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(54) Title: CDK2 INHIBITORS AND METHODS OF USING THE SAME

(57) Abstract: The present disclosure relates generally to Cyclin-dependent kinase 2 (CDK2) inhibiting chemical compounds and uses thereof in the inhibition of the activity of CDK2. The disclosure also provides pharmaceutically acceptable compositions comprising compounds disclosed herein and methods of using said compounds and compositions in the treatment of various disorders related to CDK2 activity.



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CDK2 INHIBITORS AND METHODS OF USING THE SAME

CROSS REFERENCE TO RELATED APPLICATION

[0001] This application claims the benefit of U.S. Provisional Application No. 63/202,844, filed June 26, 2021, which is hereby incorporated by reference in its entirety.

FIELD

[0002] The present disclosure relates generally to Cyclin-dependent kinase 2 (CDK2) inhibiting chemical compounds and uses thereof in the inhibition of the activity of CDK2. The disclosure also provides pharmaceutically acceptable compositions comprising compounds disclosed herein and methods of using said compounds and compositions in the treatment of various disorders related to CDK2 activity.

BACKGROUND

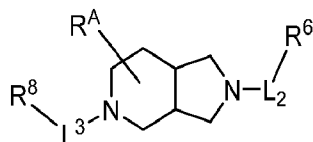
[0003] Cell cycle dysregulation, including uncontrolled cell growth, impaired cell differentiation and abnormal apoptosis have been shown to be caused by over activity of Cyclin-dependent kinases (CDKs). CDKs are important serine/threonine protein kinases that become active when combined with a specific cyclin partner. There are various subtypes of CDKs, each having a different role during the cell cycle, with varying levels of activity during each of the phases. CDK1, CDK2, CDK4 and CDK6 have been found to be specifically important subtypes, where over activity of one or more of these subtypes may lead to dysregulation of the cell cycle and the development of a variety of cancers. The S phase of the cell cycle is responsible for DNA replication and is the phase where aberrant DNA replication may occur. The CDK2/cyclin E complex is required for the cell cycle transition from the G1 phase to the S phase and the CDK2/cyclin A complex is required for the cell cycle transition from the S phase to the G2 phase. Therefore, selective inhibition of the CDK2/cyclin E and/or CDK2/cyclin A complexes can prevent aberrant DNA replication and can be used to treat certain cancers.

[0004] Accordingly, there is a need for the development of compounds capable of inhibiting the activity of CDK2/cyclin complexes, and pharmaceutical compositions thereof, for the prevention, and treatment of CDK2 related diseases or disorders.

SUMMARY

[0005] The present disclosure is based at least in part on the identification of compounds that bind and inhibit Cyclin-dependent kinase 2 (CDK2) and methods of using the same to treat diseases

associated with CDK2 activity. Disclosed herein is a compound according to Formula I or a pharmaceutically acceptable salt thereof:



I

wherein each variable is as defined and described herein.

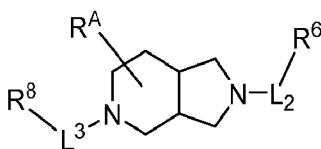
[0006] Compounds of the present disclosure, and pharmaceutically acceptable compositions thereof, are useful for treating a variety of diseases, disorders or conditions, associated with CDK2 activity. Such diseases, disorders, or conditions include those described herein.

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS

1. General Description of Compounds of the Disclosure:

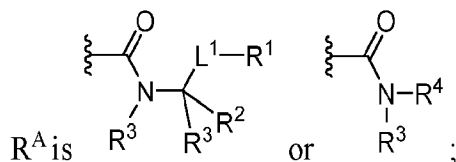
[0007] The present disclosure provides compounds capable of inhibiting Cyclin-dependent kinase 2 (CDK2) and/or CDK2/cyclin complexes.

[0008] In some embodiments, provided herein are compounds according to Formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:



L^1 is a covalent bond or a saturated or unsaturated, straight or branched, optionally substituted bivalent C_{1-6} hydrocarbon chain, wherein 0-2 methylene units of L^1 are independently replaced by -O-, -NR-, -S-, -OC(O)-, -C(O)O-, -C(O)-, -S(O)-, -S(O)₂-, -C(S)-, -NRS(O)₂-, -S(O)₂NR-, -NRC(O)-, -C(O)NR-, -OC(O)NR-, -NRC(O)O-, or -NRC(O)NR-;

R^1 is hydrogen, an optionally substituted C_{1-6} aliphatic group, or an optionally substituted cyclic group selected from a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, a 7-12 membered saturated or partially unsaturated bicyclic carbocyclic ring, phenyl, an 8-10 membered bicyclic aromatic carbocyclic ring, a 3-8 membered saturated or partially unsaturated monocyclic heterocyclic ring (having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur), a 7-12 membered saturated or partially unsaturated bicyclic heterocyclic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), a 5-6 membered monocyclic heteroaromatic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), and an 8-10 membered bicyclic heteroaromatic ring (having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur);

R^2 is hydrogen, an optionally substituted C_{1-6} aliphatic group, $-C(O)OR$, $-C(O)NR_2$, or an optionally substituted cyclic group selected from phenyl and a 5-6 membered monocyclic heteroaromatic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur);

each instance of R^3 is independently hydrogen or an optionally substituted C_{1-6} aliphatic group;

R^4 is a cyclic group selected from a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, a 7-12 membered saturated or partially unsaturated bicyclic carbocyclic ring, phenyl, an 8-10 membered bicyclic aromatic carbocyclic ring, a 3-8 membered saturated or partially unsaturated monocyclic heterocyclic ring (having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur), a 7-12 membered saturated or partially unsaturated bicyclic heterocyclic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), a 5-6 membered monocyclic heteroaromatic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), and an 8-10 membered bicyclic heteroaromatic ring (having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur), wherein the cyclic group is optionally substituted with one or more instances of R^5 ;

each instance of R^5 is independently halogen, $-CN$, $-NO_2$, $-OR$, $-SR$, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, $-S(O)R$, $-S(O)NR_2$, $-C(O)R$, $-C(O)OR$, $-C(O)NR_2$, $-C(O)N(R)OR$, $-OC(O)R$, $-OC(O)NR_2$, -

N(R)C(O)OR, -N(R)C(O)R, -N(R)C(O)NR₂, -N(R)C(NR)NR₂, -N(R)S(O)₂NR₂, -N(R)S(O)₂R, an optionally substituted C₁₋₆ aliphatic group, or an optionally substituted -C₁₋₆ aliphatic-Cy group;

L² is a saturated or unsaturated, straight or branched, optionally substituted bivalent C₁₋₄ hydrocarbon chain, wherein 0-2 methylene units of L² are independently replaced by -O-, -NR-, -S-, -OC(O)-, -C(O)O-, -C(O)-, -S(O)-, -S(O)₂-, -C(S)-, -NRS(O)₂-, -S(O)₂NR-, -NRC(O)-, -C(O)NR-, -OC(O)NR-, -NRC(O)O-, or -NRC(O)NR-;

R⁶ is an optionally substituted C₁₋₆ aliphatic group, or a cyclic group selected from a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, a 7-12 membered saturated or partially unsaturated bicyclic carbocyclic ring, phenyl, an 8-10 membered bicyclic aromatic carbocyclic ring, a 3-8 membered saturated or partially unsaturated monocyclic heterocyclic ring (having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur), a 7-12 membered saturated or partially unsaturated bicyclic heterocyclic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), a 5-6 membered monocyclic heteroaromatic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), and an 8-10 membered bicyclic heteroaromatic ring (having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur), wherein the cyclic group is optionally substituted with one or more instances of R⁷;

each instance of R⁷ is independently halogen, -CN, -NO₂, -OR, -SR, -NR₂, -S(O)₂R, -S(O)₂NR₂, -S(O)R, -S(O)NR₂, -C(O)R, -C(O)OR, -C(O)NR₂, -C(O)N(R)OR, -OC(O)R, -OC(O)NR₂, -N(R)C(O)OR, -N(R)C(O)R, -N(R)C(O)NR₂, -N(R)C(O)S(O)₂R, -N(R)C(NR)NR₂, -N(R)S(O)₂NR₂, -N(R)S(O)₂R, an optionally substituted C₁₋₆ aliphatic group, or Cy, or two instances of R⁶ on the same carbon atom are taken together to form an oxo group;

