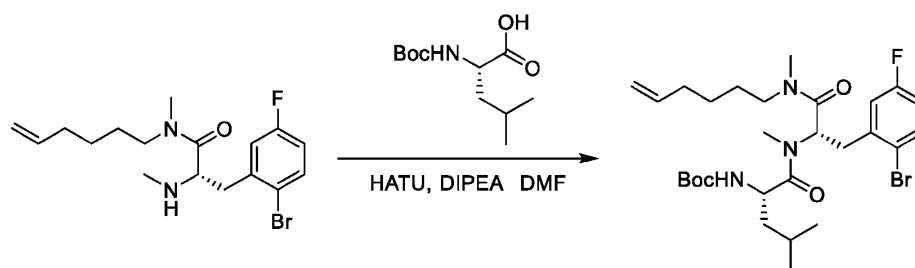
- [0476]** To a solution of **Int. 31** (32 g, 85 mmol, 1 eq) and **Int. 3** (11.5 g, 112 mmol, 1.3 eq) in DMF (1000 mL) was added HATU (48.5 g, 127.5 mmol, 1.5 eq) and DIPEA (55.0 g, 425.3 mmol, 74.1 mL, 5 eq) at 0 °C. The mixture was removed from the cooling bath and stirred at 25 °C until LCMS analysis showed the complete consumption of starting material. The reaction was added into ice water 2000 mL, then extracted with EtOAc (2000 mL × 2), the combined organic layers were washed with brine, dried over MgSO₄ and filtered. The filtrate was concentrated under reduced pressure to give crude product which was purified by column chromatography (SiO₂, EtOAc:Hexanes; 0-60%) to yield **201**: (37 g, 78.5 mmol, 92.3% yield) as a yellow oil. LCMS (ESI⁺): m/z 493.1 (M+Na⁺)

Step 2: (S)-3-(2-bromo-5-fluorophenyl)-N-(hex-5-en-1-yl)-N-methyl-2-((tert-butoxycarbonyl)(methyl)amino)propanamide TFA salt (202):



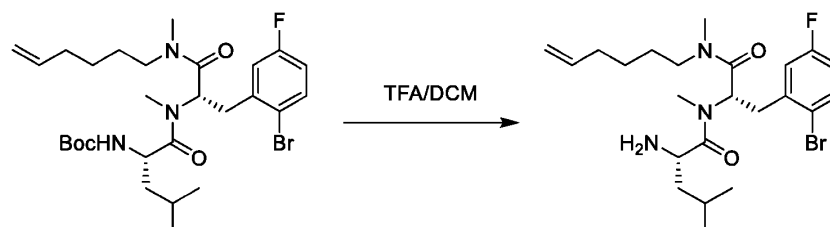
- [0477]** To a solution of **201** (37 g, 78.5 mmol, 1 eq) in DCM (400 mL) was added TFA (80 mL) at 0 °C. The mixture was removed from the cooling bath and stirred at 25 °C until LCMS analysis showed the complete consumption of starting material. The reaction mixture was concentrated under reduced pressure to give **202** (38 g, crude, TFA) as a light-yellow oil. LCMS (ESI⁺): m/z 371.1 (M+H⁺)

Step 3: Tert-butyl ((S)-1-(((S)-3-(2-bromo-5-fluorophenyl)-1-(hex-5-en-1-yl(methyl)amino)-1-oxopropan-2-yl(methyl)amino)-4-methyl-1-oxopentan-2-yl)carbamate (203):



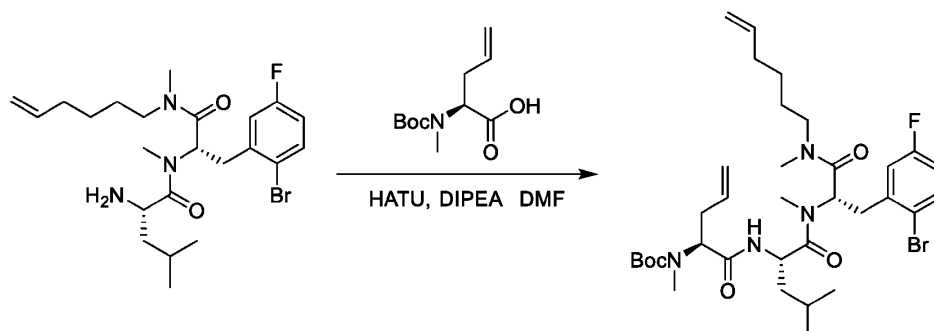
[0478] To a solution of **202** (38 g, 78.3 mmol, 1 eq, TFA salt) and **Int. 151** (19.9 g, 86. mmol, 1.1 eq) in DMF (1000 mL) was added HATU (44.7 g, 117.5 mmol, 1.5 eq) and DIEPA (50.6 g, 391.5 mmol, 68.2 mL, 5 eq) at 0 °C. The mixture was removed from the cooling bath and stirred at 25 °C until LCMS analysis showed the complete consumption of starting material. The reaction was added into ice water 2000 mL, then extracted with EtOAc (2000 mL × 2), the combined organic layers were washed with brine, dried over MgSO₄ and filtered. The filtrate was concentrated under reduced pressure to give crude product which was purified by column chromatography (SiO₂, EtOAc:Hexanes 0-50%) to give **203** (45 g) as a yellow oil. LCMS (ESI⁺): m/z 606.2 (M+Na⁺)

Step 4: (S)-2-amino-N-((S)-3-(2-bromo-5-fluorophenyl)-1-(hex-5-en-1-yl(methyl)amino)-1-oxopropan-2-yl)-N,4-dimethylpentanamide TFA salt (204):



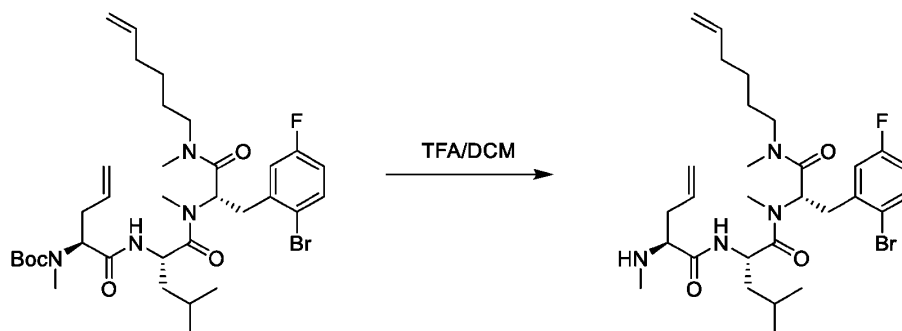
[0479] To a solution of **203** (45 g, 76.9 mmol, 1 eq) in DCM (500 mL) was added TFA (100 mL) at 0 °C. The mixture was removed from the cooling bath and stirred at 25 °C until LCMS analysis showed the complete consumption of starting material. The reaction mixture was concentrated under reduced pressure to give **204** (46 g, crude) as a light-yellow oil. LCMS (ESI⁺): m/z 484.1 (M+H⁺)

Step 5: Tert-butyl ((S)-1-(((S)-1-(((S)-3-(2-bromo-5-fluorophenyl)-1-(hex-5-en-1-yl(methyl)amino)-1-oxopropan-2-yl)(methyl)amino)-4-methyl-1-oxopentan-2-yl)amino)-1-oxopent-4-en-2-yl)(methyl)carbamate (205):



- [0480]** To a solution of **204** (46 g, 76.9 mmol, 1 eq, TFA) and **Int. 152** (19.38 g, 84.6 mmol, 1.1 eq) in DMF (1300 mL) was added HATU (43.8 g, 115.3 mmol, 1.5 eq) and DIEPA (49.7 g, 384.32 mmol, 66.94 mL, 5 eq) at 0 °C. The mixture was removed from the cooling bath and stirred at 25 °C until LCMS analysis showed the complete consumption of starting material. The reaction was added into ice water 2000 mL, then extracted with EtOAc (2000 mL × 2), the combined organic layers were washed with brine, dried over MgSO₄ and filtered. The filtrate was concentrated under reduced pressure to give crude product which was purified by column chromatography (SiO₂, EtOAc:Hexanes; 0-60%) to give **205** (46 g, 66.1 mmol, 78 % yield) as a yellow oil. LCMS (ESI+): m/z 717.4 (M+Na⁺)

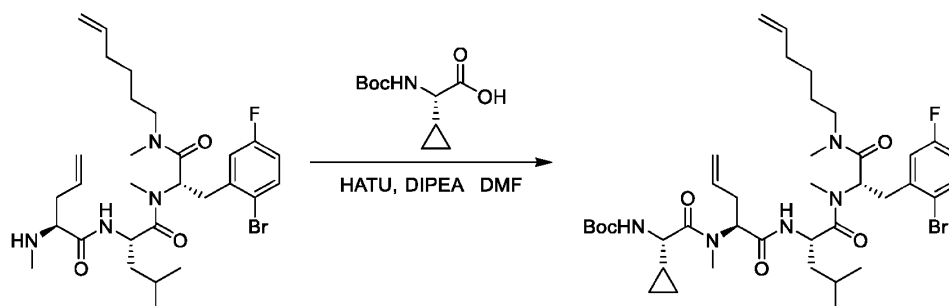
Step 6: (S)-N-((S)-1-(((S)-3-(2-bromo-5-fluorophenyl)-1-(hex-5-en-1-yl(methyl)amino)-1-oxopropan-2-yl)(methyl)amino)-4-methyl-1-oxopentan-2-yl)-2-(methylamino)pent-4-enamide TFA salt (206**):**



- [0481]** To a solution of **205** (46 g, 66.1 mmol, 1 eq) in DCM (500 mL) was added TFA (100 mL) at 0 °C. The mixture was removed from the cooling bath and stirred at 25 °C until LCMS analysis showed the complete consumption of starting material. The reaction mixture

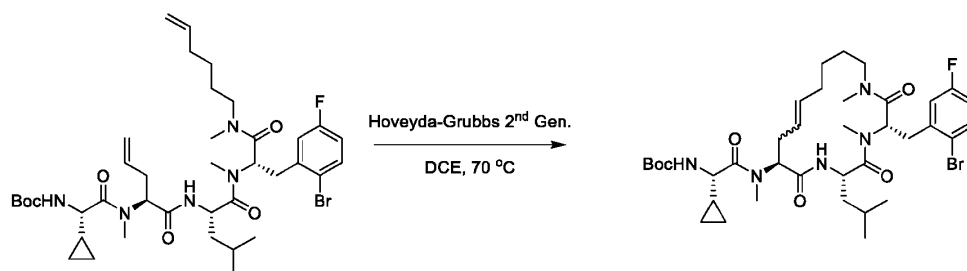
was concentrated under reduced pressure to give **206** (47 g,) as a yellow oil. LCMS (ESI+): m/z 595.1 ($M+H^+$)

Step 7: Tert-butyl ((1S,4S,7S,10S)-4-allyl-10-(2-bromo-5-fluorobenzyl)-1-cyclopropyl-7-isobutyl-3,9,12-trimethyl-2,5,8,11-tetraoxo-3,6,9,12-tetraazaoctadec-17-en-1-yl)carbamate (207):



[0482] To a solution **206** (47 g, 66.2 mmol, 1 eq, TFA) and **Int. 153** (16.4 g, 76.2 mmol, 1.15 eq) in DMF (1300 mL) was added HATU (37.8 g, 99.4 mmol, 1.5 eq) and DIEPA (85.6 g, 662.3 mmol, 115.4 mL, 10 eq) at 0 °C. The mixture was removed from the cooling bath and stirred at 25 °C until LCMS analysis showed the complete consumption of starting material. The reaction was added into ice water 2000 mL, then extracted with EtOAc (2000 mL $\times$ 2), the combined organic layers were washed with brine, dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure to give crude product which was purified by column chromatography (SiO_2 , EtOAc:Hexanes; 0-60%) to give **207** (44 g, 55.5 mmol, 70 % yield) as a yellow oil. LCMS (ESI+): m/z 814.5 ($M+Na^+$). 1H NMR (400 MHz, $DMSO-d_6$) δ 0.34 (br s, 2 H) 0.42 (br d, J = 7.87 Hz, 2 H) 0.85 (br d, J = 6.32 Hz, 6 H) 1.11 (br d, J = 7.15 Hz, 1 H) 1.29 (br d, J = 6.44 Hz, 3 H) 1.38 (s, 9 H) 1.45 (br s, 3 H) 1.52-1.63 (m, 1 H) 2.02 (br d, J = 6.68 Hz, 2 H) 2.30-2.40 (m, 1 H) 2.83 (s, 3 H) 2.94 (br s, 2 H) 3.00 (s, 3 H) 3.03 (br d, J = 9.06 Hz, 1 H) 3.06 (s, 3 H) 3.09-3.24 (m, 2 H) 3.26-3.47 (m, 1 H) 4.14 (br s, 1 H) 4.66-4.76 (m, 1 H) 4.81-5.23 (m, 5 H) 5.67 (br s, 1 H) 5.70-5.85 (m, 2 H) 6.21-6.69 (m, 1 H) 6.92-7.01 (m, 1 H) 7.03-7.15 (m, 1 H) 7.54 (br dd, J = 8.52, 5.54 Hz, 1 H)

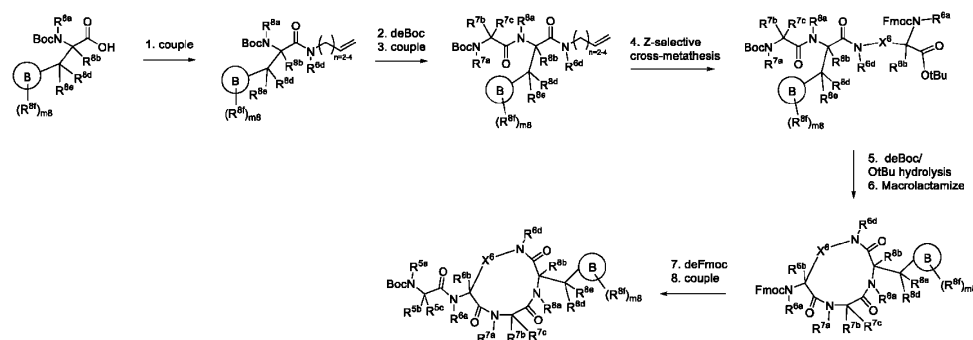
Step 8: Tert-butyl ((S)-2-(((3S,6S,9S)-3-(2-bromo-5-fluorobenzyl)-6-isobutyl-1,4-dimethyl-2,5,8-trioxo-1,4,7-triazacyclohexadec-11-en-9-yl)(methyl)amino)-1-cyclopropyl-2-oxoethyl)carbamate (208):

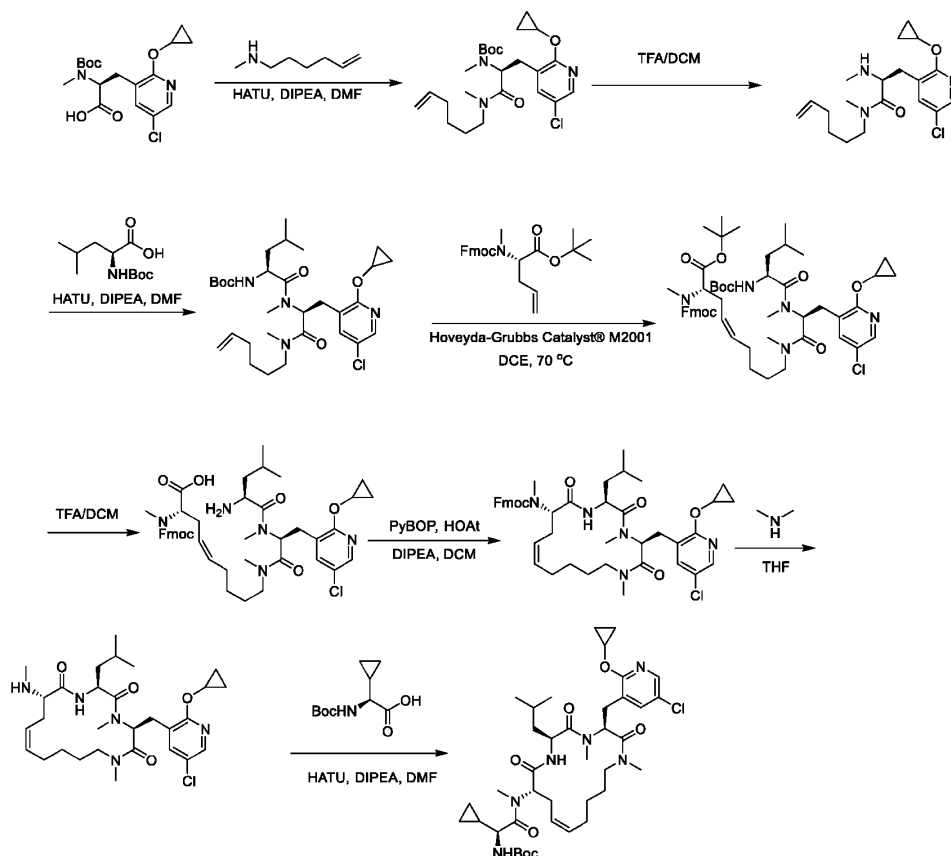


- [0483]** A mixture the pre-cyclized peptide **207** (8 g, 10.1 mmol, 1 eq), [1,3-bis(2,4,6-trimethylphenyl)imidazolidin-2-ylidene]-dichloro-[(2-isopropoxyphenyl)methylene]ruthenium (695.5 mg, 1.11 mmol, 0.11 eq) in DCE (1600 mL) was degassed and purged with N₂ for 0.5 hr. The mixture was capped and stirred at 70 °C until LCMS analysis showed the complete consumption of starting material. The reaction mixture was concentrated under reduced pressure to give a thick residue. The crude product was purified by reversed phase HPLC flash C18 gel chromatography (ISCO; 330g SepaFlash C18 Flash Column, eluent of 50-100% MeCN in H₂O buffered with 0.1% TFA) **208** (5.41 g, 6.8 mmol, 67 % yield) as an off white solid. Compound was isolated as a mix of *cis/trans* isomers LCMS (ESI+): *m/z* 764.4 (M+H). ¹H NMR of major isomer (400 MHz, DMSO-*d*₆) δ 0.25-0.47 (m, 4 H) 0.70-0.86 (m, 6 H) 1.05-1.13 (m, 1 H) 1.29 (br s, 3 H) 1.40 (br s, 9 H) 1.43-1.62 (m, 3 H) 1.78-2.16 (m, 3 H) 2.47-2.49 (m, 1 H) 2.51-2.56 (m, 1 H) 2.60-3.03 (m, 11 H) 3.09-3.29 (m, 2 H) 4.10-4.32 (m, 2 H) 4.53-5.07 (m, 2 H) 5.19-5.40 (m, 1 H) 5.41-5.58 (m, 1 H) 6.25-6.60 (m, 1 H) 6.95-7.06 (m, 1 H) 7.07-7.16 (m, 1 H) 7.53-7.63 (m, 1 H) 7.74-7.98 (m, 1 H)

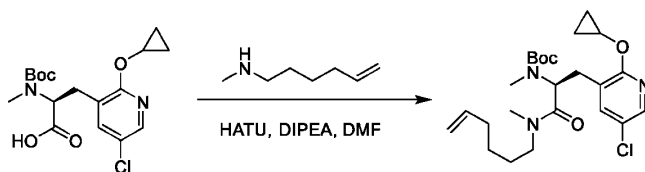
b. Method B

Generic Procedure for Method B: Z-Selective Macrocycle Formation:



Representative Procedure for Method B:**Representative Experimental for Method B:**

Step 1: Tert-butyl (S)-(3-(5-chloro-2-cyclopropoxy-pyridin-3-yl)-1-(hex-5-en-1-yl(methyl)amino)-1-oxopropan-2-yl)(methyl)carbamate (209):

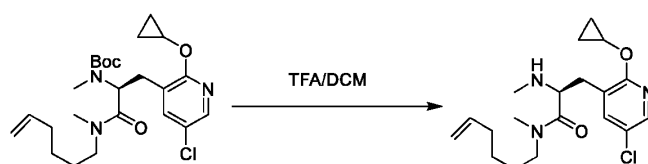


[0484] To a solution of **Int. 7** (7.0 g, 1 Eq, 19 mmol) and **Int. 3** (2.8 g, 1.3 Eq, 25 mmol) in DMF (94 mL) was added HATU (9.3 g, 1.3 Eq, 25 mmol) and DIPEA (9.8 g, 13 mL, 4 Eq, 76 mmol) at 0 °C. The mixture was removed from the cooling bath and stirred at 25 °C until LCMS analysis showed the complete consumption of starting material. The reaction was

added into ice water 400 mL, then extracted with EtOAc (300 mL $\times$ 2), the combined organic layers were washed with brine, dried over MgSO₄ and filtered. The filtrate was concentrated under reduced pressure to give crude product which was purified by column chromatography (SiO₂, EtOAc:Hexanes; 0-60%) to yield **209** (8.0 g, 17 mmol, 91 % yield) as a yellow oil.

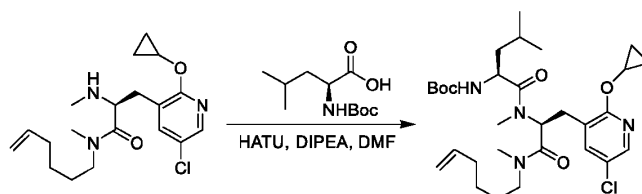
5 **LCMS** (ESI⁺): m/z 466.4 (M+H⁺)

Step 2: (S)-3-(5-chloro-2-cyclopropoxy-pyridin-3-yl)-N-(hex-5-en-1-yl)-N-methyl-2-(methylamino)propanamide TFA salt (210):



10 **[0485]** To a solution of **209** (8.0 g, 17 mmol, 1 eq) in DCM (80 mL) was added TFA (16 mL) at 0 °C. The mixture was removed from the cooling bath and stirred at 25 °C until LCMS analysis showed the complete consumption of starting material. The reaction mixture was concentrated under reduced pressure to give **210** (8.8 g, crude, TFA) as a light-yellow oil. **LCMS** (ESI⁺): m/z 366.2 (M+H⁺)

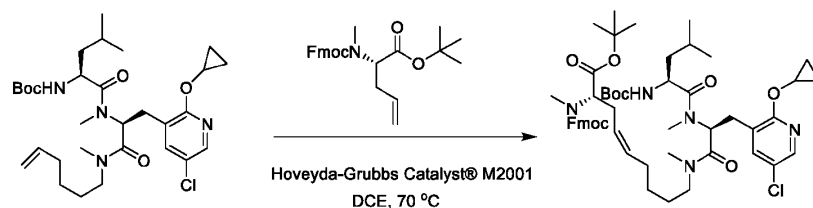
15 **Step 3: Tert-butyl ((S)-1-(((S)-3-(5-chloro-2-cyclopropoxy-pyridin-3-yl)-1-(hex-5-en-1-yl(methyl)amino)-1-oxopropan-2-yl)(methyl)amino)-4-methyl-1-oxopentan-2-yl)carbamate (211):**



20 **[0486]** To a solution of **210** (8.0 g, 17 mmol, 1 eq, TFA) and **Int. 151** (5.1 g, 1.2 Eq, 21 mmol) in DMF (86 mL) was added DIPEA (8.9 g, 12 mL, 4 Eq, 69 mmol) and HATU (7.8 g, 1.2 Eq, 21 mmol) at 0 °C. The mixture was removed from the cooling bath and stirred at 25 °C until LCMS analysis showed the complete consumption of starting material. The reaction was added into ice water 400 mL, then extracted with EtOAc (300 mL $\times$ 2), the combined organic layers were washed with brine, dried over MgSO₄ and filtered. The filtrate was concentrated under reduced pressure to give crude product which was purified by column

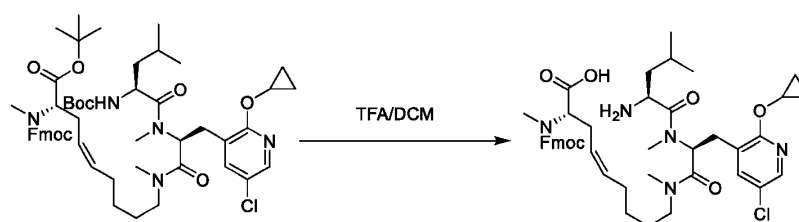
chromatography (SiO₂, EtOAc:Hexanes; 0-100%) to yield **211** (9.2 g, 16 mmol, 93 % yield) as a yellow oil. LCMS (ESI⁺): *m/z* 579.7 (M+H⁺)

Step 4: Tert-butyl (6S,9S,19S,Z)-19-((((9H-fluoren-9-yl)methoxy)carbonyl)(methyl)amino)-9-((5-chloro-2-cyclopropoxy)pyridin-3-yl)methyl)-6-isobutyl-2,2,8,11-tetramethyl-4,7,10-trioxo-3-oxa-5,8,11-triazaicos-16-en-20-oate (212):



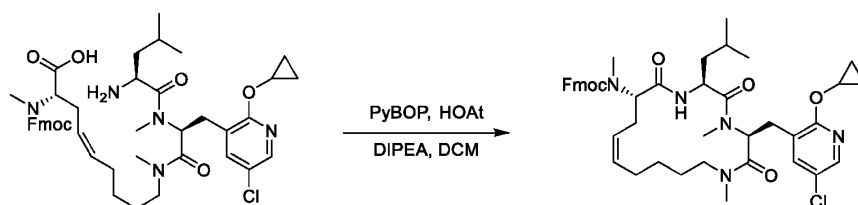
[0487] A mixture of **Int. 154** (2.5 g, 1 Eq, 4.3 mmol) **211** (5.3 g, 3 Eq, 13 mmol) in DCE (22 mL) was degassed and purged with Ar for 0.5 hr, and Hoveyda-Grubbs Catalyst® M2001 (0.41 g, 0.15 Eq, 0.65 mmol) was added to the mixture. The mixture was stirred at 70 °C until LCMS analysis showed the complete consumption of starting material. The reaction mixture was concentrated under reduced pressure to give a thick residue. The crude product was purified by column chromatography (SiO₂, EtOAc:Hexanes; 0-100%) to give **212** (1.8 g, 1.9 mmol, 44 % yield, crude, *Trans/Cis* =1:4) as brown syrup. LCMS (ESI⁺): *m/z* 958.8 (M+H).

Step 5: (S,Z)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)(methyl)amino)-9-((S)-2-((S)-2-(12-azaneyl)-N,4-dimethylpentanamido)-3-(5-chloro-2-cyclopropoxy)pyridin-3-yl)-N-methylpropanamido)non-4-enoic acid TFA salt (213):



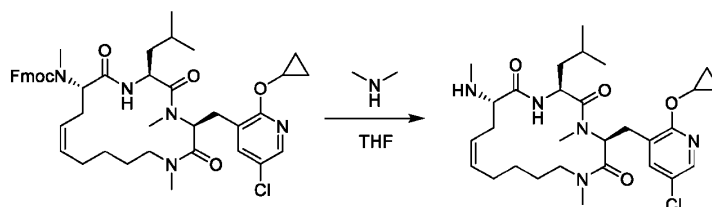
[0488] To a solution of peptide **212** (1.8 g, 1.9 mmol, 1 eq) in DCM (15 mL) was added TFA (7 mL) at 0 °C. The mixture was removed from the cooling bath and stirred at 25 °C until LCMS analysis showed the complete consumption of starting material. The reaction mixture was concentrated under reduced pressure to give **213** (2 g, crude, TFA) as a brown oil. LCMS (ESI⁺): *m/z* 858.6 (M+H⁺)

Step 6: (9H-fluoren-9-yl)methyl ((3S,6S,9S,Z)-3-((5-chloro-2-cyclopropoxypyridin-3-yl)methyl)-6-isobutyl-1,4-dimethyl-2,5,8-trioxo-1,4,7-triazacyclohexadec-11-en-9-yl)(methyl)carbamate (214):



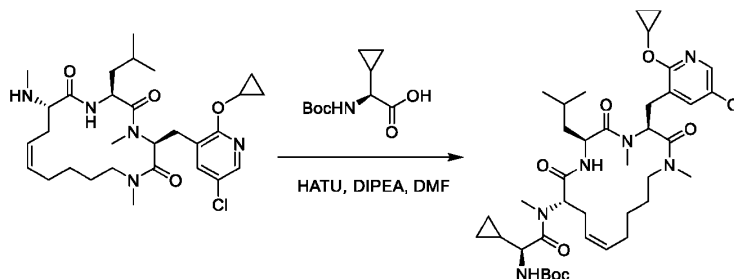
- 5 **[0489]** To a solution of the deprotected peptide **213** (1.8 g, 1.9 mmol, 1 eq, TFA) in DCM (0.37 L), add DIEPA (0.87 g, 1.2 mL, 3 Eq, 6.7 mmol). Separately, dissolve 1-Hydroxy-7-azabenzotriazole (0.37 g, 0.38 mL, 1.2 Eq, 2.7 mmol) and PyBOP (1.4 g, 1.2 Eq, 2.7 mmol) in DCM (0.37 L) and add DIEPA (0.87 g, 1.2 mL, 3 Eq, 6.7 mmol). Add the second solution into the first solution dropwise by additional funnel. The mixture was stirred at 25 °C until
- 10 LCMS analysis showed the complete consumption of starting material. The reaction mixture was concentrated under reduced pressure to give a thick residue. The crude product was purified by column chromatography (SiO₂, EtOAc:Hexanes; 0-100%) to give **214** (0.5 g, 0.6 mmol, 30 % yield, 99% purity) as brown solid. LCMS (ESI+): *m/z* 784.5 (M+H⁺)

- Step 7: (3S,6S,9S,Z)-3-((5-chloro-2-cyclopropoxypyridin-3-yl)methyl)-6-isobutyl-1,4-dimethyl-9-(methylamino)-1,4,7-triazacyclohexadec-11-ene-2,5,8-trione (215):**
- 15



- [0490]** To peptide **214** (0.5 g, 0.6 mmol, 1 eq) was added dimethylamine in THF (6.76 g, 10.4 mL, 2.0 molar, 32.6 Eq, 20.8 mmol) at 0 °C. The mixture was removed from the cooling bath and stirred at 25 °C until LCMS analysis showed the complete consumption of starting
- 20 material. The reaction mixture was concentrated under reduced pressure to give a thick residue. The crude product was purified by reversed phase HPLC flash C18 gel chromatography (ISCO; 12 g C18 Flash Column, eluent of 20-100% MeCN in H₂O buffered with 0.1% TFA) to give **215** (0.35 g, 0.64 mmol, 100 % yield) LCMS (ESI+): *m/z* 562.5 (M+H⁺)

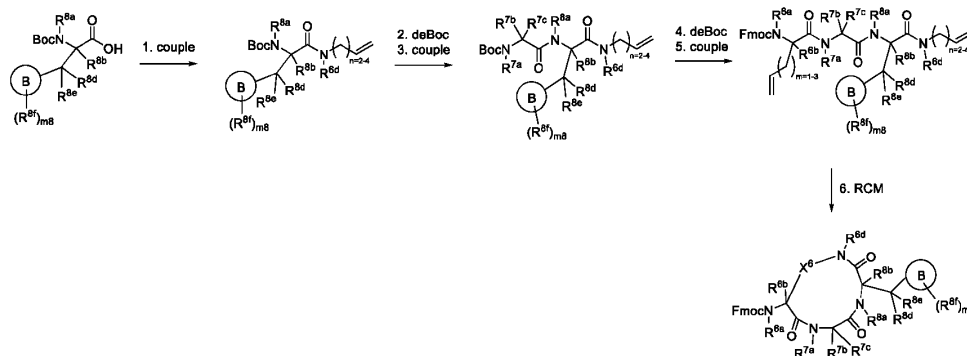
Step 8: Tert-butyl ((S)-2-(((3S,6S,9S,Z)-3-((5-chloro-2-cyclopropoxy)pyridin-3-yl)methyl)-6-isobutyl-1,4-dimethyl-2,5,8-trioxo-1,4,7-triazacyclohexadec-11-en-9-yl)(methyl)amino)-1-cyclopropyl-2-oxoethyl)carbamate (216**):**



- 5 **[0491]** To a solution of deprotected starting material **215** (350 mg, 0.64 mmol, 1 eq) and **Int. 153** (164 mg, 1.2 Eq, 764 μ mol) in DMF (3.18 mL) was added DIPEA (494 mg, 666 μ L, 6 Eq, 3.82 mmol) and HATU (291 mg, 1.2 Eq, 764 μ mol) at 0 °C. The mixture was removed from the cooling bath and stirred at 25 °C until LCMS analysis showed the complete consumption of starting material. The mixture was neutralized to pH ~ 7 with 1N HCl and
- 10 directly purified by RP-HPLC (C18, 50% to 80% MeCN/H₂O with 0.5% formic acid) to yield **216** (120 mg, 158 μ mol, 25 %) as off-white solid. LCMS (ESI⁺): *m/z* 759.5 (M+H⁺)

c. Method C

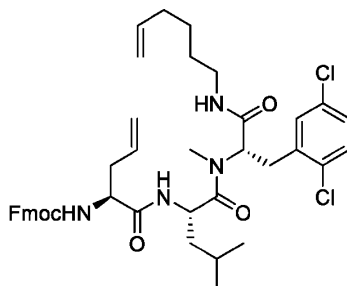
Generic Procedure for Method C



- 15 **[0492]** As seen when comparing Method A and Method C, Steps 1-5 follow similar synthetic procedures.

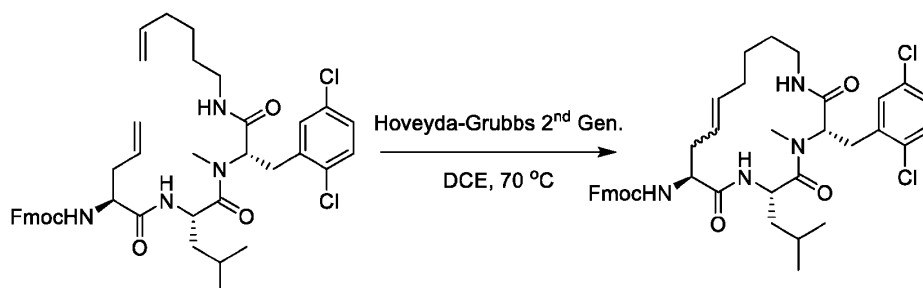
Representative Experimental for Method C:

(9H-fluoren-9-yl)methyl ((S)-1-(((S)-1-(((S)-3-(1,4-dichloro-115-chlorinin-3-yl)-1-(hex-5-en-1-ylamino)-1-oxopropan-2-yl)(methyl)amino)-4-methyl-1-oxopentan-2-yl)amino)-1-oxopent-4-en-2-yl)carbamate (217):

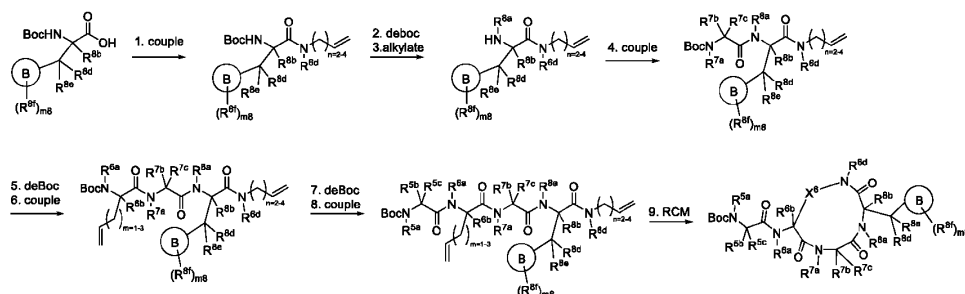
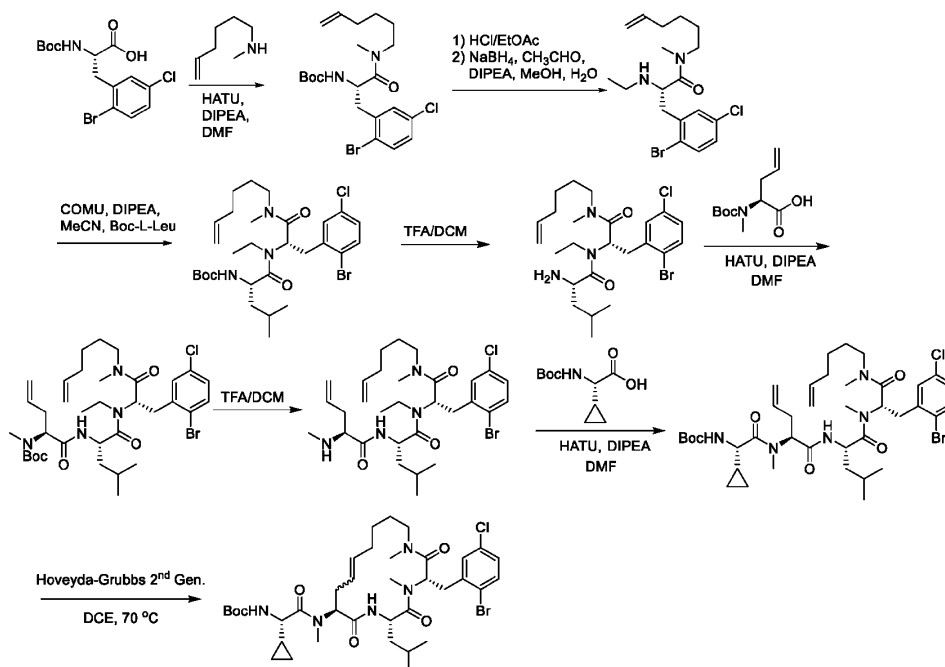


- 5 [0493] Compound **217** was prepared according to Steps 1-5 of Method A with starting materials **Int. 1**, **6**, **151** and **21**. LCMS (ESI+): m/z 761.1 (M+H).

Step 6: (9H-fluoren-9-yl)methyl ((3S,6S,9S)-3-(2,5-dichlorobenzyl)-6-isobutyl-4-methyl-2,5,8-trioxo-1,4,7-triazacyclohexadec-11-en-9-yl)carbamate (**218**):



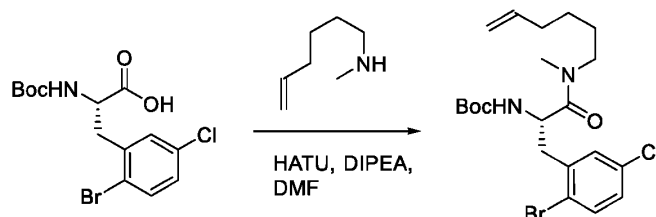
- 10 [0494] **217** (200 mg, 1 Eq, 263 μ mol) was dissolved in DCE (80 mL) and degassed for 30 min with a stream of nitrogen. Dichloro(1,3-dimesityl-2-imidazolidinylidene)(2-isopropoxybenzylidene)ruthenium (32 mg, 0.19 Eq, 51 μ mol) was added rapidly and the reaction was degassed for an additional 10 min. reaction was then heated to 50 °C and continued until the complete consumption of starting material (monitored by LCMS). The
- 15 reaction was cooled, concentrated, and purified by normal phase purification Methanol/DCM (0 to 15%, over 10 min.). **218** (121 mg, 165 μ mol, 63 %) was isolated as a brown solid. It was used as a mixture of *E/Z* isomers (~7:3). LCMS (ESI+): m/z 733.4 (M+H).

d. Method D**Generic procedure for Method D****Representative Procedure for Method D:**

5

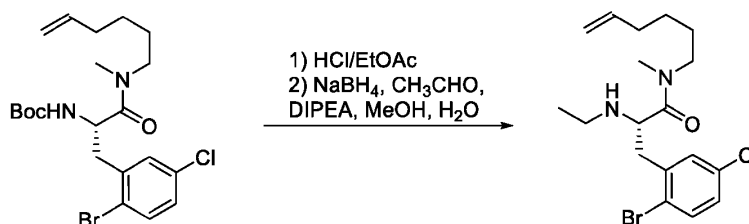
Representative Experimental for Method D:

Step 1: tert-butyl (S)-(3-(2-bromo-5-chlorophenyl)-1-(hex-5-en-1-yl(methyl)amino)-1-oxopropan-2-yl)carbamate (249):



[0495] **Int. 238** (3.73 g, 1 Eq, 10.02 mmol) was dissolved in DMF (10 mL) along with **Int. 3** (1.36 g, 1.8 mL, 1.2 Eq, 12.03 mmol), HATU (4.5 g, 1.2 Eq, 12.03 mmol), and DIPEA (4.53 g, 6.11 mL, 3.5 Eq, 35.08 mmol). The pH was checked by indicator paper and DIPEA was added until the pH was confirmed to be basic. The reaction was stirred for 1 hour, diluted with water, and extracted with EtOAc (3 x 100 mL). The combined organics were washed with brine, dried over MgSO₄, filtered, and concentrated by rotary evaporation. The crude product was purified by silica gel chromatography (0 to 100% ethyl acetate in hexanes) to yield **249** (1.195 g, 2.52 mmol, 25% yield). LCMS (ESI⁺): m/z 473.2 (M+H⁺).

10 **Steps 2-3: (S)-3-(2-bromo-5-chlorophenyl)-2-(ethylamino)-N-(hex-5-en-1-yl)-N-methylpropanamide (250):**



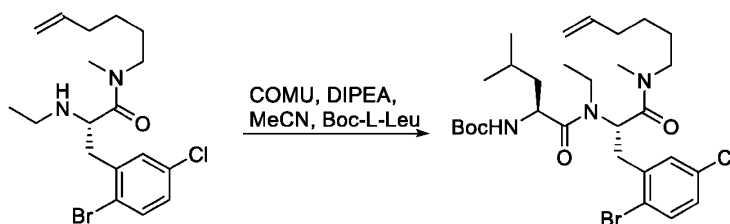
[0496] **249** (1.195 g, 1 Eq, 2.522 mmol) was dissolved in 4M HCl/EtOAc and stirred for 1 hour. The reaction was diluted in saturated sodium bicarbonate EtOAc (3 x 30 mL). The combined organics were washed with brine, dried over MgSO₄, filtered, and concentrated by rotary evaporation. The residue was carried on without further purification. LCMS (ESI⁺): m/z 373.5 (M+H⁺).