L³ is a saturated or unsaturated, straight or branched, optionally substituted bivalent C₁₋₄ hydrocarbon chain, wherein 0-2 methylene units of L³ are independently replaced by -O-, -NR-, -S-, -OC(O)-, -C(O)O-, -C(O)-, -S(O)-, -S(O)₂-, -C(S)-, -NRS(O)₂-, -S(O)₂NR-, -NRC(O)-, -C(O)NR-, -OC(O)NR-, -NRC(O)O-, or -NRC(O)NR-;

R⁸ is a cyclic group selected from a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, a 7-12 membered saturated or partially unsaturated bicyclic carbocyclic ring, phenyl, an 8-10 membered bicyclic aromatic carbocyclic ring, a 3-8 membered

saturated or partially unsaturated monocyclic heterocyclic ring (having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur), a 7-12 membered saturated or partially unsaturated bicyclic heterocyclic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), a 5-6 membered monocyclic heteroaromatic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), and an 8-10 membered bicyclic heteroaromatic ring (having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur), wherein the cyclic group is optionally substituted with one or more instances of R⁹;

each instance of R⁹ is independently halogen, -CN, -NO₂, -OR, -SR, -NR₂, -S(O)₂R, -S(O)₂NR₂, -S(O)R, -S(O)NR₂, -C(O)R, -C(O)OR, -C(O)NR₂, -C(O)N(R)OR, -OC(O)R, -OC(O)NR₂, -N(R)C(O)OR, -N(R)C(O)R, -N(R)C(O)NR₂, -N(R)C(NR)NR₂, -N(R)S(O)₂NR₂, -N(R)S(O)₂R, an optionally substituted C₁₋₆ aliphatic group, an optionally substituted C₁₋₆ aliphatic-Cy group, or Cy;

each Cy is independently an optionally substituted cyclic group selected from a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, phenyl, a 3-8 membered saturated or partially unsaturated monocyclic heterocyclic ring (having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur), and a 5-6 membered monocyclic heteroaromatic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur); and

each R is independently hydrogen, or an optionally substituted C₁₋₆ aliphatic group, an optionally substituted phenyl, an optionally substituted 3-7 membered saturated or partially unsaturated carbocyclic ring, an optionally substituted 3-7 membered saturated or partially unsaturated heterocyclic ring (having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur), or an optionally substituted 5-6 membered heteroaryl ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur); or

two R groups on the same nitrogen are taken together with their intervening atoms to form an optionally substituted 4-7 membered saturated, partially unsaturated, or heteroaryl ring (having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur);

wherein the compound is not Compound X, wherein Compound X is defined herein.

[0009] Overexpression of CDK2 is associated with abnormal regulation of the cell-cycle. The cyclin E/CDK2 complex plays an important role in regulation of the G1/S transition, histone biosynthesis and centrosome duplication. Progressive phosphorylation of retinoblastoma (Rb) by cyclin D/Cdk4/6 and cyclin E/Cdk2 releases the G1 transcription factor, E2F, and promotes S-phase entry. Activation of cyclin A/CDK2 during early S-phase promotes phosphorylation of endogenous substrates that permit DNA replication and inactivation of E2F, for S-phase completion. (Asghar et al., *Nat. Rev. Drug. Discov.* 2015; 14(2): 130-146).

[0010] Cyclin E, the regulatory cyclin for CDK2, is frequently overexpressed in cancer. Cyclin E amplification or overexpression has long been associated with poor outcomes in breast cancer. (Keyomarsi et al., *Cyclin E and survival in patients with breast cancer. N Engl J Med.* (2002) 347:1566-75). Cyclin E2 (CCNE2) overexpression is associated with endocrine resistance in breast cancer cells and CDK2 inhibition has been reported to restore sensitivity to tamoxifen or CDK4 inhibitors in tamoxifen-resistant and CCNE2 overexpressing cells. (Caldon et al., *Mol. Cancer Ther.* (2012) 11:1488-99; Herrera-Abreu et al., *Cancer Res.* (2016) 76: 2301-2313). Cyclin E amplification also reportedly contributes to trastuzumab resistance in HER2+ breast cancer. (Scaltriti et al., *Proc Natl Acad Sci.* (2011) 108: 3761-6). Cyclin E overexpression has also been reported to play a role in basal-like and triple negative breast cancer (TNBC), as well as inflammatory breast cancer. (Elsawaf & Sinn, *Breast Care* (2011) 6:273-278; Alexander et al., *Oncotarget* (2017) 8: 14897-14911.)

[0011] Amplification or overexpression of cyclin E1 (CCNE1) is also associated with poor outcomes in ovarian, gastric, endometrial and other cancers. (Nakayama et al., *Gene amplification CCNE1 is related to poor survival and potential therapeutic target in ovarian cancer, Cancer* (2010) 116: 2621-34; Etemadmoghadam et al., *Clin Cancer Res* (2013) 19: 5960-71; Au-Yeung et al., *Clin. Cancer Res.* (2017) 23:1862-1874; Ayhan et al., *Modern Pathology* (2017) 30: 297-303; Ooi et al., *Hum Pathol.* (2017) 61: 58-67; Noske et al., *Oncotarget* (2017) 8: 14794-14805).

[0012] There remains a need in the art for CDK inhibitors, especially selective CDK2 inhibitors, which may be useful for the treatment of cancer or other proliferative diseases or conditions. In particular, CDK2 inhibitors may be useful in treating CCNE1 or CCNE2 amplified tumors.

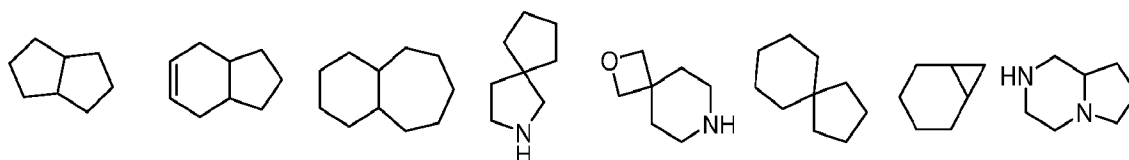
2. *Compounds and Definitions:*

[0013] Compounds of this present disclosure include those described generally herein, and are further illustrated by the classes, subclasses, and species disclosed herein. As used herein, the following definitions shall apply unless otherwise indicated. For purposes of this disclosure, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 101st Ed. Additionally, general principles of organic chemistry are described in “Organic Chemistry”, Thomas Sorrell, University Science Books, Sausalito: 2005, and “March’s Advanced Organic Chemistry: Reactions Mechanisms and Structure”, 8th Ed., Ed.: Smith, M.B., John Wiley & Sons, New York: 2019, the entire contents of which are hereby incorporated by reference.

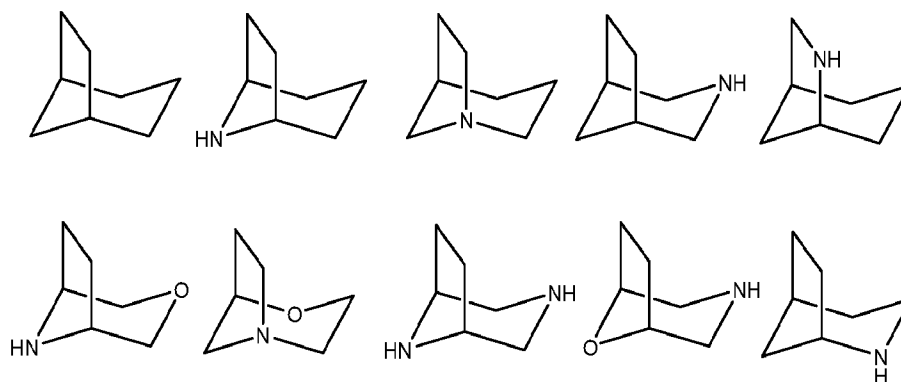
[0014] The term “aliphatic” or “aliphatic group”, as used herein, means a straight-chain (i.e., unbranched) or branched, substituted or unsubstituted hydrocarbon chain that is completely saturated or that contains one or more units of unsaturation, or a monocyclic hydrocarbon or bicyclic hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic (also referred to herein as “carbocycle,” “cycloaliphatic” or “cycloalkyl”), that has a single point of attachment to the rest of the molecule. Unless otherwise specified, aliphatic groups contain 1 to 6 aliphatic carbon atoms. In some embodiments, aliphatic groups contain 1 to 5 aliphatic carbon atoms. In other embodiments, aliphatic groups contain 1 to 4 aliphatic carbon atoms. In still other embodiments, aliphatic groups contain 1 to 3 aliphatic carbon atoms, and in yet other embodiments, aliphatic groups contain 1 to 2 aliphatic carbon atoms. In some embodiments, “cycloaliphatic” (or “carbocycle” or “cycloalkyl”) refers to a monocyclic C₃-C₆ hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic, that has a single point of attachment to the rest of the molecule. Suitable aliphatic groups include, but are not limited to, linear or branched, substituted or unsubstituted alkyl, alkenyl, alkynyl groups and hybrids thereof such as (cycloalkyl)alkyl, (cycloalkenyl)alkyl or (cycloalkyl)alkenyl.

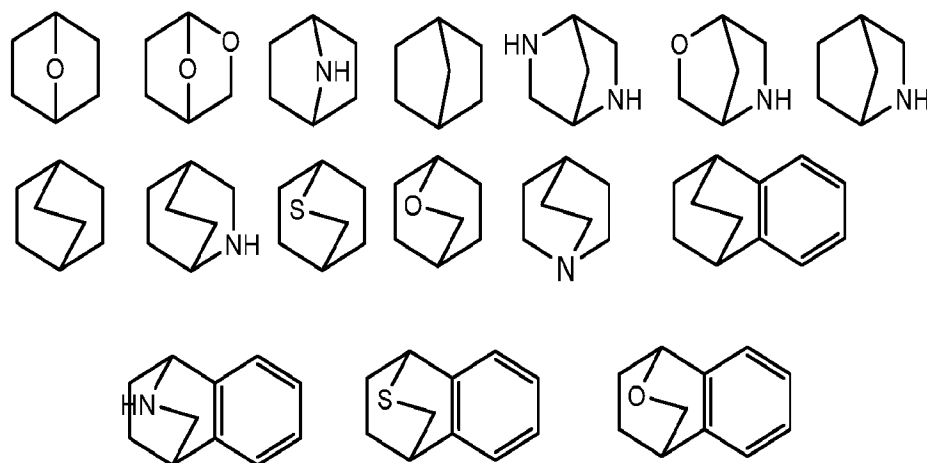
[0015] As used herein, the term “bicyclic ring” or “bicyclic ring system” refers to any bicyclic ring system, i.e. carbocyclic or heterocyclic, saturated or having one or more units of unsaturation, having one or more atoms in common between the two rings of the ring system. Thus, the term includes any permissible ring fusion, such as *ortho*-fused or spirocyclic. As used herein, the term

“heterobicyclic” is a subset of “bicyclic” that requires that one or more heteroatoms are present in one or both rings of the bicycle. Such heteroatoms may be present at ring junctions and are optionally substituted, and may be selected from nitrogen (including N-oxides), oxygen, sulfur (including oxidized forms such as sulfones and sulfonates), phosphorus (including oxidized forms such as phosphonates and phosphates), boron, etc. In some embodiments, a bicyclic group has 7-12 ring members and 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. As used herein, the term “bridged bicyclic” refers to any bicyclic ring system, i.e. carbocyclic or heterocyclic, saturated or partially unsaturated, having at least one bridge. As defined by IUPAC, a “bridge” is an unbranched chain of atoms or an atom or a valence bond connecting two bridgeheads, where a “bridgehead” is any skeletal atom of the ring system which is bonded to three or more skeletal atoms (excluding hydrogen). In some embodiments, a bridged bicyclic group has 7-12 ring members and 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. Such bridged bicyclic groups are well known in the art and include those groups set forth below where each group is attached to the rest of the molecule at any substitutable carbon or nitrogen atom. Unless otherwise specified, a bridged bicyclic group is optionally substituted with one or more substituents as set forth for aliphatic groups. Additionally or alternatively, any substitutable nitrogen of a bridged bicyclic group is optionally substituted. Exemplary bicyclic rings include:

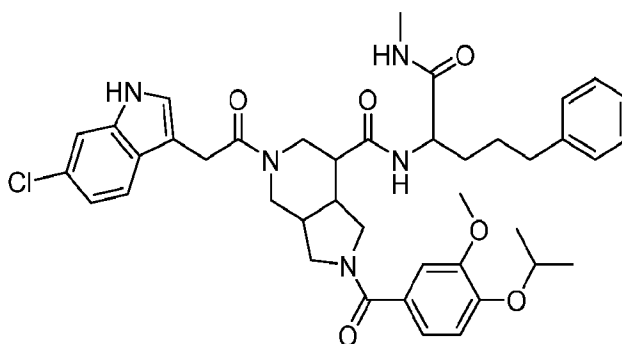


[0016] Exemplary bridged bicyclics include:





[0017] The term “Compound X” refers to 5-(2-(6-chloro-1H-indol-3-yl)acetyl)-2-(4-isopropoxy-3-methoxybenzoyl)-N-(1-(methylamino)-1-oxo-5-phenylpentan-2-yl)octahydro-1H-pyrrolo[3,4-c]pyridine-7-carboxamide. Compound X may also be depicted as



[0018] The term “lower alkyl” refers to a C₁₋₄ straight or branched alkyl group. Exemplary lower alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, and tert-butyl.

[0019] The term “lower haloalkyl” refers to a C₁₋₄ straight or branched alkyl group that is substituted with one or more halogen atoms.

[0020] The term “heteroatom” means one or more of oxygen, sulfur, nitrogen, phosphorus, or silicon (including, any oxidized form of nitrogen, sulfur, phosphorus, or silicon; the quaternized form of any basic nitrogen; or an oxygen, sulfur, nitrogen, phosphorus, or silicon atom in a heterocyclic ring).

[0021] The term “unsaturated,” as used herein, means that a moiety has one or more units of unsaturation.

[0022] As used herein, the term “bivalent C₁₋₈ (or C₁₋₆) saturated or unsaturated, straight or branched, hydrocarbon chain”, refers to bivalent alkylene, alkenylene, and alkynylene chains that are straight or branched as defined herein.

[0023] The term “alkylene” refers to a bivalent alkyl group. An “alkylene chain” is a polymethylene group, i.e., $-(CH_2)_n-$, wherein n is a positive integer, preferably from 1 to 6, from 1 to 4, from 1 to 3, from 1 to 2, or from 2 to 3. A substituted alkylene chain is a polymethylene group in which one or more methylene hydrogen atoms are replaced with a substituent. Suitable substituents include those described below for a substituted aliphatic group.

[0024] The term “alkenylene” refers to a bivalent alkenyl group. A substituted alkenylene chain is a polymethylene group containing at least one double bond in which one or more hydrogen atoms are replaced with a substituent. Suitable substituents include those described below for a substituted aliphatic group.

[0025] The term “halogen” means F, Cl, Br, or I.

[0026] The term “aryl” used alone or as part of a larger moiety as in “aralkyl,” “aralkoxy,” or “aryloxyalkyl,” refers to monocyclic or bicyclic ring systems having a total of 4 to 14 ring members, wherein at least one ring in the system is aromatic and wherein each ring in the system contains three to seven ring members. The term “aryl” may be used interchangeably with the term “aryl ring”. In certain embodiments of the present disclosure, “aryl” refers to an aromatic ring system which includes, but not limited to, phenyl, biphenyl, naphthyl, anthracyl and the like, which may bear one or more substituents. Also included within the scope of the term “aryl,” as it is used herein, is a group in which an aromatic ring is fused to one or more non-aromatic rings, such as indanyl, phthalimidyl, naphthimidyl, phenanthridinyl, or tetrahydronaphthyl, and the like.