[0497] The residue in was dissolved in MeOH (20 mL) and Water (2.0 mL). To this solution was added DIPEA (2.1 g, 2.8 mL, 6.4 Eq, 16 mmol), followed by a solution of acetaldehyde (433 mg, 550 μ L, 3.90 Eq, 9.84 mmol) in ethanol. Sodium borohydride (400 mg, 4.19 Eq, 10.6 mmol) was added and the reaction was stirred overnight. Additional DIPEA (2.1 g, 2.8 mL, 6.4 Eq, 16 mmol), solution of acetaldehyde (433 mg, 550 μ L, 3.90 Eq, 9.84 mmol) in ethanol, and sodium borohydride (400 mg, 4.19 Eq, 10.6 mmol) were added

and the reaction was stirred for 2 hr. The reaction was concentrated by rotary evaporation and the crude product, **250** (1.01 g, 2.522 mmol, quant.), was used without further purification.

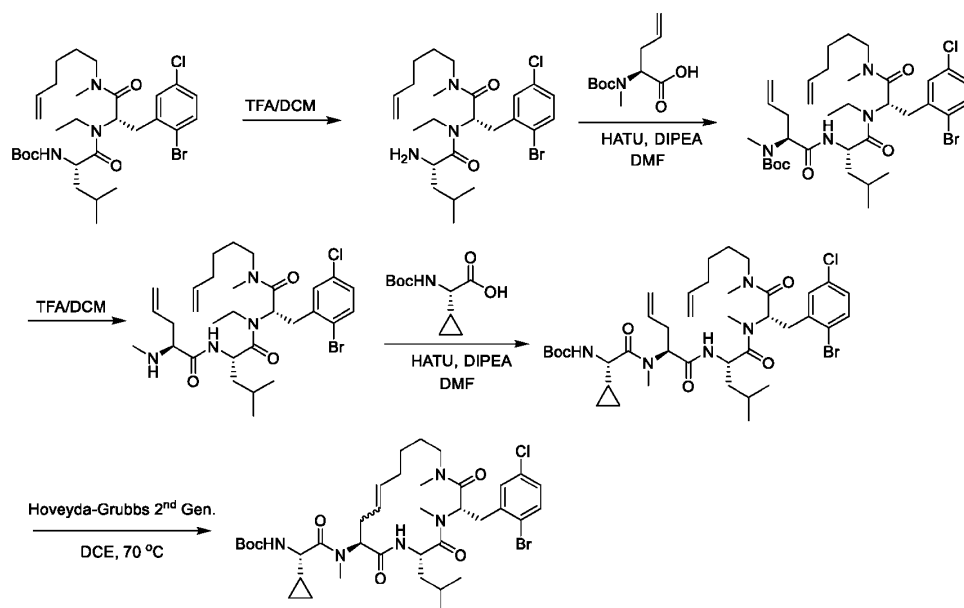
LCMS (ESI+): m/z 401.2 ($M+H^+$).

Step 4: tert-butyl ((S)-1-(((S)-3-(2-bromo-5-chlorophenyl)-1-(hex-5-en-1-yl(methyl)amino)-1-oxopropan-2-yl)(ethyl)amino)-4-methyl-1-oxopentan-2-yl)carbamate (251):



[0498] **250** (1.01 g, 1 Eq, 2.51 mmol) was dissolved in MeCN (25 mL) along with COMU (8 g, 7.4 Eq, 19 mmol), Boc-L-Leucine monohydrate (4.5 g, 7.2 Eq, 18 mmol), and DIPEA (5.6 g, 7.5 mL, 17 Eq, 43 mmol). The reaction was refluxed at 85° C for 24 hours and allowed to cool to room temperature before being concentrated by rotary evaporation. The residue was partitioned between water (20 mL) and EtOAc (20 mL), and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organics were washed with brine, dried over MgSO₄, filtered, and concentrated by rotary evaporation. The crude product was purified by silica gel chromatography (0 to 100% EtOAc in hexanes) to yield **251** (440 mg, 2.51 mmol, 25%). LCMS (ESI+): m/z 617.8 ($M+H^+$).

Steps 5-9: tert-butyl ((S)-2-(((3S,6S,9S)-3-(2-bromo-5-chlorobenzyl)-6-isobutyl-1,4-dimethyl-2,5,8-trioxo-1,4,7-triazacyclohexadec-11-en-9-yl)(methyl)amino)-1-cyclopropyl-2-oxoethyl)carbamate (252):

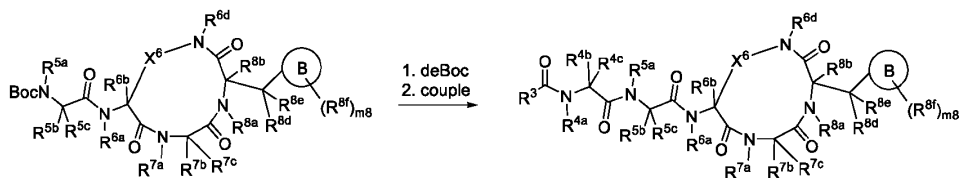


[0499] Steps 5-9 for the synthesis of **252** were carried out using reaction sequences and procedures outlined in Method A, Steps 4-8. LCMS (ESI): m/z 780.4 ($M+H^+$).

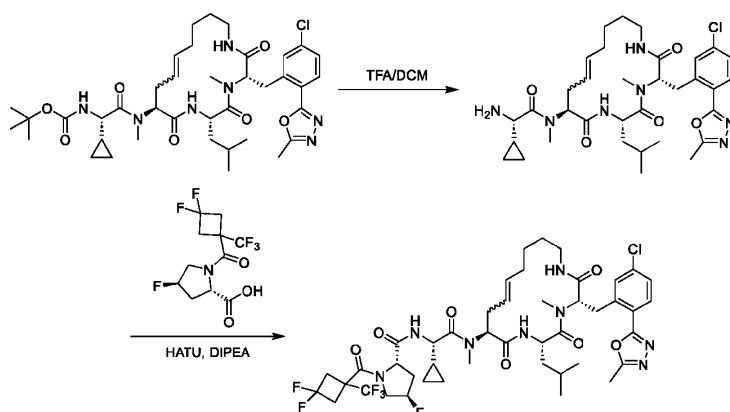
2. Final Synthesis Procedures to prepare Compounds of Formula (I)

5

a. Method 1

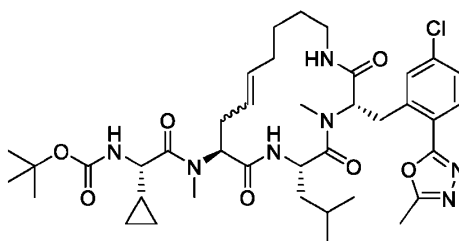


Representative Procedure for Method 1: Example 118



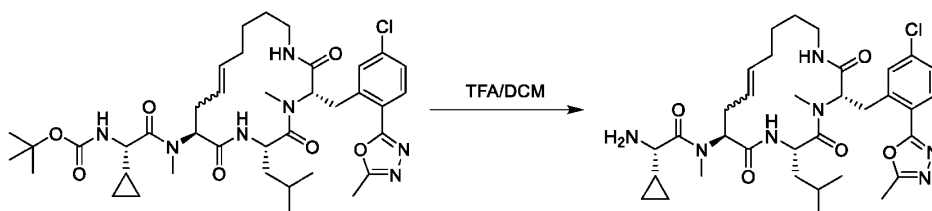
Representative Experimental for Method 1: Example 118

- Tert-butyl ((S)-2-(((3S,6S,9S)-3-(5-chloro-2-(5-methyl-1,3,4-oxadiazol-2-yl)benzyl)-6-isobutyl-4-methyl-2,5,8-trioxo-1,4,7-triazacyclohexadec-11-en-9-yl)(methylamino)-1-cyclopropyl-2-oxoethyl)carbamate (219):**



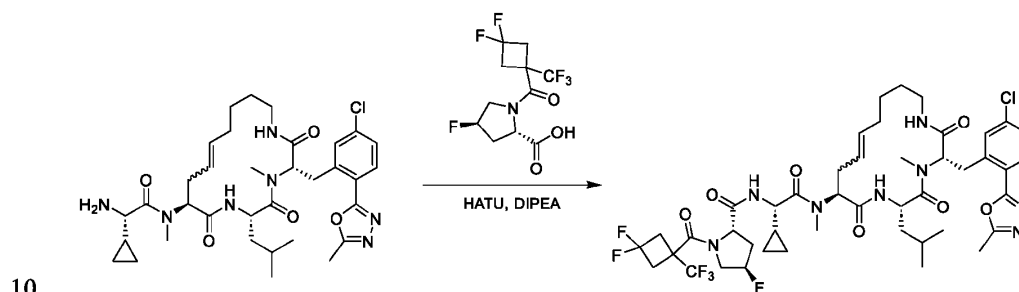
[0500] The macrocyclic starting material for Method 1 was synthesized Using Method A with **Int. 1**, and **8**. It was used as a mixture of *E/Z* isomers. **LCMS (ESI+):** *m/z* 770.4 (M+H).

- Step 1: (S)-2-amino-N-((3S,6S,9S)-3-(5-chloro-2-(5-methyl-1,3,4-oxadiazol-2-yl)benzyl)-6-isobutyl-4-methyl-2,5,8-trioxo-1,4,7-triazacyclohexadec-11-en-9-yl)-2-cyclopropyl-N-methylacetamide (220):**



[0501] **219** (112 mg, 1 Eq, 145 μ mol) was dissolved in DCM/TFA (3:1) and stirred until the deprotection was complete (monitored via LCMS). The volatile solvent was completely removed to afford a quantitative yield of **220** (97.4 mg, 145 μ mol, 100 %) as the TFA salt. LCMS (ESI+): m/z 732.4 (M+H).

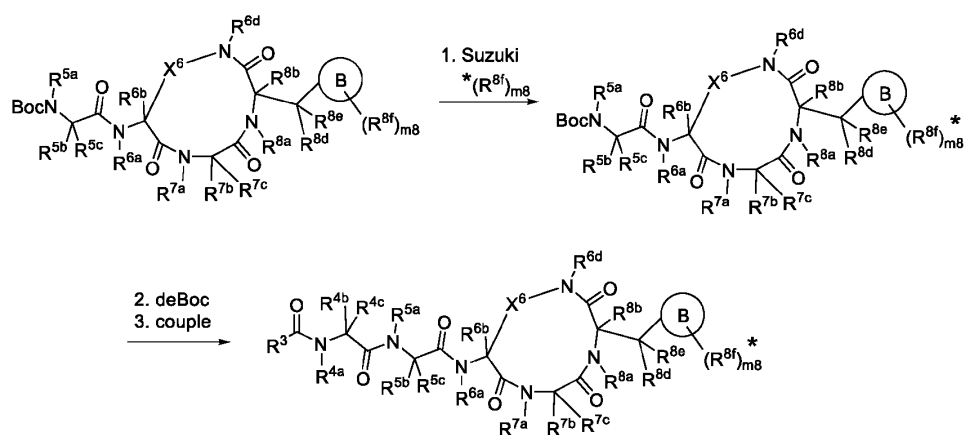
- 5 **Step 2: (2S,4R)-N-((S)-2-(((3S,6S,9S)-3-(5-chloro-2-(5-methyl-1,3,4-oxadiazol-2-yl)benzyl)-6-isobutyl-4-methyl-2,5,8-trioxo-1,4,7-triazacyclohexadec-11-en-9-yl)(methyl)amino)-1-cyclopropyl-2-oxoethyl)-1-(3,3-difluoro-1-(trifluoromethyl)cyclobutane-1-carbonyl)-4-fluoropyrrolidine-2-carboxamide (Example 118):**



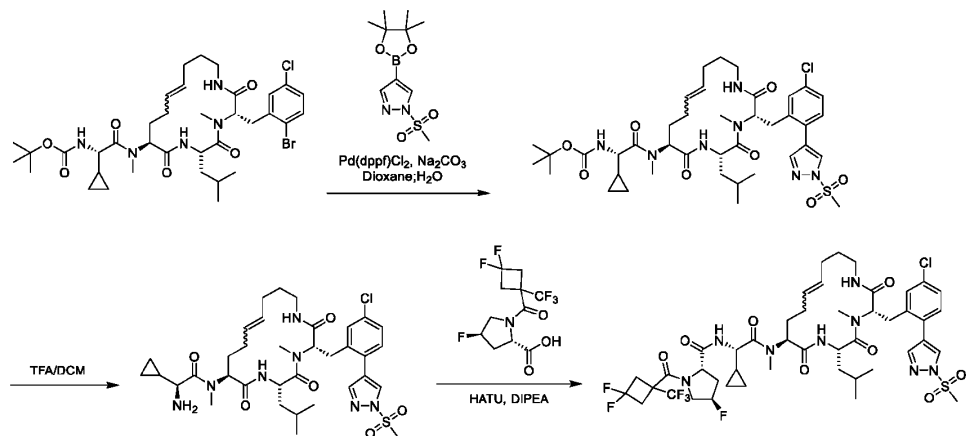
- [0502] **220** (48.7 mg, 1 Eq, 72.7 μ mol) and **Int. 141** (27.8 mg, 1.2 Eq, 87.2 μ mol) were dissolved in DMF (2.0 mL). DIPEA (56.3 mg, 75.9 μ L, 6 equiv., 436 μ mol) and HATU (33.2 mg, 1.2 Eq, 87.2 μ mol) were added sequentially and the reaction was continued until the consumption of starting material (monitored via LCMS). The reaction mixture was
- 15 neutralized to pH ~7 with 1N HCl and directly purified by RP-HPLC (C18, 40 % to 75% MeCN/H₂O with 0.5% formic acid). **Example 118** was isolated as two peaks. The first eluting (28.5 mg, 29.3 μ mol, 40.4 %) and the second eluting peak (18.2 mg, 18.7 μ mol, 25.7 %) were isolated as a white solid after lyophilization. Stereochemistry of isolated peaks was not assigned. LCMS data was identical for both peaks. LCMS (ESI+): m/z 971.3 (M+H).

20

b. Method 2

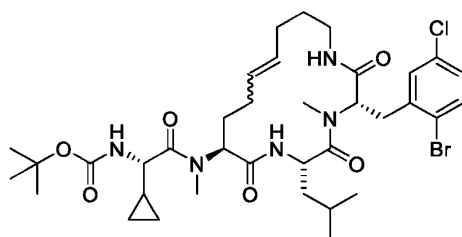


Representative Procedure for Method 2: Example 273



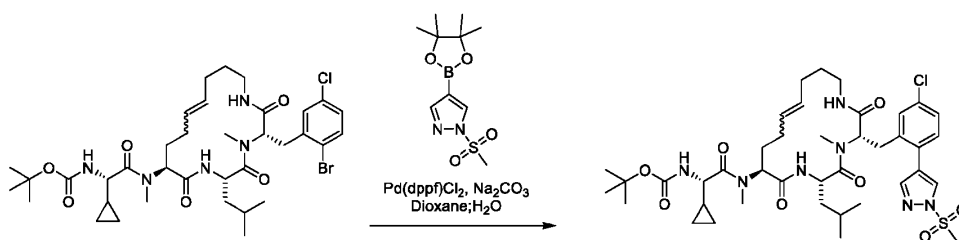
Representative Experimental for Method 2: Example 273

- 5 **Tert-butyl ((S)-2-(((3S,6S,9S)-3-(2-bromo-5-chlorobenzyl)-6-isobutyl-4-methyl-2,5,8-trioxo-1,4,7-triazacyclohexadec-12-en-9-yl)(methyl)amino)-1-cyclopropyl-2-oxoethyl)carbamate (221):**



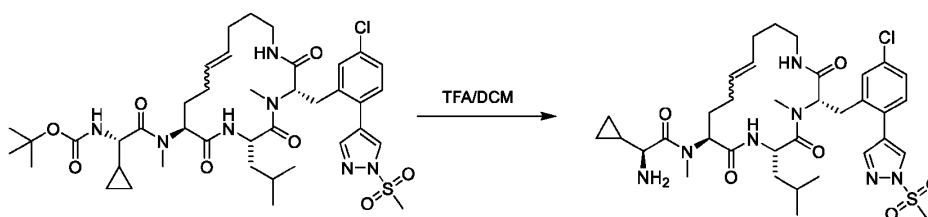
[0503] The macrocyclic Starting material for Method 2 was synthesized Using Method A with Int. 2, 30, and 42. It was used as a mixture of *E/Z* isomers. LCMS (ESI+): *m/z* 766.2 (M+H).

Step 1: *tert*-butyl ((*S*)-2-(((3*S*,6*S*,9*S*)-3-(5-chloro-2-(1-(methylsulfonyl)-1*H*-pyrazol-4-yl)benzyl)-6-isobutyl-4-methyl-2,5,8-trioxo-1,4,7-triazacyclohexadec-12-en-9-yl)(methyl)amino)-1-cyclopropyl-2-oxoethyl)carbamate (222):



[0504] 221 (124 mg, 2 Eq, 456 μ mol), PdCl₂(dppf)-DCM adduct (186 mg, 1 Eq, 228 μ mol), Int. 64, and sodium carbonate (96.7 mg, 4 equiv., 912 μ mol) were dissolved in 4:1 Dioxane/Water (6.3 mL). The reaction was degassed for 10 min with Ar and then heated to 80 °C until the complete consumption of starting material monitored by LCMS. The vial was then cooled and adjusted to pH ~7 with 1N HCl. The solution was filtered and directly purified by RP-HPLC (C18, 50% to 80% MeCN/H₂O with 0.5% formic acid) to obtain 222 (150 mg, 180 μ mol, 79 %) as a white solid after lyophilization. LCMS (ESI+): *m/z* 832.4 (M+H).

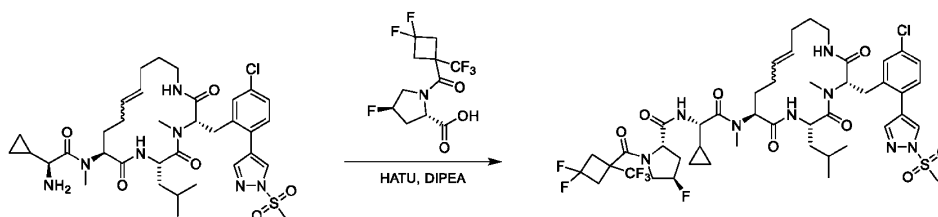
Step 2: (*S*)-2-amino-*N*-((3*S*,6*S*,9*S*)-3-(5-chloro-2-(1-(methylsulfonyl)-1*H*-pyrazol-4-yl)benzyl)-6-isobutyl-4-methyl-2,5,8-trioxo-1,4,7-triazacyclohexadec-12-en-9-yl)-2-cyclopropyl-*N*-methylacetamide (223):



[0505] 222 (126.6 mg, 1 Eq, 152.1 μ mol) was dissolved in DCM/TFA (3:1) and stirred until the deprotection was complete (monitored via LCMS). The volatile solvent was

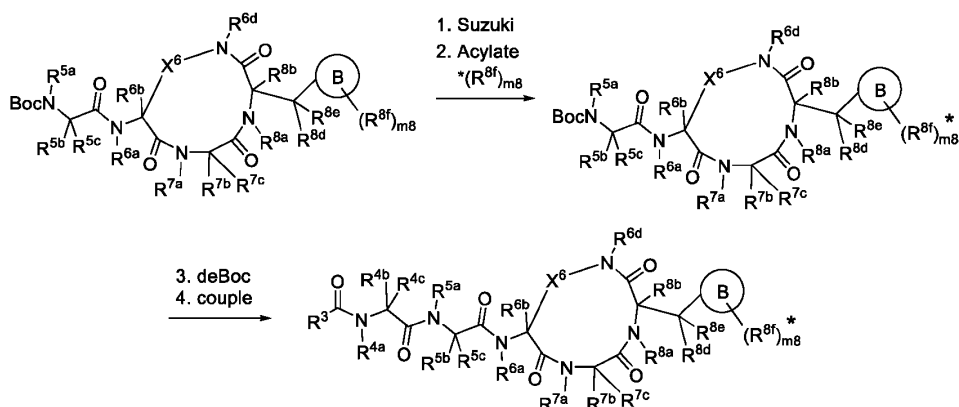
completely removed to afford a quantitative yield of **223** (111.4 mg, 152.1 μmol , 100.0 %) as the TFA salt. LCMS (ESI+): m/z 732.4 (M+H).

- Step 3: (2S,4R)-N-((S)-2-(((3S,6S,9S)-3-(5-chloro-2-(1-(methylsulfonyl)-1H-pyrazol-4-yl)benzyl)-6-isobutyl-4-methyl-2,5,8-trioxo-1,4,7-triazacyclohexadec-12-en-9-yl)(methyl)amino)-1-cyclopropyl-2-oxoethyl)-1-(3,3-difluoro-1-(trifluoromethyl)cyclobutane-1-carbonyl)-4-fluoropyrrolidine-2-carboxamide (Example 273):**

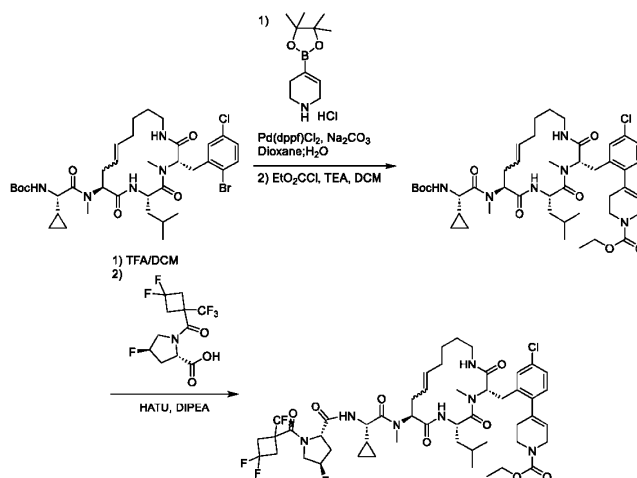


- [0506] 223** as the TFA salt (111.4 mg, 1 Eq, 152.1 μmol) and **Int. 141** (58.27 mg, 1.2 Eq, 182.5 μmol) were dissolved in DMF (5.0 mL). DIPEA (118.0 mg, 159 μL , 6 Eq, 912.7 μmol) and HATU (69.41 mg, 1.2 Eq, 182.5 μmol) was added sequentially and the reaction was continued until consumption of starting material (monitored by LCMS). The reaction mixture was neutralized to pH $\sim$ 7 with 1N HCl and directly purified by RP-HPLC (C18, 40% to 70% MeCN/H₂O with 0.5% formic acid). **Example 273** (31.72 mg, 30.69 μmol , 20.18 %) was obtained as a white solid after lyophilization. LCMS (ESI+): m/z 1033.4 (M+H).

c. Method 3

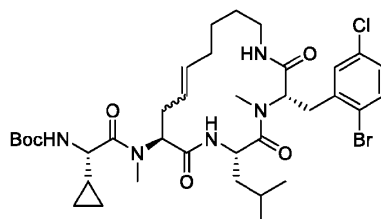


Representative Procedure for Method 3: Example 53



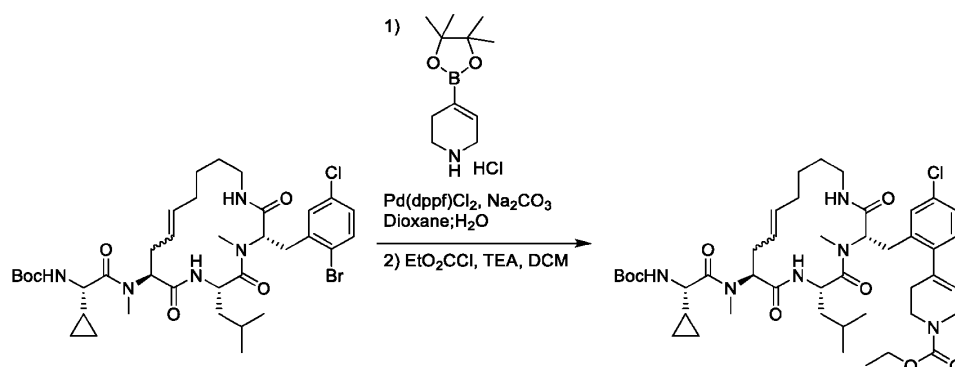
Representative Experimental for Method 3: Example 53

Tert-butyl ((S)-2-(((3S,6S,16S)-16-(2-bromo-5-chlorobenzyl)-3-isobutyl-1-methyl-2,5,15-trioxo-113-chloro-4,14-diazacyclohexadec-8-en-6-yl)(methyl)amino)-1-cyclopropyl-2-oxoethyl)carbamate (224):



[0507] The starting material for Method 3, **224**, was synthesized according to method A using **Int. 1** and **30**. LCMS (ESI+): 766.2 m/z (M+H).

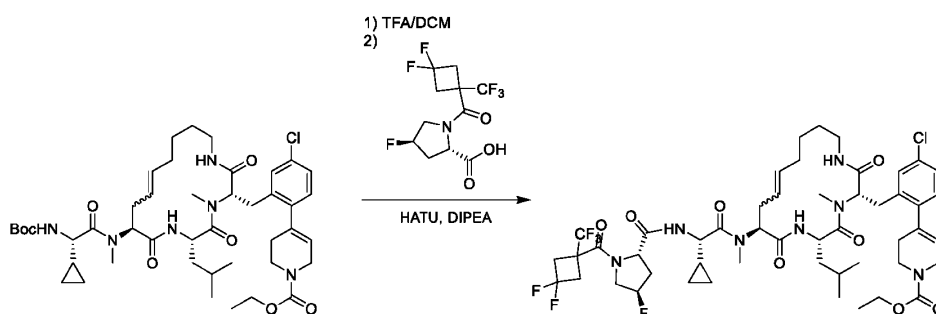
Steps 1-2: Ethyl 4-(2-(((3S,6S,9S)-9-((S)-2-((tert-butoxycarbonyl)amino)-2-cyclopropyl-N-methylacetamido)-6-isobutyl-4-methyl-2,5,8-trioxo-1,4,7-triazacyclohexadec-11-en-3-yl)methyl)-4-chlorophenyl)-3,6-dihydropyridine-1(2H)-carboxylate (225):



[0508] **224** (100 mg, 1 Eq, 127 μ mol), **Int. 67** (31.1 mg, 1 Eq, 127 μ mol), Na_2CO_3 (40.3 mg, 3 Eq, 380 μ mol) and $\text{PdCl}_2(\text{dppf})$ (10.4 mg, 0.1 Eq, 12.7 μ mol) were dissolved in 4:1 Dioxane/Water (4 mL). The reaction was degassed for 10 min with Ar and then heated to 80 $^\circ\text{C}$. The reaction was stopped by the addition of 5 mL water upon the consumption of starting material (monitored by LCMS). The aqueous layer was extracted EtOAc (2x 10 mL). The combined organic layer was washed with brine, dried over MgSO_4 , filtered, and concentrated. The material could either be purified by RP-HPLC (C18, 10% to 50% MeCN/ H_2O with 0.5% formic acid) or used directly in the next reaction.

[0509] The crude reaction product was dissolved in DCM (2 mL), cooled in an ice bath before the addition of TEA (64.2 mg, 88.4 μL , 5 Eq, 634 μ mol). ethyl chloroformate (20.6 mg, 18.3 μL , 1.5 Eq, 190 μ mol) was added slowly to the cooled solution. The reaction was stirred at 0 $^\circ\text{C}$ until the complete consumption of starting material. Once complete the volatile solvents were completely removed and the crude residue was purified directly by RP-HPLC (C18, 50% to 80% MeCN/ H_2O with 0.5% formic acid) which afforded **225** (54 mg, 64 μ mol, 51 %) as an off-white solid. **LCMS** (ESI+): 841.3 m/z (M+H).

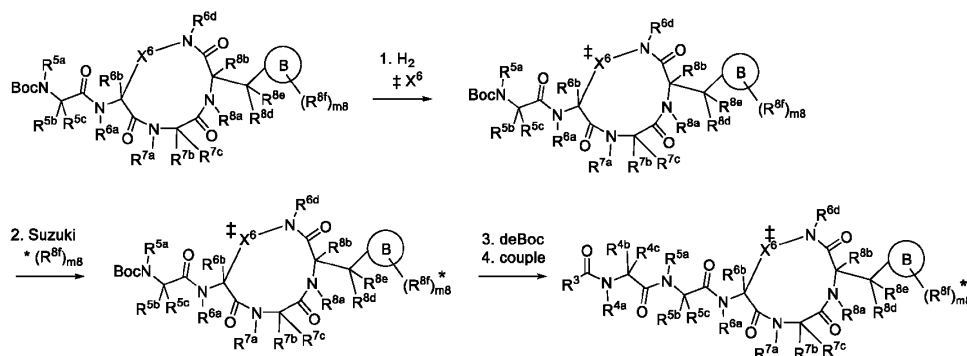
Steps 3-4: Ethyl 4-(4-chloro-2-(((3S,6S,9S)-9-((S)-2-cyclopropyl-2-((2S,4R)-1-(3,3-difluoro-1-(trifluoromethyl)cyclobutane-1-carbonyl)-4-fluoropyrrolidine-2-carboxamido)-N-methylacetamido)-6-isobutyl-4-methyl-2,5,8-trioxo-1,4,7-triazacyclohexadec-11-en-3-yl)methyl)phenyl)-3,6-dihydropyridine-1(2H)-carboxylate (Example 53):



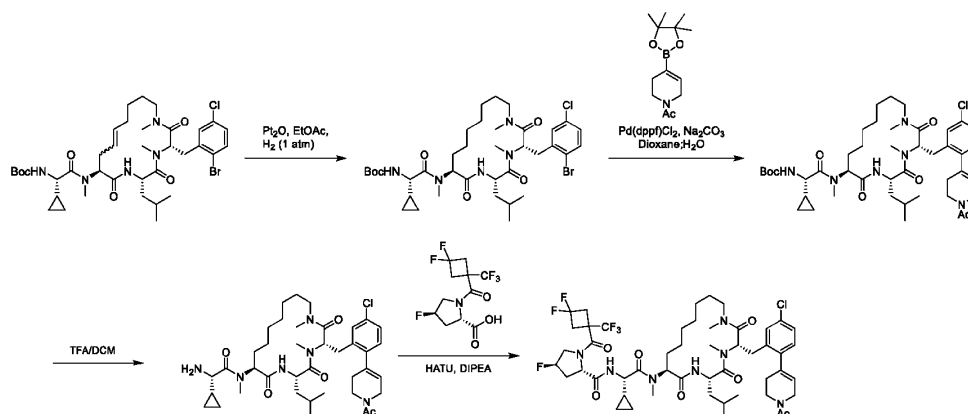
[0510] **225** (107 mg, 1 Eq, 127 μmol) was dissolved in DCM/ TFA (3:1) and stirred until the deprotection was complete (monitored by LCMS). The volatile solvent was completely removed to afford a quantitative yield of the free amine.

- 5 **[0511]** The deprotected amine and **Int. 141** (44.8 mg, 1.1 Eq, 140 μmol) were dissolved in DMF (1 mL). DIPEA (98.9 mg, 133 μL , 6 Eq, 765 μmol) and HATU (53.3 mg, 1.1 Eq, 140 μmol) were added sequentially. and the reaction continued until the consumption of my starting material by LCMS. The reaction mixture was neutralized to pH ~ 7 with 1 N HCl and directly purified by RP-HPLC(C18, 40% to 70% MeCN/H₂O with 0.5% formic acid).
- 10 **Example 53** (48.8 mg, 46.8 μmol , 37%) was obtained as a white solid after lyophilization. LCMS (ESI+): m/z 1043.6 (M+H).

d. Method 4

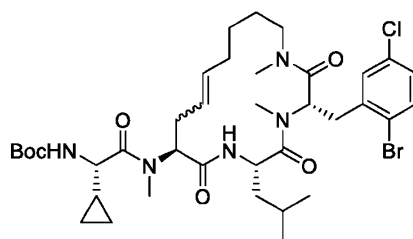


Representative Procedure for Method 4: Example 50



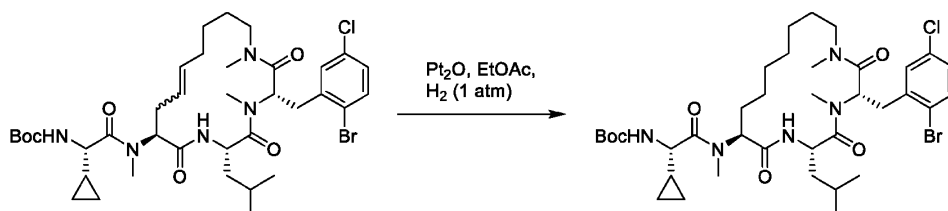
Representative Experimental for Method 4: Example 50

- Tert-butyl ((S)-2-(((3S,6S,9S)-3-(2-bromo-5-chlorobenzyl)-6-isobutyl-1,4-dimethyl-2,5,8-trioxo-1,4,7-triazacyclohexadec-11-en-9-yl)(methyl)amino)-1-cyclopropyl-2-oxoethyl)carbamate (226):**



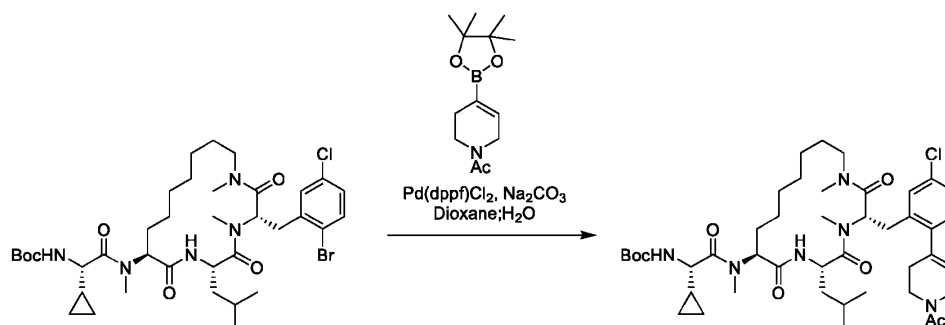
[0512] The macrocycle starting material for method 4 (226), was synthesized using Method A with **Int. 30**. It was used as a mixture of *E/Z* isomers (~9:1) LCMS: *m/z* [M+H]. LCMS (ESI+): 780.3 *m/z* (M+H).

- Step 1: ((S)-2-(((3S,6S,9S)-3-(2-bromo-5-chlorobenzyl)-6-isobutyl-4-methyl-2,5,8-trioxo-1,4,7-triazacyclohexadecan-9-yl)(methyl)amino)-1-cyclopropyl-2-oxoethyl)carbamate (227):**

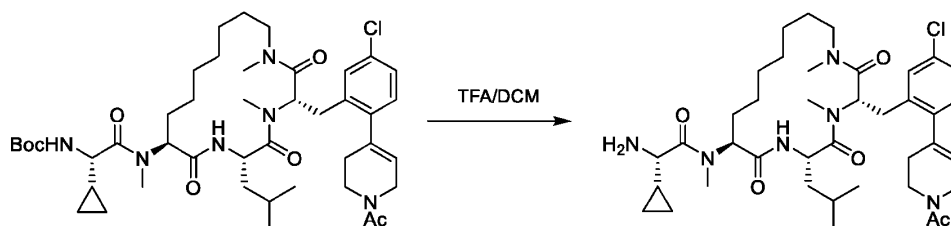


- [0513] **226** (12.0 g, 1 Eq, 15.6 mmol) was dissolved in EtOAc (80 ml) by stirring at ambient temperature. platinum(IV) oxide (284 mg, 0.08 Eq, 1.25 mmol) was added to the stirring reaction mixture. The reaction was then placed under an atmosphere of hydrogen and stirred vigorously until LCMS analysis showed complete consumption of starting material.
- 5 The reaction mixture was filtered over a pad of Celite. The Filter was washed with EtOAc (2 x 50 mL). The organic solvent was concentrated to afford **227** (11.8 g, 15.3 mmol, 98 %) as an off white solid. The reaction was used without further purification. LCMS: m/z 782.2 [M+H]⁺

- Step 2: tert-butyl ((S)-2-(((3S,6S,9S)-3-(2-(1-acetyl-1,2,3,6-tetrahydropyridin-4-yl)-5-chlorobenzyl)-6-isobutyl-1,4-dimethyl-2,5,8-trioxo-1,4,7-triazacyclohexadecan-9-yl)(methyl)amino)-1-cyclopropyl-2-oxoethyl)carbamate (**228**):
- 10

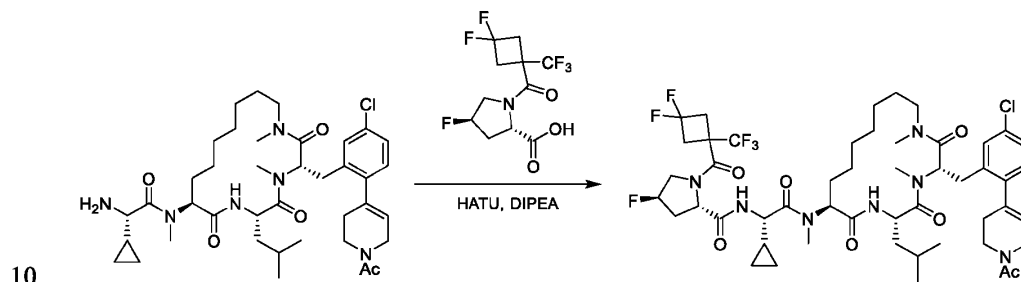


- [0514] **227** (34.5 mg, 1.0 Eq, 44.0 μ mol), Na₂CO₃ (14.0 mg, 3 Eq, 132 μ mol), **Int. 47** (22.1 mg, 2.0 Eq, 88.1 μ mol) and PdCl₂(dppf)-CH₂Cl₂ adduct (3.60 mg, 0.1 Eq, 4.40 μ mol) were dissolved in 4:1 Dioxane/Water (4 mL). The reaction was degassed for 10 min with Ar and then heated to 80 °C until the complete consumption of starting material. The vial was then cooled and adjusted to pH ~7 with 1 N HCl. The homogeneous solution was directly purified by RP-HPLC (C18, 50% to 85% MeCN/H₂O with 0.5% formic acid) to obtain **228** (31.6 mg, 44.0 μ mol, 86.7 %) as a white solid after lyophilization. LCMS (ESI⁺): m/z 827.4 (M+H).
- 15
- 20 Step 3: (S)-N-(((3S,6S,9S)-3-(2-(1-acetyl-1,2,3,6-tetrahydropyridin-4-yl)-5-chlorobenzyl)-6-isobutyl-1,4-dimethyl-2,5,8-trioxo-1,4,7-triazacyclohexadecan-9-yl)-2-amino-2-cyclopropyl-N-methylacetamide TFA salt (**229**):



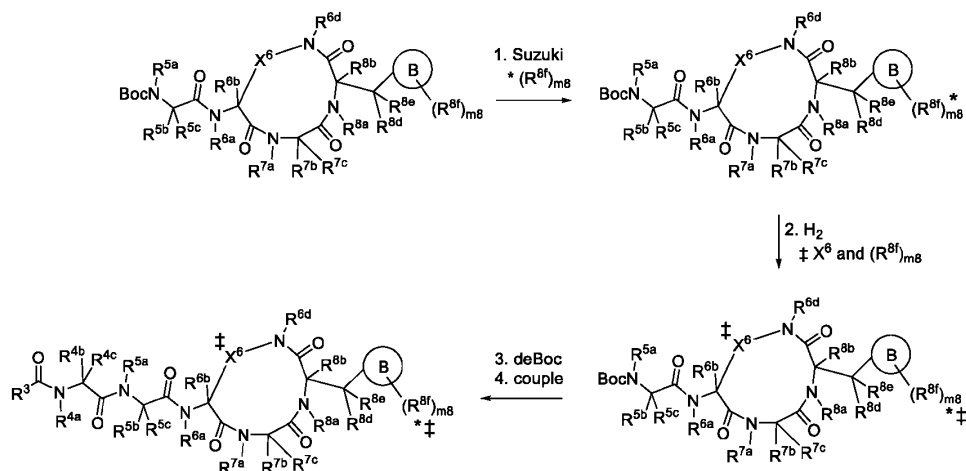
[0515] **228** (31.6 mg, 1 Eq, 38.2 μmol) was dissolved in 6 mL DCM/TFA (3:1) and stirred until the deprotection was complete (monitored by LCMS). The volatile solvent was completely removed to afford a quantitative yield of **229**. LCMS (ESI⁺): m/z 727.4 (M+H).

- 5 **Step 4: (2S,4R)-N-((S)-2-(((3S,6S,9S)-3-(2-(1-acetyl-1,2,3,6-tetrahydropyridin-4-yl)-5-chlorobenzyl)-6-isobutyl-1,4-dimethyl-2,5,8-trioxo-1,4,7-triazacyclohexadecan-9-yl)(methyl)amino)-1-cyclopropyl-2-oxoethyl)-1-(3,3-difluoro-1-(trifluoromethyl)cyclobutane-1-carbonyl)-4-fluoropyrrolidine-2-carboxamide (Example 50):**

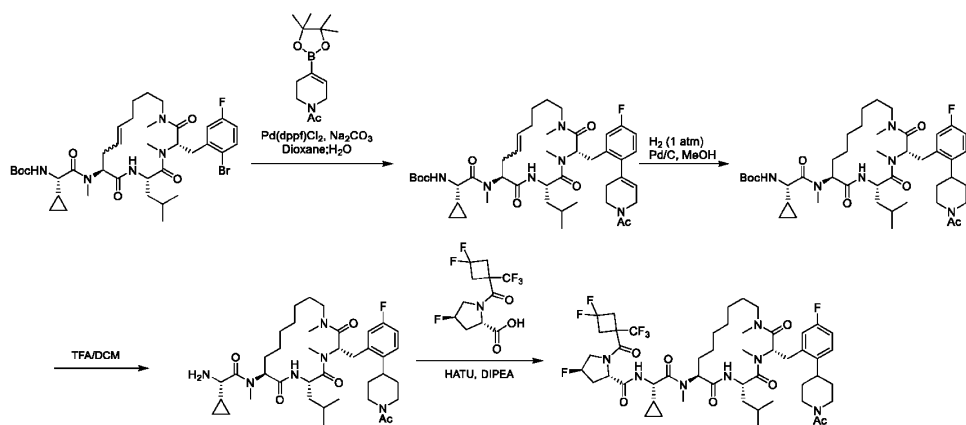


- [0516]** The deprotected amine and **Int. 141** (13.4 mg, 1.1 Eq, 42.1 μmol) were dissolved in DMF (1 mL). DIPEA (29.7 mg, 40.0 μL , 6 Eq, 229 μmol) and HATU (16.0 mg, 1.1 Eq, 42.1 μmol) were added sequentially and the reaction was continued until the consumption of starting material (monitored by LCMS). The reaction mixture was neutralized to pH ~7 with 1N HCl and directly purified by RP-HPLC (C18, 45% to 75% MeCN/H₂O with 0.5% formic acid). **Example 50** (25.0 mg, 24.3 μmol , 64 %) was obtained as a white solid after lyophilization. LCMS (ESI⁺): m/z 1028.6.4 (M+H).
- 15

e. Method 5

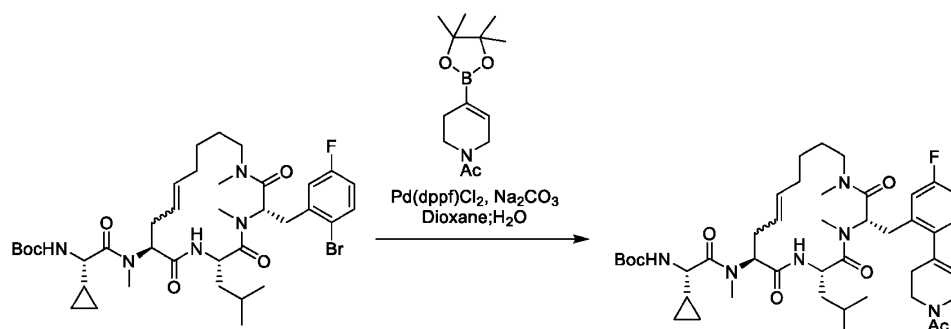


Representative Procedure for Method 5: Example 45

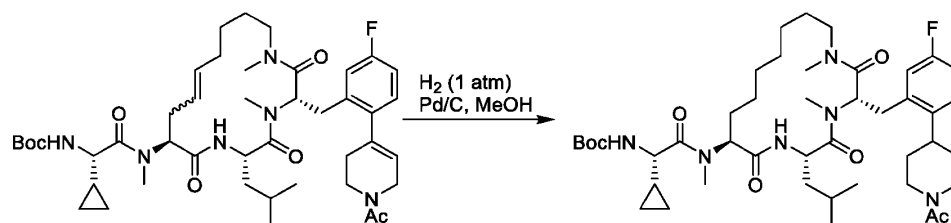


Representative Experimental for Method 5: Example 45

- 5 **Step 1: Tert-butyl ((S)-2-(((3S,6S,9S)-3-(2-(1-acetyl-1,2,3,6-tetrahydropyridin-4-yl)-5-fluorobenzyl)-6-isobutyl-1,4-dimethyl-2,5,8-trioxo-1,4,7-triazacyclohexadec-11-en-9-yl)(methyl)amino)-1-cyclopropyl-2-oxoethyl)carbamate (230):**

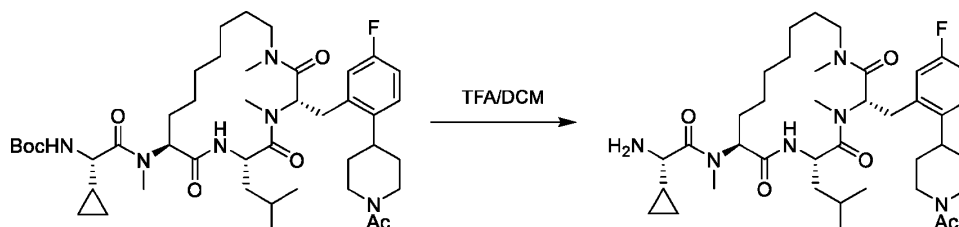


- [0517]** **208** (300 mg, 1 Eq, 392 μmol), **Int. 47** (128 mg, 1.3 Eq, 510 μmol), Na_2CO_3 (125 mg, 3 Eq, 1.18 mmol) and $\text{PdCl}_2(\text{dppf})\text{-DCM}$ adduct (32.0 mg, 0.1 Eq, 39.2 μmol) were dissolved in 4:1 Dioxane/Water (10 mL). The reaction was degassed for 10 min with Ar and then heated to 80 $^\circ\text{C}$ until the complete consumption of starting material monitored by LCMS. The vial was then cooled and adjusted to pH ~ 7 with 1N HCl. The solution was concentrated to $\sim 4\text{mL}$, filtered, then directly purified by RP-HPLC (C18, 50% to 80% MeCN/ H_2O with 0.5% formic acid) to obtain **Int. 430** (200 mg, 247 μmol , 63 %). **LCMS**: m/z 809.4 $[\text{M}+\text{H}]$.
- 10 Step 2: Tert-butyl ((S)-2-(((3S,6S,9S)-3-(2-(1-acetyl-1,2,3,6-tetrahydropyridin-4-yl)-5-fluorobenzyl)-6-isobutyl-1,4-dimethyl-2,5,8-trioxo-1,4,7-triazacyclohexadecan-9-yl)(methyl)amino)-1-cyclopropyl-2-oxoethyl)carbamate (231):**



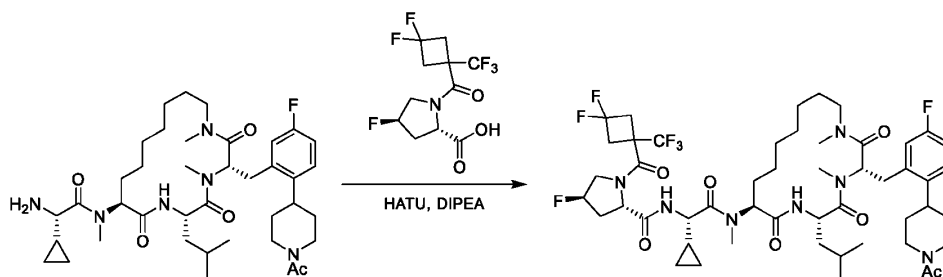
- [0518]** **230** (100 mg, 1 Eq, 124 μmol) was dissolved in MeOH (2 mL). Pd/C (100 mg) was carefully added, and the reaction was stirred under an atmosphere of H_2 . Upon the consumption of starting material (monitored by LCMS), the reaction was filtered over a pad of celite. The filter cake was washed with EtOAc (2 x 20 mL). the filtrate was concentrated to afford **231** (85.7 mg, 105 μmol , 85 %) d as an off-white solid. It was used without any further purification. **LCMS**: m/z 813.5 $[\text{M}+\text{H}]$.

Step 3: (S)-N-((3S,6S,9S)-3-(2-(1-acetylpiperidin-4-yl)-5-fluorobenzyl)-6-isobutyl-1,4-dimethyl-2,5,8-trioxo-1,4,7-triazacyclohexadecan-9-yl)-2-amino-2-cyclopropyl-N-methylacetamide (232):



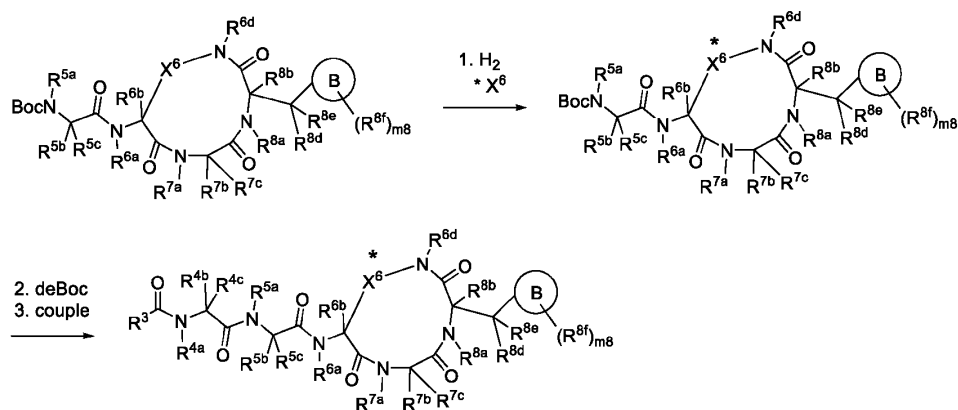
- 5 **[0519]** **231** (40.0 mg, 1 Eq, 49.2 μ mol) was dissolved in 2 ml DCM/TFA (3:1) and stirred until the deprotection was complete (monitored by LCMS). The volatile solvent was completely removed to afford a quantitative yield of **232** as the TFA salt. **LCMS**: m/z 713.4 [M+H].

Step 4: (2S,4R)-N-((S)-2-(((3S,6S,9S)-3-(2-(1-acetylpiperidin-4-yl)-5-fluorobenzyl)-6-isobutyl-1,4-dimethyl-2,5,8-trioxo-1,4,7-triazacyclohexadecan-9-yl)(methyl)amino)-1-cyclopropyl-2-oxoethyl)-1-(3,3-difluoro-1-(trifluoromethyl)cyclobutane-1-carbonyl)-4-fluoropyrrolidine-2-carboxamide (Example 45):

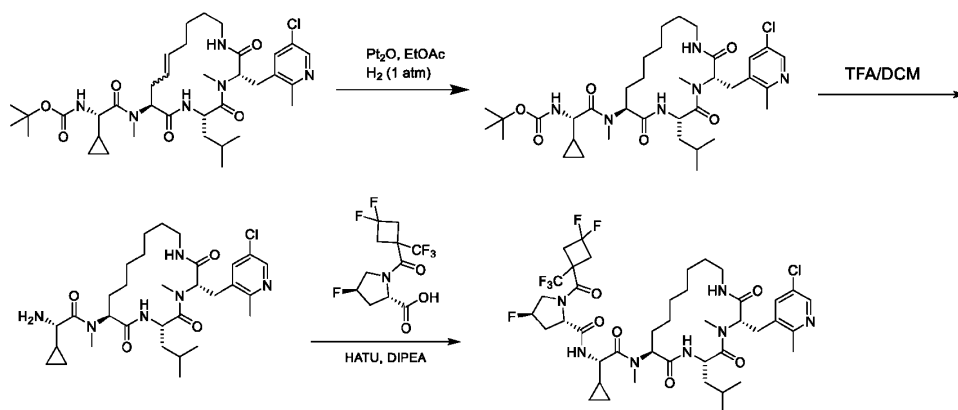


- 15 **[0520]** **232** as the TFA salt (40.0 mg), **Int. 141** (17.3 mg, 1.1 Eq, 54.1 μ mol) and HATU (20.6 mg, 1.1 Eq, 54.1 μ mol) were dissolved in DMF (2 mL). The reaction was stirred and DIPEA (38.2 mg, 51.4 μ L, 6 Eq, 295 μ mol) was added slowly. The reaction continued until the consumption of starting material (monitored by LCMS). The reaction mixture was neutralized to pH $\sim$ 7 with 1N HCl and directly purified by RP-HPLC (C18, 40% to 70% MeCN/H₂O with 0.5% formic acid). **Example 45** (22.0 mg, 21.7 μ mol, 44 %) was isolated as
- 20 a white solid upon lyophilization. **LCMS**: m/z 1015.5[M+H].

f. Method 6

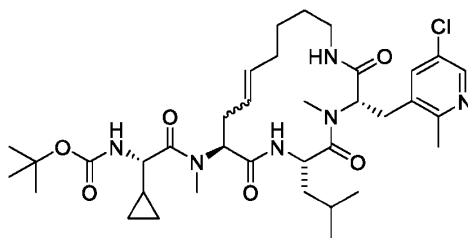


Representative Procedure for Method 6: Example 331



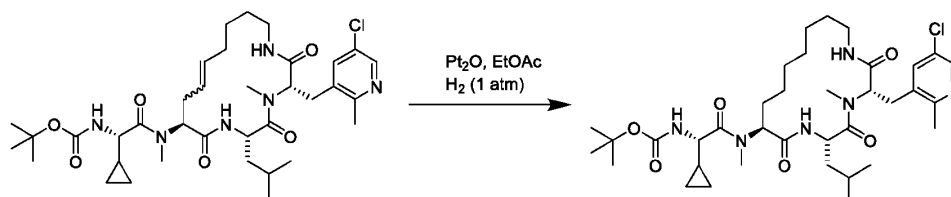
Representative Experimental For Method 6: Example 331

- 5 **Tert-butyl ((S)-2-(((3S,6S,9S)-3-((5-chloro-2-methylpyridin-3-yl)methyl)-6-isobutyl-4-methyl-2,5,8-trioxo-1,4,7-triazacyclohexadec-11-en-9-yl)(methyl)amino)-1-cyclopropyl-2-oxoethyl)carbamate (233):**



[0521] The macrocycle starting material for Method 6, **233**, was synthesized using Method A with **Int. 1** and **27**. It was used as a mixture of *E/Z* isomers. LCMS (ESI+): 703.3 *m/z* (M+H).

Step 1: *tert*-butyl ((*S*)-2-(((3*S*,6*S*,9*S*)-3-((5-chloro-2-methylpyridin-3-yl)methyl)-6-isobutyl-4-methyl-2,5,8-trioxo-1,4,7-triazacyclohexadecan-9-yl)(methyl)amino)-1-cyclopropyl-2-oxoethyl)carbamate (**234**):



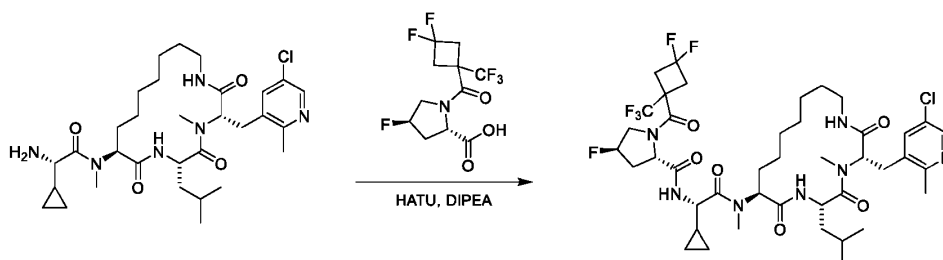
[0522] **233** (230.6 mg, 1 Eq, 327.9 μmol) was dissolved in EtOAc (5.0 mL) by stirring at ambient temperature. Platinum(IV) oxide (11.17 mg, 0.15 equiv., 49.18 μmol) was added to the stirring reaction mixture. The reaction was then placed under an atmosphere of hydrogen and stirred vigorously until LCMS analysis showed complete consumption of starting material. The reaction mixture was filtered over a pad of Celite. The filter was washed with EtOAc (2x50 mL). The organic solvent was concentrated to afford **234** (220 mg, 312 μmol , 95 %) as an off white solid. The reaction was used without further purification. LCMS: *m/z* 705.3 [M+H].

Step 2: (*S*)-2-amino-N-((3*S*,6*S*,9*S*)-3-((5-chloro-2-methylpyridin-3-yl)methyl)-6-isobutyl-4-methyl-2,5,8-trioxo-1,4,7-triazacyclohexadecan-9-yl)-2-cyclopropyl-N-methylacetamide (**235**):



[0523] **234** (231.3 mg, 1 Eq, 327.9 μmol) was dissolved in 6 mL DCM/TFA (3:1) and stirred until the deprotection was complete (monitored via LCMS). The volatile solvent was completely removed to afford a quantitative yield of **235** as the TFA salt. LCMS (ESI+): *m/z* 605.7 (M+H).

Step 3: (2S,4R)-N-((S)-2-(((3S,6S,9S)-3-((5-chloro-2-methylpyridin-3-yl)methyl)-6-isobutyl-4-methyl-2,5,8-trioxo-1,4,7-triazacyclohexadecan-9-yl)(methyl)amino)-1-cyclopropyl-2-oxoethyl)-1-(3,3-difluoro-1-(trifluoromethyl)cyclobutane-1-carbonyl)-4-fluoropyrrolidine-2-carboxamide (Example 331):

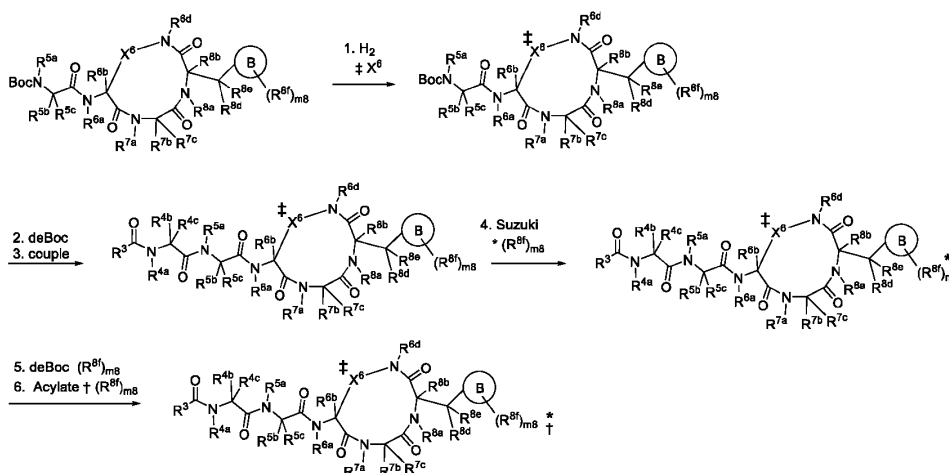


5

[0524] **235** as the TFA salt (198.5 mg, 1 Equiv., 328.0 μmol) and **Int. 141** (125.6 mg, 1.2 Equiv., 393.6 μmol) were dissolved in DMF (2.0 mL). DIPEA (254.3 mg, 343 μL , 6 Equiv., 1.968 mmol) and HATU (149.7 mg, 1.2 Equiv., 393.6 μmol) were added sequentially and the reaction was continued until the consumption of starting material (monitored via LCMS). The reaction mixture was neutralized to pH ~ 7 with 1N HCl and directly purified by RP-HPLC (C18, 40% to 80% MeCN/H₂O with 0.5% formic acid). **Example 331** (83.25 mg, 91.85 μmol , 28 %) was obtained as a white solid after lyophilization. **LCMS** (ESI⁺): m/z 906.6 (M+H).

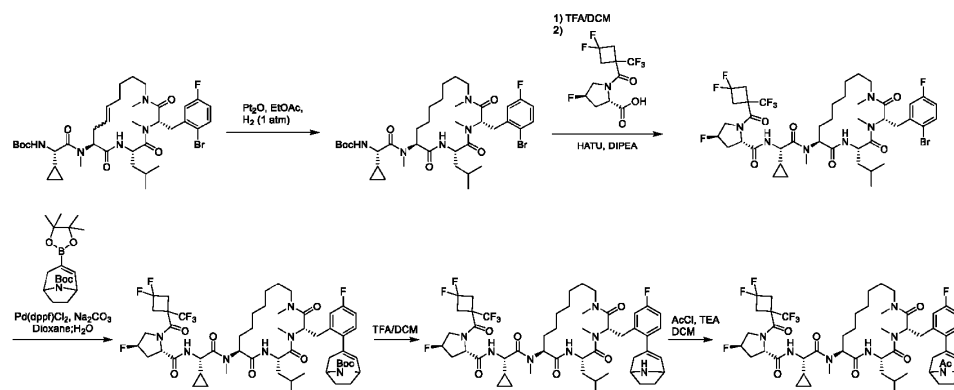
10

g. Method 7



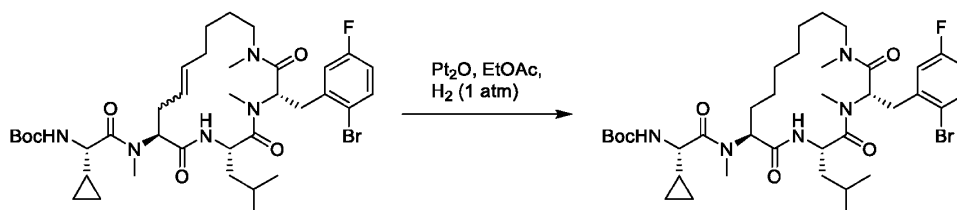
15

Representative Procedure for Method 7: Example 165 and Example 58



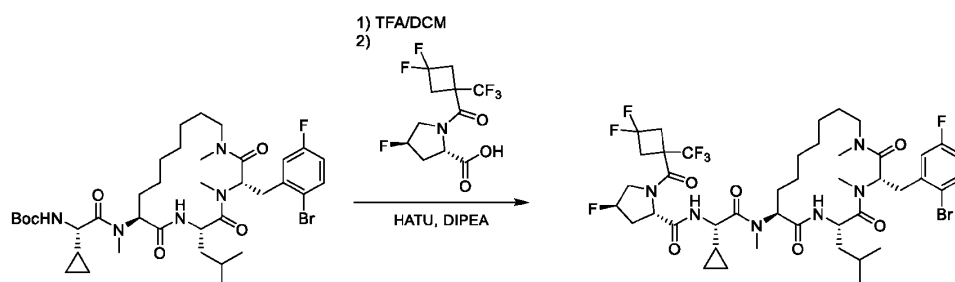
Representative Experimental for Method 7: Example 165 and Example 58

Step 1: tert-butyl ((1S)-2-(((3S,6S,9S)-4-acetyl-3-(2-bromo-5-fluorobenzyl)-6-isobutyl-1,4-dimethyl-2,5,8-trioxo-1,4,7-triazacyclohexadecan-9-yl)(methyl)amino)-1-cyclopropyl-2-oxoethyl)carbamate (236):



[0525] 208 (14 g, 1 Equiv., 18 mmol) was dissolved in EtOAc (180 mL) and platinum (IV) oxide (0.33 g, 0.08 Equiv., 1.5 mmol) was added. The reaction was placed under a hydrogen atmosphere and vigorously stirred. The reaction was run rt overnight. The reaction was filtered over a bed of celite and the solvent was reduced and **236** was isolated as an off-white solid (Quant. 14.0 g). The reaction was used in the next step without any further purification. LCMS (ESI+): m/z 766.4 (M+H).

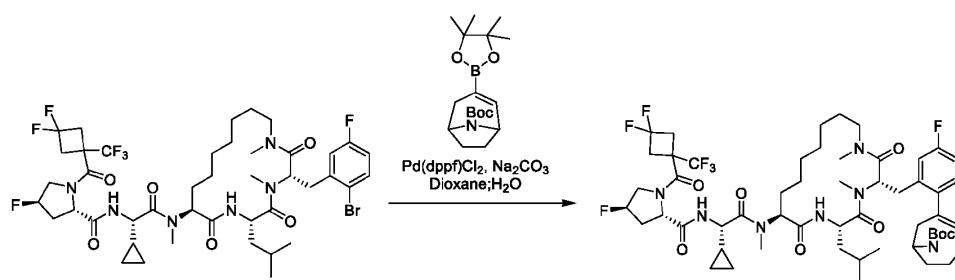
Step 2-3: (2S,4R)-N-((S)-2-(((3S,6S,9S)-3-(2-bromo-5-fluorobenzyl)-6-isobutyl-1,4-dimethyl-2,5,8-trioxo-1,4,7-triazacyclohexadecan-9-yl)(methyl)amino)-1-cyclopropyl-2-oxoethyl)-1-(3,3-difluoro-1-(trifluoromethyl)cyclobutane-1-carbonyl)-4-fluoropyrrolidine-2-carboxamide (237):



[0526] **236** (300 mg, 1 Equiv., 391 μ mol) was dissolved in 6 mL DCM/TFA (3:1) and stirred until the deprotection was complete (monitored via LCMS). The volatile solvent was completely removed to afford a quantitative yield of free amine. The crude deprotected amine was used in the next step without any further purification.

[0527] The deprotected amine, **Int. 141** (137 mg, 1.1 Equiv., 430 μ mol) and HATU (164 mg, 1.1 Equiv., 430 μ mol) were dissolved in DMF (4 mL) and DIPEA (253 mg, 341 μ L, 5 Equiv., 1.96 mmol) was added slowly. The reaction was stopped by the addition of 15 mL water upon the consumption of starting material (monitored by LCMS). The aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic layer was washed with brine, dried with MgSO_4 , filtered, and concentrated. **237** (300 mg, 310 μ mol, 79 %) was isolated as an off-white solid and used without further purification. LCMS (ESI+): m/z 967.3 (M+H).

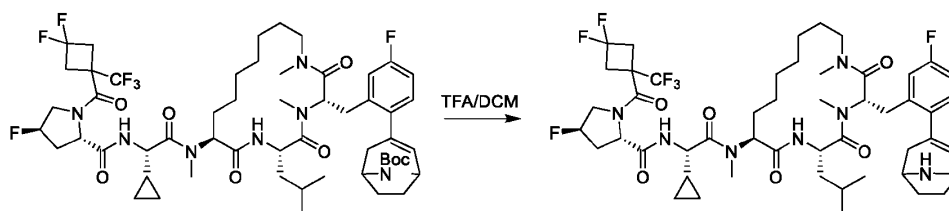
Step 4: Tert-butyl 3-(2-(((3S,6S,9S)-9-((S)-2-cyclopropyl-2-((2S,4R)-1-(3,3-difluoro-1-(trifluoromethyl)cyclobutane-1-carbonyl)-4-fluoropyrrolidine-2-carboxamido)-N-methylacetamido)-6-isobutyl-1,4-dimethyl-2,5,8-trioxo-1,4,7-triazacyclohexadecan-3-yl)methyl)-4-fluorophenyl)-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate (238**):**



[0528] **237** (54.0 mg, 1.2 Equiv., 161 μ mol), Na_2CO_3 (47.0 mg, 222 μ L, 2.0 molar, 3.3 Equiv., 443 μ mol), **Int. 134** (31.2 mg, 2 Equiv., 93.0 μ mol) and $\text{PdCl}_2(\text{dppf})$ -DCM adduct (16.5 mg, 0.15 Equiv., 20.1 μ mol) were dissolved in 4:1 Dioxane/Water (4 mL). The reaction

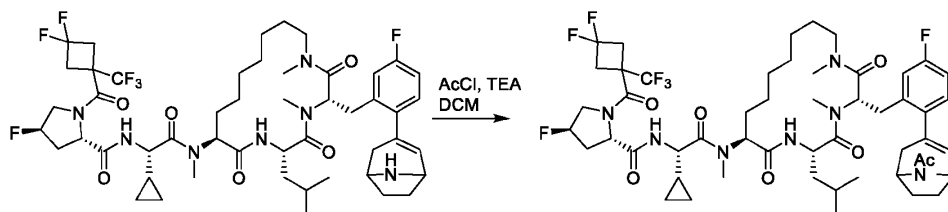
was degassed for 10 min with Ar and then heated to 80 °C until the complete consumption of starting material (monitored by LCMS). The reaction mixture was diluted with water (5 mL) and extracted with EtOAc (2 x 10 mL). The combined organic layer was washed with brine, dried over MgSO₄, filtered, and concentrated. **208** (as a mixture of diastereomers) was used in the next reaction without any additional purification. LCMS (ESI⁺): m/z 1097.5 (M+H).

Step 5: (2S,4R)-N-((1S)-2-(((3S,6S,9S)-3-(2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)-5-fluorobenzyl)-6-isobutyl-1,4-dimethyl-2,5,8-trioxo-1,4,7-triazacyclohexadecan-9-yl)(methyl)amino)-1-cyclopropyl-2-oxoethyl)-1-(3,3-difluoro-1-(trifluoromethyl)cyclobutane-1-carbonyl)-4-fluoropyrrolidine-2-carboxamide (Example 165):



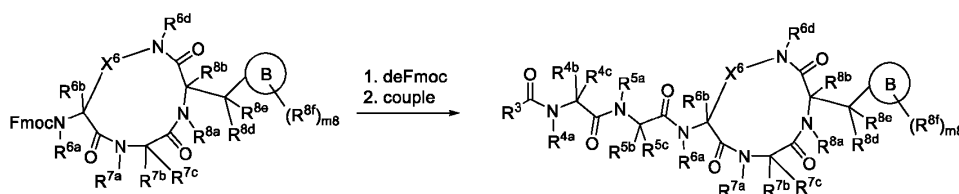
[0529] The crude Suzuki product was dissolved in 2 mL DCM/TFA (3:1) and stirred until the deprotection was complete (monitored via LCMS). The volatile solvent was completely removed to afford the crude deprotection product. The remaining TFA was removed by co-evaporation with toluene. The material can be used without any further purification in the next reaction. A portion of the crude reaction mixture was isolated via RP-HPLC (C18, 15% to 50% MeCN/H₂O with 0.5% formic acid) to afford **Example 165** (as a mixture of diastereomers, Formic Acid Salt) as a white powder after lyophilization. The remaining unpurified material was used in the next reaction directly. LCMS (ESI⁺): m/z 996.47 (M+H).

Step 6: (2S,4R)-N-((1S)-2-(((3S,6S,9S)-3-(2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)-5-fluorobenzyl)-6-isobutyl-1,4-dimethyl-2,5,8-trioxo-1,4,7-triazacyclohexadecan-9-yl)(methyl)amino)-1-cyclopropyl-2-oxoethyl)-1-(3,3-difluoro-1-(trifluoromethyl)cyclobutane-1-carbonyl)-4-fluoropyrrolidine-2-carboxamide (Example 58):



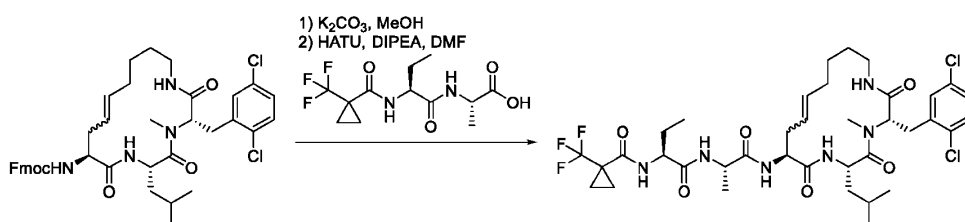
- [0530] Example 165** was dissolved in DCM (4 mL), TEA was added to adjust the pH to ~8.0 (~4 equiv.). Next, the reaction was cooled with an ice bath and AcCl (2.4 mg, 2.1 μ L, 1 Equiv., 30 μ mol) was added. Upon the complete consumption of starting material, the reaction was concentrated and directly purified by RP-HPLC (C18, 50% to 80% MeCN/H₂O with 0.5% formic acid) to afford **Example 58** as a mixture of diastereomers (13 mg, 12 μ mol, 40 %) as a white solid after lyophilization. LCMS (ESI+): m/z 1038.59 (M+H).

h. Method 8



10 Representative Experimental for Method 8: Example 1

Step 1: N-((S)-1-(((S)-1-(((3S,6S,9S)-3-(2,5-dichlorobenzyl)-6-isobutyl-4-methyl-2,5,8-trioxo-1,4,7-triazacyclohexadec-11-en-9-yl)amino)-1-oxopropan-2-yl)amino)-1-oxobutan-2-yl)-1-(trifluoromethyl)cyclopropane-1-carboxamide (Example 1):

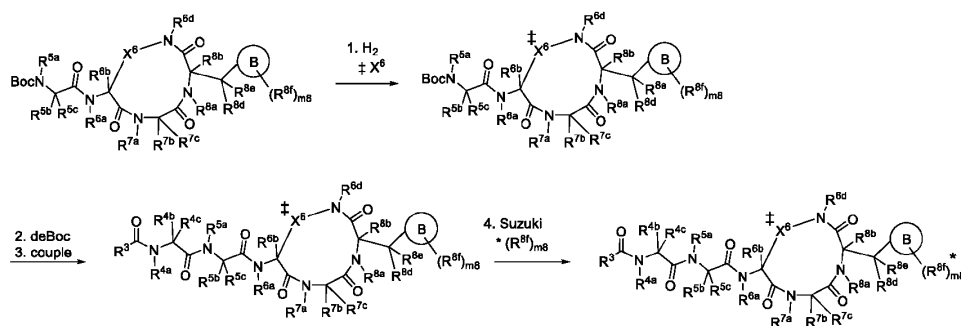
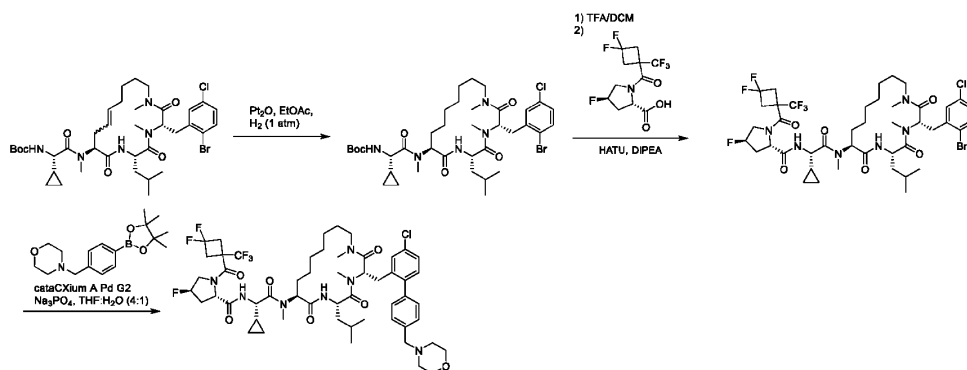


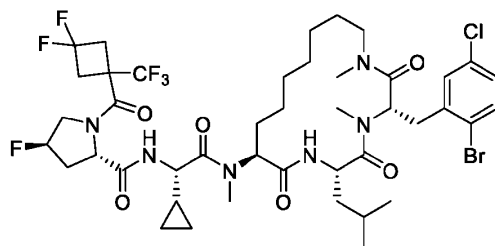
- [0531] 218** (30 mg, 1 Equiv., 41 μ mol) was dissolved in MeOH (2 ml), and K₂CO₃ (7.0 mg, 1.2 Equiv., 51 μ mol) was added while stirring. The reaction continued until the complete removal of the Fmoc protecting group (monitored by LCMS). Upon completion, the reaction was concentrated and DCE (2 x 4 mL) was used to dissolve the deprotected amine.

The DCE was filtered and concentrated. The crude amine was used directly in the next reaction.

[0532] The deprotected amine from above, **Int. 34** (15 mg, 1.2 Equiv., 48 μmol), and HATU (16 mg, 1 Equiv., 41 μmol) were dissolved in DMF (2 mL). DIPEA (35.5 μL , 1 equiv., 205 μmol) was added and the reaction was continued until the complete consumption of starting material (monitored by LCMS). Upon completion, the reaction mixture was neutralized with minimal 1N HCl and directly purified by RP-HPLC (C18, 40% to 70% MeCN/H₂O with 0.5% formic acid). **Example 1** (4.5 mg, 5.6 μmol , 14 %) was isolated after lyophilization as a white solid. LCMS (ESI⁺): m/z 803.4 (M+H).

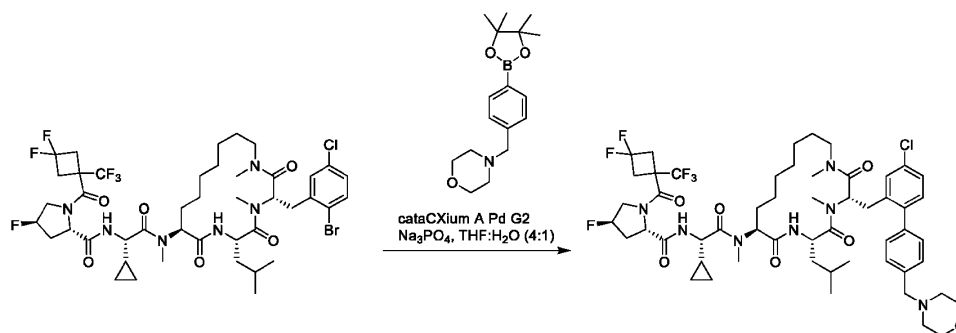
10

i. Method 9**Representative Procedure for Method 9: Example 359****Representative Experimental for Method 9: Example 359**



[0533] The starting material for Method 9, **239**, was synthesized using identical procedures for steps 1-3 of Method 7 using **226** and **Int. 141** LCMS (ESI): m/z 985.5 [M+H].

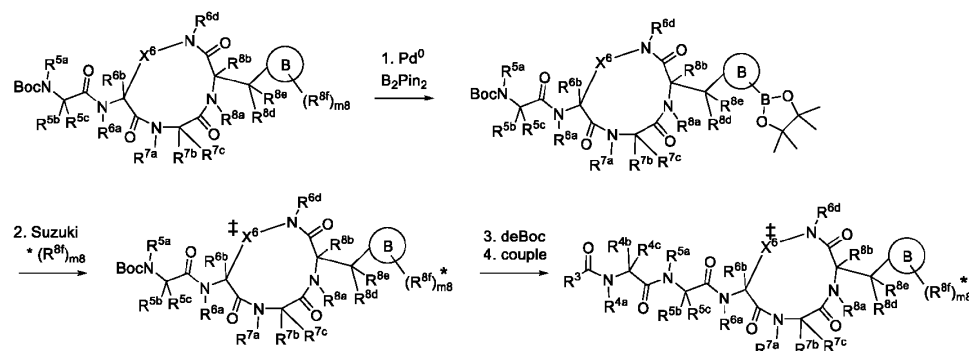
Step 4: (2S,4R)-N-((S)-2-(((3S,6S,9S)-3-((4-chloro-4'-(morpholinomethyl)-[1,1'-biphenyl]-2-yl)methyl)-6-isobutyl-1,4-dimethyl-2,5,8-trioxo-1,4,7-triazacyclohexadecan-9-yl)(methyl)amino)-1-cyclopropyl-2-oxoethyl)-1-(3,3-difluoro-1-(trifluoromethyl)cyclobutane-1-carbonyl)-4-fluoropyrrolidine-2-carboxamide (Example 359):



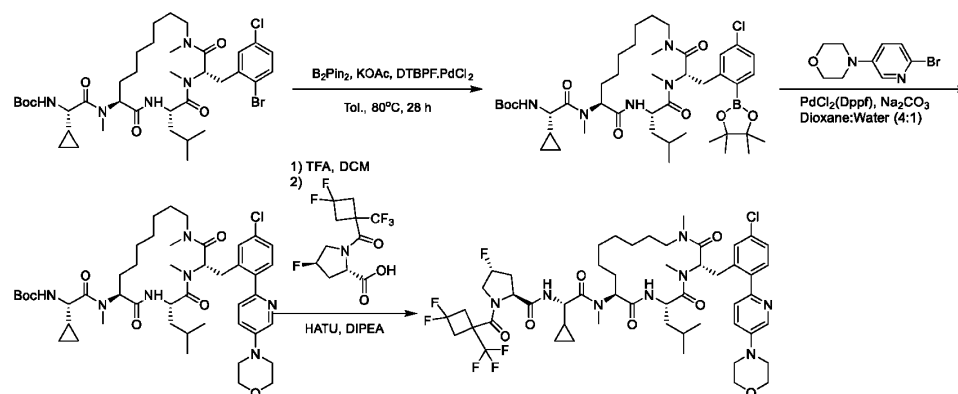
[0534] **239** (125 mg, 1 Equiv. 127 μ mol), 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)morpholine (38.5 mg, 1 Equiv. 127 μ mol), and Chloro[(di(1-adamantyl)-N-butylphosphine)-2-(2-aminobiphenyl)]palladium(II) (8.49 mg, 0.1 Equiv. 12.7 μ mol) were dissolved in 1.0 mL THF and Na_3PO_4 (267 μ L, 1.0 molar, 2.1 Equiv. 267 μ mol). The mixture was degassed with a stream of Argon, then sealed and stirred at 70 °C until the complete consumption of starting material (monitored by LCMS). The reaction was then cooled to room temperature and adjusted to pH ~7 with 1N HCl. The reaction mixture was filtered and directly purified by RP-HPLC (C18, 30% to 60% MeCN/ H_2O with 0.5% formic acid). **Example 359** (48.8 mg, 45.2 μ mol, 35.6 %) was isolated as a white solid after lyophilization. LCMS (ESI): m/z 1080.3 [M+H].

20

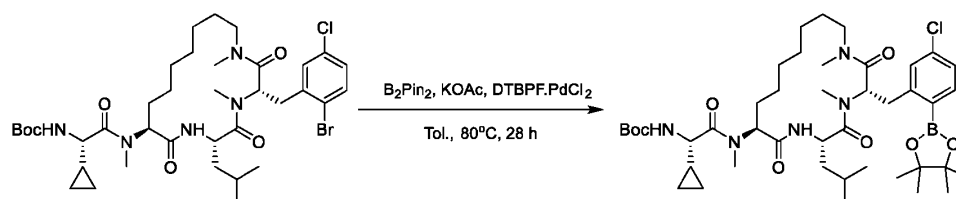
j. Method 10



Representative Procedure for Method 10: Example 382



Step 1: tert-butyl ((S)-2-(((3S,6S,9S)-3-(5-chloro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-6-isobutyl-1,4-dimethyl-2,5,8-trioxo-1,4,7-triazacyclohexadecan-9-yl)(methylamino)-1-cyclopropyl-2-oxoethyl)carbamate (240):

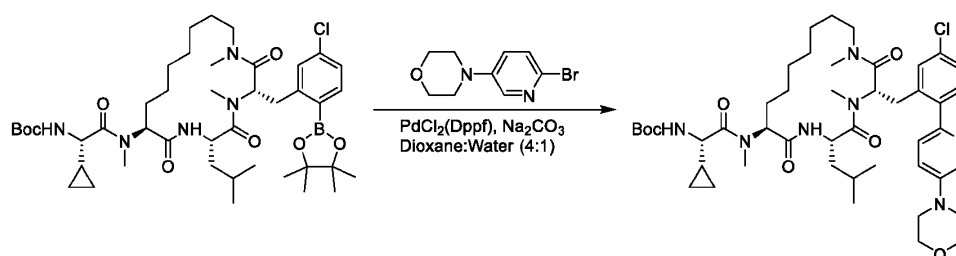


[0535] To a solution of macrocycle **227** (300 mg, 383.03 μmol , 1 eq) and B_2Pin_2 (194.53 mg, 766.06 μmol , 2 eq) in Toluene (5 mL) was added KOAc (75.18 mg, 766.06 μmol , 2 eq) and ditert-butyl(cyclopentyl)phosphane;dichloropalladium;iron (24.96 mg, 38.30 μmol , 0.1 eq) under N_2 atmosphere. The reaction mixture was heated to 80°C and stirred for 28hr. The reaction mixture was cooled to room temperature and quenched by water (10 mL), extracted

with EtOAc (10 mL x 2). The combined organic layer was washed with brine (15 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The residue was first purified by flash column chromatography (SiO₂, 0 to 50% EtOAc / Pet. Ether). Then by prep-HPLC (C18, using H₂O (10mM NH₄HCO₃) with MeCN 50 to 80% over 8.0 min).