[0027] The terms “heteroaryl” and “heteroar-,” used alone or as part of a larger moiety, e.g., “heteroaralkyl,” or “heteroaralkoxy,” refer to groups having 5 to 10 ring atoms, preferably 5, 6, or 9 ring atoms; having 6, 10, or 14 π electrons shared in a cyclic array; and having, in addition to carbon atoms, from one to five heteroatoms. The term “heteroatom” in the context of “heteroaryl” particularly includes, but is not limited to, nitrogen, oxygen, or sulfur, and includes any oxidized form of nitrogen or sulfur, and any quaternized form of a basic nitrogen. Heteroaryl groups include, without limitation, thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyridazinyl,

pyrimidinyl, pyrazinyl, indolizinyl, purinyl, naphthyridinyl, and pteridinyl. The terms “heteroaryl” and “heteroar-”, as used herein, also include groups in which a heteroaromatic ring is fused to one or more aryl, cycloaliphatic, or heterocyclyl rings, where the radical or point of attachment is on the heteroaromatic ring. Nonlimiting examples include indolyl, isoindolyl, benzothienyl, benzofuranyl, dibenzofuranyl, indazolyl, benzimidazolyl, benzthiazolyl, quinolyl, isoquinolyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 4*H*-quinolizinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, and pyrido[2,3-*b*]-1,4-oxazin-3(4*H*)-one. A heteroaryl group may be monocyclic or bicyclic. A heteroaryl ring may include one or more oxo (=O) or thioxo (=S) substituent. The term “heteroaryl” may be used interchangeably with the terms “heteroaryl ring,” “heteroaryl group,” or “heteroaromatic,” any of which terms include rings that are optionally substituted. The term “heteroaralkyl” refers to an alkyl group substituted by a heteroaryl, wherein the alkyl and heteroaryl portions independently are optionally substituted.

[0028] As used herein, the terms “heterocycle,” “heterocyclyl,” “heterocyclic radical,” and “heterocyclic ring” are used interchangeably and refer to a stable 5- to 7-membered monocyclic or 7 to 10-membered bicyclic heterocyclic moiety that is either saturated or partially unsaturated, and having, in addition to carbon atoms, one or more, preferably 1 to 4, heteroatoms, as defined above. When used in reference to a ring atom of a heterocycle, the term “nitrogen” includes a substituted nitrogen. As an example, in a saturated or partially unsaturated ring (having 0 to 3 heteroatoms selected from oxygen, sulfur and nitrogen).

[0029] A heterocyclic ring can be attached to a provided compound at any heteroatom or carbon atom that results in a stable structure and any of the ring atoms can be optionally substituted. Examples of such saturated or partially unsaturated heterocyclic radicals include, without limitation, tetrahydrofuranyl, tetrahydrothiophenyl pyrrolidinyl, piperidinyl, pyrrolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, oxazolidinyl, piperazinyl, dioxanyl, dioxolanyl, diazepinyl, oxazepinyl, thiazepinyl, morpholinyl, and quinuclidinyl. The terms “heterocycle,” “heterocyclyl,” “heterocyclyl ring,” “heterocyclic group,” “heterocyclic moiety,” and “heterocyclic radical,” are used interchangeably herein, and also include groups in which a heterocyclyl ring is fused to one or more aryl, heteroaryl, or cycloaliphatic rings, such as indolinyl, 3*H*-indolyl, chromanyl, phenanthridinyl, or tetrahydroquinolinyl. A heterocyclyl group may be monocyclic or bicyclic, bridged bicyclic, or spirocyclic. A heterocyclic ring may include

one or more oxo (=O) or thioxo (=S) substituent. The term “heterocyclalkyl” refers to an alkyl group substituted by a heterocycl, wherein the alkyl and heterocycl portions independently are optionally substituted.

[0030] As used herein, the term “partially unsaturated” refers to a ring moiety that includes at least one double or triple bond. The term “partially unsaturated” is intended to encompass rings having multiple sites of unsaturation, but is not intended to include aryl or heteroaryl moieties, as herein defined.

[0031] As described herein, compounds of the present disclosure may contain “substituted” moieties. In general, the term “substituted” means that one or more hydrogens of the designated moiety are replaced with a suitable substituent. Unless otherwise indicated, an “optionally substituted” group may have a suitable substituent at one or more substitutable position of the group, and when more than one position in any given structure is substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. Combinations of substituents envisioned by the present disclosure are preferably those that result in the formation of stable or chemically feasible compounds. The term “stable,” as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and, in certain embodiments, their recovery, purification, and use for one or more of the purposes disclosed herein.

[0032] Suitable monovalent substituents on a substitutable carbon atom of an “optionally substituted” group are independently halogen; $-(CH_2)_{0-6}R^\circ$; $-(CH_2)_{0-6}OR^\circ$; $-O(CH_2)_{0-6}R^\circ$; $-O-(CH_2)_{0-6}C(O)OR^\circ$; $-(CH_2)_{0-6}CH(OR^\circ)_2$; $-(CH_2)_{0-6}SR^\circ$; $-(CH_2)_{0-6}Ph$, which Ph may be substituted with R° ; $-(CH_2)_{0-46}O(CH_2)_{0-1}Ph$ which Ph may be substituted with R° ; $-CH=CHPh$, which Ph may be substituted with R° ; $-(CH_2)_{0-6}O(CH_2)_{0-1}$ -pyridyl which pyridyl may be substituted with R° ; $-NO_2$; $-CN$; $-N_3$; $-(CH_2)_{0-6}N(R^\circ)_2$; $-(CH_2)_{0-6}N(R^\circ)C(O)R^\circ$; $-N(R^\circ)C(S)R^\circ$; $-(CH_2)_{0-6}N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)C(S)NR^\circ_2$; $-(CH_2)_{0-6}N(R^\circ)C(O)OR^\circ$; $-N(R^\circ)N(R^\circ)C(O)R^\circ$; $-N(R^\circ)N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)N(R^\circ)C(O)OR^\circ$; $-(CH_2)_{0-6}C(O)R^\circ$; $-C(S)R^\circ$; $-(CH_2)_{0-6}C(O)OR^\circ$; $-(CH_2)_{0-6}C(O)SR^\circ$; $-(CH_2)_{0-6}C(O)OSiR^\circ_3$; $-(CH_2)_{0-6}OC(O)R^\circ$; $-OC(O)(CH_2)_{0-6}SR^\circ$; $-(CH_2)_{0-6}SC(O)R^\circ$; $-(CH_2)_{0-6}C(O)NR^\circ_2$; $-C(S)NR^\circ_2$; $-C(S)SR^\circ$; $-SC(S)SR^\circ$; $-(CH_2)_{0-6}OC(O)NR^\circ_2$; $-C(O)N(OR^\circ)R^\circ$; $-C(O)C(O)R^\circ$; $-C(O)CH_2C(O)R^\circ$; $-C(NOR^\circ)R^\circ$; $-(CH_2)_{0-6}SSR^\circ$; $-(CH_2)_{0-6}S(O)_2R^\circ$; $-(CH_2)_{0-6}S(O)_2OR^\circ$; $-(CH_2)_{0-6}OS(O)_2R^\circ$; $-S(O)_2NR^\circ_2$; $-(CH_2)_{0-6}$

$6S(O)R^\circ$; $-N(R^\circ)S(O)_2NR^\circ_2$; $-N(R^\circ)S(O)_2R^\circ$; $-N(OR^\circ)R^\circ$; $-C(NH)NR^\circ_2$; $-P(O)_2R^\circ$; $-P(O)R^\circ_2$; $-P(O)(OR^\circ)_2$; $-OP(O)(R^\circ)OR^\circ$; $-OP(O)R^\circ_2$; $-OP(O)(OR^\circ)_2$; SiR°_3 ; $-(C_{1-4}$ straight or branched alkylene) $O-N(R^\circ)_2$; or $-(C_{1-4}$ straight or branched alkylene) $C(O)O-N(R^\circ)_2$, wherein each R° may be substituted as defined below and is independently hydrogen, C_{1-6} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, $-CH_2$ -(5- to 6-membered heteroaryl ring), or a 3- to 6-membered saturated, partially unsaturated, or aryl ring (having 0 to 4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), or, notwithstanding the definition above, two independent occurrences of R° , taken together with their intervening atom(s), form a 3- to 12-membered saturated, partially unsaturated, or aryl mono- or bicyclic ring (having 0 to 4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), which may be substituted as defined below.