- 5 The product was lyophilized to give **240** (20 mg, 5.78 μmol, 1.51% yield) as a white solid. LCMS (ESI): 730.6 (M-Boc)

Step 2: tert-butyl ((S)-2-(((3S,6S,9S)-3-(5-chloro-2-(5-morpholinopyridin-2-yl)benzyl)-6-isobutyl-1,4-dimethyl-2,5,8-trioxo-1,4,7-triazacyclohexadecan-9-yl)(methylamino)-1-cyclopropyl-2-oxoethyl)carbamate (241):

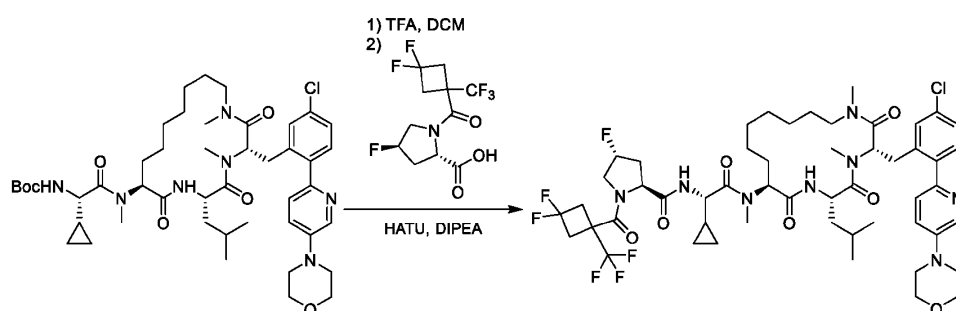


10

[0536] **240** 200 mg, 1 Equiv. 241 μmol), 4-(6-bromopyridin-3-yl)morpholine (82.0 mg, 1.4 Equiv. 337 μmol), and PdCl₂(dppf) (19.7 mg, 0.1 Equiv. 24.1 μmol) were dissolved in mixture of 1,4-Dioxane (1.3 mL) and 2M Na₂CO₃ (58.7 mg, 277 μL, 2.3 Equiv. 554 μmol). The reaction was degassed with a stream of Ar then heated to 100 °C for 6hr. The reaction was then cooled and adjusted to pH~7 with Formic Acid. The crude reaction mixture was then diluted in MeOH (2 mL), filtered, and directly purified by RP-HPLC (C18, 50% to 100% MeCN/H₂O with 0.5% formic acid) to obtain **241** (95 mg, 0.11 mmol, 46 %) as an off-white powder after lyophilization. LCMS (ESI): m/z 966.3 [M+H].

15

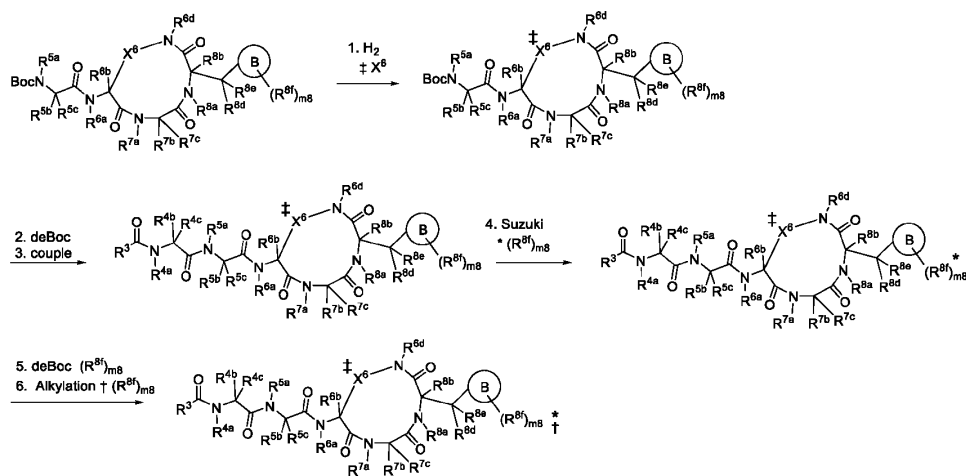
Steps 3-4: Example 382



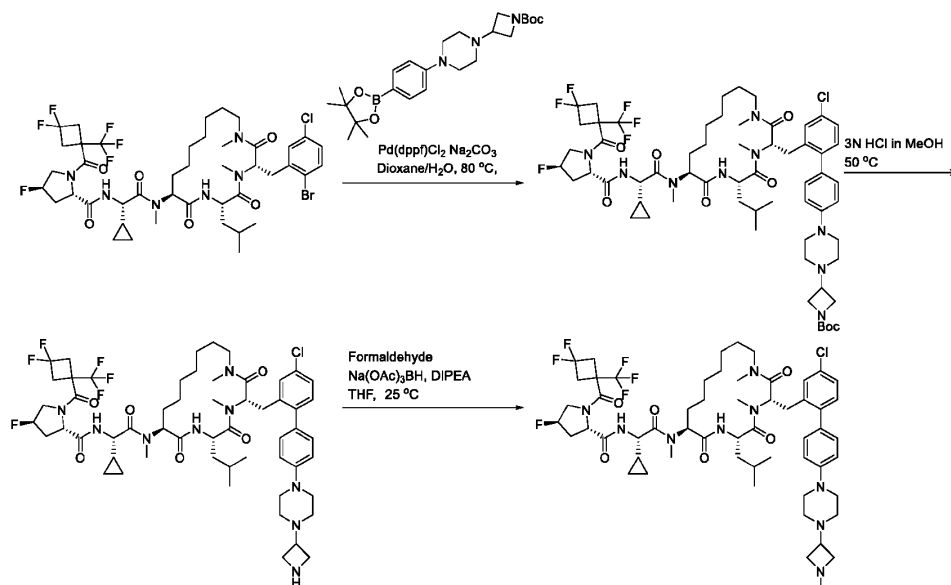
20

[0537] **Example 382** was synthesized using identical procedures for Method 4 (Steps 3-4) using **241** and **Int. 141**. LCMS (ESI): m/z 1068.2 [M+H].

k. Method 11

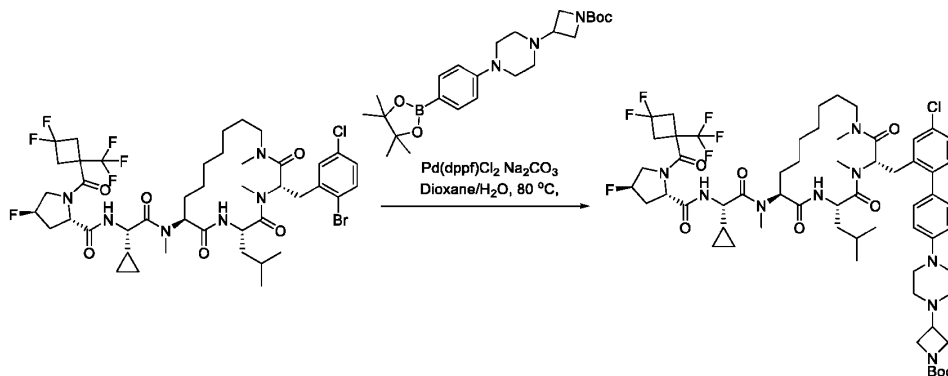


5 Representative Procedure for Method 11: Example 383



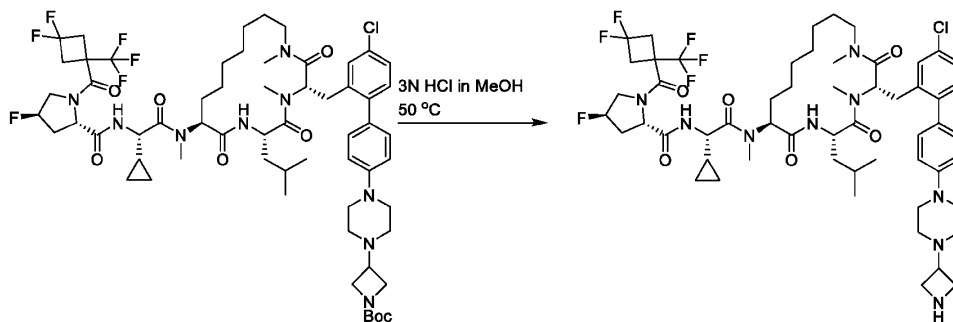
Step 1: tert-butyl 3-(4-(4'-chloro-2'-((3S,6S,9S)-9-((S)-2-cyclopropyl-2-((2S,4R)-1-(3,3-difluoro-1-(trifluoromethyl)cyclobutane-1-carbonyl)-4-fluoropyrrolidine-2-carboxamido)-N-methylacetamido)-6-isobutyl-1,4-dimethyl-2,5,8-trioxo-1,4,7-

triazacyclohexadecan-3-yl)methyl)-[1,1'-biphenyl]-4-yl)piperazin-1-yl)azetidine-1-carboxylate (**242**):



- [0538]** **239** (550 mg, 1 Equiv. 559 μmol), **Int. 193** (496 mg, 2 Equiv. 1.12 mmol), Na_2CO_3 (237 mg, 4 Equiv. 2.24 mmol) and $\text{PdCl}_2(\text{dppf})$ (45.6 mg, .1 Equiv. 55.9 μmol) were dissolved in Dioxane:Water (4:1) (5.59 mL). The reaction was degassed for 10 min with Ar and then heated to 80 °C until the complete consumption of starting material (monitored by LCMS). The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (2 x 10 mL). The combined organic layer was washed with brine, dried over MgSO_4 , filtered, and concentrated. The crude reaction mixture was isolated via RP-HPLC (C18, 30% to 80% MeCN/ H_2O with 0.5% formic acid) to afford **242** (400 mg, 328 μmol , 58.6 %) as a white powder after lyophilization. LCMS (ESI+): m/z 1220.7 (M+H).

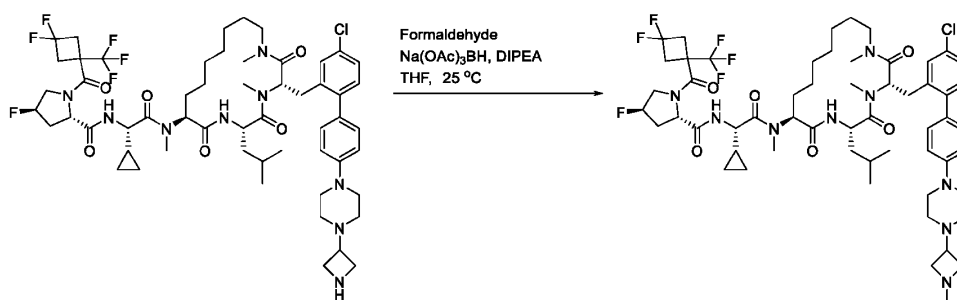
- Step 2: (2S,4R)-N-((S)-2-(((3S,6S,9S)-3-((4'-4-(azetidin-3-yl)piperazin-1-yl)-4-chloro-[1,1'-biphenyl]-2-yl)methyl)-6-isobutyl-1,4-dimethyl-2,5,8-trioxo-1,4,7-triazacyclohexadecan-9-yl)(methyl)amino)-1-cyclopropyl-2-oxoethyl)-1-(3,3-difluoro-1-(trifluoromethyl)cyclobutane-1-carbonyl)-4-fluoropyrrolidine-2-carboxamide (**243**):**



[0539] **242** (400 mg, 328 μmol , 1 Eq) was dissolved in 2 mL 3N HCl in MeOH and stirred at 50 °C until the deprotection was complete (monitored via LCMS). The volatile solvent was completely removed to afford the crude deprotection product, **243**, as the HCl salt. The material can be used without any further purification in the next reaction. LCMS 1120.7

5 (ESI+): m/z (M+H).

Step 3: (2S,4R)-N-((S)-2-(((3S,6S,9S)-3-((4-chloro-4'-(4-(1-methylazetidin-3-yl)piperazin-1-yl)-[1,1'-biphenyl]-2-yl)methyl)-6-isobutyl-1,4-dimethyl-2,5,8-trioxo-1,4,7-triazacyclohexadecan-9-yl)(methyl)amino)-1-cyclopropyl-2-oxoethyl)-1-(3,3-difluoro-1-(trifluoromethyl)cyclobutane-1-carbonyl)-4-fluoropyrrolidine-2-carboxamide
 10 (Example 383):



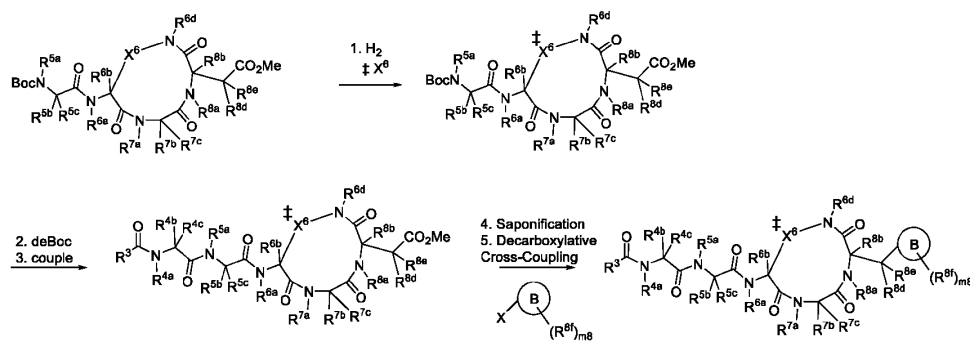
[0540] **243** (300 mg, 1 Equiv. 268 μmol), formaldehyde (43.5 mg, 39.9 μL , 37% Wt, 2 Equiv. 535 μmol) and DIPEA (138 mg, 187 μL , 4 Equiv. 1.07 mmol) was dissolved in THF (2.68 mL) stirred at 25 °C for 15 mins. Then, sodium triacetoxyborohydride (113 mg, 2 Equiv. 535 μmol) was added portion-wise to the reaction mixture. The reaction was carried on at 25 °C for 1 hour. The starting material was completely consumed (monitored by LCMS). The reaction mixture was diluted with water (15 mL) and extracted with EtOAc (2 x 15 mL). The combined organic layer was washed with brine, dried over MgSO_4 , filtered, and concentrated. The crude reaction mixture was purified via RP-HPLC (C18, 30% to 70% MeCN/ H_2O with 0.5% formic acid) to afford **Example 383** (150 mg, 132 μmol , 49.4 %) as a white powder after lyophilization. LCMS (ESI+): m/z 1135.25 (M+H).

15

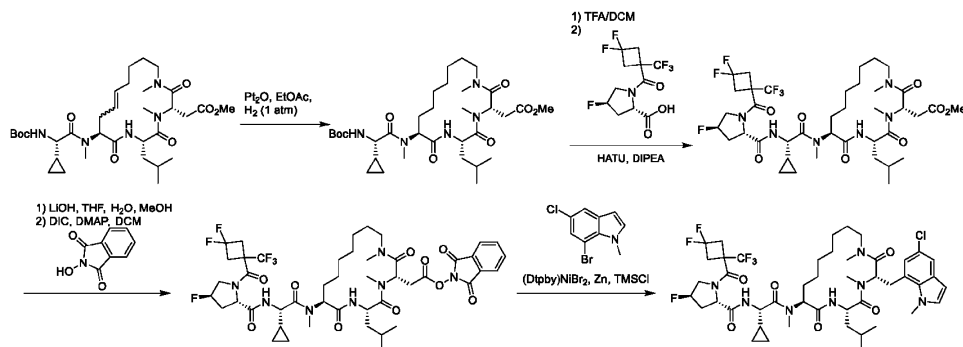
20

1. Method 12

Generic procedure for Method 12

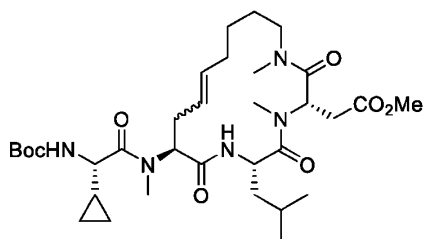


Representative Procedure for Method 12: Example 392



5

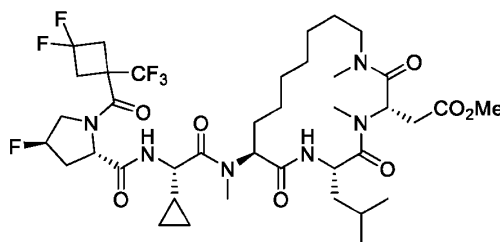
Representative Experimental for Method 12: Example 392:



[0541] The starting material for Method 12, **244**, was synthesized using Method A with **int.**

206. LCMS (ESI): m/z 652.4 ($M+H^+$).

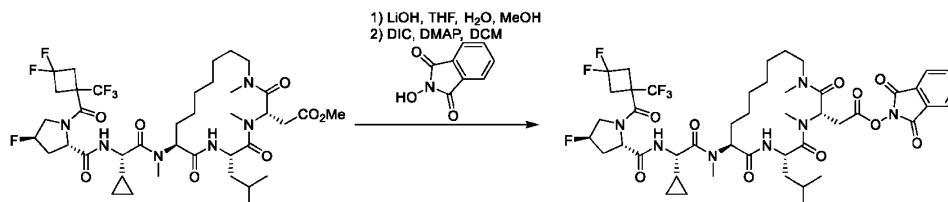
Steps 1-3: Methyl 2-((3S,6S,9S)-9-((S)-2-cyclopropyl-2-((2S,4R)-1-(3,3-difluoro-1-(trifluoromethyl)cyclobutane-1-carbonyl)-4-fluoropyrrolidine-2-carboxamido)-N-methylacetamido)-6-isobutyl-1,4-dimethyl-2,5,8-trioxo-1,4,7-triazacyclohexadecan-3-yl)acetate (245):



5

[0542] 245 was synthesized using identical procedures for steps 1-3 of Method 7 using 244 and Int. 141. LCMS (ESI): m/z 854.1 ($M+H^+$).

Steps 4-5: 1,3-Dioxoisindolin-2-yl 2-((3S,6S,9S)-9-((S)-2-cyclopropyl-2-((2S,4R)-1-(3,3-difluoro-1-(trifluoromethyl)cyclobutane-1-carbonyl)-4-fluoropyrrolidine-2-carboxamido)-N-methylacetamido)-6-isobutyl-1,4-dimethyl-2,5,8-trioxo-1,4,7-triazacyclohexadecan-3-yl)acetate (246):



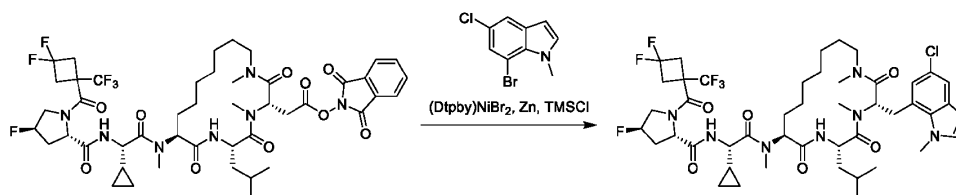
[0543] 245 (2.0 g, 1 Eq, 2.345 mmol), was dissolved in THF (16.4 mL). In a separate vial, LiOH (112.3 mg, 2 Eq, 4.690 mmol) was dissolved in Water (10.9 mL) and the LiOH solution was added to the stirring THF solution. MeOH (~1 mL) was added until the solution became homogeneous. The reaction was stirred at 25 °C until the complete consumption of starting material (monitored by LCMS). upon completion, the solution was acidified to pH~3 with 1N HCl. The acidified mixture was diluted with water (50 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude carboxylic acid product was used directly in the next reaction. LCMS (ESI): m/z 839.3 ($M+H^+$).

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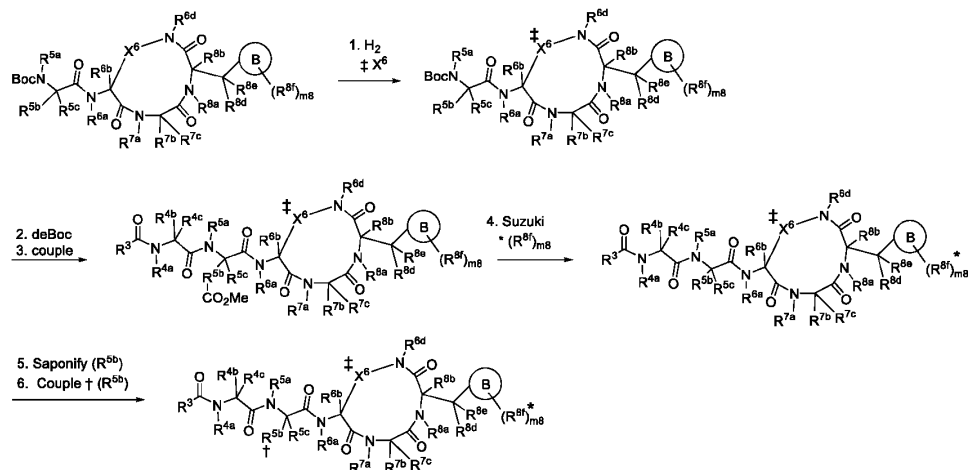
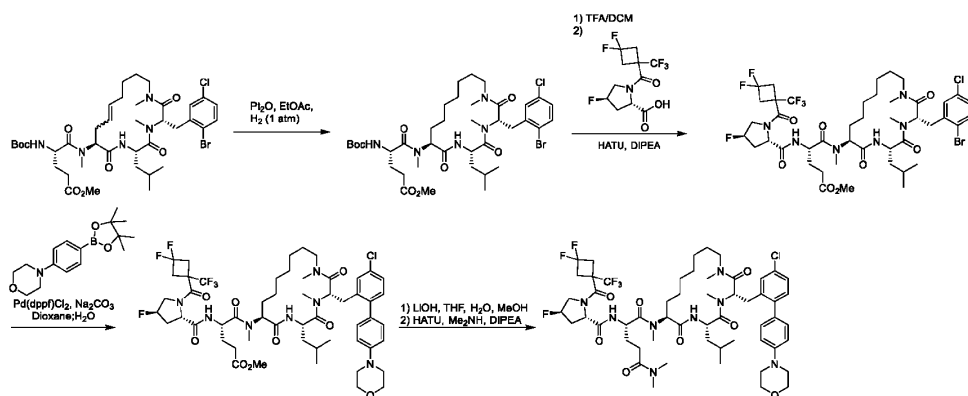
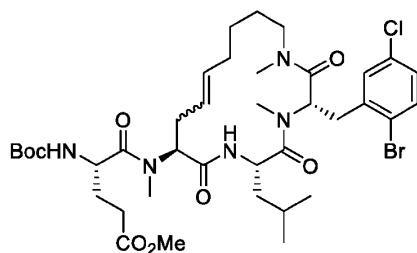
20

- [0544] The crude carboxylic acid (590 mg, 1 Eq, 703 μmol), 2-hydroxyisoindoline-1,3-dione (126 mg, 1.1 Eq, 774 μmol) and DMAP (8.59 mg, 0.1 Eq, 70.3 μmol) were dissolved in DCM (4.0 mL) and DIC (97.6 mg, 121 μL , 1.1 Eq, 774 μmol) was added. the reaction was stirred until the consumption of starting material was observed (TLC 50% EtOAc in hexane).
- 5 The reaction was filtered over a pad of SiO_2 which was washed with EtOAc (2 x 10 mL). The organic solvent was removed and the product, **246** (692 mg, 703 μmol , quant.), was used without further purification. Product decomposed to the carboxylic acid on LCMS.

- Step 6: (2S,4R)-N-((S)-2-(((3S,6S,9S)-3-((5-chloro-1-methyl-1H-indol-7-yl)methyl)-6-isobutyl-1,4-dimethyl-2,5,8-trioxo-1,4,7-triazacyclohexadecan-9-yl)(methyl)amino)-1-cyclopropyl-2-oxoethyl)-1-(3,3-difluoro-1-(trifluoromethyl)cyclobutane-1-carbonyl)-4-fluoropyrrolidine-2-carboxamide (Example 392)**
- 10

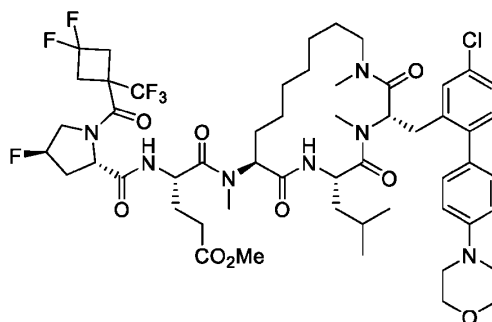


- [0545] DMA (2.0 mL) was added to a vial containing **246** (175 mg, 1 Eq, 178 μmol), 7-bromo-5-chloro-1-methyl-1H-indole (87.0 mg, 2 Eq, 356 μmol). Then, TMS-Cl (4.3 mg, 5.0 μL , 0.22 Eq, 39 μmol) was added and the mixture was degassed with a stream of Ar for 5 min. (Dtpby)NiBr₂ (21.6 mg, 0.25 Eq, 44.5 μmol) was added, while degassing was continued for an additional 5 min. Next, the vial was quickly capped, and the mixture was stirred overnight at ambient temperature. LCMS showed the consumption of starting material, and the reaction was filtered and directly purified by RP-HPLC. **Example 392** was isolated as a
- 20 fluffy white solid (15.7 mg, 16.4 μmol , 9.21 %). LCMS (ESI): m/z 958.48 ($M+H^+$).

m. Method 13**Representative Procedure for Method 13: Example 419****5 Representative Experimental for Method 13: Example 419**

[0546] The starting material for Method 13, **247**, Method A with **Int. 30**, **207**. LCMS (ESI): m/z 826.4 ($M+H^+$).

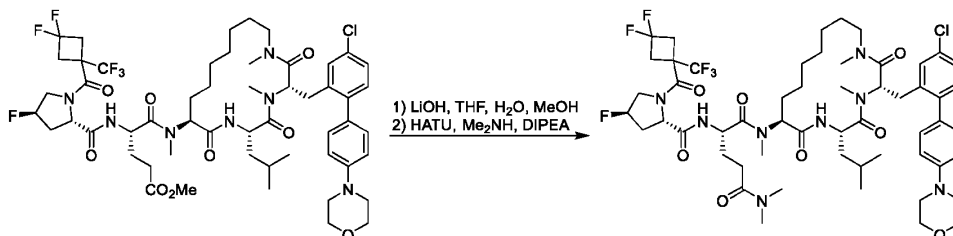
Steps 1-4: ethyl (S)-5-(((3S,6S,9S)-3-((4-chloro-4'-morpholino-[1,1'-biphenyl]-2-yl)methyl)-6-isobutyl-1,4-dimethyl-2,5,8-trioxo-1,4,7-triazacyclohexadecan-9-yl)(methylamino)-4-((2S,4R)-1-(3,3-difluoro-1-(trifluoromethyl)cyclobutane-1-carbonyl)-4-fluoropyrrolidine-2-carboxamido)-5-oxopentanoate (248):



5

[0547] Example 415 was synthesized using identical procedures from Method 7 Steps 1-4 using 247, Int. 117 and 141 as starting materials. LCMS (ESI): m/z 1113.11 (M+H⁺).

Steps 5-6: (S)-N1-(((3S,6S,9S)-3-((4-chloro-4'-morpholino-[1,1'-biphenyl]-2-yl)methyl)-6-isobutyl-1,4-dimethyl-2,5,8-trioxo-1,4,7-triazacyclohexadecan-9-yl)-2-((2S,4R)-1-(3,3-difluoro-1-(trifluoromethyl)cyclobutane-1-carbonyl)-4-fluoropyrrolidine-2-carboxamido)-N1,N5,N5-trimethylpentanediamide (Example 419):



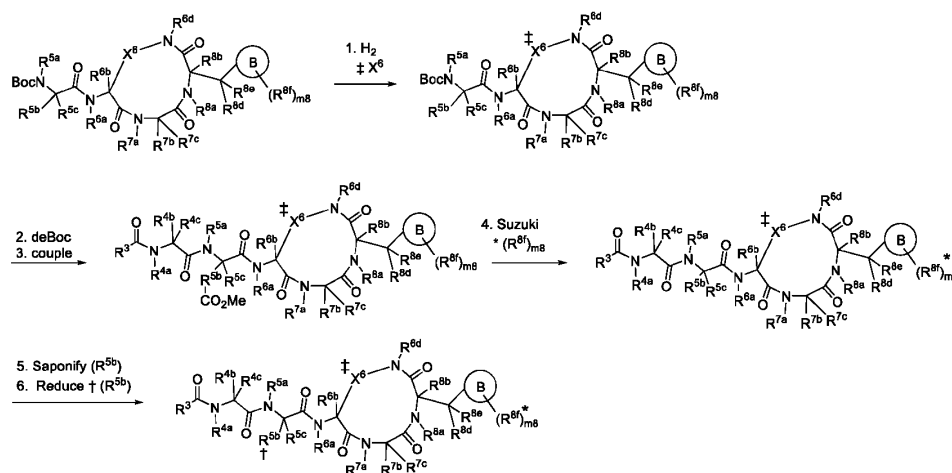
[0548] Example 415 (300 mg, 1 Eq, 270 μmol) was dissolved in THF (4.0 mL). In a separate vial, LiOH•water (23.8 mg, 2.1 Eq, 566 μmol) was dissolved in Water (1.0 mL). The LiOH solution was added into the stirring THF solution. MeOH (~0.1 mL) was added dropwise to ensure a homogeneous reaction mixture. The reaction was quenched with 1N HCl (4 mL) upon the consumption of starting material (monitored by LCMS). The reaction was extracted with EtOAc (10 mL x 2). The combined organic layers were washed with brine, dried with MgSO₄, filtered, and concentrated to afford Example 418 (296 mg, 270

μmol , 100 %) as a white solid. The reaction was carried on without further purification. A small portion (~ 15 mg) was purified by RP-HPLC for biological evaluation. LCMS (ESI): m/z 1090.02 ($M+H^+$).

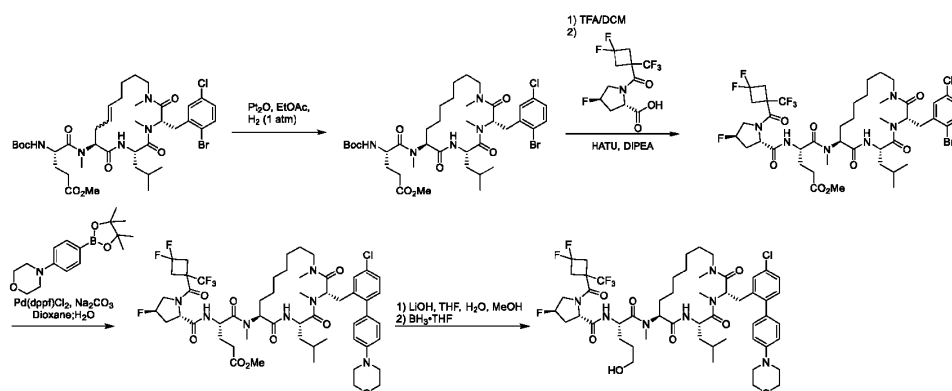
[0549] Example 418 (35 mg, 1 Eq, 32 μmol) was dissolved in DMF (1.0 mL). HATU (13 mg, 1.1 Eq, 35 μmol) and DIPEA (25 mg, 33 μL , 6 Eq, 0.19 mmol) were subsequently added. The reaction was stirred for 5 min. Then, 1M dimethylamine in THF (14 mg, 0.32 mL, 10 Eq, 0.32 mmol) was added. The reaction was continued until the complete consumption of starting material (monitored by LCMS). The reaction mixture was neutralized to pH ~ 4 , with 1N HCl filtered, and directly purified by RP-HPLC. **Example 419** (20.9 mg, 18.6 μmol , 58 %)

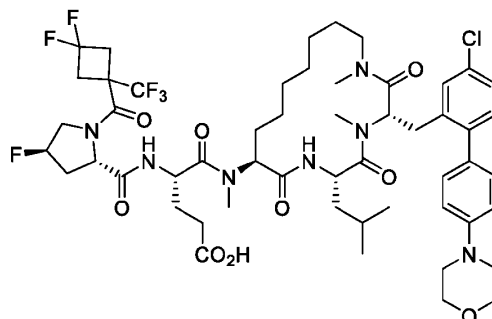
was isolated as white solid after lyophilization. LCMS (ESI): m/z 1126.12 ($M+H^+$).

n. Method 14



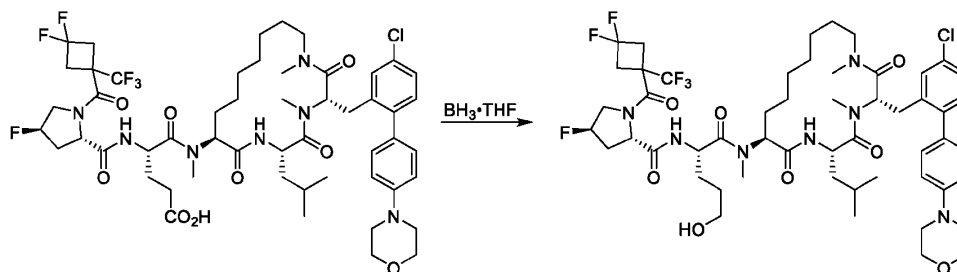
Representative Procedure for Method 14: Example 420



Representative Experimental for Method 14: Example 420

[0550] The intermediate for Method 14, **Example 418**, was synthesized using Method 13 steps 1-5.

- 5 **Step 6:** (2S,4R)-N-((S)-1-(((3S,6S,9S)-3-((4-chloro-4'-morpholino-[1,1'-biphenyl]-2-yl)methyl)-6-isobutyl-1,4-dimethyl-2,5,8-trioxo-1,4,7-triazacyclohexadecan-9-yl)(methylamino)-5-hydroxy-1-oxopentan-2-yl)-1-(3,3-difluoro-1-(trifluoromethyl)cyclobutane-1-carbonyl)-4-fluoropyrrolidine-2-carboxamide (**Example 420**):



10

- [0551] **Example 418** (35 mg, 1 Eq, 32 μ mol) was dissolved in THF 2 mL and was cooled to 0 °C. $\text{BH}_3 \cdot \text{THF}$ (8.2 mg, 96 μ L, 1.0 molar in THF, 3 Eq, 96 μ mol) was added. The reaction was slowly warmed to RT and stirred overnight. The reaction mixture was quenched with the addition of sat. NaHCO_3 , filtered, and directly purified by RP-HPLC. **Example 420** (7.8 mg, 7.2 μ mol, 23 %) was isolated as a white solid after lyophilization. LCMS (ESI): m/z 1085.25 ($\text{M} + \text{H}^+$).

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3. Exemplary Compounds – Preparation Summary Tables

[0552] Table 2, below, provides information on the methods used to prepare the exemplified compounds in the current application. This table includes a column listing the Example Number, Macrocyclic Synthesis procedure, and Final Synthesis procedure. Chemical structures for the exemplified compounds are shown in Table 4, while analytical data for these compounds are shown in Table 3.

[0553] Certain examples in the following tables include a P1 or a P2 after the example number. This indicates that two isomers of an exemplary compound were isolated using HPLC purification, but the absolute stereochemistry for each isolated isomer was not determined. P1 refers to the first eluting peak, and P2 refers to the second eluting peak.

10 Table 2: Summary Table Procedures for Compound Preparation

Example Number	Macrocyclic Synthesis	Final Synthesis
1	Method C	Method 8 with Int. 34
2	Method C	Method 8 with Int. 35
3	Method C	Method 8 with Int. 33
4	Method C	Method 8 with Int. 127
5-P1	Method A with Int. 1, Int. 6	Method 1 with Int. 140
5-P2	Method A with Int. 1, Int. 6	Method 1 with Int. 140
6-P1	Method A with Int. 1, Int. 6	Method 1
6-P2	Method A with Int. 1, Int. 6	Method 1
7	Method A with Int. 1, Int. 6	Method 6
8	Method C	Method 8 with Int. 127
9	Method A with Int. 1, Int. 6	Method 6 with Int. 140
10	Method A with Int. 1, Int. 6	Method 6 with Int. 142
11	Method A with Int. 6	Method 1 with Int. 140
12	Method C with Int. 3	Method 8 with Int. 127
13	Method C with Int. 3	Method 8 with Int. 35
14	Method A with Int. 6	Method 1
15	Method A with Int. 6	Method 1 with Int. 143
16-P1	Method A with Int. 1, Int. 6	Method 1 with Int. 143
16-P2	Method A with Int. 1, Int. 6	Method 1 with Int. 143
17	Method A with Int. 1, Int. 30	Method 2 with Int. 46
18	Method A with Int. 1, Int. 30	Method 2 with Int. 47
19	Method A with Int. 1, Int. 30	Method 2 with Int. 48
20	Method A with Int. 1, Int. 30	Method 4
21	Method A with Int. 1, Int. 30	Method 4 with Int. 46
22	Method A with Int. 1, Int. 30	Method 2 with Int. 49
23	Method A with Int. 1, Int. 30	Method 2 with Int. 50
24	Method A with Int. 1, Int. 30	Method 2 with Int. 51

Example Number	Macrocycle Synthesis	Final Synthesis
25	Method A with Int. 6	Method 6
26	Method A with Int. 1, Int. 30	Method 2 with Int. 52
27	Method A with Int. 1, Int. 30	Method 2 with Int. 53
28	Method A with Int. 1, Int. 30	Method 2 with Int. 54
29	Method A with Int. 30	Method 2 with Int. 52
30	Method A with Int. 30	Method 2 with Int. 55
31	Method A with Int. 30	Method 2 with Int. 47
32	Method A with Int. 1, Int. 30	Method 2 with Int. 144, Int. 53
33	Method A with Int. 1, Int. 30	Method 2 with Int. 144, Int. 54
34	Method A with Int. 30	Method 2 with Int. 144, Int. 52
35	Method A with Int. 30	Method 2 with Int. 144, Int. 55
36	Method A with Int. 30	Method 2 with Int. 144, Int. 47
37	Method A	Method 2 with Int. 52
38	Method A	Method 2 with Int. 55
39	Method A	Method 2 with Int. 47
40	Method A	Method 2 With Int. 144, Int. 52
41	Method A	Method 2 with Int. 144, Int. 55
42	Method A	Method 2 with Int. 144, Int. 47
43	Method A with Int. 1, Int. 30	Method 2 with Int. 56
44	Method A with Int. 30	Method 2 with Int. 56
45	Method A	Method 5
46	Method A	Method 2 with Int. 57
47	Method A	Method 2 with Int. 51
48	Method A with Int. 6	Method 1 with Int. 144
49	Method A with Int. 30	Method 4 with Int. 52
50	Method A with Int. 30	Method 4
51	Method A with Int. 30	Method 4 with Int. 46
52	Method A with Int. 30	Method 5
53	Method A with Int. 1, Int. 30	Method 3 with Int. 67, Int. 36
54	Method A with Int. 1, Int. 6, Int. 32	Method 1
55	Method A with Int. 1, Int. 6, Int. 32	Method 6
56-P1	Method A with Int. 1, Int. 30	Method 2 with Int. 58
56-P2	Method A with Int. 1, Int. 30	Method 2 with Int. 58
57-P1	Method A with Int. 30	Method 7 with Int. 134
57-P2	Method A with Int. 30	Method 7 with Int. 134
58	Method A	Method 7 with Int. 134
59-P1	Method A	Method 5 With Int. 45
59-P2	Method A	Method 5 With Int. 45
60	Method A with Int. 30	Method 7 with Int. 137

Example Number	Macrocycle Synthesis	Final Synthesis
61	Method A with Int. 1, Int. 30	Method 4 with Int. 68
62	Method A with Int. 1, Int. 30	Method 4 with Int. 69
63	Method A with Int. 1, Int. 30	Method 5 with Int. 68
64	Method A with Int. 1, Int. 30	Method 5 with Int. 69
65	Method A	Method 4 with Int. 52
66	Method A with Int. 1, Int. 30	Method 4 with Int. 52
67	Method A with Int. 1, Int. 30	Method 4 with Int. 59
68	Method A	Method 4 with Int. 59
69	Method A	Method 4 with Int. 144, Int. 52
70	Method A with Int. 1, Int. 30	Method 4 with Int. 144, Int. 52
71	Method A with Int. 4, Int. 30	Method 4 with Int. 46
72	Method A with Int. 4, Int. 30	Method 4 with Int. 52
73	Method A with Int. 4, Int. 30	Method 4 with Int. 59
74	Method A with Int. 4, Int. 30	Method 4
75	Method A with Int. 30	Method 4 with Int. 70
76	Method A with Int. 30	Method 4 with Int. 145, Int. 52
77	Method A with Int. 30	Method 4 with Int. 146, Int. 52
78	Method A with Int. 30	Method 2 with Int. 59
79	Method A with Int. 30	Method 2 with Int. 60
80	Method A with Int. 30	Method 2 with Int. 144, Int. 60
81	Method A with Int. 30	Method 2 with Int. 144, Int. 59
82	Method A with Int. 30	Method 4 with Int. 147, Int. 52
83	Method A	Method 2 with Int. 144, Int. 61
84	Method A	Method 2 with Int. 62
85	Method A	Method 2 with Int. 63
86	Method A	Method 2 with Int. 59
87	Method A	Method 2 with Int. 64
88	Method A	Method 2 with Int. 65
89	Method A with Int. 1, Int. 30	Method 2 with Int. 66
90	Method A with Int. 1, Int. 30	Method 3 with Int. 67, Int. 37
91	Method A with Int. 1, Int. 30	Method 3 with Int. 67, Int. 38
92	Method A	Method 4 with Int. 144, Int. 61
93	Method A	Method 4 with Int. 62
94	Method A	Method 4 with Int. 63
95	Method A	Method 4 with Int. 64
96	Method A	Method 4 with Int. 65
97	Method A with Int. 1, Int. 30	Method 4 with Int. 66
98	Method A with Int. 1, Int. 30	Method 7 with Int. 138
99	Method A with Int. 1, Int. 30	Method 7 with Int. 138
100	Method A	Method 4 with Int. 50
101	Method A	Method 5 with Int. 66

Example Number	Macrocycle Synthesis	Final Synthesis
102-P1	Method A with Int. 1, Int. 7	Method 1
102-P2	Method A with Int. 1, Int. 7	Method 1
103	Method A with Int. 1, Int. 7	Method 6
104	Method A with Int. 7	Method 1
105	Method A with Int. 7	Method 6
106	Method A with Int. 7	Method 1 with Int. 144
107-P1	Method A with Int. 1, Int. 7	Method 1 with Int. 144
107-P2	Method A with Int. 1, Int. 7	Method 1 with Int. 144
108	Method A with Int. 1, Int. 7	Method 6 with Int. 144
109	Method A with Int. 7	Method 6 with Int. 144
110	Method A with Int. 30	Method 4 with Int. 59
111	Method A with Int. 30	Method 4 with Int. 71
112	Method A with Int. 30	Method 4 with Int. 65
113	Method A with Int. 30	Method 4 with Int. 63
114	Method A with Int. 30	Method 4 with Int. 62
115	Method A with Int. 8	Method 1 with Int. 144
116	Method A with Int. 8	Method 1
117-P1	Method A with Int. 1, Int. 8	Method 1 with Int. 144
117-P2	Method A with Int. 1, Int. 8	Method 1 with Int. 144
118-P1	Method A with Int. 1, Int. 8	Method 1
118-P2	Method A with Int. 1, Int. 8	Method 1
119	Method A with Int. 10	Method 6 with Int. 144
120	Method A with Int. 10	Method 6
121	Method A	Method 4 with Int. 72
122	Method A	Method 4 with Int. 147, Int. 59
123	Method A	Method 4 with Int. 130
124	Method A	Method 7 with Int. 135
125	Method A with Int. 1, Int. 9	Method 1
126	Method A with Int. 9	Method 1
127	Method A with Int. 1, Int. 9	Method 6
128	Method A with Int. 9	Method 6
129	Method A with Int. 1, Int. 10	Method 1
130	Method A with Int. 10	Method 1
131	Method A with Int. 1, Int. 10	Method 6
132	Method A with Int. 1, Int. 9	Method 1 with Int. 144
133	Method A with Int. 9	Method 1 with Int. 144
134	Method A with Int. 1, Int. 9	Method 6 with Int. 144
135	Method A with Int. 9	Method 6 with Int. 144
136-P1	Method A with Int. 1, Int. 10	Method 1 with Int. 144
136-P2	Method A with Int. 1, Int. 10	Method 1 with Int. 144
137	Method A with Int. 10	Method 1 with Int. 144

Example Number	Macrocycle Synthesis	Final Synthesis
138	Method A with Int. 1, Int. 10	Method 6 with Int. 144
139	Method A with Int. 12	Method 6 with Int. 144
140	Method A with Int. 12	Method 6
141	Method A with Int. 1, Int. 12	Method 6 with Int. 144
142	Method A with Int. 1, Int. 12	Method 6
143	Method A with Int. 30	Method 7 with Int. 138, Int. 37
144	Method A with Int. 30	Method 7 with Int. 138, Int. 38
145	Method A with Int. 30	Method 7 with Int. 138, Int. 36
146	Method A	Method 4 with Int. 148, Int. 59
147	Method A	Method 4 with Int. 149, Int. 59
148	Method A	Method 4 with Int. 73
149	Method A	Method 7 with Int. 134
150	Method A	Method 7 with Int. 134
151	Method A	Method 7 with Int. 135
152	Method A with Int. 1, Int. 11	Method 1
153	Method A with Int. 11	Method 1
154	Method A with Int. 1, Int. 11	Method 6
155	Method A with Int. 11	Method 6
156-P1	Method A with Int. 1, Int. 11	Method 1 with Int. 144
156-P2	Method A with Int. 1, Int. 11	Method 1 with Int. 144
157	Method A with Int. 11	Method 1 with Int. 144
158	Method A with Int. 1, Int. 11	Method 6 with Int. 144
159	Method A with Int. 11	Method 6 with Int. 144
160	Method A with Int. 1, Int. 8	Method 6
161	Method A with Int. 1, Int. 8	Method 6 with Int. 144
162	Method A with Int. 8	Method 6
163	Method A with Int. 8	Method 6 with Int. 144
164	Method A	Method 4 with Int. 74
165	Method A	Method 7
166	Method A	Method 7 with Int. 135
167	Method A with Int. 30	Method 4 with Int. 75
168	Method B with Int. 30	Method 2 with Int. 52
169	Method A with Int. 30	Method 4 with Int. 131
170	Method A with Int. 30	Method 4 with Int. 76
171	Method A with Int. 30	Method 4 with Int. 77
172	Method A with Int. 30	Method 4 with Int. 78
173	Method B with Int. 30	Method 2 with Int. 144, Int. 52
174	Method B with Int. 30	Method 2 with Int. 149, Int. 52
175	Method B with Int. 30	Method 2 with Int. 59
176	Method B with Int. 30	Method 2 with Int. 144, Int. 59
177	Method A with Int. 30	Method 4 with Int. 79

Example Number	Macrocycle Synthesis	Final Synthesis
178	Method A with Int. 30	Method 4 with Int. 80
179	Method A with Int. 30	Method 4 with Int. 81
180	Method A with Int. 30	Method 4 with Int. 132
181	Method A with Int. 30	Method 4 with Int. 82
182	Method A with Int. 30	Method 4 with Int. 83
183	Method A with Int. 30	Method 4 with Int. 148, Int. 52
184	Method A with Int. 30	Method 4 with Int. 149, Int. 52
185	Method A with Int. 30	Method 4 with Int. 144, Int. 52
186	Method A	Method 4 with Int. 144, Int. 59
187	Method A with Int. 30	Method 4 with Int. 84
188	Method A with Int. 1, Int. 30	Method 4 with Int. 144, Int. 59
189	Method A with Int. 1, Int. 30	Method 2 with Int. 59
190	Method A with Int. 30	Method 4 with Int. 73
191	Method A with Int. 30	Method 4 with Int. 85
192	Method A with Int. 30	Method 4 with Int. 86
193	Method A with Int. 1, Int. 30	Method 7 with Int. 134
194	Method A with Int. 1, Int. 30	Method 7 with Int. 135
195	Method A with Int. 1	Method 2 with Int. 52
196	Method A with Int. 30	Method 4 with Int. 121
197	Method A with Int. 30	Method 4 with Int. 87
198	Method A with Int. 30	Method 4 with Int. 88
199	Method A with Int. 30	Method 4 with Int. 87
200	Method A with Int. 30	Method 4 with Int. 90
201	Method A with Int. 30	Method 4 with Int. 91
202	Method A with Int. 30	Method 4 with Int. 92
203	Method A with Int. 30	Method 4 with Int. 143, Int. 52
204	Method A with Int. 30	Method 4 with Int. 150, Int. 52
205	Method A with Int. 30	Method 4 with Int. 93
206	Method A with Int. 30	Method 4 with Int. 94
207	Method A with Int. 30	Method 4 with Int. 95
208	Method A with Int. 30	Method 4 with Int. 96
209	Method A with Int. 30	Method 4 with Int. 97
210	Method A with Int. 30	Method 4 with Int. 98
211	Method A with Int. 30	Method 4 with Int. 99
212	Method A with Int. 30	Method 4 with Int. 100
213	Method A with Int. 1	Method 4 with Int. 59
214	Method A with Int. 1	Method 4 with Int. 73
215	Method A with Int. 1	Method 4 with Int. 52
216	Method A with Int. 30	Method 4 with Int. 101
217	Method A with Int. 1	Method 4
218	Method A with Int. 30	Method 4 with Int. 52

Example Number	Macrocycle Synthesis	Final Synthesis
219	Method A with Int. 7, Int. 41	Method 6
220	Method A with Int. 7, Int. 41	Method 6 with Int. 144
221	Method A with Int. 7, Int. 41	Method 6 with Int. 149
222	Method A with Int. 13	Method 6
223	Method A with Int. 13	Method 6 with Int. 149
224	Method A with Int. 13	Method 6 with Int. 144
225	Method A with Int. 14	Method 6
226	Method A with Int. 14	Method 6 with Int. 149
227	Method A with Int. 14	Method 6 with Int. 144
228	Method A with Int. 15	Method 6
229	Method A with Int. 15	Method 6 with Int. 149
230	Method A with Int. 15	Method 6 with Int. 144
231	Method A with Int. 30	Method 4 with Int. 102
232	Method A with Int. 30	Method 4 with Int. 103
233	Method A with Int. 30	Method 4 with Int. 85
234	Method A with Int. 30	Method 4 with Int. 104
235	Method A with Int. 30	Method 4 with Int. 105
236	Method A with Int. 30	Method 4 with Int. 106
237	Method A with Int. 30	Method 4 with Int. 107
238	Method A with Int. 30	Method 4 with Int. 64
239	Method A with Int. 30	Method 4 with Int. 108
240	Method A with Int. 16	Method 6
241	Method A with Int. 1	Method 7 with Int. 135
242	Method A with Int. 30	Method 4 with Int. 74
243	Method A with Int. 17	Method 6
244	Method A with Int. 18	Method 6
245	Method A with Int. 18	Method 6 with Int. 144
246	Method A with Int. 19	Method 6
247	Method A with Int. 19	Method 6 with Int. 144
248	Method A with Int. 19	Method 6 with Int. 148
249	Method A with Int. 30	Method 4 with Int. 109
250	Method A with Int. 30	Method 4 with Int. 110
251	Method A with Int. 30	Method 4 with Int. 111
252	Method A	Method 4 with Int. 112
253	Method A with Int. 30	Method 4 with Int. 113
254	Method A with Int. 30	Method 4 with Int. 112
255	Method A with Int. 30	Method 4 with Int. 114
256	Method A with Int. 30	Method 4 with Int. 115
257	Method A with Int. 30	Method 4 with Int. 116
258	Method B	Method 1
259	Method A with Int. 20	Method 6

Example Number	Macrocycle Synthesis	Final Synthesis
260	Method A with Int. 20	Method 6 with Int. 148
261	Method A with Int. 30	Method 4 with Int. 117
262	Method A with Int. 30	Method 4 with Int. 118
263	Method A with Int. 30	Method 4 with Int. 130
264	Method A with Int. 1	Method 4 with Int. 130
265	Method A with Int. 30	Method 4 with Int. 119
266	Method A with Int. 30	Method 4 with Int. 120
267	Method A with Int. 2, Int. 30, Int. 42	Method 2 with Int. 47
268	Method A with Int. 13	Method 6 with Int. 150
269	Method A with Int. 14	Method 6 with Int. 150
270	Method A with Int. 1, Int. 30	Method 4 with Int. 130
271	Method A	Method 4 with Int. 121
272	Method A with Int. 30	Method 4 with Int. 89
273	Method A with Int. 2, Int. 30, Int. 42	Method 2 with Int. 64
274	Method A with Int. 1, Int. 13	Method 6 with Int. 148
275	Method A with Int. 1, Int. 13	Method 6
276	Method A with Int. 1, Int. 30	Method 4 with Int. 133
277	Method A with Int. 1, Int. 30	Method 4 with Int. 122
278	Method B with Int. 31	Method 2 with Int. 64
279	Method A	Method 4 with Int. 123
280	Method A with Int. 1	Method 4 with Int. 133
281	Method A with Int. 1	Method 4 with Int. 112
282	Method A	Method 4 with Int. 112, Int. 39
283	Method A with Int. 30	Method 4 with Int. 112, Int. 39
284	Method A with Int. 1, Int. 30	Method 4 with Int. 50
285	Method A with Int. 5, Int. 30, Int. 43	Method 2 with Int. 52
286	Method A with Int. 5, Int. 30, Int. 43	Method 2 with Int. 47
287	Method A with Int. 5, Int. 30, Int. 43	Method 2 with Int. 59
288	Method A with Int. 1, Int. 30	Method 4 with Int. 40
289	Method A with Int. 30	Method 4 with Int. 40
290	Method A with Int. 1	Method 4 with Int. 123
291	Method A with Int. 1, Int. 30	Method 4 with Int. 123
292	Method A with Int. 30	Method 4 with Int. 123
293	Method A	Method 4 with Int. 124
294	Method A with Int. 1	Method 4 with Int. 124
295	Method A with Int. 1, Int. 30	Method 4 with Int. 124

Example Number	Macrocycle Synthesis	Final Synthesis
296	Method A with Int. 30	Method 4 with Int. 124
297	Method A with Int. 30	Method 4 with Int. 125
298	Method B with Int. 30	Method 2 with Int. 64
299	Method A with Int. 30	Method 4 with Int. 148, Int. 64
300	Method A with Int. 1, Int. 30	Method 4 with Int. 112
301	Method A with Int. 30	Method 4 with Int. 150, Int. 64
302	Method A with Int. 1, Int. 22	Method 6
303	Method A	Method 4 with Int. 148, Int. 64
304	Method A	Method 4 with Int. 150, Int. 64
305	Method A with Int. 30	Method 4 with Int. 126
306	Method A	Method 4 with Int. 64
307	Method A with Int. 30	Method 4 with Int. 64
308	Method A with Int. 30	Method 7 with Int. 128
309	Method A with Int. 30	Method 4 with Int. 44
310	Method A	Method 4 with Int. 126
311	Method A with Int. 1, Int. 23	Method 6
312	Method A with Int. 1, Int. 30	Method 7 with Int. 134
313	Method A with Int. 1, Int. 30	Method 7 with Int. 134
314	Method A with Int. 23	Method 6
315	Method A with Int. 1	Method 7 with Int. 134
316	Method A with Int. 1	Method 7 with Int. 134
317	Method A	Method 7 with Int. 134
318	Method A	Method 7 with Int. 134
319	Method A with Int. 24	Method 6
320	Method A with Int. 25	Method 6
321	Method A with Int. 26	Method 6
322	Method A with Int. 27	Method 6
323	Method A with Int. 28	Method 6
324	Method A with Int. 29	Method 6
325	Method A with Int. 1	Method 7 with Int. 135
326	Method A	Method 7 with Int. 135
327	Method A with Int. 1, Int. 30	Method 7 with Int. 135
328	Method A	Method 7 with Int. 135
329	Method A	Method 7 with Int. 135
330	Method A with Int. 1, Int. 26	Method 6
331	Method A with Int. 1, Int. 27	Method 6
332	Method A with Int. 28	Method 6 with Int. 148
333	Method A with Int. 1, Int. 30	Method 4 with Int. 117
334	Method A with Int. 1	Method 4 with Int. 117
335	Method A with Int. 30	Method 4 with Int. 117, Int. 150
336	Method A with Int. 30	Method 4 with Int. 157

Example Number	Macrocycle Synthesis	Final Synthesis
337	Method A	Method 9 with Int. 117
338	Method A with Int. 30	Method 7 (Steps 1- 4) with Int. 161
339	Method A with Int. 30	Method 9 with Int. 164
340	Method A with Int. 30	Method 7 (Steps 1- 4) with Int. 167
341	Method A with Int. 30	Method 4 with Int. 168
342	Method A with Int. 30	Method 9 with Int. 165
343	Method A with Int. 30	Method 4 with Int. 52, Int. 162
344	Method A with Int. 30	Method 9 with Int. 163
345	Method A with Int. 30	Method 9 with Int. 166
346	Method A with Int. 30	Method 7 (Steps 1- 4) with Int. 199
347	Method A with Int. 30	Method 7 (Steps 1- 4) with Int. 169
348	Method A with Int. 30	Method 7 (Steps 1- 4) with Int. 171
349	Method A with Int. 30	Method 9 with Int. 173
350	Method A with Int. 30	Method 4 with Int. 117, Int. 174
351	Method A with Int. 30	Method 9 with Int. 177
352	Method A with Int. 30	Method 7 with Int. 404
353	Method A	Method 9 with Int. 159
354	Method A with Int. 30	Method 9 with Int. 160
355	Method A with Int. 30	Method 7 (Steps 1- 4) with Int. 172
356	Method A with Int. 30	Method 9 with Int. 403
357	Method A with Int. 30	Method 9 with Int. 179
358	Method A with Int. 30	Method 9 with Int. 170
359	Method A with Int. 30	Method 9 with Int. 155
360	Method A with Int. 30	Method 9 (Steps 1- 4) with Int. 156
361	Method A with Int. 30	Method 9 with Int. 402
362	Method A with Int. 30	Method 9 with Int. 178
363	Method A with Int. 30	Method 7 (Steps 1- 4) with Int. 400
364	Method A with Int. 30	Method 7 (Steps 1- 4) with Int. 401
365	Method A with Int. 30	Method 4 with Int. 117, Int. 180
366	Method A with Int. 30	Method 9 with Int. 181
367	Method A with Int. 30	Method 9 with Int. 182
368	Method A with Int. 30	Method 7 (Steps 1- 4) with Int. 183
369	Method A with Int. 30	Method 7 (Steps 1- 4) with Int. 176
370	Method A with Int. 30	Method 7 (Steps 1- 4) with Int. 186
371	Method A with Int. 30	Method 7 (Steps 1- 4) with Int. 175
372	Method A with Int. 30	Method 7 with Int. 405
373	Method A with Int. 30	Method 7 (Steps 1- 4) with Int. 184
374	Method A with Int. 30	Method 7 (Steps 1- 4) with Int. 185
375	Method A with Int. 30	Method 7 (Steps 1- 4) with Int. 158
376	Method A with Int. 30	Method 7 (Steps 1- 4) with Int. 188
377	Method A with Int. 30	Method 4 with Int. 117, Int. 189

Example Number	Macrocycle Synthesis	Final Synthesis
378	Method A with Int. 30	Method 7 (Steps 1- 4) with Int. 190
379	Method A with Int. 30	Method 7 (Steps 1- 4) with Int. 187
380	Method A with Int. 30	Method 7 (Steps 1- 4) with Int. 191
381	Method A with Int. 30	Method 7 (Steps 1- 4) with Int. 194
382	Method A with Int. 30	Method 10
383	Method A with Int. 30	Method 11
384	Method A with Int. 30	Method 7 (Steps 1- 4) with Int. 196
385	Method A with Int. 30	Method 7 (Steps 1- 4) with Int. 197
386	Method A with Int. 30	Method 7 (Steps 1- 4) with Int. 198
387	Method A with Int. 30, Int. 195	Method 7 (Steps 1- 4) with Int. 195, Int. 157
388	Method A with Int. 30, Int. 41	Method 7 (Steps 1- 4) with Int. 157
389	Method A with Int. 30	Method 7 (Steps 1- 4) with Int. 192
390	Method A with Int. 30	Method 9 with Int. 209
391	Method A	Method 9 with Int. 210
392	Method A with int. 206	Method 12 with Int. 211
393	Method A with int. 206	Method 12 with Int. 212
394	Method A with int. 206	Method 12 with Int. 213
395	Method A with Int. 1, 30	Method 9 with Int.172
396	Method A with Int. 30	Method 9 with Int. 214
397	Method B with Int. 3, 30	Method 9 with Int. 159
398	Method A with Int. 30	Method 4 with Int. 117, Int. 215
399	Method A with Int. 30	Method 4 with Int. 117, Int. 215
400	Method A with Int. 30	Method 4 with Int. 117, Int. 217
401	Method A	Method 9 with Int. 218
402	Method A with Int. 30	Method 9 with Int. 219
403	Method A with Int. 30	Method 9 With Int. 220
404	Method A with Int. 30, 195	Method 4 with Int. 117
405	Method D	Method 4 with Int. 159
406	Method A with Int. 30	Method 9 with Int. 221
407	Method A with Int. 30	Method 9 with Int. 222
408	Method A with Int. 30	Method 9 with Int. 223
409	Method A with Int. 30	Method 9 with Int. 225
410	Method A with Int. 30	Method 9 with Int. 226
411	Method A with Int. 30	Method 9 with Int. 227
412	Method A with Int. 30	Method 9 with Int. 228
413	Method A with Int. 30	Method 9 with Int. 229
414	Method A with Int. 30	Method 9 with int. 230
415	Method A with Int. 30, 207	Method 4 with int. 117
416	Method A with Int. 30, 207	Method 12 with Int. 236
417	Method A with Int. 30	Method 4 with Int. 231

Example Number	Macrocycle Synthesis	Final Synthesis
418	Method A with Int. 30, 207	Method 13 steps 1-5
419	Method A with Int. 30, 207	Method 13
420	Method A with Int. 30, 207	Method 13 with Int. 237
421	Method A with Int. 30, 207	Method 14
422	Method A with Int. 30, 208	Method 4 with Int. 159
423	Method A with int. 206	Method 12 with Int. 232
424	Method A with int. 206	Method 12 with Int. 233
425	Method A with int. 206	Method 12 with Int. 234
426	Method A with int. 206	Method 12 with Int. 235

[0554] Table 3, below, provides the expected (Exact Mass) and observed molecular weight for each exemplary compound listed in Table 2.

Table 3: Analytical Data for Exemplary Compounds of Table 2

Ex. Number	Exact Mass	Observed m/z
1	802.32	803.33
2	846.33	847.49
3	818.29	819.44
4	908.32	909.43
5-P1	872.34	873.46
5-P2	872.34	873.46
6-P1	922.34	923.42
6-P2	922.34	923.42
7	924.35	925.48
8	910.34	911.44
9	874.36	875.5
10	878.35	879.48
11	872.34	873.37
12	922.34	923.38
13	860.34	861.36
14	936.35	937.43
15	940.4	941.43
16-P1	926.39	927.45
16-P2	926.39	927.45
17	970.42	971.42
18	1011.45	1012.45
19	998.37	999.34
20	1013.46	1014.51

Ex. Number	Exact Mass	Observed m/z
21	972.44	973.49
22	1004.42	1005.41
23	1047.41	1048.43
24	984.44	985.42
25	938.37	939.5
26	968.42	969.45
27	1010.43	1011.48
28	998.43	999.48
29	982.43	983.49
30	980.42	981.49
31	1025.46	1026.52
32	974.44	975.51
33	962.44	963.5
34	946.45	947.5
35	944.43	945.49
36	989.48	990.53
37	966.46	967.49
38	964.44	965.51
39	1009.49	1010.54
40	930.48	931.53
41	928.46	929.51
42	973.51	974.54
43	1012.44	1013.55
44	1026.46	1027.61
45	1013.52	1014.56
46	952.47	953.52
47	982.48	983.51
48	900.37	901.46
49	984.45	985.5
50	1027.48	1028.55
51	986.45	987.49
52	1029.49	1030.56
53	1041.46	1042.57
54	896.32	897.42
55	898.34	897.42
56-P1	983.45	984.51
56-P2	983.45	984.51
57-P1	1053.49	1054.58
57-P2	1053.49	1054.58
58	1037.52	1038.59
59-P1	1039.54	1040.62

Ex. Number	Exact Mass	Observed m/z
59-P2	1039.54	1040.62
60	1041.49	1042.6
61	930.42	931.48
62	944.44	945.52
63	932.44	933.48
64	946.46	947.5
65	968.48	969.51
66	970.43	971.46
67	996.45	997.49
68	994.49	995.53
69	932.49	933.54
70	934.45	935.51
71	972.44	973.49
72	970.43	971.47
73	996.45	997.53
74	1013.46	1014.55
75	1001.41	1002.47
76	930.47	931.53
77	966.46	967.51
78	1008.45	1009.51
79	1012.44	1013.52
80	976.46	977.55
81	972.47	973.51
82	905.47	906.55
83	980.48	981.69
84	1036.5	1037.7
85	1022.49	1023.64
86	992.48	993.68
87	1030.42	1031.58
88	1006.49	1007.67
89	1037.46	1038.64
90	1039.48	1040.68
91	1053.49	1054.71
92	982.49	983.67
93	1038.52	1039.71
94	1024.5	1025.71
95	1032.44	1033.62
96	1008.51	1009.68
97	1039.48	1040.69
98	1041.49	1042.71
99	1055.51	1056.73

Ex. Number	Exact Mass	Observed m/z
100	1047.47	1048.67
101	1039.54	1038.7
102-P1	945.4	946.3
102-P2	945.4	946.3
103	947.41	948.31
104	959.41	960.33
105	961.43	962.36
106	923.43	924.36
107-P1	909.42	910.34
107-P2	909.42	910.34
108	911.43	912.34
109	925.45	926.37
110	1010.46	1011.38
111	1012.48	1013.4
112	1024.48	1025.39
113	1040.47	1041.4
114	1054.49	1055.43
115	948.43	949.36
116	984.41	985.34
117-P1	934.41	935.32
117-P2	934.41	935.32
118-P1	970.39	971.3
118-P2	970.39	971.3
119	927.46	928.44
120	963.45	964.44
121	928.47	929.45
122	915.52	916.48
123	902.45	903.41
124	1053.52	1054.52
125	929.43	930.4
126	943.44	944.45
127	931.44	932.43
128	945.46	946.46
129	947.41	948.39
130	961.43	962.44
131	949.43	950.41
132	893.45	894.43
133	907.46	908.45
134	895.46	895.45
135	909.48	910.48
136-P1	911.43	912.39

Ex. Number	Exact Mass	Observed m/z
136-P2	911.43	912.39
137	925.45	926.44
138	913.45	914.41
139	939.46	940.43
140	975.45	976.44
141	925.45	926.42
142	961.43	962.4
143	1055.51	1056.51
144	1069.52	1070.54
145	1057.49	1058.49
146	988.52	989.52
147	988.52	989.52
148	994.49	995.49
149	1037.52	1038.54
150	1065.55	1066.59
151	1081.55	1082.58
152	982.39	983.32
153	996.41	997.36
154	984.41	985.34
155	998.43	999.39
156-P1	946.41	947.34
156-P2	946.41	947.34
157	960.43	961.36
158	948.43	949.36
159	962.44	963.37
160	972.41	973.35
161	936.43	937.36
162	986.43	987.36
163	950.44	951.38
164	968.48	969.41
165	995.51	996.47
166	1011.51	1012.46
167	970.43	971.46
168	982.43	983.43
169	1037.41	1038.43
170	1022.43	1023.45
171	1023.42	1024.45
172	1021.44	1022.45
173	946.45	947.45
174	976.46	977.47
175	1008.45	1009.47

Ex. Number	Exact Mass	Observed m/z
176	972.47	973.48
177	1035.46	1036.5
178	1021.44	1022.46
179	1021.44	1022.47
180	997.43	998.45
181	1041.44	1042.46
182	1025.46	1026.49
183	978.48	979.49
184	978.48	979.5
185	948.47	949.94
186	958.51	959.67
187	1026.49	1027.66
188	960.47	960.82
189	994.43	995.56
190	1010.46	1010.9
191	1026.46	1027.3
192	981.44	982.16
193	1067.51	1068.73
194	1083.5	1084.68
195	952.44	953.22
196	981.44	982.42
197	1011.45	1012.45
198	999.43	1000.43
199	1011.45	1012.46
200	1020.43	1021.43
201	1059.41	1060.43
202	1027.42	1028.45
203	988.5	989.5
204	936.47	937.45
205	984.45	985.48
206	985.43	986.46
207	1015.42	1016.46
208	997.43	998.46
209	972.44	973.42
210	999.45	1000.47
211	984.45	985.49
212	985.43	986.42
213	980.48	981.51
214	980.48	981.46
215	954.46	955.45
216	1009.44	1010.45

Ex. Number	Exact Mass	Observed m/z
217	997.49	998.5
218	970.43	971.45
219	975.45	976.46
220	939.46	940.48
221	969.48	970.49
222	935.41	936.46
223	929.44	930.49
224	899.43	900.48
225	949.43	950.47
226	943.46	944.49
227	913.45	914.48
228	977.46	978.51
229	971.49	972.52
230	941.48	942.52
231	1094.5	1095.53
232	1021.44	1022.47
233	1026.46	1027.45
234	998.46	999.5
235	998.46	999.51
236	1020.45	1021.47
237	1013.46	1014.47
238	1048.41	1049.41
239	987.47	988.48
240	1012.44	1013.41
241	1067.53	1068.56
242	984.45	985.47
243	1045.49	1046.53
244	969.47	970.49
245	933.49	934.52
246	985.44	986.46
247	949.46	950.49
248	979.47	980.49
249	1035.46	1036.48
250	1035.46	1036.49
251	1034.46	1035.3
252	1058.45	1059.44
253	1088.44	1089.44
254	1074.42	1075.44
255	1074.42	1075.44
256	1083.51	1084.52
257	1076.44	1077.46

Ex. Number	Exact Mass	Observed m/z
258	959.41	960.41
259	974.45	975.46
260	968.48	969.48
261	1065.49	1066.4
262	1058.42	1059.31
263	918.42	919.136
264	888.44	889.37
265	1038.46	1039.37
266	1113.46	1114.36
267	1011.45	1012.36
268	887.43	888.33
269	901.45	902.4
270	904.41	905.52
271	965.46	966.5
272	1036.44	1037.31
273	1032.38	1033.3
274	915.43	916.35
275	921.4	922.31
276	967.42	968.34
277	1041.49	1042.43
278	1030.42	1031.28
279	966.46	967.32
280	951.45	952.33
281	1044.44	1045.27
282	1052.48	1053.32
283	1068.45	1069.28
284	1049.43	1050.25
285	968.42	969.28
286	1011.45	1012.29
287	994.43	995.29
288	1027.48	1028.2
289	1041.49	1042.2
290	952.44	953.32
291	968.42	969.27
292	982.43	983.32
293	980.48	981.35
294	966.46	967.38
295	982.43	983.31
296	996.45	997.31
297	1021.44	1022.28
298	1046.39	1047.25

Ex. Number	Exact Mass	Observed m/z
299	1042.44	1043.25
300	1060.41	1061.21
301	1000.43	1001.2
302	1014.46	1015.12
303	1026.47	1027.23
304	984.46	985.22
305	1021.44	1022.17
306	1031.44	1032.23
307	1047.41	1048.15
308	1013.46	1014.2
309	1049.43	1050.16
310	1005.47	1006.21
311	946.42	947.27
312	1067.51	1068.31
313	1067.51	1068.3
314	960.44	961.29
315	1051.54	1052.35
316	1051.54	1052.33
317	1065.55	1066.34
318	1065.55	1066.37
319	989.46	990.28
320	990.46	991.27
321	962.41	963.25
322	919.42	920.26
323	1001.44	1002.29
324	1018.45	1019.27
325	1067.53	1068.37
326	1067.53	1068.36
327	1083.5	1084.35
328	1081.55	1082.39
329	1081.55	1082.38
330	948.4	949.22
331	905.4	906.26
332	995.47	996.3
333	1051.48	1052.32
334	1035.51	1036.36
335	1017.51	1018.20
336	1078.52	1079.30
337	1049.52	1050.14
338	1060.48	1062.12
339	1109.52	1110.17

Ex. Number	Exact Mass	Observed m/z
340	1080.49	1081.14
341	1064.51	1065.18
342	1051.48	1052.17
343	1002.44	1003.14
344	1079.51	1080.13
345	1099.45	1100.08
346	1120.54	1121.16
347	1106.56	1107.18
348	1083.48	1084.13
349	1084.48	1085.14
350	1047.5	1048.12
351	1075.51	1076.21
352	1128.52	1129.12
353	1062.55	1063.26
354	1129.45	1130.17
355	1077.49	1079.03
356	1166.58	1167.33
357	1090.52	1091.26
358	1077.53	1078.23
359	1079.51	1080.26
360	1092.54	1093.70
361	1095.5	1096.21
362	1104.54	1105.27
363	1091.51	1093.21
364	1120.54	1121.90
365	1011.52	1012.93
366	1093.52	1095.00
367	1095.5	1096.98
368	1155.55	1157.08
369	1077.49	1078.99
370	1095.52	1097.03
371	1093.52	1095.01
372	1158.56	1160.05
373	1109.52	1110.93
374	1092.54	1093.94
375	1057.47	1059.09
376	1082.56	1084.03
377	1021.49	1022.82
378	1102.49	1103.88
379	1090.49	1092.09
380	1143.55	1145.14

Ex. Number	Exact Mass	Observed m/z
381	1118.56	1120.01
382	1066.49	1068.17
383	1133.57	1135.25
384	1106.56	1108.21
385	1073.46	1074.99
386	1101.47	1103.21
387	1092.54	1094.09
388	1092.54	1094.08
389	1093.52	1095.13
390	1106.52	1107.98
391	1063.55	1064.89
392	957.44	958.48
393	957.44	958.38
394	944.4	945.46
395	1063.48	1064.97
396	1094.52	1096
397	1076.51	1077.72
398	981.47	982.73
399	997.51	998.91
400	997.51	998.92
401	1080.54	1081.93
402	1068.48	1069.98
403	1093.52	1094.98
404	1079.51	1080.7
405	1092.54	1093.73
406	1049.5	1050.95
407	1049.5	1050.95
408	1079.47	1080.68
409	1092.54	1093.52
410	1122.55	1123.67
411	1077.53	1078.7
412	1077.53	1078.67
413	1124.55	1125.74
414	1079.51	1080.56
415	1111.5	1112.66
416	1155.51	1156.35
417	1077.53	1078.7
418	1097.48	1098.73
419	1124.53	1125.69
420	1179.57	1180.49
421	1083.5	1084.68

Ex. Number	Exact Mass	Observed <i>m/z</i>
422	1081.54	1082.82
423	939.45	940.41
424	958.43	959.47
425	954.42	955.42
426	910.37	911.44

[0555] Table 4, below, provides the full chemical structure for each exemplified compound in Table 2.

Table 4: Chemical Structure for Exemplary
Compounds Described in Table 2

Ex. No.	Chemical Structure	Ex. No.	Chemical Structure
1		2	
3		4	
5-P1 /5-P2		6-P1 /6-P2	
7		8	
9		10	

Ex. No.	Chemical Structure	Ex. No.	Chemical Structure
11		12	
13		14	
15		16-P1 / 16-P2	
17		18	
19		20	
21		22	
23		24	

Ex. No.	Chemical Structure	Ex. No.	Chemical Structure
25		26	
27		28	
29		30	
31		32	
33		34	
35		36	
37		38	

Ex. No.	Chemical Structure	Ex. No.	Chemical Structure
39		40	
41		42	
43		44	
45		46	
47		48	
49		50	
51		52	

Ex. No.	Chemical Structure	Ex. No.	Chemical Structure
53		54	
55		56-P1 / 56-P2	
57-P1 / 57-P2		58	
59-P1 / 59-P2		60	
61		62	
63		64	
65		66	
67		68	

Ex. No.	Chemical Structure	Ex. No.	Chemical Structure
69		70	
71		72	
73		74	
75		76	
77		78	
79		80	
81		82	
83		84	

Ex. No.	Chemical Structure	Ex. No.	Chemical Structure
85		86	
87		88	
89		90	
91		92	
93		94	
95		96	
97		98	

Ex. No.	Chemical Structure	Ex. No.	Chemical Structure
99		100	
101		102 - P1 / 102 -P2	
103		104	
105		106	
107 - P1 /10 7- P2		108	
109		110	
111		112	

Ex. No.	Chemical Structure	Ex. No.	Chemical Structure
113		114	
115		116	
117 - P1 /117 - P2		118 - P1 / 118 - P2	
119		120	
121		122	
123		124	
125		126	
127		128	

Ex. No.	Chemical Structure	Ex. No.	Chemical Structure
129		130	
131		132	
133		134	
135		136 - P1 / 136 -P2	
137		138	
139		140	
141		142	

Ex. No.	Chemical Structure	Ex. No.	Chemical Structure
143		144	
145		146	
147		148	
149		150	
151		152	
153		154	
155		156 - P1 / 156 - P2	

Ex. No.	Chemical Structure	Ex. No.	Chemical Structure
157		158	
159		160	
161		162	
163		164	
165		166	
167		168	
169		170	
171		172	

Ex. No.	Chemical Structure	Ex. No.	Chemical Structure
173		174	
175		176	
177		178	
179		180	
181		182	
183		184	
185		186	
187		188	

Ex. No.	Chemical Structure	Ex. No.	Chemical Structure
189		190	
191		192	
193		194	
195		196	
197		198	
199		200	
201		202	
203		204	

Ex. No.	Chemical Structure	Ex. No.	Chemical Structure
205		206	
207		208	
209		210	
211		212	
213		214	
215		216	
217		218	
219		220	

Ex. No.	Chemical Structure	Ex. No.	Chemical Structure
221		222	
223		224	
225		226	
227		228	
229		230	
231		232	
233		234	

Ex. No.	Chemical Structure	Ex. No.	Chemical Structure
235		236	
237		238	
239		240	
241		242	
243		244	
245		246	
247		248	
249		250	

Ex. No.	Chemical Structure	Ex. No.	Chemical Structure
251		252	
253		254	
255		256	
257		258	
259		260	
261		262	
263		264	

Ex. No.	Chemical Structure	Ex. No.	Chemical Structure
265		266	
267		268	
269		270	
271		272	
273		274	
275		276	
277		278	

Ex. No.	Chemical Structure	Ex. No.	Chemical Structure
279		280	
281		282	
283		284	
285		286	
287		288	
289		290	
291		292	

Ex. No.	Chemical Structure	Ex. No.	Chemical Structure
293		294	
295		296	
297		298	
299		300	
301		302	
303		304	
305		306	
307		308	

Ex. No.	Chemical Structure	Ex. No.	Chemical Structure
309		310	
311		312	
313		314	
315		316	
317		318	
319		320	
321		322	

Ex. No.	Chemical Structure	Ex. No.	Chemical Structure
323		324	
325		326	
327		328	
329		330	
331		332	
333		334	
335		336	

Ex. No.	Chemical Structure	Ex. No.	Chemical Structure
337		338	
339		340	
341		342	
343		344	
345		346	
347		348	

Ex. No.	Chemical Structure	Ex. No.	Chemical Structure
349		350	
351		352	
353		354	
355		356	
357		358	

Ex. No.	Chemical Structure	Ex. No.	Chemical Structure
359		360	
361		362	
363		364	
365		366	
367		368	
369		370	

Ex. No.	Chemical Structure	Ex. No.	Chemical Structure
371		372	
373		374	
375		376	
377		378	
379		380	
381		382	

Ex. No.	Chemical Structure	Ex. No.	Chemical Structure
383		384	
385		386	
387		388	
389		390	
391		392	
393		394	

Ex. No.	Chemical Structure	Ex. No.	Chemical Structure
395		396	
397		398	
399		400	
401		402	
403		404	
405		406	
407		408	

Ex. No.	Chemical Structure	Ex. No.	Chemical Structure
409		410	
411		412	
413		414	
415		416	
417		418	
419		420	

Ex. No.	Chemical Structure	Ex. No.	Chemical Structure
421		422	
423		424	
425		426	

C. Biological Examples

1. Fluorescence Polarization Assay

- [0556] Binding affinity for the compounds of Formula (I) were determined by
- 5 Fluorescence Polarization (FP) competitive assay based on previously established protocols (Andrews et. al., *Org Biomol Chem.*, **2004**, 2(19):2735-41.; Premnath et. al., *J Med Chem.*, **2015**, 58(1):433-42.) with modifications as described below. Cyclin/CDK protein complexes were sourced as follows: CyclinA2/CDK2 (CRELUX Protein Services), CyclinB1/CDK1 (Eurofins, discovery. Cat. No. 14-450) and CyclinE1/CDK2 (Eurofins, discovery. Cat. No.
- 10 14-475).
- [0557] FP binding assays were performed in 25 mM HEPES pH 7.5, 100 mM NaCl, 1mM DTT, 0.01% NP-40 and 1 mg/mL BSA for all 3 protein complexes in black 96-well plates. After experimental plates are set, they were equilibrated by gentle mixing by placing them on an orbital shaker at 100 rpm for 2 hours at rt and then read on a SpectraMax i3X Multi-Mode
- 15 Microplate Detection platform.

[0558] Affinity of the Cyclin/Cdk complexed for the fluorescent labeled probe was determined by adding increasing concentration of each protein complex in buffer containing a carboxyfluorescein labeled probe (FAM probe) at 2 nM (preparation of FAM probe is described below). The half maximal concentration of protein needed for the maximal FP signal were 2 nM for Cyclin A2/Cdk2, 9 nM for Cyclin B1/Cdk1 and 3 nM for Cyclin E1/Cdk2. Methods to prepare the FAM probe are described in the heading below.

[0559] The protein concentration used for the competitive FP assays were 8 nM for Cyclin A2/Cdk2 and 10 nM for Cyclin B1/Cdk1 and Cyclin E1/Cdk2 with 2 nM of FAM probe. Under these conditions, the dynamic range was about 120 mP 100% binding of FAM probe and complete inhibition of binding by excess of an unlabeled competitor compound, with all experiment showing a Z' factor > 0.80. IC₅₀ for test compounds were determined in eight-point serial dilution dose response curves. Reported IC₅₀ are the average of 2-3 independent experiments. Data from these assays are reported in **Table 5**.