[0033] Suitable monovalent substituents on R° (or the ring formed by taking two independent occurrences of R° together with their intervening atoms), are independently halogen, $-(CH_2)_{0-2}R^\bullet$, $-(haloR^\bullet)$, $-(CH_2)_{0-2}OH$, $-(CH_2)_{0-2}OR^\bullet$, $-(CH_2)_{0-2}CH(OR^\bullet)_2$, $-O(haloR^\bullet)$, $-CN$, $-N_3$, $-(CH_2)_{0-2}C(O)R^\bullet$, $-(CH_2)_{0-2}C(O)OH$, $-(CH_2)_{0-2}C(O)OR^\bullet$, $-(CH_2)_{0-2}SR^\bullet$, $-(CH_2)_{0-2}SH$, $-(CH_2)_{0-2}NH_2$, $-(CH_2)_{0-2}NHR^\bullet$, $-(CH_2)_{0-2}NR^\bullet_2$, $-NO_2$, $-SiR^\bullet_3$, $-OSiR^\bullet_3$, $-C(O)SR^\bullet$, $-(C_{1-4}$ straight or branched alkylene) $C(O)OR^\bullet$, or $-SSR^\bullet$ wherein each $R^\bullet$ is unsubstituted or where preceded by “halo” is substituted only with one or more halogens, and is independently selected from C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5 to 6-membered saturated, partially unsaturated, or aryl ring (having 0 to 4 heteroatoms independently selected from nitrogen, oxygen, and sulfur). Suitable divalent substituents on a saturated carbon atom of R° include $=O$ and $=S$.

[0034] Suitable divalent substituents on a saturated carbon atom of an “optionally substituted” group include the following: $=O$, $=S$, $=NNR^*_2$, $=NNHC(O)R^*$, $=NNHC(O)OR^*$, $=NNHS(O)_2R^*$, $=NR^*$, $=NOR^*$, $-O(C(R^*_2))_{2-3}O-$, or $-S(C(R^*_2))_{2-3}S-$, wherein each independent occurrence of R^* is selected from hydrogen, C_{1-6} aliphatic which may be substituted as defined below, and an unsubstituted 5 to 6-membered saturated, partially unsaturated, or aryl ring (having 0 to 4 heteroatoms independently selected from nitrogen, oxygen, and sulfur). Suitable divalent substituents that are bound to vicinal substitutable carbons of an “optionally substituted” group include: $-O(CR^*_2)_{2-3}O-$, wherein each independent occurrence of R^* is selected from hydrogen, C_{1-6} aliphatic which may be substituted as defined below, and an unsubstituted 5 to 6-membered

saturated, partially unsaturated, or aryl ring (having 0 to 4 heteroatoms independently selected from nitrogen, oxygen, and sulfur).

[0035] Suitable substituents on the aliphatic group of R^* include halogen, $-R^\bullet$, $-(\text{halo}R^\bullet)$, $-\text{OH}$, $-\text{OR}^\bullet$, $-\text{O}(\text{halo}R^\bullet)$, $-\text{CN}$, $-\text{C}(\text{O})\text{OH}$, $-\text{C}(\text{O})\text{OR}^\bullet$, $-\text{NH}_2$, $-\text{NHR}^\bullet$, $-\text{NR}^{\bullet 2}$, or $-\text{NO}_2$, wherein each $R^\bullet$ is unsubstituted or where preceded by “halo” is substituted only with one or more halogens, and is independently C_{1-4} aliphatic, $-\text{CH}_2\text{Ph}$, $-\text{O}(\text{CH}_2)_{0-1}\text{Ph}$, or a 5 to 6-membered saturated, partially unsaturated, or aryl ring (having 0 to 4 heteroatoms independently selected from nitrogen, oxygen, and sulfur).

[0036] Suitable substituents on a substitutable nitrogen of an “optionally substituted” group include $-\text{R}^\dagger$, $-\text{NR}^{\dagger 2}$, $-\text{C}(\text{O})\text{R}^\dagger$, $-\text{C}(\text{O})\text{OR}^\dagger$, $-\text{C}(\text{O})\text{C}(\text{O})\text{R}^\dagger$, $-\text{C}(\text{O})\text{CH}_2\text{C}(\text{O})\text{R}^\dagger$, $-\text{S}(\text{O})_2\text{R}^\dagger$, $-\text{S}(\text{O})_2\text{NR}^{\dagger 2}$, $-\text{C}(\text{S})\text{NR}^{\dagger 2}$, $-\text{C}(\text{NH})\text{NR}^{\dagger 2}$, or $-\text{N}(\text{R}^\dagger)\text{S}(\text{O})_2\text{R}^\dagger$; wherein each $\text{R}^\dagger$ is independently hydrogen, C_{1-6} aliphatic which may be substituted as defined below, unsubstituted $-\text{OPh}$, or an unsubstituted 5 to 6-membered saturated, partially unsaturated, or aryl ring (having 0 to 4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), or, notwithstanding the definition above, two independent occurrences of $\text{R}^\dagger$, taken together with their intervening atom(s) form an unsubstituted 3 to 12-membered saturated, partially unsaturated, or aryl mono- or bicyclic ring (having 0 to 4 heteroatoms independently selected from nitrogen, oxygen, and sulfur).

[0037] Suitable substituents on the aliphatic group of $\text{R}^\dagger$ are independently halogen, $-\text{R}^\bullet$, $-(\text{halo}R^\bullet)$, $-\text{OH}$, $-\text{OR}^\bullet$, $-\text{O}(\text{halo}R^\bullet)$, $-\text{CN}$, $-\text{C}(\text{O})\text{OH}$, $-\text{C}(\text{O})\text{OR}^\bullet$, $-\text{NH}_2$, $-\text{NHR}^\bullet$, $-\text{NR}^{\bullet 2}$, or $-\text{NO}_2$, wherein each $\text{R}^\bullet$ is unsubstituted or where preceded by “halo” is substituted only with one or more halogens, and is independently C_{1-4} aliphatic, $-\text{CH}_2\text{Ph}$, $-\text{O}(\text{CH}_2)_{0-1}\text{Ph}$, or a 5 to 6-membered saturated, partially unsaturated, or aryl ring (having 0 to 4 heteroatoms independently selected from nitrogen, oxygen, and sulfur).

[0038] As used herein, the term “provided compound” or “compound of the present disclosure” refers to any genus, subgenus, and/or species set forth herein.

[0039] As used herein, the term “pharmaceutically acceptable salt” refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well

known in the art. For example, S. M. Berge et al., describe pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences*, 1977, 66, 1–19, which is incorporated herein by reference. Pharmaceutically acceptable salts of the compounds of this disclosure include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like.

[0040] Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4}alkyl)_4$ salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, lower alkyl sulfonate, and aryl sulfonate.

[0041] Unless otherwise stated, structures depicted herein are also meant to include all isomeric (e.g., enantiomeric, diastereomeric, and geometric (or conformational)) forms of the structure; for example, the R and S configurations for each asymmetric center, Z and E double bond isomers, and Z and E conformational isomers. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, and geometric (or conformational) mixtures of the present compounds are within the scope of the disclosure. Unless otherwise stated, all tautomeric forms of the compounds of the disclosure are within the scope of the disclosure. Additionally, unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the

present structures including the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ^{13}C - or ^{14}C -enriched carbon are within the scope of this disclosure. Such compounds are useful, for example, as analytical tools, as probes in biological assays, or as therapeutic agents in accordance with the present disclosure.