Table 5: Cyclin A, B, and E Activity Data of Exemplary Compounds

Example Number	Cyclin A FP IC ₅₀ (μ M)	Cyclin B FP IC ₅₀ (μ M)	Cyclin E FP IC ₅₀ (μ M)
1	0.21	0.02	0.44
2	0.11	0.02	0.10
3	0.62	0.02	0.68
4	0.09	0.02	0.10
5-P1	0.79	0.02	0.70
5-P2	0.56	0.02	0.46
6-P1	0.16	0.02	0.50
6-P2	0.10	0.02	0.24
7	0.06	0.02	0.29
8	0.03	0.02	0.10
9	0.25	0.02	0.40
10	0.10	0.02	0.12
11	0.17	0.02	0.10
12	0.06	0.02	0.10
13	0.10	0.02	0.10
14	0.10	0.02	0.34
15	0.28	0.02	1.04
16-P1	0.74	0.02	3.15
16-P2	0.60	0.02	2.71
17	0.09	0.02	4.11
18	0.09	0.02	6.19

Example Number	Cyclin A FP IC50 (μ M)	Cyclin B FP IC50 (μ M)	Cyclin E FP IC50 (μ M)
19	0.43	0.02	20.00
20	0.02	0.02	1.52
21	0.02	0.02	1.13
22	0.21	0.02	20.00
23	0.12	0.02	5.47
24	0.06	0.02	1.60
25	0.04	0.02	0.23
26	0.06	0.02	1.17
27	0.09	0.02	1.90
28	0.04	0.02	0.74
29	0.03	0.02	0.69
30	0.24	0.02	5.05
31	0.03	0.02	2.20
32	0.05	0.02	0.59
33	0.02	0.02	0.27
34	0.02	0.02	0.21
35	0.12	0.02	1.69
36	0.03	0.02	0.82
37	0.05	0.02	0.37
38	0.18	0.02	1.76
39	0.06	0.02	0.94
40	0.05	0.02	0.24
41	0.16	0.02	0.81
42	0.04	0.02	0.44
43	0.04	0.02	0.37
44	0.03	0.02	0.27
45	0.10	0.02	0.33
46	0.02	0.02	0.35
47	0.04	0.02	0.80
48	0.08	0.02	0.13
49	0.02	0.02	0.35
50	0.02	0.02	1.22
51	0.02	0.02	0.89
52	0.04	0.02	1.13
53	0.09	0.02	12.40
54	0.39	0.03	3.39
55	0.70	0.08	3.93
56-P1	0.86	0.04	20.00
56-P2	0.59	0.03	20.00
57-P1	0.02	0.02	1.41

Example Number	Cyclin A FP IC50 (μ M)	Cyclin B FP IC50 (μ M)	Cyclin E FP IC50 (μ M)
57-P2	0.02	0.02	1.31
58	0.02	0.02	0.62
59-P1	0.12	0.02	0.85
59-P2	0.18	0.02	0.87
60	0.02	0.02	0.74
61	0.02	0.02	1.01
62	0.03	0.02	0.39
63	0.12	0.02	3.51
64	0.38	0.02	20.00
65	0.02	0.02	0.27
66	0.02	0.02	0.45
67	0.02	0.02	0.50
68	0.02	0.02	0.12
69	0.02	0.02	0.11
70	0.02	0.02	0.29
71	0.02	0.02	1.59
72	0.03	0.02	1.05
73	0.03	0.02	0.93
74	0.05	0.02	3.62
75	0.02	0.02	0.44
76	0.02	0.02	0.88
77	0.02	0.02	1.71
78	0.04	0.02	0.64
79	0.05	0.02	0.63
80	0.04	0.02	0.30
81	0.04	0.02	0.30
82	0.02	0.02	0.22
83	0.04	0.02	0.10
84	0.05	0.02	0.29
85	0.06	0.02	0.28
86	0.06	0.02	0.25
87	0.18	0.02	0.89
88	0.05	0.02	0.20
89	0.12	0.02	5.41
90	0.09	0.02	3.70
91	0.10	0.02	5.73
92	0.02	0.02	0.10
93	0.02	0.02	0.14
94	0.02	0.02	0.18
95	0.05	0.02	0.53

Example Number	Cyclin A FP IC50 (μ M)	Cyclin B FP IC50 (μ M)	Cyclin E FP IC50 (μ M)
96	0.02	0.02	0.12
97	0.02	0.02	1.45
98	0.02	0.02	1.10
99	0.02	0.02	1.54
100	0.02	0.02	0.45
101	0.03	0.02	0.47
102-P1	0.31	0.02	1.11
102-P2	0.12	0.02	0.31
103	0.06	0.02	0.35
104	0.16	0.02	0.49
105	0.05	0.02	0.29
106	0.12	0.02	0.24
107-P1	0.25	0.02	0.54
107-P2	0.11	0.02	0.18
108	0.05	0.02	0.18
109	0.04	0.02	0.17
110	0.02	0.02	0.33
111	0.02	0.02	0.28
112	0.02	0.02	0.34
113	0.02	0.02	0.31
114	0.02	0.02	0.40
115	0.04	0.02	0.17
116	0.04	0.02	0.33
117-P1	0.08	0.02	0.34
117-P2	0.06	0.02	0.16
118-P1	0.11	0.02	0.74
118-P2	0.06	0.02	0.30
119	0.03	0.02	0.10
120	0.03	0.02	0.21
121	0.05	0.02	0.13
122	0.02	0.02	0.10
123	0.03	0.02	0.12
124	0.02	0.02	0.54
125	1.01	0.02	1.14
126	0.50	0.02	0.62
127	0.08	0.02	0.23
128	0.08	0.02	0.19
129	0.21	0.02	0.82
130	0.07	0.02	0.31
131	0.03	0.02	0.24

Example Number	Cyclin A FP IC50 (μ M)	Cyclin B FP IC50 (μ M)	Cyclin E FP IC50 (μ M)
132	0.71	0.02	0.45
133	0.47	0.02	0.34
134	0.10	0.02	0.12
135	0.08	0.02	0.12
136-P1	0.14	0.02	0.32
136-P2	0.08	0.02	0.12
137	0.06	0.02	0.13
138	0.03	0.02	0.11
139	0.02	0.02	0.10
140	0.02	0.02	0.12
141	0.04	0.02	0.10
142	0.04	0.02	0.15
143	0.02	0.02	0.94
144	0.02	0.02	0.84
145	0.02	0.02	1.30
146	0.03	0.02	0.10
147	0.02	0.02	0.10
148	0.03	0.02	0.31
149	0.02	0.02	0.56
150	0.02	0.02	0.21
151	0.02	0.02	0.22
152	1.02	0.02	1.90
153	0.47	0.02	1.00
154	0.15	0.02	0.48
155	0.10	0.02	0.41
156-P1	0.89	0.02	0.83
156-P2	0.35	0.02	0.24
157	0.36	0.02	0.41
158	0.10	0.02	0.21
159	0.08	0.02	0.20
160	0.02	0.02	0.27
161	0.02	0.02	0.12
162	0.02	0.02	0.22
163	0.02	0.02	0.10
164	0.07	0.02	0.93
165	0.11	0.02	5.47
166	0.06	0.02	2.30
167	0.02	0.02	0.28
168	0.02	0.02	0.16
169	0.03	0.02	1.09

Example Number	Cyclin A FP IC50 (μ M)	Cyclin B FP IC50 (μ M)	Cyclin E FP IC50 (μ M)
170	0.05	0.02	2.22
171	0.08	0.02	4.21
172	0.06	0.02	2.43
173	0.02	0.02	0.10
174	0.02	0.02	0.10
175	0.02	0.02	0.13
176	0.02	0.02	0.10
177	0.02	0.02	0.46
178	0.05	0.02	5.46
179	0.03	0.02	1.13
180	0.03	0.02	1.86
181	0.04	0.02	1.58
182	0.02	0.02	1.17
183	0.03	0.02	0.28
184	0.02	0.02	0.10
185	0.02	0.02	0.11
186	0.02	0.02	0.10
187	0.02	0.02	0.34
188	0.02	0.02	0.23
189	0.05	0.02	0.85
190	0.02	0.02	0.66
191	0.02	0.02	0.26
192	0.02	0.02	1.14
193	0.02	0.02	0.71
194	0.02	0.02	0.54
195	0.04	0.02	0.18
196	0.03	0.02	0.74
197	0.02	0.02	0.31
198	0.05	0.02	1.45
199	0.03	0.02	0.91
200	0.03	0.02	0.89
201	0.03	0.02	1.95
202	0.05	0.02	1.49
203	0.04	0.02	1.26
204	0.02	0.02	0.16
205	0.03	0.02	0.48
206	0.02	0.02	0.20
207	0.05	0.02	2.73
208	0.21	0.02	6.40
209	0.02	0.02	0.54

Example Number	Cyclin A FP IC50 (μ M)	Cyclin B FP IC50 (μ M)	Cyclin E FP IC50 (μ M)
210	0.42	0.02	20.00
211	0.05	0.02	1.11
212	0.07	0.02	4.16
213	0.03	0.02	0.19
214	0.05	0.02	0.50
215	0.02	0.02	0.20
216	0.03	0.02	0.47
217	0.03	0.02	0.76
218	0.10	0.02	2.22
219	0.10	0.02	1.43
220	0.09	0.02	0.68
221	0.06	0.02	0.18
222	0.04	0.02	0.23
223	0.02	0.02	0.10
224	0.03	0.02	0.10
225	0.03	0.02	0.19
226	0.02	0.02	0.10
227	0.03	0.02	0.12
228	0.03	0.02	0.25
229	0.02	0.02	0.10
230	0.03	0.02	0.14
231	0.06	0.02	2.94
232	0.05	0.02	2.87
233	0.05	0.02	1.60
234	0.03	0.02	0.83
235	0.14	0.02	6.08
236	0.03	0.02	0.78
237	0.02	0.02	1.14
238	0.03	0.02	0.99
239	0.02	0.02	0.42
240	0.02	0.02	0.14
241	0.02	0.02	0.20
242	0.03	0.02	0.70
243	0.05	0.02	0.69
244	0.06	0.02	0.58
245	0.04	0.02	0.22
246	0.02	0.02	0.64
247	0.02	0.02	0.31
248	0.02	0.02	0.10
249	0.02	0.02	0.59

Example Number	Cyclin A FP IC50 (μ M)	Cyclin B FP IC50 (μ M)	Cyclin E FP IC50 (μ M)
250	0.03	0.02	1.62
251	0.04	0.02	0.93
252	0.03	0.02	0.38
253	0.02	0.02	0.33
254	0.03	0.02	0.97
255	0.02	0.02	0.21
256	0.03	0.02	0.48
257	0.02	0.02	0.12
258	0.07	0.02	0.12
259	0.07	0.02	0.28
260	0.05	0.02	0.10
261	0.02	0.02	0.43
262	0.02	0.02	0.91
263	0.03	0.02	0.20
264	0.09	0.02	0.29
265	0.02	0.02	0.64
266	0.02	0.02	2.22
267	0.02	0.02	1.95
268	0.06	0.02	0.10
269	0.06	0.02	0.10
270	0.06	0.02	0.37
271	0.03	0.02	0.24
272	0.05	0.02	1.60
273	0.05	0.02	1.94
274	0.03	0.02	0.10
275	0.05	0.02	0.23
276	0.03	0.02	0.70
277	0.60	0.02	20.00
278	0.07	0.02	0.28
279	0.10	0.02	1.92
280	0.04	0.02	0.32
281	0.04	0.02	0.53
282	0.03	0.02	0.10
283	0.03	0.02	0.18
284	0.02	0.02	1.74
285	0.06	0.02	1.70
286	0.08	0.02	4.02
287	0.06	0.02	1.94
288	0.03	0.02	0.36
289	0.03	0.02	0.32

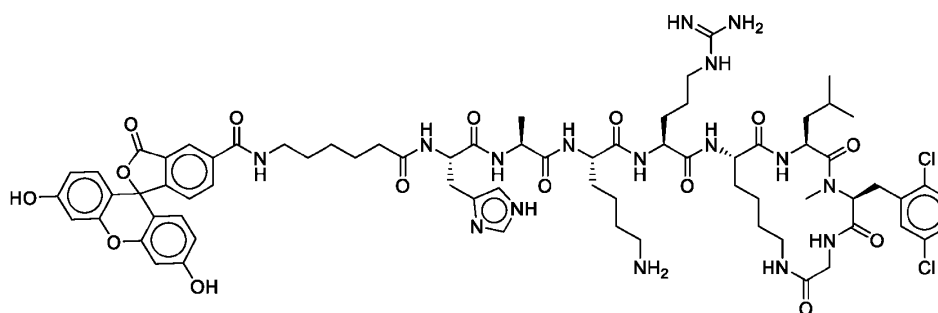
Example Number	Cyclin A FP IC50 (μ M)	Cyclin B FP IC50 (μ M)	Cyclin E FP IC50 (μ M)
290	0.12	0.02	1.79
291	0.07	0.02	5.16
292	0.06	0.02	2.88
293	0.10	0.02	1.99
294	0.08	0.02	1.44
295	0.07	0.02	3.69
296	0.07	0.02	2.81
297	0.04	0.02	1.27
298	0.05	0.02	0.44
299	0.02	0.02	0.13
300	0.03	0.02	0.68
301	0.04	0.02	0.32
302	0.05	0.02	3.56
303	0.03	0.02	0.10
304	0.04	0.02	0.19
305	0.05	0.02	1.75
306	0.02	0.02	0.20
307	0.02	0.02	0.44
308	0.02	0.02	0.84
309	0.02	0.02	0.93
310	0.08	0.02	0.99
311	0.05	0.02	0.20
312	0.02	0.02	0.74
313	0.02	0.02	0.64
314	0.03	0.02	0.14
315	0.03	0.02	0.42
316	0.02	0.02	0.29
317	0.03	0.02	0.25
318	0.02	0.02	0.28
319	0.03	0.02	1.35
320	0.03	0.02	1.45
321	0.02	0.02	0.10
322	0.08	0.02	0.53
323	0.03	0.02	0.24
324	0.06	0.02	0.52
325	0.02	0.02	0.30
326	0.02	0.02	0.15
327	0.02	0.02	0.40
328	0.02	0.02	0.21
329	0.02	0.02	0.25

Example Number	Cyclin A FP IC50 (μ M)	Cyclin B FP IC50 (μ M)	Cyclin E FP IC50 (μ M)
330	0.03	0.02	0.10
331	0.17	0.02	1.14
332	0.02	0.02	0.10
333	0.02	0.02	1.15
334	0.02	0.02	0.19
335	0.02	0.02	0.16
336	0.02	0.02	0.42
337	0.02	0.02	0.19
338	0.03	0.02	1.70
339	0.02	0.02	0.40
340	0.02	0.02	1.65
341	0.02	0.02	0.51
342	0.02	0.02	0.59
343	0.02	0.02	0.67
344	0.02	0.02	1.27
345	0.03	0.02	3.05
346	0.02	0.02	0.36
347	0.02	0.02	0.65
348	0.02	0.02	0.88
349	0.02	0.02	0.23
350	0.02	0.02	0.88
351	0.02	0.02	0.97
352	0.02	0.02	0.51
353	0.02	0.02	0.22
354	0.03	0.02	1.34
355	0.02	0.02	1.76
356	0.02	0.02	0.34
357	0.03	0.02	1.97
358	0.02	0.02	0.55
359	0.02	0.02	0.68
360	0.02	0.02	0.86
361	0.05	0.02	1.84
362	0.02	0.02	0.60
363	0.02	0.02	0.47
364	0.02	0.02	0.43
365	0.02	0.02	1.17
366	0.02	0.02	1.05
367	0.02	0.02	1.10
368	0.02	0.02	0.48
369	0.02	0.02	1.49

Example Number	Cyclin A FP IC50 (μ M)	Cyclin B FP IC50 (μ M)	Cyclin E FP IC50 (μ M)
370	0.02	0.02	0.78
371	0.02	0.02	0.92
372	0.02	0.02	0.43
373	0.02	0.02	0.48
374	0.02	0.02	0.87
375	0.02	0.02	1.73
376	0.02	0.02	1.33
377	0.02	0.02	0.34
378	0.02	0.02	1.12
379	0.03	0.02	2.73
380	0.03	0.02	2.17
381	0.02	0.02	1.31
382	0.04	0.02	2.49
383	0.02	0.02	0.53
384	0.02	0.02	0.59
385	0.02	0.02	1.63
386	0.02	0.02	0.90
387	0.03	0.02	1.89
388	0.02	0.02	3.93
389	0.02	0.02	0.79
390	0.02	0.02	0.87
391	0.03	0.02	0.61
392	0.23	0.02	0.83
393	6.67	0.047	1.69
394	0.15	0.02	0.50
395	0.06	0.02	2.81
396	0.03	0.02	2.53
397	0.02	0.02	0.26
398	0.02	0.02	0.59
399	0.07	0.02	3.00
400	0.02	0.02	0.49
401	0.02	0.02	0.38
402	0.02	0.02	0.96
403	0.02	0.02	0.67
404	0.02	0.02	1.53
405	0.05	0.02	2.56
406	0.02	0.02	1.78
407	0.02	0.02	1.46
408	0.02	0.02	0.51
409	0.02	0.02	0.67

Example Number	Cyclin A FP IC50 (μ M)	Cyclin B FP IC50 (μ M)	Cyclin E FP IC50 (μ M)
410	0.02	0.02	0.65
411	0.02	0.02	0.76
412	0.02	0.02	1.39
413	0.02	0.02	1.31
414	0.03	0.02	0.94
415	0.02	0.02	0.30
416	0.04	0.02	3.98
417	0.03	0.02	2.65
418	0.12	0.02	5.26
419	0.02	0.02	0.54
420	0.02	0.02	0.19
421	0.02	0.02	0.51
422	0.02	0.02	0.42
423	0.72	0.02	0.71
424	20.00	0.0455	3.82
425	0.15	0.02	0.21
426	0.11	0.02	2.06

Preparation of Fluorescent Probe (FAM Probe)



[0560] The fluorescent probe was synthesized via solid phase peptide synthesis followed by cyclization, fluorescent labeling, and deprotection in solution.

- 5 **[0561]** To load Fmoc-Glycine onto ~50 mg of CTC resin, Fmoc-Glycine (G), CAS#29022-11-5, (4 equiv.) was dissolved in 1.0 mL of anhydrous NMP. Neat DIEA (8 equiv.) was added to the Fmoc-amino acid solution. The solution was dispensed in a peptide reactor vessel containing 50 mg of 2-chlorotrityl chloride (CTC) resin and was agitated for 2 hours at rt. The amino acid solution was drained then the resin was washed with 1.0 mL DMF three
- 10 times. Unreacted CTC resin was capped with 1.0 mL solution of methanol:DMF (50:50), and

DIEA (8 equiv.) for 10 min at rt. The methanol solution was drained then the resin was washed with 1.0 mL DMF three times. To remove Fmoc, A mixture of piperidine:DMF (20:80, 1 mL) was added to the resin and agitated for 10 to 15 min at rt. The piperidine solution was drained and then the resin was washed with 1.0 mL DMF three times.

- 5 **[0562]** A solution of Fmoc-L-2,5-dichlorophenylalanine-OH (25CIF), CAS#1260614-80-9, (4 equiv.), HATU (4 equiv.), and DIEA (8 equiv.) in 1.0 mL of anhydrous NMP was prepared. The mixture was allowed to pre-activate at rt for 5 min, and then was added to the resin and agitated at 35°C for 30 min. The mixture was drained then the resin was washed with 1.0 mL of DMF three times. To remove Fmoc, A mixture of piperidine:DMF (20:80, 1
10 mL) was added to the resin and agitated for 10 to 15 min at rt. The piperidine solution was drained and then the resin was washed with 1.0 mL DMF three times.

- [0563]** To N-Methylate the amine of 25CIF, 2,6-lutidine (6 equiv.) dissolved in 0.5 mL of anhydrous DCE was added to the resin. 2-nitrobenzenesulfonyl chloride (5 equiv.) dissolved in 0.5 mL anhydrous toluene was added to the resin and then was agitated at 40 to 45°C for
15 10 to 15 min. The mixture was drained, then the resin was washed with 1.0 mL of anhydrous toluene three times. The method was repeated twice. Triphenylphosphine (10 equiv.) dissolved in 0.7 mL anhydrous toluene was added to the resin. Dry methanol (MeOH), (20 equiv.) was added to the resin. Azodicarboxylate (10 equiv.) was added to the resin and the mixture was agitated at 45°C for 30 min. The mixture was drained and the resin was washed
20 with 1.0 mL of anhydrous DMF three times. Alkylation was repeated twice. The nosyl group was then deprotected. A solution of 2-mercaptoethanol (5 equiv.) and 1,8-Diazabicyclo[5.4.0]undec-7-ene (5 equiv.) in 1.0 mL NMP was added to the resin and the mixture was agitated at 45°C for 10 min. The mixture was drained and then the resin was washed with 1.0 mL of anhydrous DMF three times. Deprotection was repeated twice.

- 25 **[0564]** Fmoc-L-Leucine-OH (L), CAS# 35661-60-0 (12 equiv.), HATU (4 equiv.), and DIEA (8 equiv.) in 1.0 mL of anhydrous NMP was prepared. The mixture was allowed to pre-activate at rt for 5 min, and then was added to the resin and agitated at 35°C for 30 min. The mixture was drained then the resin was washed with 1.0 mL of DMF three times. To remove Fmoc, A mixture of piperidine:DMF (20:80, 1 mL) was added to the resin and
30 agitated for 15 min at rt. The piperidine solution was drained and then the resin was washed with 1.0 mL DMF three times.

[0565] Fmoc-L-Lysine(Mtt)-OH (KMtt), CAS#167393-62-6, (4 equiv.), HATU (4 equiv.), and DIEA (8 equiv.) in 1.0 mL of anhydrous NMP was prepared. The mixture was allowed to pre-activate at rt for 5 min, and then was added to the resin and agitated at 35°C for 30 min. The mixture was drained then the resin was washed with 1.0 mL of DMF three times. To
5 remove Fmoc, A mixture of piperidine:DMF (20:80, 1 mL) was added to the resin and agitated for 15 min at rt. The piperidine solution was drained and then the resin was washed with 1.0 mL DMF three times.

[0566] Fmoc-L-Arginine(Pbf)-OH (RPbf), CAS#154445-77-9, (4 equiv.), HATU (4 equiv.), and DIEA (8 equiv.) in 1.0 mL of anhydrous NMP was prepared. The mixture was
10 allowed to pre-activate at rt for 5 min, and then was added to the resin and agitated at 35°C for 30 min. The mixture was drained then the resin was washed with 1.0 mL of DMF three times. To remove Fmoc, A mixture of piperidine:DMF (20:80, 1 mL) was added to the resin and agitated for 15 min at rt. The piperidine solution was drained and then the resin was washed with 1.0 mL DMF three times.

[0567] Fmoc-L-Lysine(Boc)-OH (KBoc), CAS#71989-26-9, (4 equiv.), HATU (4 equiv.), and DIEA (8 equiv.) in 1.0 mL of anhydrous NMP was prepared. The mixture was allowed to pre-activate at rt for 5 min, and then was added to the resin and agitated at 35°C for 30 min. The mixture was drained then the resin was washed with 1.0 mL of DMF three times. To
15 remove Fmoc, A mixture of piperidine:DMF (20:80, 1 mL) was added to the resin and
20 agitated for 15 min at rt. The piperidine solution was drained and then the resin was washed with 1.0 mL DMF three times.

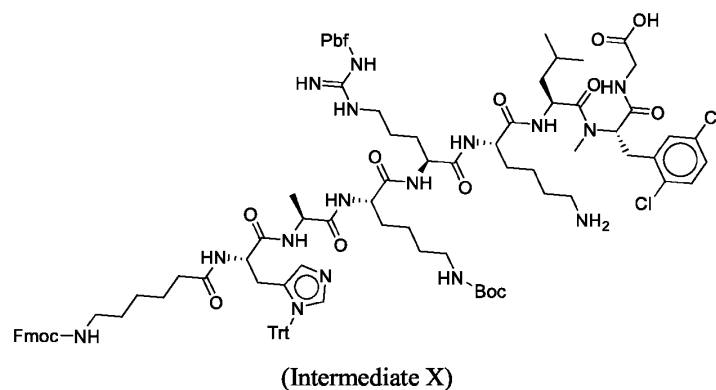
[0568] Fmoc-L-Alanine-OH (A), CAS#35661-39-3, (4 equiv.), HATU (4 equiv.), and DIEA (8 equiv.) in 1.0 mL of anhydrous NMP was prepared. The mixture was allowed to pre-activate at rt for 5 min, and then was added to the resin and agitated at 35°C for 30 min.
25 The mixture was drained then the resin was washed with 1.0 mL of DMF three times. To remove Fmoc, A mixture of piperidine:DMF (20:80, 1 mL) was added to the resin and agitated for 15 min at rt. The piperidine solution was drained and then the resin was washed with 1.0 mL DMF three times.

[0569] Fmoc-L-Histidine(Trt)-OH (HTrt), CAS#109425-51-6, (4 equiv.), HATU (4 equiv.), and DIEA (8 equiv.) in 1.0 mL of anhydrous NMP was prepared. The mixture was
30 allowed to pre-activate at rt for 5 min, and then was added to the resin and agitated at 35°C for 30 min. The mixture was drained then the resin was washed with 1.0 mL of DMF three

times. To remove Fmoc, A mixture of piperidine:DMF (20:80, 1 mL) was added to the resin and agitated for 15 min at rt. The piperidine solution was drained and then the resin was washed with 1.0 mL DMF three times.

5 [0570] Fmoc-6-aminohexanoic acid (Ahx), CAS#88574-06-5, (4 equiv.), HATU (4 equiv.), and DIEA (8 equiv) in 1.0 mL of anhydrous NMP was prepared. The mixture was allowed to pre-activate at rt for 5 min, and then was added to the resin and agitated at 35°C for 30 min. The mixture was drained and then the resin was washed with 1.0 mL of DMF three times.

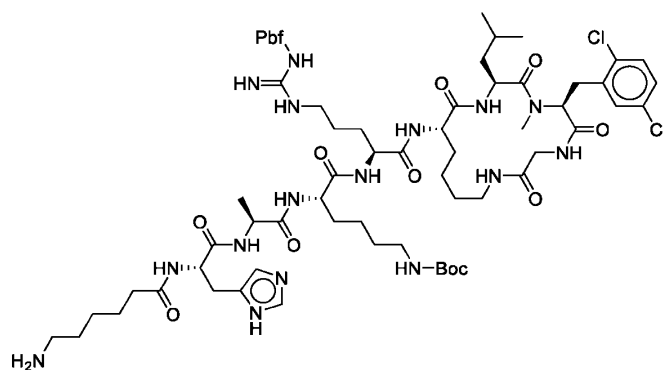
[0571] To cleave peptide from CTC resin and simultaneously deprotect the Mtt protecting group, approximately 2 mL of a solution of 24% HFIP, 2% TIPS, in DCM was added to the polystyrene resin in a solid phase reaction vessel. The contents were shaken for 1 hour. The
10 cleavage solution was filtered into a 50 mL conical vial. The cleaved resin was washed with an additional 2 mL of DCM and the wash was collected in the conical vial. The solution was evaporated in a Genevac. The linear peptide was purified via reverse-phase HPLC using an Acetonitrile/Water gradient with 0.05% formic acid and the purified fractions were pooled
15 and lyophilized to yield white powder of intermediate X (M/z observed = 1968.65 $[M+H]^+$).



[0572] The linear intermediate X (~15 mg) was cyclized using a medium volume, T3P solution cyclization method. The deprotected and purified linear product was transferred to a
20 50 mL conical vial and dissolved in 1 mL NMP followed by the addition of DIEA (0.5 mL) and DCM (35 mL). T3P (3 eqv) was added to the solution and the reaction pH was adjusted to pH 9 via dropwise addition of DIEA. The closed conical vial was agitated at rt for 2 hours at 150 rotations per minute. The solution was concentrated at 45°C under reduced pressure in a Genevac system. The Fmoc group was then removed with the addition of a 10% of
25 KOH/Water solution (5 mL) heated at 70°C for 30 min. The resulting LCMS trace revealed

that the trityl group had been unexpectedly removed during the cyclization and Fmoc-deprotection steps. The cyclic peptide was then purified via reverse phase HPLC using an Acetonitrile/Water gradient with 0.05% formic acid. The purified fractions were pooled and lyophilized to yield intermediate **Y** (M/z observed = 1485.94 $[M+Z]^+$).

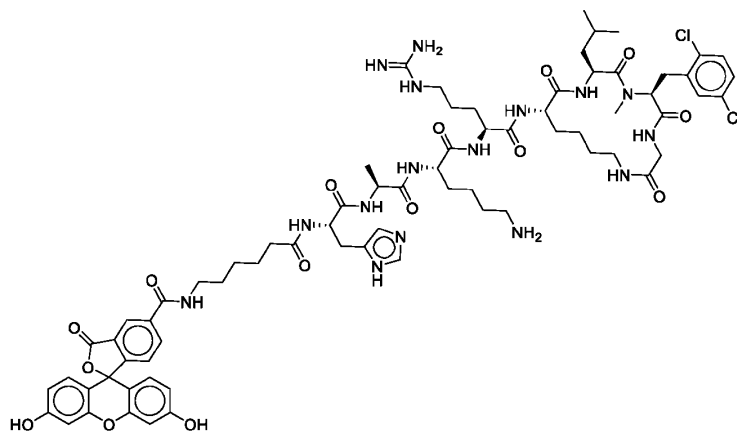
5



(Intermediate Y)

[0573] The probe was fluorescently labeled via a peptide coupling in solution. A solution of 5-carboxyfluorescein (CAS#76823-03-5, FAM) (4 equiv.), EDC (4 equiv.), HOAt (3.9 equiv.) and DIEA (8 equiv.) in 1.0 mL of anhydrous DCM was prepared. The mixture was allowed to pre-activate at rt for 5 min. Intermediate **Y** was added to the coupling solution, and the reaction was agitated at rt until starting material was not observed by LCMS, resulting in the formation of Intermediate **Z** (M/z observed = 1844.29 $[M+Z]^+$).

10



(Intermediate Z)

[0574] The Boc and Pbf protecting groups were removed from the cyclic intermediate **Z** by dissolving the cyclic peptide in a 1 mL solution of 90% TFA, 5% TIPS, 5% DCM and agitating for 1 hour. The reaction was monitored by LCMS for the disappearance of starting material. Upon completion, the reaction was concentrated. The crude material was co-
 5 evaporated with DCE (5 mL x 2), and then purified via reverse phase-HPLC to yield fluorescent probe (FAM probe) (M/z observed = 1492.14 [M+Z]⁺, 0.7 mg, 99% purity by HPLC).

2. MTT Proliferation Assay

[0575] MTT proliferation assay was used to determine the 50% growth inhibition (GI₅₀) of
 10 disclosed compounds. 5 x 10³ cells were seeded into 96 well plates. 24 hours later, cells were dosed with compound in an 8- or 10-point 1:3 serial dilution starting at 10 μM. Cells were exposed to compound for a sufficient time to allow 3-4 cell doublings (3 days (WI-38); 5 days (NCI-H1048 and OVCAR3)). Roscovitine and staurosporine were used as plate controls. At the end of the compound incubation, MTT reagent (TACS MTT Cell
 15 Proliferation Assay R&D Systems Catalog #4890-025-K) was added and assay carried out. Results are summarized in Table 6

Table 6: Cellular Activity Data of Exemplary Compounds

Example Number	H1048 GI ₅₀ (μM)	OVCAR3 GI ₅₀ (μM)	WI-38 GI ₅₀ (μM)
1	4.00	6.61	14.59
2	0.38	0.41	20.00
3	0.46	0.72	20.00
4	0.12	0.06	20.00
5-P1	0.39	0.69	20.00
5-P2	0.29	0.56	20.00
6-P1	0.05	0.09	16.37
6-P2	0.04	0.07	15.60
7	0.02	0.05	20.00
8	0.02	0.03	20.00
9	0.08	0.11	20.00
10	0.02	0.03	20.00
11	0.08	0.21	20.00
12	0.03	0.04	20.00
13	0.07	0.24	20.00
14	0.10	0.20	20.00
15	0.18	0.55	7.85

Example Number	H1048 GI50 (μM)	OVCAR3 GI50 (μM)	WI-38 GI50 (μM)
16-P1	0.34	0.88	20.00
16-P2	0.35	0.99	20.00
17	0.24	0.56	17.94
18	0.17	0.34	9.03
19	0.55	1.76	20.00
20	0.02	0.02	11.06
21	0.01	0.02	6.85
22	1.10	1.80	20.00
23	0.18	0.21	20.00
24	0.09	0.17	20.00
25	0.03	0.04	8.07
26	0.11	0.17	8.74
27	0.09	0.37	11.41
28	0.08	0.17	20.00
29	0.04	0.07	20.00
30	0.13	0.14	20.00
31	0.08	0.15	20.00
32	0.14	0.25	11.77
33	0.09	0.17	15.55
34	0.06	0.11	13.07
35	0.17	0.35	12.41
36	0.11	0.35	15.97
37	0.04	0.05	20.00
38	0.06	0.16	20.00
39	0.09	0.21	20.00
40	0.06	0.05	15.39
41	0.10	0.13	20.00
42	0.07	0.21	20.00
43	0.03	0.04	8.57
44	0.02	0.04	6.60
45	0.02	0.04	20.00
46	0.72	0.79	20.00
47	0.03	0.13	12.93
48	0.04	0.05	15.80
49	0.01	0.01	11.54
50	0.01	0.01	20.00
51	0.01	0.01	18.81
52	0.01	0.01	13.14
53	0.18	0.18	4.50
54	0.47	0.70	20.00
55	0.56	0.71	20.00

Example Number	H1048 GI50 (μM)	OVCAR3 GI50 (μM)	WI-38 GI50 (μM)
56-P1	0.47	1.02	5.76
56-P2	0.19	0.43	3.76
57-P1	0.01	0.01	13.77
57-P2	0.01	0.01	16.87
58	0.01	0.01	20.00
59-P1	0.02	0.02	20.00
59-P2	0.06	0.05	20.00
60	0.01	0.01	5.72
61	0.02	0.04	20.00
62	0.06	0.07	20.00
63	0.11	0.24	3.17
64	0.51	1.24	20.00
65	0.01	0.01	20.00
66	0.01	0.01	12.89
67	0.01	0.01	20.00
68	0.01	0.01	12.81
69	0.01	0.01	17.57
70	0.01	0.01	10.11
71	0.07	0.09	13.82
72	0.04	0.06	14.87
73	0.04	0.06	3.65
74	0.11	0.17	20.00
75	0.01	0.02	5.89
76	0.08	0.12	20.00
77	0.06	0.07	20.00
78	0.03	0.04	4.52
79	0.03	0.04	20.00
80	0.03	0.03	11.63
81	0.04	0.05	4.30
82	0.03	0.07	20.00
83	0.02	0.01	20.00
84	0.02	0.01	20.00
85	0.02	0.02	20.00
86	0.02	0.02	20.00
87	0.05	0.06	20.00
88	0.03	0.03	7.64
89	0.31	0.38	4.34
90	0.26	0.23	4.13
91	0.23	0.26	20.00
92	0.01	0.01	20.00
93	0.01	0.01	20.00

Example Number	H1048 GI50 (μM)	OVCAR3 GI50 (μM)	WI-38 GI50 (μM)
94	0.01	0.01	20.00
95	0.01	0.02	20.00
96	0.01	0.01	8.92
97	0.02	0.03	20.00
98	0.02	0.02	16.45
99	0.02	0.03	20.00
100	0.02	0.02	20.00
101	0.02	0.03	20.00
102-P1	0.35	0.81	20.00
102-P2	0.08	0.13	20.00
103	0.03	0.05	20.00
104	0.16	0.26	20.00
105	0.02	0.03	18.78
106	0.41	0.54	6.39
107-P1	0.70	1.01	5.29
107-P2	0.19	0.32	20.00
108	0.02	0.03	20.00
109	0.02	0.02	9.52
110	0.01	0.01	4.80
111	0.01	0.01	8.13
112	0.01	0.01	20.00
113	0.01	0.01	7.24
114	0.01	0.01	7.19
115	0.07	0.06	11.00
116	0.04	0.05	20.00
117-P1	0.23	0.18	20.00
117-P2	0.09	0.06	20.00
118-P1	0.18	0.17	20.00
118-P2	0.05	0.05	20.00
119	0.25	0.30	8.71
120	0.10	0.13	9.28
121	0.04	0.07	7.61
122	0.05	0.05	20.00
123	0.02	0.02	20.00
124	0.02	0.02	20.00
125	0.49	0.55	20.00
126	0.38	0.31	20.00
127	0.03	0.03	20.00
128	0.03	0.03	20.00
129	1.46	2.58	6.88
130	0.70	1.55	8.99

Example Number	H1048 GI50 (μM)	OVCAR3 GI50 (μM)	WI-38 GI50 (μM)
131	0.29	0.40	20.00
132	0.57	0.38	20.00
133	0.34	0.26	20.00
134	0.03	0.04	20.00
135	0.03	0.02	20.00
136-P1	0.83	1.77	3.96
136-P2	0.45	0.64	6.67
137	0.60	0.76	4.58
138	0.20	0.28	6.67
139	0.07	0.15	6.42
140	0.05	0.13	9.25
141	0.09	0.19	3.39
142	0.11	0.19	10.20
143	0.01	0.02	5.18
144	0.07	0.07	20.00
145	0.07	0.08	10.14
146	0.02	0.02	20.00
147	0.01	0.01	1.24
148	0.01	0.01	20.00
149	0.03	0.04	20.00
150	0.02	0.04	20.00
151	0.01	0.01	20.00
152	0.50	0.45	20.00
153	0.11	0.14	20.00
154	0.02	0.02	20.00
155	0.01	0.02	20.00
156-P1	0.48	0.53	20.00
156-P2	0.09	0.10	20.00
157	0.08	0.14	20.00
158	0.02	0.02	20.00
159	0.01	0.02	9.45
160	0.02	0.02	11.46
161	0.02	0.02	20.00
162	0.01	0.01	20.00
163	0.01	0.01	20.00
164	0.03	0.03	20.00
165	0.34	1.67	20.00
166	0.04	0.10	20.00
167	0.01	0.01	19.74
168	0.01	0.01	13.10
169	0.02	0.03	20.00

Example Number	H1048 GI50 (μM)	OVCAR3 GI50 (μM)	WI-38 GI50 (μM)
170	0.13	0.20	20.00
171	0.15	0.21	20.00
172	0.03	0.06	13.70
173	0.01	0.01	12.74
174	0.01	0.01	6.98
175	0.01	0.01	6.85
176	0.01	0.01	5.48
177	0.01	0.01	8.96
178	1.18	2.57	20.00
179	0.01	0.03	11.61
180	0.73	1.22	20.00
181	0.24	0.42	20.00
182	0.06	0.13	20.00
183	0.01	0.02	5.07
184	0.01	0.01	3.65
185	0.01	0.01	10.35
186	0.01	0.01	8.68
187	0.01	0.01	8.66
188	0.01	0.02	3.08
189	0.13	0.08	3.67
190	0.01	0.01	1.98
191	0.01	0.01	2.05
192	0.02	0.02	3.51
193	0.01	0.02	7.58
194	0.01	0.01	5.61
195	0.01	0.01	20.00
196	0.01	0.01	20.00
197	0.05	0.10	20.00
198	0.05	0.05	20.00
199	0.03	0.05	20.00
200	0.04	0.03	20.00
201	0.06	0.06	20.00
202	0.04	0.06	9.11
203	0.06	0.05	3.70
204	0.01	0.01	20.00
205	0.02	0.03	20.00
206	0.01	0.02	20.00
207	0.03	0.04	4.94
208	0.83	1.96	20.00
209	0.01	0.02	20.00
210	0.10	0.11	20.00

Example Number	H1048 GI50 (μM)	OVCAR3 GI50 (μM)	WI-38 GI50 (μM)
211	0.02	0.03	20.00
212	0.08	0.08	20.00
213	0.01	0.01	20.00
214	0.01	0.01	20.00
215	0.01	0.01	20.00
216	0.01	0.01	15.55
217	0.01	0.02	20.00
218	0.23	0.39	20.00
219	0.04	0.08	14.06
220	0.03	0.07	5.20
221	0.02	0.03	16.64
222	0.01	0.01	20.00
223	0.01	0.01	7.76
224	0.01	0.01	12.41
225	0.02	0.03	8.53
226	0.02	0.03	8.39
227	0.02	0.04	14.09
228	0.06	0.08	9.54
229	0.01	0.02	20.00
230	0.04	0.09	5.05
231	0.02	0.04	13.36
232	0.05	0.08	11.61
233	0.03	0.03	15.15
234	0.01	0.01	10.66
235	0.10	0.09	13.15
236	0.01	0.02	7.33
237	0.01	0.04	20.00
238	0.01	0.02	17.27
239	0.02	0.02	14.31
240	0.01	0.01	8.73
241	0.01	0.01	12.45
242	0.03	0.02	20.00
243	0.05	0.04	13.29
244	0.10	0.04	20.00
245	0.08	0.02	20.00
246	0.03	0.01	20.00
247	0.05	0.04	20.00
248	0.04	0.02	20.00
249	0.01	0.01	20.00
250	0.03	0.03	5.55
251	0.01	0.01	13.92

Example Number	H1048 GI50 (μM)	OVCAR3 GI50 (μM)	WI-38 GI50 (μM)
252	0.01	0.02	20.00
253	0.04	0.02	9.93
254	0.02	0.02	20.00
255	0.04	0.03	15.76
256	0.01	0.01	13.19
257	0.01	0.01	13.26
258	0.07	0.07	14.19
259	0.11	0.11	10.43
260	0.04	0.04	6.39
261	0.01	0.01	14.10
262	0.01	0.02	16.21
263	0.03	0.04	20.00
264	0.04	0.03	20.00
265	0.01	0.02	20.00
266	0.03	0.05	20.00
267	0.05	0.04	20.00
268	0.02	0.01	20.00
269	0.03	0.03	20.00
270	0.08	0.07	13.38
271	0.01	0.01	20.00
272	0.09	0.43	20.00
273	0.03	0.04	20.00
274	0.01	0.01	10.48
275	0.01	0.01	20.00
276	0.02	0.02	23.38
277	0.33	0.36	3.82
278	0.01	0.01	20.00
279	0.08	0.09	20.00
280	0.01	0.01	20.00
281	0.01	0.02	20.00
282	0.01	0.01	20.00
283	0.01	0.01	14.18
284	0.01	0.01	20.00
285	0.05	0.03	20.00
286	0.06	0.05	6.50
287	0.04	0.04	20.00
288	0.02	0.02	13.81
289	0.01	0.01	3.78
290	0.08	0.15	20.00
291	0.12	0.15	20.00
292	0.07	0.11	20.00

Example Number	H1048 GI50 (μM)	OVCAR3 GI50 (μM)	WI-38 GI50 (μM)
293	0.05	0.09	20.00
294	0.08	0.13	20.00
295	0.08	0.16	20.00
296	0.07	0.10	20.00
297	0.02	0.03	9.15
298	0.01	0.02	20.00
299	0.01	0.01	14.29
300	0.03	0.04	20.00
301	0.02	0.02	20.00
302	0.14	0.12	20.00
303	0.01	0.01	20.00
304	0.01	0.01	20.00
305	0.01	0.02	19.20
306	0.01	0.01	20.00
307	0.01	0.01	20.00
308	0.01	0.01	20.00
309	0.01	0.01	20.00
310	0.01	0.01	20.00
311	0.02	0.03	20.00
312	0.02	0.03	20.00
313	0.01	0.01	36.59
314	0.01	0.01	20.00
315	0.02	0.02	20.00
316	0.01	0.01	20.00
317	0.01	0.01	20.00
318	0.01	0.01	9.92
319	0.01	0.02	20.00
320	0.01	0.02	15.50
321	0.01	0.01	89.76
322	0.03	0.06	20.00
323	0.01	0.01	20.00
324	0.04	0.08	20.00
325	0.01	0.01	20.00
326	0.01	0.01	20.00
327	0.01	0.01	83.88
328	0.01	0.01	20.00
329	0.01	0.01	20.00
330	0.01	0.01	18.46
331	0.06	0.05	20.00
332	0.01	0.01	20.00
333	0.01	0.01	20.00

Example Number	H1048 GI50 (μM)	OVCAR3 GI50 (μM)	WI-38 GI50 (μM)
334	0.01	0.01	20.00
335	0.01	0.01	4.75
336	0.01	0.01	2.48
337	0.01	0.01	18.7
338	0.02	0.02	18.9
339	0.01	0.01	5.62
340	0.02	0.02	17.3
341	0.01	0.01	2.44
342	0.01	0.01	20
343	0.01	0.01	20
344	0.01	0.02	20
345	0.02	0.04	20
346	0.01	0.01	3.68
347	0.01	0.01	1.81
348	0.01	0.01	18
349	0.01	0.01	20
350	0.01	0.01	20
351	0.01	0.01	1.78
352	0.01	0.01	20
353	0.01	0.01	3.49
354	0.01	0.02	20
355	0.01	0.01	2.77
356	0.01	0.01	3.43
357	0.02	0.05	3.14
358	0.01	0.01	2.13
359	0.01	0.01	4.56
360	0.01	0.01	2.72
361	0.03	0.01	14.3
362	0.01	0.01	1.28
363	0.01	0.01	1.43
364	0.01	0.01	3.25
365	0.01	0.01	3.18
366	0.02	0.02	20
367	0.02	0.01	14.7
368	0.01	0.01	15.2
369	0.02	0.02	4.54
370	0.02	0.02	1.21
371	0.01	0.01	1.44
372	0.01	0.01	2.84
373	0.01	0.01	20
374	0.01	0.01	2.22

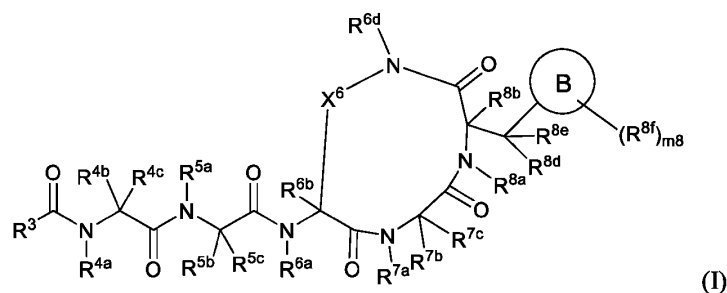
Example Number	H1048 GI50 (μM)	OVCAR3 GI50 (μM)	WI-38 GI50 (μM)
375	0.01	0.02	16.8
376	0.01	0.01	3.45
377	0.01	0.01	8.16
378	0.01	0.02	20
379	0.03	0.02	20
380	0.02	0.03	1.17
381	0.02	0.04	2.3
382	0.09	0.04	20
383	0.01	0.01	2.7
384	0.01	0.01	2.21
385	0.03	0.02	20
386	0.03	0.02	20
387	0.03	0.02	3.08
388	0.02	0.02	3.5
389	0.02	0.01	17.6
390	0.03	0.02	9.24
391	0.01	0.01	7.82
392	0.17	0.17	14.70
393	1.79	1.31	13.70
394	0.09	0.05	20.00
395	0.02	0.01	
396	0.02	0.01	
397	0.01	0.01	3.56
398	0.14	0.19	3.64
399	0.22	0.11	3.65
400	0.01	0.01	4.61
401	0.01	0.01	
402	0.04	0.01	20.00
403	0.01	0.01	3.99
404	0.02	0.03	20.00
405	0.04	0.05	2.16
406	0.02	0.04	3.35
407	0.01	0.02	3.01
408	0.01	0.01	5.53
409	0.01	0.01	2.46
410	0.01	0.01	2.00
411	0.01	0.01	1.61
412	0.01	0.01	1.06
413	0.01	0.01	1.60
414	0.01	0.01	20.00

Example Number	H1048 GI50 (μM)	OVCAR3 GI50 (μM)	WI-38 GI50 (μM)
415	0.01	0.01	14.10
416	0.03	0.04	20.00
417	0.01	0.01	1.16
418	1.42	1.15	20.00
419	0.02	0.02	1.99
420	0.01	0.02	3.51
421	0.01	0.01	19.10
422	0.01	0.01	2.36
423	0.20	0.07	20.00
424	2.51	1.78	20.00
425	0.16	0.24	20.00
426	0.09	0.15	20.00

[0576] Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, one of skill in the art will appreciate that certain changes and modifications may be practiced within the scope of the appended claims. In addition, each reference provided herein is incorporated by reference in its entirety to the same extent as if each reference was individually incorporated by reference. Where a conflict exists between the instant application and a reference provided herein, the instant application shall dominate.