[0042] As used herein, the term “inhibitor” is defined as a compound that binds to and/or inhibits CDK2 with measurable affinity. In certain embodiments, an inhibitor has an IC_{50} and/or binding constant of less than about 50 μM , less than about 1 μM , less than about 500 nM, less than about 100 nM, less than about 10 nM, or less than about 1 nM, when measured in an appropriate assay.

[0043] The term “patient,” as used herein, means an animal, preferably a mammal, and most preferably a human.

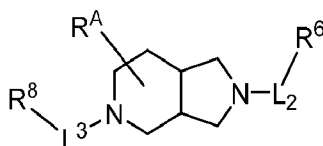
[0044] The term “pharmaceutically acceptable carrier, adjuvant, or vehicle” refers to a non-toxic carrier, adjuvant, or vehicle that does not destroy the pharmacological activity of the compound with which it is formulated. Pharmaceutically acceptable carriers, adjuvants or vehicles that may be used in the compositions of this disclosure include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

[0045] A “pharmaceutically acceptable derivative” means any non-toxic salt, ester, salt of an ester or other derivative of a compound of this disclosure that, upon administration to a recipient, is capable of providing, either directly or indirectly, a compound of this disclosure or an inhibitorily or degranatorily active metabolite or residue thereof.

[0046] As used herein, the term “inhibitorily active metabolite or residue thereof” means that a metabolite or residue thereof is also an inhibitor of a CDK2 protein, or a mutant thereof.

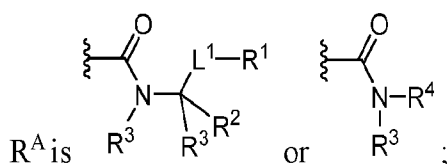
3. Description of Exemplary Embodiments:

[0047] In some embodiments, provided herein are compounds according to Formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:



L^1 is a covalent bond or a saturated or unsaturated, straight or branched, optionally substituted bivalent C_{1-6} hydrocarbon chain, wherein 0-2 methylene units of L^1 are independently replaced by -O-, -NR-, -S-, -OC(O)-, -C(O)O-, -C(O)-, -S(O)-, -S(O)₂-, -C(S)-, -NRS(O)₂-, -S(O)₂NR-, -NRC(O)-, -C(O)NR-, -OC(O)NR-, -NRC(O)O-, or -NRC(O)NR-;

R^1 is hydrogen, an optionally substituted C_{1-6} aliphatic group, or an optionally substituted cyclic group selected from a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, a 7-12 membered saturated or partially unsaturated bicyclic carbocyclic ring, phenyl, an 8-10 membered bicyclic aromatic carbocyclic ring, a 3-8 membered saturated or partially unsaturated monocyclic heterocyclic ring (having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur), a 7-12 membered saturated or partially unsaturated bicyclic heterocyclic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), a 5-6 membered monocyclic heteroaromatic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), and an 8-10 membered bicyclic heteroaromatic ring (having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur);

R^2 is hydrogen, an optionally substituted C_{1-6} aliphatic group, -C(O)OR, -C(O)NR₂, or an optionally substituted cyclic group selected from phenyl and a 5-6 membered monocyclic heteroaromatic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur);

each instance of R^3 is independently hydrogen or an optionally substituted C_{1-6} aliphatic group;

R^4 is a cyclic group selected from a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, a 7-12 membered saturated or partially unsaturated bicyclic carbocyclic ring, phenyl, an 8-10 membered bicyclic aromatic carbocyclic ring, a 3-8 membered saturated or partially unsaturated monocyclic heterocyclic ring (having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur), a 7-12 membered saturated or partially unsaturated bicyclic heterocyclic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), a 5-6 membered monocyclic heteroaromatic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), and an 8-10 membered bicyclic heteroaromatic ring (having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur), wherein the cyclic group is optionally substituted with one or more instances of R^5 ;

each instance of R^5 is independently halogen, $-CN$, $-NO_2$, $-OR$, $-SR$, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, $-S(O)R$, $-S(O)NR_2$, $-C(O)R$, $-C(O)OR$, $-C(O)NR_2$, $-C(O)N(R)OR$, $-OC(O)R$, $-OC(O)NR_2$, $-N(R)C(O)OR$, $-N(R)C(O)R$, $-N(R)C(O)NR_2$, $-N(R)C(NR)NR_2$, $-N(R)S(O)_2NR_2$, $-N(R)S(O)_2R$, an optionally substituted C_{1-6} aliphatic group, or an optionally substituted $-C_{1-6}$ aliphatic-Cy group;

L^2 is a saturated or unsaturated, straight or branched, optionally substituted bivalent C_{1-4} hydrocarbon chain, wherein 0-2 methylene units of L^2 are independently replaced by $-O-$, $-NR-$, $-S-$, $-OC(O)-$, $-C(O)O-$, $-C(O)-$, $-S(O)-$, $-S(O)_2-$, $-C(S)-$, $-NRS(O)_2-$, $-S(O)_2NR-$, $-NRC(O)-$, $-C(O)NR-$, $-OC(O)NR-$, $-NRC(O)O-$, or $-NRC(O)NR-$;

R^6 is an optionally substituted C_{1-6} aliphatic group, or a cyclic group selected from a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, a 7-12 membered saturated or partially unsaturated bicyclic carbocyclic ring, phenyl, an 8-10 membered bicyclic aromatic carbocyclic ring, a 3-8 membered saturated or partially unsaturated monocyclic heterocyclic ring (having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur), a 7-12 membered saturated or partially unsaturated bicyclic heterocyclic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), a 5-6 membered monocyclic heteroaromatic ring (having 1-4 heteroatoms independently selected from nitrogen,

oxygen, and sulfur), and an 8-10 membered bicyclic heteroaromatic ring (having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur), wherein the cyclic group is optionally substituted with one or more instances of R^7 ;

each instance of R^7 is independently halogen, $-CN$, $-NO_2$, $-OR$, $-SR$, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, $-S(O)R$, $-S(O)NR_2$, $-C(O)R$, $-C(O)OR$, $-C(O)NR_2$, $-C(O)N(R)OR$, $-OC(O)R$, $-OC(O)NR_2$, $-N(R)C(O)OR$, $-N(R)C(O)R$, $-N(R)C(O)NR_2$, $-N(R)C(O)S(O)_2R$, $-N(R)C(NR)NR_2$, $-N(R)S(O)_2NR_2$, $-N(R)S(O)_2R$, an optionally substituted C_{1-6} aliphatic group, or Cy, or two instances of R^6 on the same carbon atom are taken together to form an oxo group;

L^3 is a saturated or unsaturated, straight or branched, optionally substituted bivalent C_{1-4} hydrocarbon chain, wherein 0-2 methylene units of L^3 are independently replaced by $-O-$, $-NR-$, $-S-$, $-OC(O)-$, $-C(O)O-$, $-C(O)-$, $-S(O)-$, $-S(O)_2-$, $-C(S)-$, $-NRS(O)_2-$, $-S(O)_2NR-$, $-NRC(O)-$, $-C(O)NR-$, $-OC(O)NR-$, $-NRC(O)O-$, or $-NRC(O)NR-$;

R^8 is a cyclic group selected from a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, a 7-12 membered saturated or partially unsaturated bicyclic carbocyclic ring, phenyl, an 8-10 membered bicyclic aromatic carbocyclic ring, a 3-8 membered saturated or partially unsaturated monocyclic heterocyclic ring (having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur), a 7-12 membered saturated or partially unsaturated bicyclic heterocyclic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), a 5-6 membered monocyclic heteroaromatic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), and an 8-10 membered bicyclic heteroaromatic ring (having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur), wherein the cyclic group is optionally substituted with one or more instances of R^9 ;

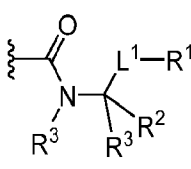
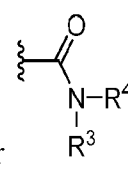
each instance of R^9 is independently halogen, $-CN$, $-NO_2$, $-OR$, $-SR$, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, $-S(O)R$, $-S(O)NR_2$, $-C(O)R$, $-C(O)OR$, $-C(O)NR_2$, $-C(O)N(R)OR$, $-OC(O)R$, $-OC(O)NR_2$, $-N(R)C(O)OR$, $-N(R)C(O)R$, $-N(R)C(O)NR_2$, $-N(R)C(NR)NR_2$, $-N(R)S(O)_2NR_2$, $-N(R)S(O)_2R$, an optionally substituted C_{1-6} aliphatic group, an optionally substituted C_{1-6} aliphatic-Cy group, or Cy;

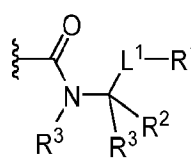
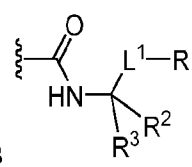
each Cy is independently an optionally substituted cyclic group selected from a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, phenyl, a 3-8 membered saturated or partially unsaturated monocyclic heterocyclic ring (having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur), and a 5-6 membered monocyclic heteroaromatic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur); and

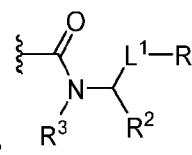
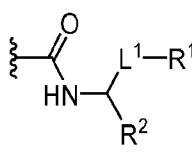
each R is independently hydrogen, or an optionally substituted C₁₋₆ aliphatic group, an optionally substituted phenyl, an optionally substituted 3-7 membered saturated or partially unsaturated carbocyclic ring, an optionally substituted 3-7 membered saturated or partially unsaturated heterocyclic ring (having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur), or an optionally substituted 5-6 membered heteroaryl ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur); or

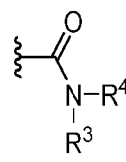
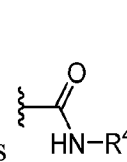
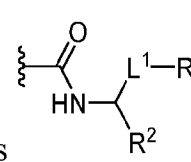
two R groups on the same nitrogen are taken together with their intervening atoms to form an optionally substituted 4-7 membered saturated, partially unsaturated, or heteroaryl ring (having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur);

wherein the compound is not Compound X, wherein Compound X is defined herein.

[0048] As defined generally above, R^A is , or . In some embodiments,

R^A is . In some embodiments, R^A is . In some embodiments, R^A

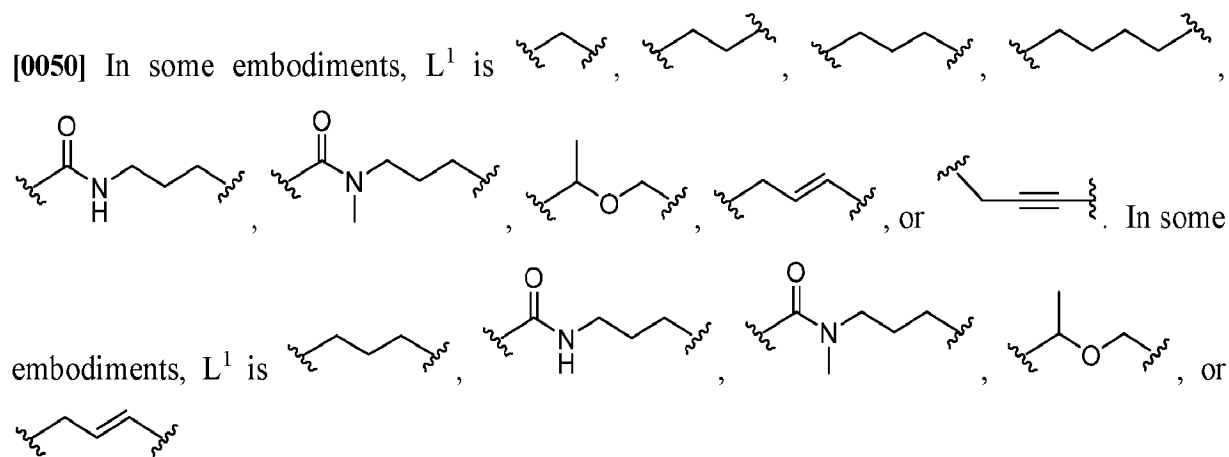
is . In some embodiments, R^A is . In some embodiments, R^A is

. In some embodiments, R^A is . In some embodiments, R^A is 

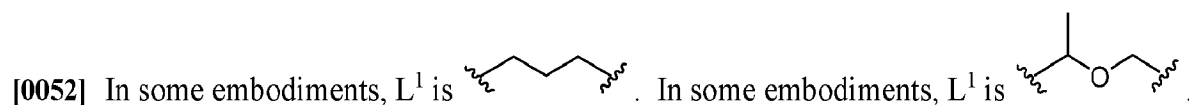

 or HN-R^A . In some embodiments, R^A is selected from those depicted in the compounds of the compounds of **Table 1**, below.

[0049] As defined generally above, L^1 is a covalent bond or a saturated or unsaturated, straight or branched, optionally substituted bivalent C_{1-6} hydrocarbon chain, wherein 0-2 methylene units of L^1 are independently replaced by -O-, -NR-, -S-, -OC(O)-, -C(O)O-, -C(O)-, -S(O)-, -S(O)₂-, -C(S)-, -NRS(O)₂-, -S(O)₂NR-, -NRC(O)-, -C(O)NR-, -OC(O)NR-, -NRC(O)O-, or -NRC(O)NR-. In some embodiments, L^1 is a covalent bond. In some embodiments, L^1 is a saturated or unsaturated, straight or branched, optionally substituted bivalent C_{1-6} hydrocarbon chain, wherein 0-2 methylene units of L^1 are independently replaced by -O-, -NR-, -S-, -OC(O)-, -C(O)O-, -C(O)-, -S(O)-, -S(O)₂-, -C(S)-, -NRS(O)₂-, -S(O)₂NR-, -NRC(O)-, -C(O)NR-, -OC(O)NR-, -NRC(O)O-, or -NRC(O)NR-. In some embodiments, L^1 is a saturated or unsaturated, straight or branched, optionally substituted bivalent C_{1-6} hydrocarbon chain. In some embodiments, L^1 is a saturated or unsaturated, straight or branched, optionally substituted bivalent C_{1-4} hydrocarbon chain. In some embodiments, L^1 is a saturated or unsaturated, straight or branched, optionally substituted bivalent C_{1-6} hydrocarbon chain, wherein 1 or 2 methylene units of L^1 are replaced by -O-, -NR-, -S-, -OC(O)-, -C(O)O-, -C(O)-, -S(O)-, -S(O)₂-, -C(S)-, -NRS(O)₂-, -S(O)₂NR-, -NRC(O)-, -C(O)NR-, -OC(O)NR-, -NRC(O)O-, or -NRC(O)NR-. In some embodiments, L^1 is an optionally substituted saturated, straight or branched, bivalent C_{1-4} hydrocarbon chain. In some embodiments, L^1 is a partially unsaturated, straight or branched, bivalent C_{1-4} hydrocarbon chain. In some embodiments, L^1 is an optionally substituted saturated, straight, bivalent C_{1-6} hydrocarbon chain, wherein 1-2 methylene units of L^1 are independently replaced by -O-, -NR-, -S-, -OC(O)-, -C(O)O-, -C(O)-, -S(O)-, -S(O)₂-, -C(S)-, -NRS(O)₂-, -S(O)₂NR-, -NRC(O)-, -C(O)NR-, -OC(O)NR-, -NRC(O)O-, or -NRC(O)NR-. In some embodiments, L^1 is an optionally substituted straight or branched C_{1-6} alkylene chain, wherein 1-2 methylene units of L^1 are independently replaced by -O-, -C(O)O-, -C(O)-, or -NRC(O)-. In some embodiments, L^1 is an optionally substituted straight or branched C_{1-4} alkylene chain, wherein 1-2 methylene units of L^1 are independently replaced by -O-, -C(O)O-, -C(O)-, or -NRC(O)-. In some embodiments, L^1 is an optionally substituted straight or branched C_{1-4} alkylene chain, wherein 1 methylene unit of L^1 is replaced by -O-. In some embodiments, L^1 is an optionally substituted straight or branched C_{1-4} alkylene chain, wherein 1 methylene unit of L^1 is replaced by -NRC(O)-. In some embodiments, L^1 is an optionally substituted straight or

branched C₁₋₄ alkylene chain, wherein 1 methylene unit of L¹ is replaced by -NHC(O)- or -N(CH₃)C(O)-. In some embodiments, L¹ is an unsubstituted straight chain C₁₋₄ alkylene. In some embodiments, L¹ is an unsubstituted straight chain C₁₋₄ alkenylene. In some embodiments, L¹ is an unsubstituted straight chain C₁₋₄ alkynylene. In some embodiments, L¹ is selected from those depicted in the compounds of **Table 1**, below.