WHAT IS CLAIMED IS:

1. A compound of Formula (I):



wherein

R^3 is

- (a) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{1-6} haloalkyl, each substituted with 0 to 5 R^{3a} ,
- (b) C_{3-12} cycloalkyl substituted with 0 to 5 R^{3b} , or
- (c) heterocycloalkyl having 3 to 12 ring members and 1 to 4 heteroatoms, each independently N, O, or S, wherein the heterocycloalkyl is substituted with 0 to 5 R^{3c} ;
- (g) heteroaryl having 5 to 6 ring members and 1 to 3 heteroatoms, each independently N, O, or S, wherein the heteroaryl is substituted with 0, 1, 2, 3, 4, or 5 R^{3g} ;

each R^{3a} is $-OH$, C_{1-6} alkoxy, C_{1-6} haloalkoxy, or $-O-C(O)C_{1-6}$ alkyl;

each R^{3b} is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $-OH$, C_{1-6} alkoxy, halo, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, or cyano;

each R^{3c} is independently C_{1-6} alkyl, halo, C_{1-6} haloalkyl, cyano, C_{3-6} cycloalkyl, or oxo;

each R^{3g} is independently C_{1-6} alkyl, halo, C_{1-6} haloalkyl, or C_{3-6} cycloalkyl;

R^{4a} is H or C_{1-6} alkyl;

R^{4b} and R^{4c} are each independently H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, $-C_{1-6}$ alkyl- C_{3-6} cycloalkyl, heterocycloalkyl, $-C_{1-6}$ alkyl-heterocycloalkyl, phenyl, $-C_{1-6}$ alkyl-phenyl, heteroaryl, or $-C_{1-6}$ alkyl-heteroaryl, wherein each heterocycloalkyl has 3 to 6 ring members and 1 to 3 heteroatoms, each

independently N, O, or S, and each heteroaryl has 5 to 6 ring members and 1 to 3 heteroatoms, each independently N, O, or S;

alternatively, R^{4c} and R^{4a} together with the carbon and nitrogen to which each is attached combine to form a heterocycloalkyl having 3 to 6 ring members and 1 to 3 heteroatoms, each independently N, O, or S, wherein the heterocycloalkyl is substituted with 0 to 4 R^{4a1};

each R^{4a1} is independently C₁₋₆ alkyl, -OH, C₁₋₆ alkyl-OH, C₁₋₆ alkoxy, or halo;

R^{5a} is H or C₁₋₆ alkyl;

R^{5b} and R^{5c} are each independently H, C₁₋₆ alkyl, -C₁₋₆ alkyl-OH, C₂₋₆ alkoxyalkyl, C₁₋₆ haloalkyl, -C₁₋₆ alkyl-C(O)NR^{5b1}R^{5b2}, -C₁₋₆ alkyl-C(O)OR^{5b1}, C₃₋₆ cycloalkyl, C₁₋₆ alkyl-C₃₋₆ cycloalkyl, heterocycloalkyl, -C₁₋₆ alkyl-heterocycloalkyl, phenyl, -C₁₋₆ alkyl-phenyl, heteroaryl, or -C₁₋₆ alkyl-heteroaryl, wherein each heterocycloalkyl has 3 to 6 ring members and 1 to 3 heteroatoms, each independently N, O, or S, and each heteroaryl has 5 to 6 ring members and 1 to 3 heteroatoms, each independently N, O, or S, and wherein each cycloalkyl, heterocycloalkyl, phenyl, and heteroaryl is substituted with 0 to 3 R^{5b5};

each R^{5b1} and R^{5b2} are independently H, C₁₋₄ alkyl, or C₁₋₄ haloalkyl;

alternatively, R^{5b1} and R^{5b2} together with the nitrogen to which each is attached combine to form a heterocycloalkyl having 3 to 6 ring members and 0 to 1 additional heteroatoms, wherein the heterocycloalkyl is substituted with 0 to 2 R^{5b3};

each R^{5b3} and R^{5b5} is independently C₁₋₆ alkyl, halo, C₁₋₆ haloalkyl, or cyano;

X⁶ is C₆₋₇ alkylene or C₆₋₇ alkenylene;

R^{6a} is H, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₂₋₆ alkoxyalkyl, C₃₋₆ cycloalkyl, -C₁₋₆ alkyl-C₃₋₆ cycloalkyl, heterocycloalkyl, -C₁₋₆ alkyl-heterocycloalkyl, phenyl, -C₁₋₆ alkyl-phenyl, heteroaryl, or -C₁₋₆ alkyl-heteroaryl, wherein the heterocycloalkyl has 3 to 6 ring members and 1 to 3 heteroatoms, each independently N, O, or S, and the heteroaryl has 5 to 6 ring members and 1 to 3 heteroatoms, each independently N, O, or S;

R^{6b} and R^{6d} are each independently H or C₁₋₆ alkyl;

R^{7a} is H or C₁₋₆ alkyl;

R^{7b} and R^{7c} are each independently H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₁₋₆ haloalkyl, C₁₋₆ alkyl-OH, C₃₋₆ cycloalkyl, or -C₁₋₆ alkyl-C₃₋₆ cycloalkyl;

R^{8a} is H, C_{1-6} alkyl, C_{2-6} alkoxyalkyl, C_{3-6} cycloalkyl or $-C_{1-6}$ alkyl- C_{3-6} cycloalkyl;
 R^{8b} , R^{8d} , and R^{8e} are each independently H or C_{1-6} alkyl;
 ring B is C_{6-12} aryl or heteroaryl having 5 to 12 ring members and 1 to 6 heteroatoms,
 each independently N, O or S;
 the subscript m8 is an integer from 0 to 5;
 each R^{8f} is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, C_{1-6}
 deutoalkoxy, halo, C_{1-6} haloalkyl, cyano, $-X^{8f}$ -cyano, C_{3-12} cycloalkyl,
 $-X^{8f}$ - C_{3-6} cycloalkyl, $-CH=CR^{8f1}R^{8f2}$, heterocycloalkyl,
 $-X^{8f}$ -heterocycloalkyl, C_{6-12} aryl, $-X^{8f}$ - C_{6-12} aryl, heteroaryl, or
 $-X^{8f}$ -heteroaryl, wherein each heterocycloalkyl has 3 to 12 ring members and
 1 to 4 heteroatoms, each independently N, O, or S, and each heteroaryl has 5
 to 10 ring members and 1 to 4 heteroatoms, each independently N, O, or S,
 wherein each alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is
 substituted with 0 to 3 R^{8f3} ;
 alternatively, two R^{8f} groups on adjacent ring vertices combine to form a C_{3-6}
 cycloalkyl or a heterocycloalkyl having 3 to 6 ring members and 1 to 3
 heteroatoms, each independently N, O or S, wherein the cycloalkyl or
 heterocycloalkyl is substituted with 0 to 3 R^{8f3} ;
 each X^{8f} is independently C_{1-6} alkylene, C_{2-6} alkenylene, $-O-C_{1-6}$ alkylene, C(O), O,
 or S;
 each R^{8f1} and R^{8f2} are combined with the carbon to which they are attached to form a
 heterocycloalkyl having 3 to 10 ring members and 1 to 3 heteroatoms, each
 independently N, O or S, wherein the heterocycloalkyl is substituted with 0 to
 3 R^{8f3} ;
 each R^{8f3} is independently C_{1-6} alkyl, $-Y^8-C_{1-6}$ alkyl, C_{1-6} deutoalkyl,
 $-Y^8-C_{1-6}$ deutoalkyl, $-OH$, $-C_{1-6}$ alkyl- $-OH$, $-Y^8-C_{1-6}$ alkyl- $-OH$,
 $-C_{1-6}$ alkyl- $-Y^8-C_{1-6}$ alkyl, $-(C_{1-2}$ alkyl- $-O)_{1-4}-C_{1-2}$ alkyl, C_{1-6} alkoxy, halo, C_{1-6}
 haloalkyl, $-Y^8-C_{1-6}$ haloalkyl, cyano, $-C_{1-6}$ alkyl-cyano, $-C_{1-6}$ alkyl- $-NR^{8g}R^{8h}$,
 oxo, C_{3-6} cycloalkyl, $-X^{8f3}-C_{3-6}$ cycloalkyl, heterocycloalkyl, $-X^{8f3}-$
 heterocycloalkyl, phenyl, $-X^{8f3}$ -phenyl, heteroaryl, or $-X^{8f3}$ -heteroaryl,
 wherein each heterocycloalkyl has 3 to 12 members and 1 to 4 heteroatoms,
 each independently N, O, S, or S(O)₂, and each heteroaryl has 5 to 10 ring
 members and 1 to 4 heteroatoms, each independently N, O, or S, and wherein

each heterocycloalkyl and heteroaryl are substituted with 0 to 2 C₁₋₄ alkyl or halo;

each X^{8f3} is independently C₁₋₆ alkylene, O, C(O), or S(O)₂;

each Y⁸ is independently C(O), C(O)O, N(R^{8f4})C(O), O, S, or S(O)₂;

each R^{8g} and R^{8h} is independently H, C₁₋₆ alkyl, or C₁₋₆ haloalkyl;

alternatively, two R^{8f3} groups on the same or adjacent ring vertices combine to form a C₃₋₆ cycloalkyl or a heterocycloalkyl having 3 to 6 ring members and 1 to 3 heteroatoms, each independently N, O or S, wherein nitrogen atom ring members in the heterocycloalkyl are substituted with 0 to 1 C₁₋₄ alkyl; and

each R^{8f4} is independently H or C₁₋₆ alkyl;

or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, or the pharmaceutically acceptable salt thereof, wherein

R³ is

- (a) C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, or C₁₋₆ haloalkyl, each substituted with 0 to 5 R^{3a},
- (b) C₃₋₁₂ cycloalkyl substituted with 0 to 5 R^{3b}, or
- (c) heterocycloalkyl having 3 to 12 ring members and 1 to 4 heteroatoms, each independently N, O, or S, wherein the heterocycloalkyl is substituted with 0 to 5 R^{3c};

each R^{3a} is -OH, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, or -O-C(O)C₁₋₆ alkyl;

each R^{3b} is independently C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, -OH, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, or cyano;

each R^{3c} is independently C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, or oxo;

R^{4a} is H or C₁₋₆ alkyl;

R^{4b} and R^{4c} are each independently H, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, -C₁₋₆ alkyl-C₃₋₆ cycloalkyl, heterocycloalkyl, -C₁₋₆ alkyl-heterocycloalkyl, phenyl, -C₁₋₆ alkyl-phenyl, heteroaryl, or -C₁₋₆ alkyl-heteroaryl, wherein each heterocycloalkyl has 3 to 6 ring members and 1 to 3 heteroatoms, each independently N, O, or S, and each heteroaryl has 5 to 6 ring members and 1 to 3 heteroatoms, each independently N, O, or S;

alternatively, R^{4c} and R^{4a} together with the carbon and nitrogen to which each is attached combine to form a heterocycloalkyl having 3 to 6 ring members, wherein the heterocycloalkyl is substituted with 0 to 4 R^{4a1};

each R^{4a1} is independently C₁₋₆ alkyl, -OH, C₁₋₆ alkyl-OH, C₁₋₆ alkoxy, or halo;

R^{5a} is H or C₁₋₆ alkyl;

R^{5b} and R^{5c} are each independently H, C₁₋₆ alkyl, -C₁₋₆ alkyl-OH, C₂₋₆ alkoxyalkyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, C₁₋₆ alkyl-C₃₋₆ cycloalkyl, heterocycloalkyl, -C₁₋₆ alkyl-heterocycloalkyl, phenyl, -C₁₋₆ alkyl-phenyl, heteroaryl, or -C₁₋₆ alkyl-heteroaryl, wherein each heterocycloalkyl has 3 to 6 ring members and 1 to 3 heteroatoms, each independently N, O, or S, and each heteroaryl has 5 to 6 ring members and 1 to 3 heteroatoms, each independently N, O, or S, and wherein each cycloalkyl, heterocycloalkyl, phenyl, and heteroaryl is substituted with 0 to 3 R^{5b5};

each R^{5b5} is independently C₁₋₆ alkyl, halo, or C₁₋₆ haloalkyl;

X⁶ is C₆₋₇ alkylene or C₆₋₇ alkenylene;

R^{6a} is H, C₁₋₆ alkyl, C₂₋₆ alkoxyalkyl, C₃₋₆ cycloalkyl, -C₁₋₆ alkyl-C₃₋₆ cycloalkyl, heterocycloalkyl, -C₁₋₆ alkyl-heterocycloalkyl, phenyl, -C₁₋₆ alkyl-phenyl, heteroaryl, or -C₁₋₆ alkyl-heteroaryl, wherein the heterocycloalkyl has 3 to 6 ring members and 1 to 3 heteroatoms, each independently N, O, or S, and the heteroaryl has 5 to 6 ring members and 1 to 3 heteroatoms, each independently N, O, or S;

R^{6b} and R^{6d} are each independently H or C₁₋₆ alkyl;

R^{7a} is H or C₁₋₆ alkyl;

R^{7b} and R^{7c} are each independently H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₁₋₆ haloalkyl, C₁₋₆ alkyl-OH, C₃₋₆ cycloalkyl, or -C₁₋₆ alkyl-C₃₋₆ cycloalkyl;

R^{8a} is H, C₁₋₆ alkyl, C₂₋₆ alkoxyalkyl, C₃₋₆ cycloalkyl or -C₁₋₆ alkyl-C₃₋₆ cycloalkyl;

R^{8b}, R^{8d}, and R^{8e} are each independently H or C₁₋₆ alkyl;

ring B is C₆₋₁₂ aryl or heteroaryl having 5 to 12 ring members and 1 to 6 heteroatoms, each independently N, O or S;

the subscript m8 is an integer from 0 to 5;

each R^{8f} is independently C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ alkoxy, C₁₋₆ deutoalkoxy, halo, C₁₋₆ haloalkyl, cyano, -X^{8f}-cyano, C₃₋₁₂ cycloalkyl, -X^{8f}-C₃₋₆ cycloalkyl, -CH=CR^{8f1}R^{8f2}, heterocycloalkyl, -X^{8f}-heterocycloalkyl, C₆₋₁₂ aryl, -X^{8f}-C₆₋₁₂ aryl, heteroaryl, or

–X^{8f}–heteroaryl, wherein each heterocycloalkyl has 3 to 12 ring members and 1 to 4 heteroatoms, each independently N, O, or S, and each heteroaryl has 5 to 10 ring members and 1 to 4 heteroatoms, each independently N, O, or S, wherein each alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is substituted with 0 to 3 R^{8f3};

alternatively, two R^{8f} groups on adjacent ring vertices combine to form a C₃₋₆ cycloalkyl or a heterocycloalkyl having 3 to 6 ring members and 1 to 3 heteroatoms, each independently N, O or S, wherein the cycloalkyl or heterocycloalkyl is substituted with 0 to 3 R^{8f3};

each X^{8f} is independently C₁₋₆ alkylene, C₂₋₆ alkenylene, –O–C₁₋₆ alkylene, O, or S;

each R^{8f1} and R^{8f2} are combined with the carbon to which they are attached to form a heterocycloalkyl having 3 to 10 ring members and 1 to 3 heteroatoms, each independently N, O or S, wherein the heterocycloalkyl is substituted with 0 to 3 R^{8f3};

each R^{8f3} is independently C₁₋₆ alkyl, –Y⁸–C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, –Y⁸–C₁₋₆ deuterioalkyl, –OH, –C₁₋₆ alkyl–OH, –Y⁸–C₁₋₆ alkyl–OH, –C₁₋₆ alkyl–Y⁸–C₁₋₆ alkyl, –(C₁₋₂ alkyl–O)₁₋₄–C₁₋₂ alkyl, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, –Y⁸–C₁₋₆ haloalkyl, cyano, –C₁₋₆ alkyl–cyano, oxo, C₃₋₆ cycloalkyl, –X^{8f3}–C₃₋₆ cycloalkyl, heterocycloalkyl, –X^{8f3}– heterocycloalkyl, phenyl, –X^{8f3}–phenyl, heteroaryl, or –X^{8f3}–heteroaryl, wherein each heterocycloalkyl has 3 to 12 members and 1 to 4 heteroatoms, each independently N, O, S, or S(O)₂, and each heteroaryl has 5 to 10 ring members and 1 to 4 heteroatoms, each independently N, O, or S, and wherein nitrogen atom ring members in each heterocycloalkyl and heteroaryl are substituted with 0 to 1 C₁₋₄ alkyl;

each X^{8f3} is independently C₁₋₆ alkylene, O, C(O), or S(O)₂;

each Y⁸ is independently C(O), C(O)O, N(R^{8f4})C(O), O, S, or S(O)₂;

alternatively, two R^{8f3} groups on the same or adjacent ring vertices combine to form a C₃₋₆ cycloalkyl or a heterocycloalkyl having 3 to 6 ring members and 1 to 3 heteroatoms, each independently N, O or S, wherein nitrogen atom ring members in the heterocycloalkyl are substituted with 0 to 1 C₁₋₄ alkyl; and

each R^{8f4} is independently H or C₁₋₆ alkyl;

or a pharmaceutically acceptable salt thereof.

3. The compound of claim 1, or the pharmaceutically acceptable salt thereof, wherein

R³ is

- (a) C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, or C₁₋₆ haloalkyl, each substituted with 0 to 5 R^{3a},
- (b) C₃₋₁₂ cycloalkyl substituted with 0 to 5 R^{3b}, or
- (c) heterocycloalkyl having 3 to 12 ring members and 1 to 4 heteroatoms, each independently N, O, or S, wherein the heterocycloalkyl is substituted with 0 to 5 R^{3c};

each R^{3a} is -OH, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, or -O-C(O)C₁₋₆ alkyl;

each R^{3b} is independently C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, -OH, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, or cyano;

each R^{3c} is independently C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, or oxo;

R^{4a} is H or C₁₋₆ alkyl;

R^{4b} and R^{4c} are each independently H, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, -C₁₋₆ alkyl-C₃₋₆ cycloalkyl, heterocycloalkyl, -C₁₋₆ alkyl-heterocycloalkyl, phenyl, -C₁₋₆ alkyl-phenyl, heteroaryl, or -C₁₋₆ alkyl-heteroaryl, wherein each heterocycloalkyl has 3 to 6 ring members and 1 to 3 heteroatoms, each independently N, O, or S, and each heteroaryl has 5 to 6 ring members and 1 to 3 heteroatoms, each independently N, O, or S;

alternatively, R^{4c} and R^{4a} together with the carbon and nitrogen to which each is attached combine to form a heterocycloalkyl having 3 to 6 ring members, wherein the heterocycloalkyl is substituted with 0 to 4 R^{4a1};

each R^{4a1} is independently C₁₋₆ alkyl, -OH, C₁₋₆ alkyl-OH, C₁₋₆ alkoxy, or halo;

R^{5a} is H or C₁₋₆ alkyl;

R^{5b} and R^{5c} are each independently H, C₁₋₆ alkyl, -C₁₋₆ alkyl-OH, C₂₋₆ alkoxyalkyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, C₁₋₆ alkyl-C₃₋₆ cycloalkyl, heterocycloalkyl, -C₁₋₆ alkyl-heterocycloalkyl, phenyl, -C₁₋₆ alkyl-phenyl, heteroaryl, or -C₁₋₆ alkyl-heteroaryl, wherein each heterocycloalkyl has 3 to 6 ring members and 1 to 3 heteroatoms, each independently N, O, or S, and each heteroaryl has 5 to 6 ring members and 1 to 3 heteroatoms, each independently N, O, or S, and wherein each cycloalkyl, heterocycloalkyl, phenyl, and heteroaryl is substituted with 0 to 3 R^{5b5};

each R^{5b5} is independently C₁₋₆ alkyl, halo, or C₁₋₆ haloalkyl;

X⁶ is C₆₋₇ alkylene or C₆₋₇ alkenylene;

R^{6a} is H, C₁₋₆ alkyl, C₂₋₆ alkoxyalkyl, C₃₋₆ cycloalkyl, -C₁₋₆ alkyl-C₃₋₆ cycloalkyl, heterocycloalkyl, -C₁₋₆ alkyl-heterocycloalkyl, phenyl, -C₁₋₆ alkyl-phenyl, heteroaryl, or -C₁₋₆ alkyl-heteroaryl, wherein the heterocycloalkyl has 3 to 6 ring members and 1 to 3 heteroatoms, each independently N, O, or S, and the heteroaryl has 5 to 6 ring members and 1 to 3 heteroatoms, each independently N, O, or S;

R^{6b} and R^{6d} are each independently H or C₁₋₆ alkyl;

R^{7a} is H or C₁₋₆ alkyl;

R^{7b} and R^{7c} are each independently H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₁₋₆ haloalkyl, C₁₋₆ alkyl-OH, C₃₋₆ cycloalkyl, or -C₁₋₆ alkyl-C₃₋₆ cycloalkyl;

R^{8a} is H, C₁₋₆ alkyl, C₂₋₆ alkoxyalkyl, C₃₋₆ cycloalkyl or -C₁₋₆ alkyl-C₃₋₆ cycloalkyl;

R^{8b}, R^{8d}, and R^{8e} are each independently H or C₁₋₆ alkyl;

ring B is aryl or heteroaryl having 5 to 12 ring members and 1 to 6 heteroatoms, each independently N, O or S;

the subscript m8 is an integer from 0 to 5;

each R^{8f} is independently C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ alkoxy, C₁₋₆ deutoalkoxy, halo, C₁₋₆ haloalkyl, cyano, -X^{8f}-cyano, C₃₋₁₂ cycloalkyl, -X^{8f}-C₃₋₆ cycloalkyl, -CH=CR^{8f1}R^{8f2}, heterocycloalkyl, -X^{8f}-heterocycloalkyl, aryl, -X^{8f}-aryl, heteroaryl, or -X^{8f}-heteroaryl, wherein each heterocycloalkyl has 3 to 12 ring members and 1 to 4 heteroatoms, each independently N, O, or S, and each heteroaryl has 5 to 10 ring members and 1 to 4 heteroatoms, each independently N, O, or S, wherein each alkynyl, cycloalkyl, heterocycloalkyl, phenyl, and heteroaryl is substituted with 0 to 3 R^{8f3};

alternatively, two R^{8f} groups on adjacent ring vertices combine to form a C₃₋₆ cycloalkyl or a heterocycloalkyl having 3 to 6 ring members and 1 to 3 heteroatoms, each independently N, O or S;

each X^{8f} is independently C₁₋₆ alkylene, C₂₋₆ alkenylene, O, or S;

each R^{8f1} and R^{8f2} are combined with the carbon to which they are attached to form a heterocycloalkyl having 3 to 10 ring members and 1 to 3 heteroatoms, each independently N, O or S, wherein the heterocycloalkyl is substituted with 0 to 3 R^{8f3};

each R^{8f3} is independently C_{1-6} alkyl, $-Y^8-C_{1-6}$ alkyl, C_{1-6} deuterioalkyl, $-Y^8-C_{1-6}$ deuterioalkyl, $-OH$, $-C_{1-6}$ alkyl- OH , $-Y^8-C_{1-6}$ alkyl- OH , $-C_{1-6}$ alkyl- Y^8-C_{1-6} alkyl, C_{1-6} alkoxy, halo, C_{1-6} haloalkyl, $-Y^8-C_{1-6}$ haloalkyl, cyano, $-C_{1-6}$ alkyl-cyano, oxo, C_{3-6} cycloalkyl, $-X^{8f3}-C_{3-6}$ cycloalkyl, heterocycloalkyl, $-X^{8f3}$ -heterocycloalkyl, phenyl, $-X^{8f3}$ -phenyl, heteroaryl, or $-X^{8f3}$ -heteroaryl, wherein each heterocycloalkyl has 3 to 12 members and 1 to 4 heteroatoms, each independently N, O, S, or $S(O)_2$, and each heteroaryl has 5 to 10 ring members and 1 to 4 heteroatoms, each independently N, O, or S, and wherein nitrogen atom ring members in each heterocycloalkyl and heteroaryl are substituted with 0 to 1 C_{1-4} alkyl;

each X^{8f3} is independently C_{1-6} alkylene, O, $C(O)$, or $S(O)_2$;

each Y^8 is independently $C(O)$, $C(O)O$, $N(R^{8f4})C(O)$, O, S, or $S(O)_2$;

alternatively, two R^{8f3} groups on adjacent ring vertices combine to form a C_{3-6} cycloalkyl or a heterocycloalkyl having 3 to 6 ring members and 1 to 3 heteroatoms, each independently N, O or S; and

each R^{8f4} is independently H or C_{1-6} alkyl.

4. The compound of any one of claims 1 to 3, or the pharmaceutically acceptable salt thereof, wherein R^3 is (a) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{1-6} haloalkyl substituted with 0 to 5 R^{3a} .

5. The compound of any one of claims 1 to 3, or the pharmaceutically acceptable salt thereof, wherein R^3 is (a) C_{1-6} alkyl or C_{1-6} haloalkyl substituted with 0 to 2 R^{3a} .

6. The compound of any one of claims 1 to 5, or the pharmaceutically acceptable salt thereof, wherein each R^{3a} is $-OH$.

7. The compound of any one of claims 1 to 3, or the pharmaceutically acceptable salt thereof, wherein R^3 is (b) C_{3-7} cycloalkyl substituted with 0 to 3 R^{3b} .

8. The compound of any one of claims 1 to 3, or the pharmaceutically acceptable salt thereof, wherein R^3 is (b) C_{3-4} cycloalkyl substituted with 0 to 2 R^{3b} .

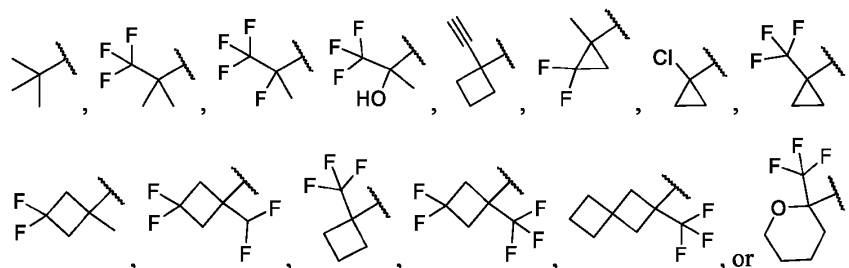
9. The compound of claim 7 or claim 8, or the pharmaceutically acceptable salt thereof, wherein each R^{3b} is halo or C_{1-4} haloalkyl.

10. The compound of any one of claims 1 to 3, or the pharmaceutically acceptable salt thereof, wherein R^3 is (c) heterocycloalkyl having 3 to 6 ring members and 1 to 3 heteroatoms, each independently N, O, or S, wherein the heterocycloalkyl is substituted with 0 to 5 R^{3c} .

11. The compound of claim 10, or the pharmaceutically acceptable salt thereof, wherein each R^{3c} is halo or C_{1-4} haloalkyl.

12. The compound of claim 10, or the pharmaceutically acceptable salt thereof, wherein each R^{3c} is fluoro or trifluoromethyl.

13. The compound of any one of claims 1 to 12, or the pharmaceutically acceptable salt thereof, wherein R^3 is



14. The compound of any one of claims 1 to 13, or the pharmaceutically acceptable salt thereof, wherein

R^{4a} , R^{4b} , and R^{4c} are each independently H or C_{1-6} alkyl;

alternatively, R^{4c} and R^{4a} together with the carbon and nitrogen to which each is attached combine to form a heterocycloalkyl having 4 to 6 ring members and 1 to 3 heteroatoms, each independently N, O, or S, wherein the heterocycloalkyl is substituted with 0 to 2 R^{4a1} ; and

each R^{4a1} is independently halo.

15. The compound of any one of claims 1 to 13, or the pharmaceutically acceptable salt thereof, wherein

R^{4a} , R^{4b} , and R^{4c} are each independently H or C_{1-6} alkyl.

16. The compound of any one of claims 1 to 13, or the pharmaceutically acceptable salt thereof, wherein

R^{4b} is H or C₁₋₆ alkyl; and

R^{4c} and R^{4a} together with the carbon and nitrogen to which each is attached combine to form a heterocycloalkyl having 4 to 6 ring members, wherein the heterocycloalkyl is substituted with 0 to 3 R^{4a1}.

17. The compound of any one of claims 1 to 16, or the pharmaceutically acceptable salt thereof, wherein

R^{4a} and R^{4b} are each H; and

R^{4c} is ethyl;

alternatively, R^{4c} and R^{4a} together with the carbon and nitrogen to which each is attached combine to form a pyrrolidinyl, substituted with 0 to 2 fluoro.

18. The compound of any one of claims 1 to 17, or the pharmaceutically acceptable salt thereof, wherein

R^{5a} is H or C₁₋₆ alkyl;

R^{5b} and R^{5c} are each independently H, C₁₋₆ alkyl, -C₁₋₆ alkyl-OH, C₂₋₆ alkoxyalkyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, or C₁₋₄ alkyl-C₃₋₆ cycloalkyl, wherein each cycloalkyl is substituted with 0 to 3 R^{5b5}; and

each R^{5b5} is independently C₁₋₄ alkyl, halo, or C₁₋₄ haloalkyl.

19. The compound of any one of claims 1 to 18, or the pharmaceutically acceptable salt thereof, wherein

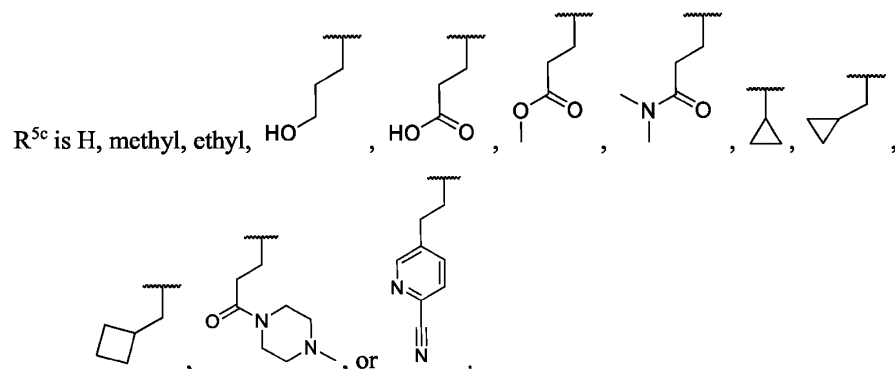
R^{5a} is H or C₁₋₆ alkyl;

R^{5b} is H; and

R^{5c} is C₃₋₆ cycloalkyl or C₁₋₄ alkyl-C₃₋₆ cycloalkyl.

20. The compound of any one of claims 1 to 19, or the pharmaceutically acceptable salt thereof, wherein

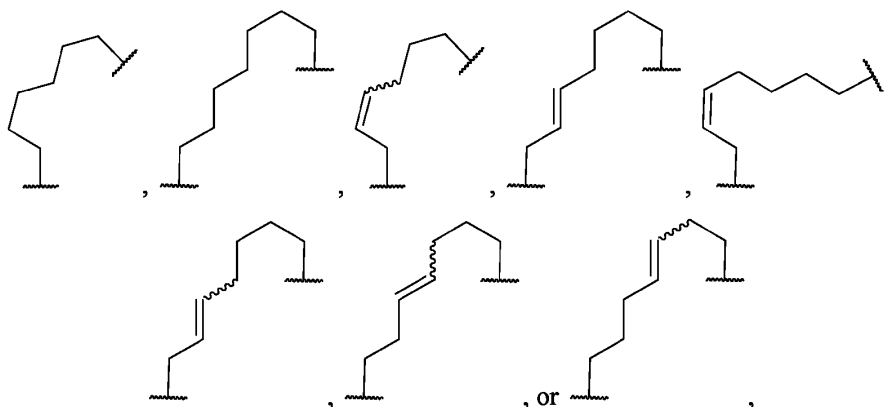
R^{5a} and R^{5b} are each H; and



21. The compound of any one of claims 1 to 20, or the pharmaceutically acceptable salt thereof, wherein X^6 is C_{6-7} alkylene.

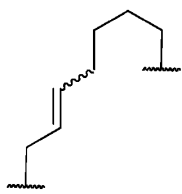
22. The compound of any one of claims 1 to 20, or the pharmaceutically acceptable salt thereof, wherein X^6 is C_{6-7} alkenylene.

23. The compound of any one of claims 1 to 22, or the pharmaceutically acceptable salt thereof, wherein X^6 is



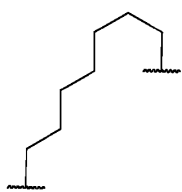
wherein the wavy bond attached to the double bond indicates E, Z, or a mixture of both isomers.

24. The compound of any one of claims 1 to 23, or the pharmaceutically acceptable salt thereof, wherein X^6 is



wherein the wavy bond attached to the double bond indicates E, Z, or a mixture of both isomers.

25. The compound of any one of claims 1 to 23, or the pharmaceutically acceptable salt thereof, wherein X^6 is

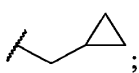


26. The compound of any one of claims 1 to 25, or the pharmaceutically acceptable salt thereof, wherein

R^{6a} is H, C_{1-4} alkyl, or $-C_{1-4}$ alkyl- C_{3-6} cycloalkyl; and

R^{6b} and R^{6d} are each independently H or C_{1-6} alkyl.

27. The compound of any one of claims 1 to 26, or the pharmaceutically acceptable salt thereof, wherein

R^{6a} is H, methyl, ethyl, or  ;

R^{6b} is H; and

R^{6d} is H, methyl, or ethyl.

28. The compound of any one of claims 1 to 27, or the pharmaceutically acceptable salt thereof, wherein

R^{7a} and R^{7b} are each independently H or C_{1-6} alkyl; and

R^{7c} is C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} haloalkyl, C_{1-6} alkyl-OH, or $-C_{1-6}$ alkyl- C_{3-6} cycloalkyl.

29. The compound of any one of claims 1 to 27, or the pharmaceutically acceptable salt thereof, wherein

R^{7a} and R^{7b} are each H; and

R^{7c} is C_{1-6} alkyl.

30. The compound of any one of claims 1 to 29, or the pharmaceutically acceptable salt thereof, wherein

R^{7a} and R^{7b} are each H; and

R^{7c} is isobutyl, , , , or .

31. The compound of any one of claims 1 to 28, or the pharmaceutically acceptable salt thereof, wherein

R^{7a} and R^{7b} are each H; and

R^{7c} is isobutyl.

32. The compound of any one of claims 1 to 31, or the pharmaceutically acceptable salt thereof, wherein

R^{8a} , R^{8b} , R^{8d} , and R^{8e} are each independently H or C_{1-6} alkyl.

33. The compound of any one of claims 1 to 31, or the pharmaceutically acceptable salt thereof, wherein

R^{8a} is H or methyl; and

R^{8b} , R^{8d} and R^{8e} are each H.

34. The compound of any one of claims 1 to 33, or the pharmaceutically acceptable salt thereof, wherein ring B is phenyl.

35. The compound of any one of claims 1 to 33, or the pharmaceutically acceptable salt thereof, wherein ring B is biphenyl.

36. The compound of any one of claims 1 to 33, or the pharmaceutically acceptable salt thereof, wherein ring B is a heteroaryl having 5 to 6 ring members and 1 to 3 heteroatoms, wherein each heteroatom is N.

37. The compound of any one of claims 1 to 33, or the pharmaceutically acceptable salt thereof, wherein ring B is naphthyl, thiophenyl, benzofuranyl, indolyl, indazolyl, or quinolinyl.

38. The compound of any one of claims **1** to **33**, or the pharmaceutically acceptable salt thereof, wherein ring B is pyrid-3-yl.

39. The compound of any one of claims **1** to **38**, or the pharmaceutically acceptable salt thereof, wherein the subscript m8 is 1, 2, or 3.

40. The compound of any one of claims **1** to **39**, or the pharmaceutically acceptable salt thereof, wherein at least one R^{8f} is halo.

41. The compound of any one of claims **1** to **40**, or the pharmaceutically acceptable salt thereof, wherein

each R^{8f} is independently C₁₋₆ alkyl, C₂₋₆ alkenyl, C₁₋₆ alkoxy, C₁₋₆ deutoalkoxy, halo, C₁₋₆ haloalkyl, cyano, or -X^{8f}-cyano.

42. The compound of any one of claims **1** to **40**, or the pharmaceutically acceptable salt thereof, wherein

each R^{8f} is independently halo, C₃₋₆ cycloalkyl, -X^{8f}-C₃₋₆ cycloalkyl, -CH=CR^{8f1}R^{8f2}, heterocycloalkyl, -X^{8f}-heterocycloalkyl, phenyl, -X^{8f}-phenyl, heteroaryl, or -X^{8f}-heteroaryl, wherein each heterocycloalkyl has 3 to 10 ring members and 1 to 3 heteroatoms, each independently N, O, or S, and each heteroaryl has 5 to 10 ring members and 1 to 3 heteroatoms, each independently N, O, or S, wherein each cycloalkyl, heterocycloalkyl, phenyl, and heteroaryl is substituted with 0 to 3 R^{8f3};

each X^{8f} is independently C₁₋₆ alkylene, C₂₋₆ alkenylene, O, or S; and

each R^{8f1} and R^{8f2} are combined with the carbon to which they are attached to form a heterocycloalkyl having 3 to 10 ring members and 1 to 3 heteroatoms, each independently N, O or S, wherein the heterocycloalkyl is substituted with 0 to 3 R^{8f3}.

43. The compound of any one of claims **1** to **42**, or the pharmaceutically acceptable salt thereof, wherein each X^{8f} is independently C₁₋₆ alkylene.

44. The compound of any one of claims **1** to **40**, or the pharmaceutically acceptable salt thereof, wherein

each R^{8f} is independently halo, C_{3-6} cycloalkyl, $-CH=CR^{8f1}R^{8f2}$, heterocycloalkyl, phenyl, or heteroaryl, wherein each heterocycloalkyl has 3 to 10 ring members and 1 to 3 heteroatoms, each independently N, O, or S, and each heteroaryl has 5 to 10 ring members and 1 to 3 heteroatoms, each independently N, O, or S, wherein each cycloalkyl, heterocycloalkyl, phenyl, and heteroaryl is substituted with 0 to 3 R^{8f3} ;

each R^{8f1} and R^{8f2} are combined with the carbon to which they are attached to form a heterocycloalkyl having 3 to 10 ring members and 1 to 3 heteroatoms, each independently N, O or S, wherein the heterocycloalkyl is substituted with 0 to 3 R^{8f3} .

45. The compound of any one of claims 1 to 40, or the pharmaceutically acceptable salt thereof, wherein

each R^{8f} is independently C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-4} alkoxy, C_{1-4} deuterioalkoxy, halo, C_{1-4} haloalkyl, cyano, or $-C_{1-2}$ alkyl-cyano.

46. The compound of any one of claims 1 to 40, or the pharmaceutically acceptable salt thereof, wherein

each R^{8f} is independently halo, C_{3-6} cycloalkyl, $-O-C_{3-6}$ cycloalkyl, heterocycloalkyl, $-C_{2-4}$ alkenyl-heterocycloalkyl, $-O$ -heterocycloalkyl, phenyl, $-O$ -phenyl, heteroaryl, or $-O$ -heteroaryl, wherein each heterocycloalkyl has 3 to 6 ring members and 1 to 2 heteroatoms, each independently N, O, or S, and each heteroaryl has 5 to 6 ring members and 1 to 3 heteroatoms, each independently N, O, or S, wherein each cycloalkyl, heterocycloalkyl, phenyl, and heteroaryl is substituted with 0 to 3 R^{8f3} .

47. The compound of any one of claims 1 to 40, or the pharmaceutically acceptable salt thereof, wherein

each R^{8f} is independently halo, C_{3-6} cycloalkyl, $-O-C_{3-6}$ cycloalkyl, heteroaryl, or $-O$ -heteroaryl, wherein each heteroaryl has 5 to 6 ring members and 1 to 3 heteroatoms, each independently N, O, or S, wherein each cycloalkyl, and heteroaryl is substituted with 0 to 3 R^{8f3} .

48. The compound of any one of claims 1 to 40, or the pharmaceutically acceptable salt thereof, wherein

each R^{8f} is independently halo, heterocycloalkyl, -O-heterocycloalkyl, phenyl, or -O-phenyl, wherein each heterocycloalkyl has 3 to 6 ring members and 1 to 2 heteroatoms, each independently N, O, or S, wherein each heterocycloalkyl and phenyl is substituted with 0 to 3 R^{8f}.

49. The compound of any one of claims 1 to 48, or the pharmaceutically acceptable salt thereof, wherein

each R^{8f3} is independently C₁₋₆ alkyl, -Y⁸-C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, -Y⁸-C₁₋₆ deuterioalkyl, -OH, -C₁₋₆ alkyl-OH, -Y⁸-C₁₋₆ alkyl-OH, -C₁₋₆ alkyl-Y⁸-C₁₋₆ alkyl, halo, C₁₋₆ haloalkyl, -Y⁸-C₁₋₆ haloalkyl, or oxo;
each Y⁸ is independently C(O), C(O)O, N(R^{8f4})C(O), O, S, or S(O)₂; and
each R^{8f4} is independently H or C₁₋₆ alkyl.

50. The compound of any one of claims 1 to 48, or the pharmaceutically acceptable salt thereof, wherein each R^{8f3} is independently C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, -OH, -C₁₋₆ alkyl-OH, halo, C₁₋₆ haloalkyl, or oxo.

51. The compound of any one of claims 1 to 48, or the pharmaceutically acceptable salt thereof, wherein

each R^{8f3} is independently C₁₋₆ alkyl or -Y⁸-C₁₋₆ alkyl.

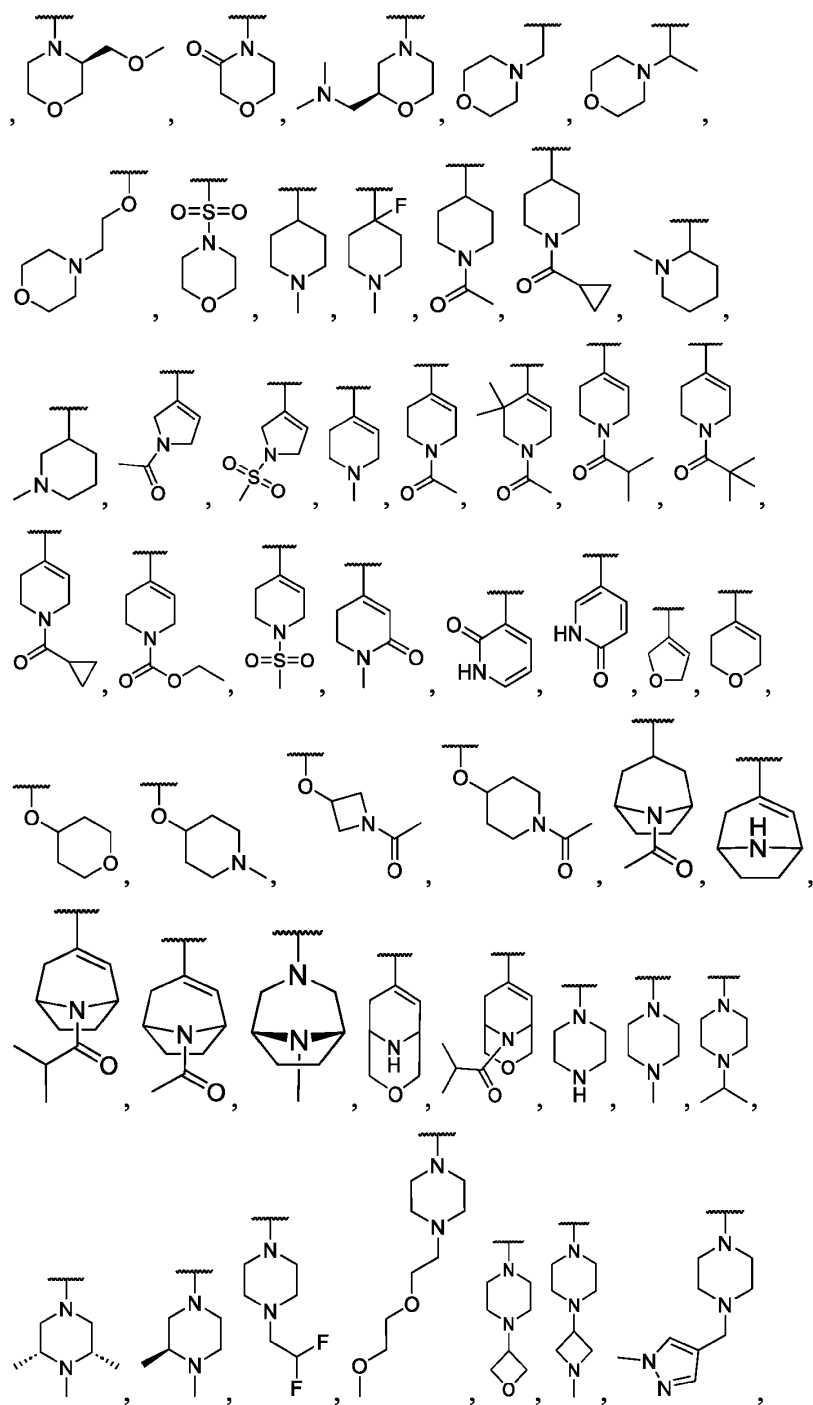
52. The compound of any one of claims 1 to 51, or the pharmaceutically acceptable salt thereof, wherein

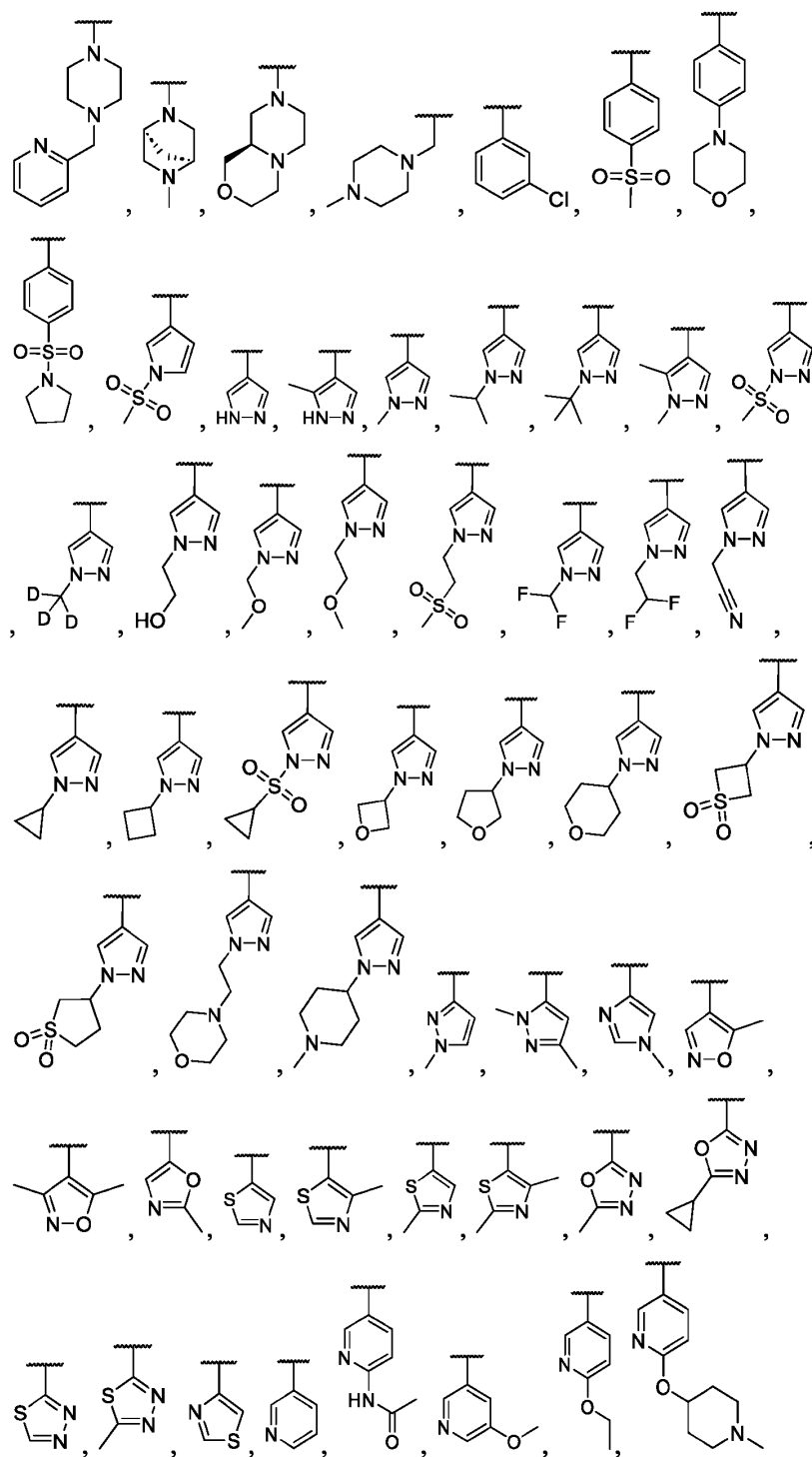
each Y⁸ is independently a C(O) or C(O)O.

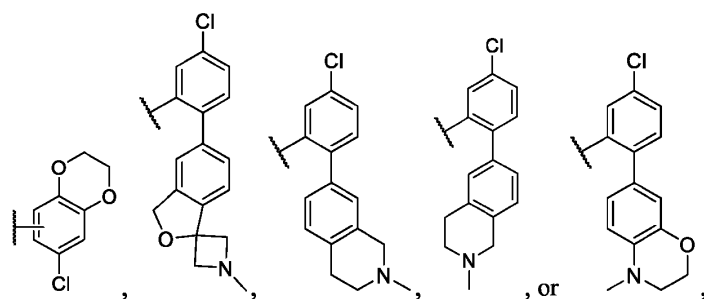
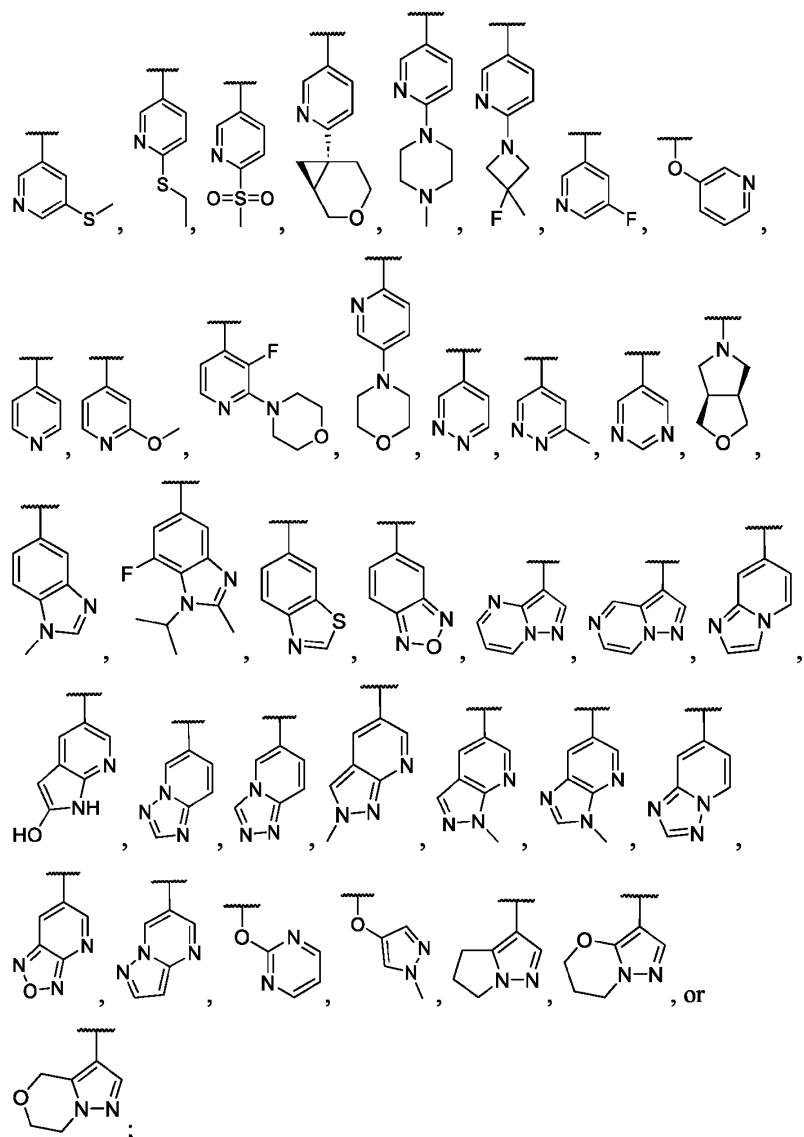
53. The compound of any one of claims 1 to 48, or the pharmaceutically acceptable salt thereof, wherein

each R^{8f3} is independently C₃₋₆ cycloalkyl, -X^{8f3}-C₃₋₆ cycloalkyl, heterocycloalkyl, or -X^{8f3}-heterocycloalkyl, wherein each heterocycloalkyl has 3 to 6 members and 1 to 2 heteroatoms, each independently N, O, S, or S(O)₂; and
each X^{8f3} is independently C₁₋₆ alkylene, C(O), or S(O)₂.

54. The compound of any one of claims 1 to 53, or the pharmaceutically acceptable salt thereof, wherein each R^{8f3} is independently C₃₋₆ cycloalkyl or heterocycloalkyl, wherein each heterocycloalkyl has 3 to 6 members and 1 to 2 heteroatoms, each independently N, O, S, or S(O)₂.



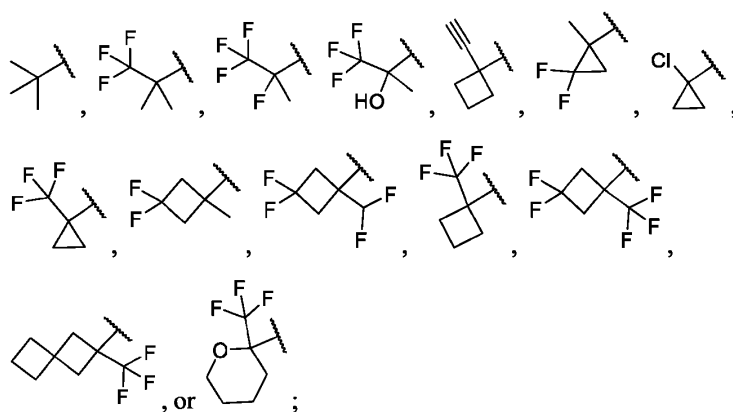




wherein the wavy line identifies attachment to the remainder of the molecule.

59. The compound of claim 1, or the pharmaceutically acceptable salt thereof, wherein

R³ is

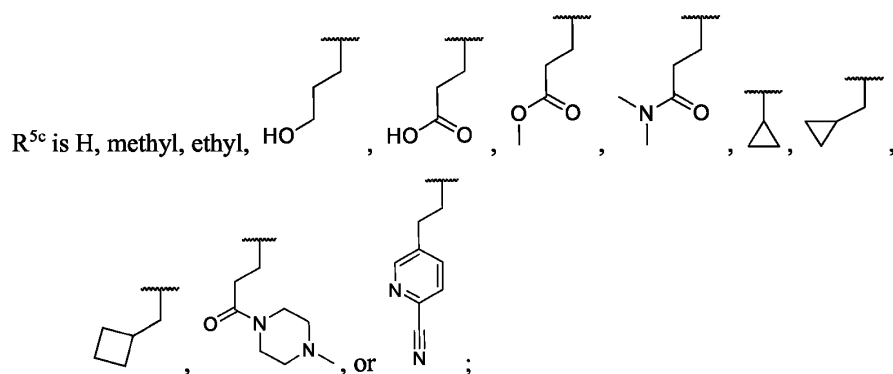


R^{4a} and R^{4b} are each H;

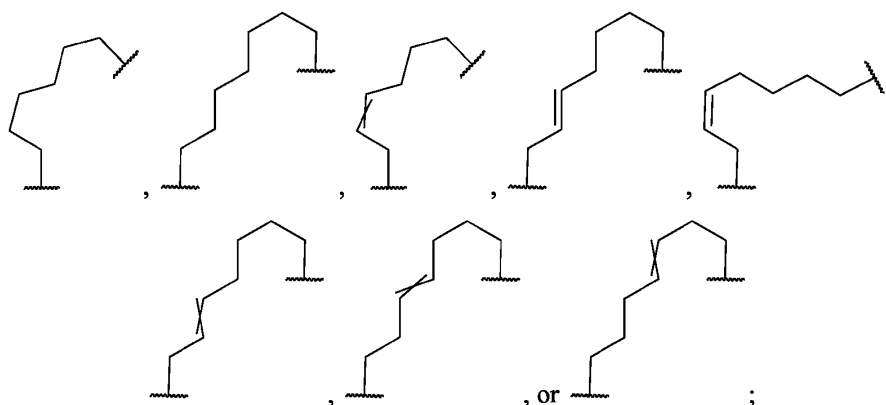
R^{4c} is ethyl;

alternatively, R^{4c} and R^{4a} together with the carbon and nitrogen to which each is attached combine to form a pyrrolidinyl, substituted with 0 to 2 fluoro;

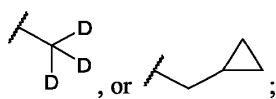
R^{5a} and R^{5b} are each H;



X⁶ is



R^{6a} is H, methyl, ethyl,

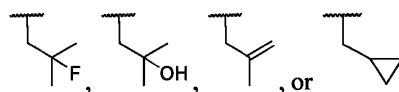


R^{6b} is H;

R^{6d} is H, methyl, or ethyl;

R^{7a} and R^{7b} are each H;

R^{7c} is isobutyl,



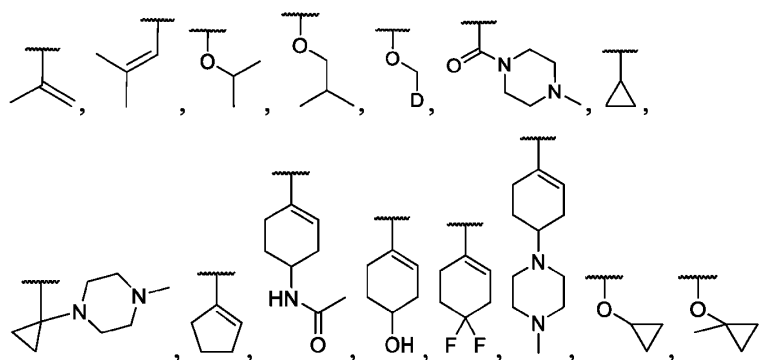
R^{8a} is H or methyl;

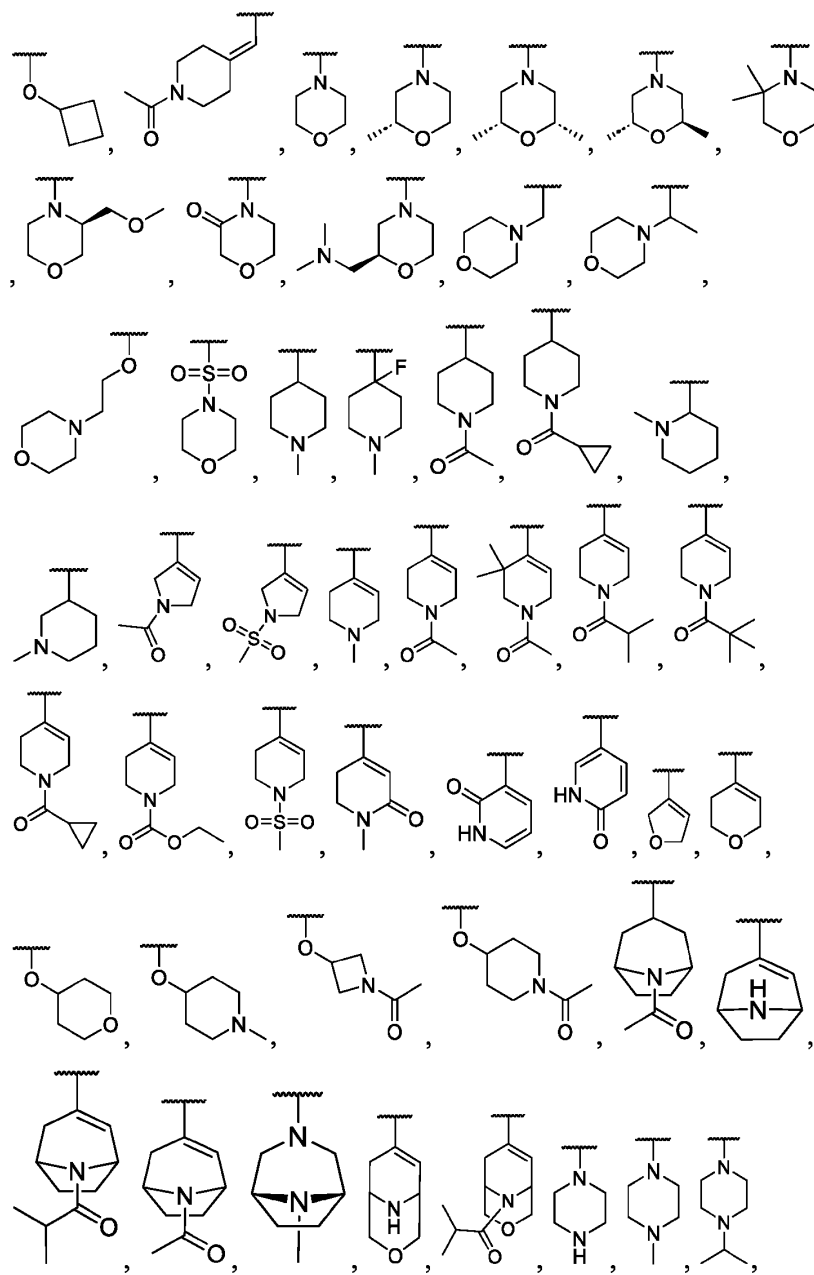
R^{8b} , R^{8d} and R^{8e} are each H;

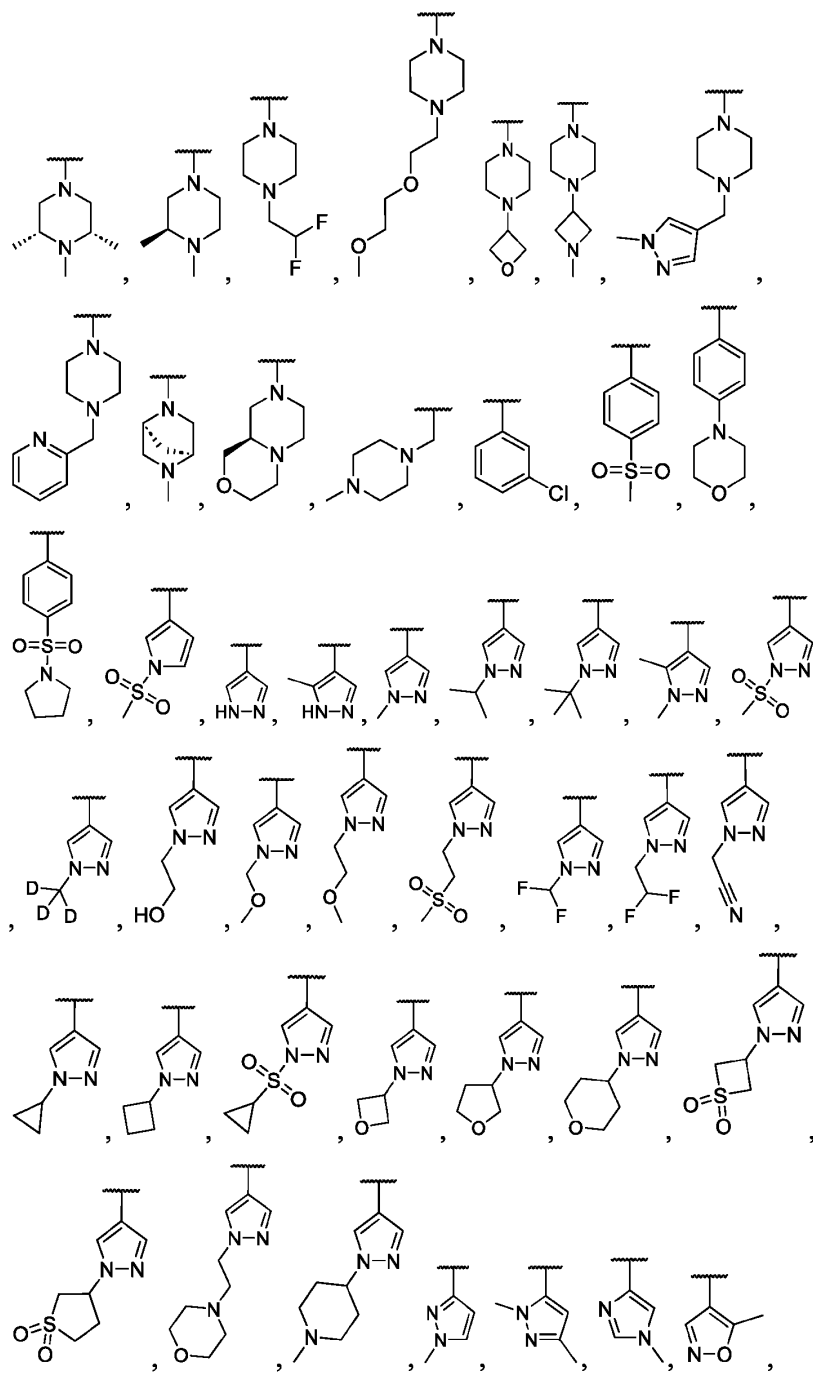
ring B is phenyl, naphthyl, biphenyl, thiophenyl, pyridyl, benzofuranyl, indolyl, indazolyl, or quinolinyl;

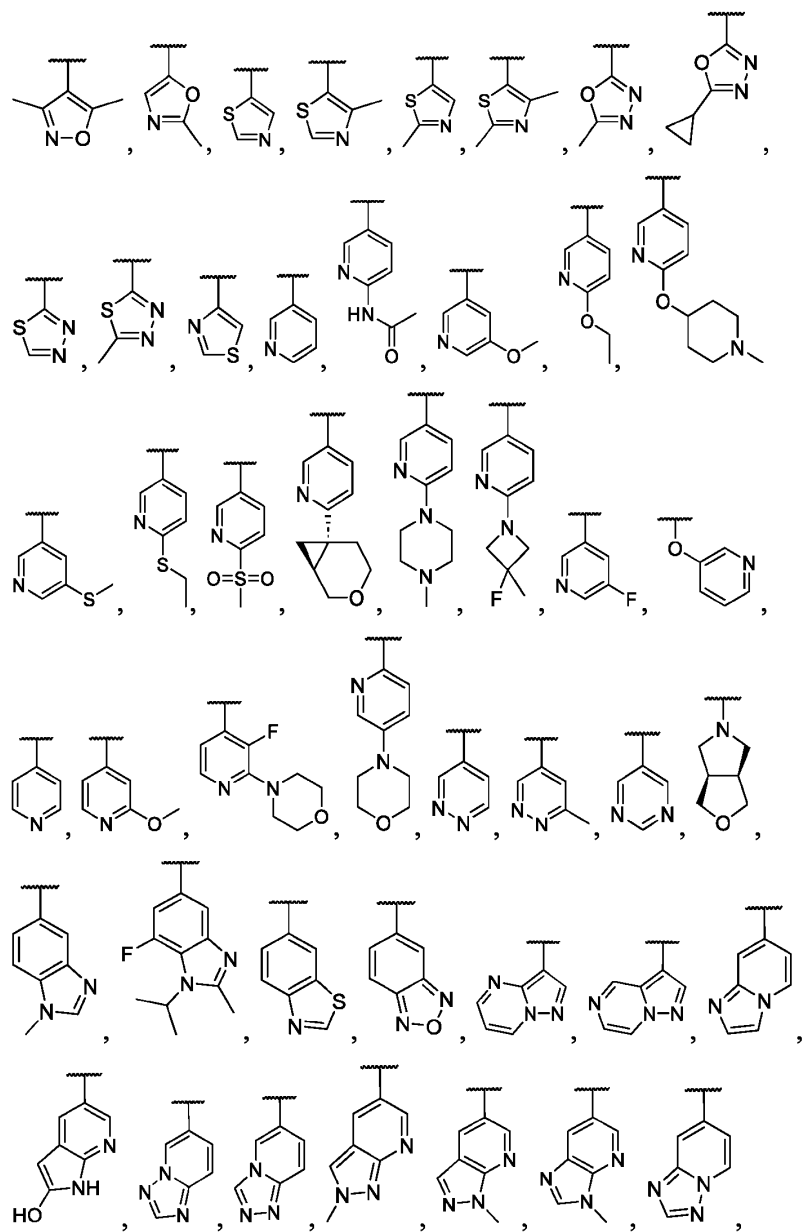
m8 is 1, 2, or 3; and

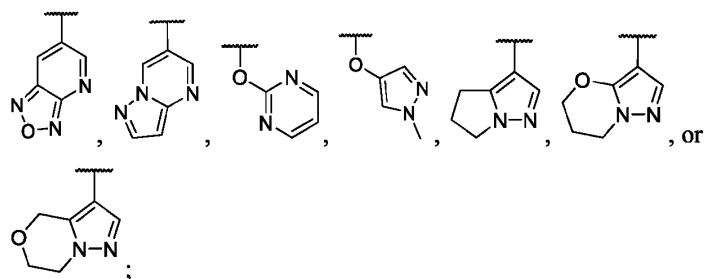
each R^{8f} is independently methyl, isopropyl, isobutyl, methoxy, ethoxy, fluoro, chloro, cyano,



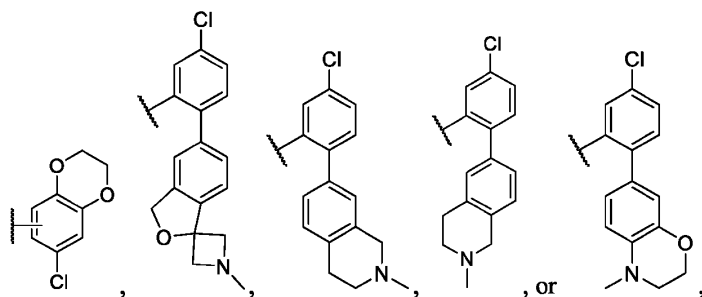






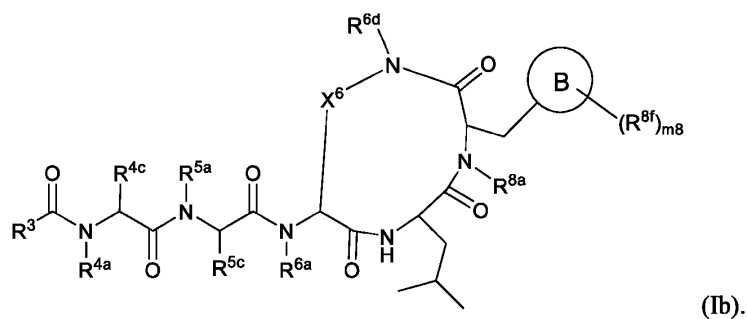


alternatively, ring B and three R^{8f} groups form the moiety

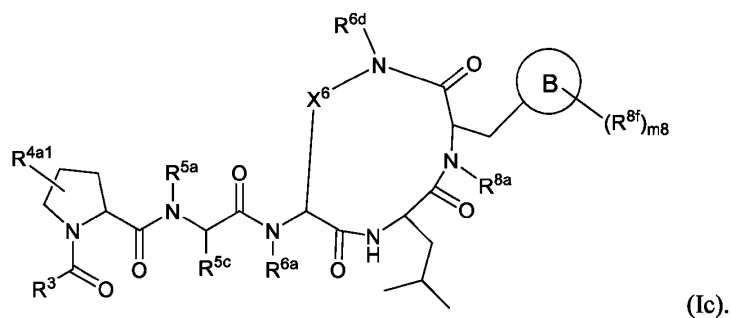


wherein the wavy line identifies attachment to the remainder of the molecule.

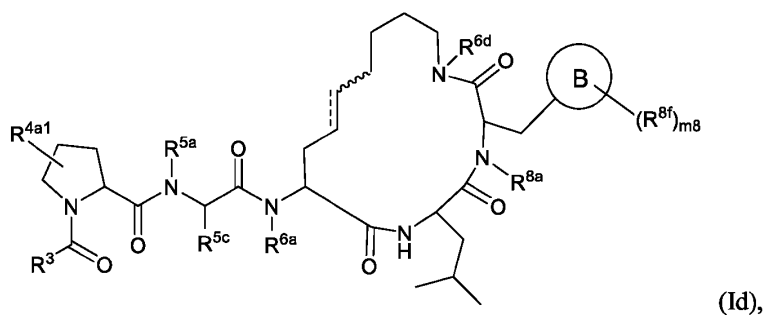
60. The compound of any one of claims 1 to 59, or the pharmaceutically acceptable salt thereof, having the compound of Formula (Ib):



61. The compound of any one of claims 1 to 59, or the pharmaceutically acceptable salt thereof, having the compound of Formula (Ic):



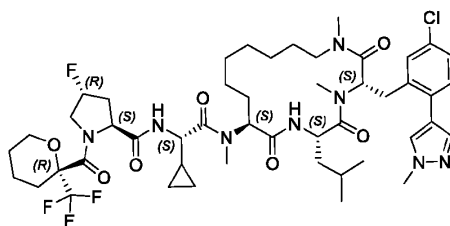
62. The compound of any one of claims 1 to 59, or the pharmaceutically acceptable salt thereof, having the compound of Formula (Id):



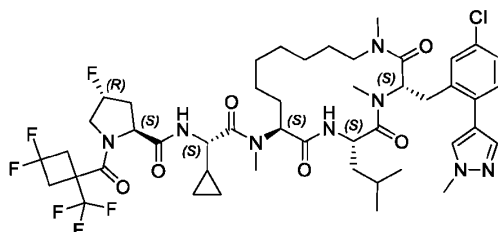
wherein the dashed bond is absent or a single bond, and wherein when the dashed line is a single bond in Formula (Id), the wavy bond attached to the double bond indicates E, Z, or a mixture of both isomers.

63. The compound of claim 1, or the pharmaceutically acceptable salt thereof, having the structure of any one of Examples 1-426.

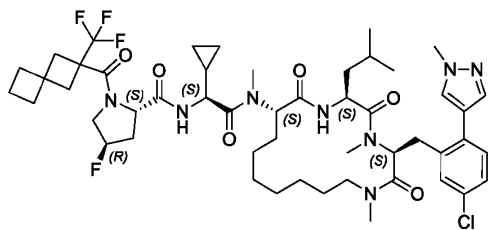
64. The compound of claim 1, or the pharmaceutically acceptable salt thereof, having the structure



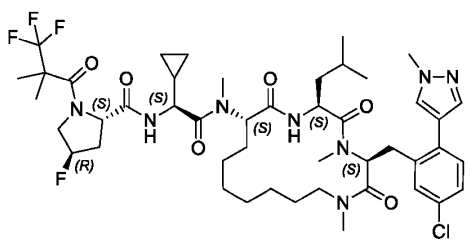
65. The compound of claim 1, or the pharmaceutically acceptable salt thereof, having the structure



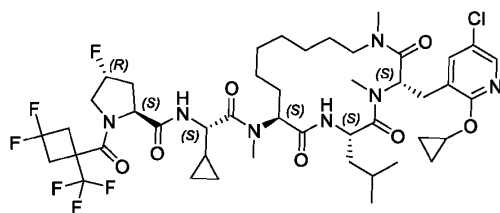
66. The compound of claim 1, or the pharmaceutically acceptable salt thereof, having the structure



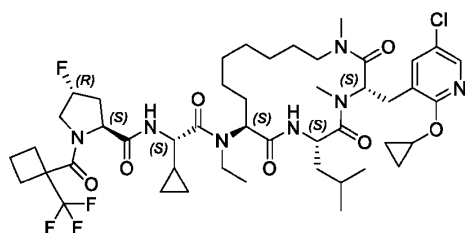
67. The compound of claim 1, or the pharmaceutically acceptable salt thereof, having the structure



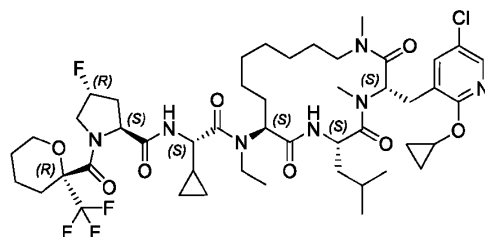
68. The compound of claim 1, or the pharmaceutically acceptable salt thereof, having the structure



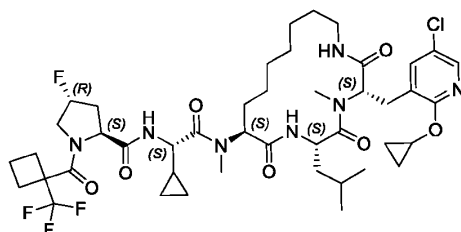
69. The compound of claim 1, or the pharmaceutically acceptable salt thereof, having the structure



70. The compound of claim 1, or the pharmaceutically acceptable salt thereof, having the structure



71. The compound of claim 1, or the pharmaceutically acceptable salt thereof, having the structure



72. A pharmaceutical composition comprising a compound of any one of claims **1** to **71** and a pharmaceutically acceptable excipient.

73. A method of treating a cancer mediated at least in part by cyclin A comprising administering a therapeutically effective amount of a compound of any one of claims **1** to **71**, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim **72**, thereby treating the disorder or condition.

74. A compound of any one of claims **1** to **71**, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim **72** for use in a method for treating a cancer mediated at least in part by cyclin A.

75. Use of a compound of any one of claims **1** to **71**, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim **72** for the manufacture of a medicament for the treatment of a cancer mediated at least in part by cyclin A.