[0051]

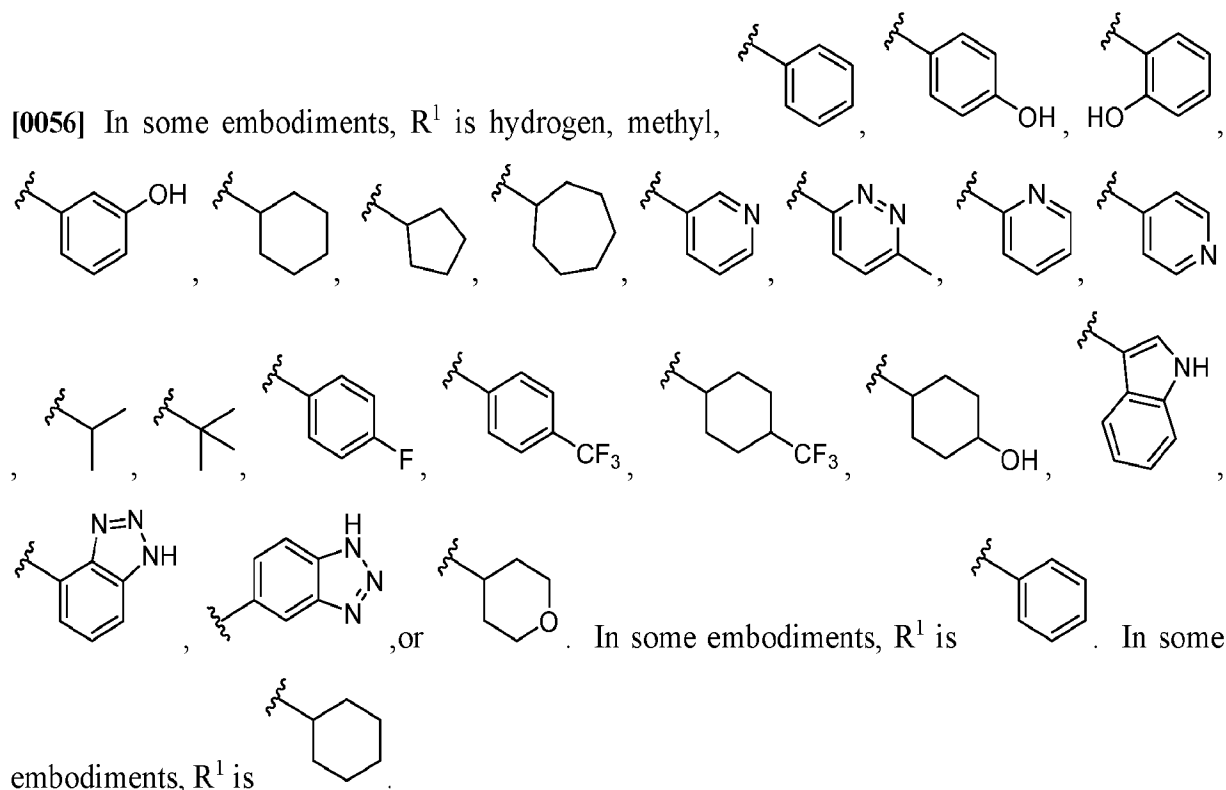


[0053] As defined generally above, R¹ is hydrogen, an optionally substituted C₁₋₆ aliphatic group, or an optionally substituted cyclic group selected from a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, a 7-12 membered saturated or partially unsaturated bicyclic carbocyclic ring, phenyl, an 8-10 membered bicyclic aromatic carbocyclic ring, a 3-8 membered saturated or partially unsaturated monocyclic heterocyclic ring (having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur), a 7-12 membered saturated or partially unsaturated bicyclic heterocyclic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), a 5-6 membered monocyclic heteroaromatic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), and an 8-10 membered bicyclic heteroaromatic ring (having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur).

[0054] In some embodiments, R¹ is hydrogen. In some embodiments, R¹ is an optionally substituted C₁₋₆ aliphatic group. In some embodiments, R¹ is an optionally substituted C₁₋₄ aliphatic group. In some embodiments, R¹ is a C₁₋₄ aliphatic group. In some embodiments, R¹ is

an isopropyl group. In some embodiments, R¹ is a tert-butyl group. In some embodiments, R¹ is methyl.

[0055] In some embodiments, R¹ is an optionally substituted cyclic group selected from a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, a 7-12 membered saturated or partially unsaturated bicyclic carbocyclic ring, phenyl, an 8-10 membered bicyclic aromatic carbocyclic ring, a 3-8 membered saturated or partially unsaturated monocyclic heterocyclic ring (having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur), a 7-12 membered saturated or partially unsaturated bicyclic heterocyclic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), a 5-6 membered monocyclic heteroaromatic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), and an 8-10 membered bicyclic heteroaromatic ring (having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur). In some embodiments, R¹ is an optionally substituted cyclic group selected from a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, phenyl, a 3-8 membered saturated or partially unsaturated monocyclic heterocyclic ring (having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur), a 5-6 membered monocyclic heteroaromatic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), and an 8-10 membered bicyclic heteroaromatic ring (having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur). In some embodiments, R¹ is an optionally substituted cyclic group selected from phenyl, cyclohexyl, cyclopentyl, cycloheptyl, tetrahydrofuranyl, tetrahydropyranyl, pyridinyl, pyridazinyl, indole, and benzotriazole. In some embodiments, R¹ is an optionally substituted phenyl group. In some embodiments, R¹ is an optionally substituted cyclohexyl group. In some embodiments, R¹ is an optionally substituted cyclopentyl group. In some embodiments, R¹ is an optionally substituted cycloheptyl group. In some embodiments, R¹ is an optionally substituted pyridinyl group. In some embodiments, R¹ is an optionally substituted pyridazinyl group. In some embodiments, R¹ is an optionally substituted tetrahydrofuranyl group. In some embodiments, R¹ is an optionally substituted tetrahydropyranyl group. In some embodiments, R¹ is an optionally substituted indole group. In some embodiments, R¹ is an optionally substituted benzotriazole group. In some embodiments, R¹ is selected from those depicted in the compounds of **Table 1**, below.



[0057] As defined generally above, R^2 is hydrogen, an optionally substituted C_{1-6} aliphatic group, $-C(O)OR$, $-C(O)NR_2$, or an optionally substituted cyclic group selected from phenyl and a 5-6 membered monocyclic heteroaromatic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur). In some embodiments, R^2 is an optionally substituted C_{1-6} aliphatic group, $-C(O)OR$, $-C(O)NR_2$, or an optionally substituted cyclic group selected from phenyl and a 5-6 membered monocyclic heteroaromatic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur). In some embodiments, R^2 is hydrogen, methyl, $-C(O)NHCH_3$, $-C(O)NH_2$, $-C(O)OCH_3$, $-C(O)OH$, or an optionally substituted 5-6 membered monocyclic heteroaromatic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur). In some embodiments, R^2 is hydrogen, methyl, $-C(O)NHCH_3$, $-C(O)NH_2$, $-C(O)OCH_3$, or $-C(O)OH$. In some embodiments, R^2 is hydrogen. In some embodiments, R^2 is methyl. In some embodiments, R^2 is $-C(O)NHCH_3$. In some embodiments, R^2 is $-C(O)NH_2$. In some embodiments, R^2 is $-C(O)OCH_3$. In some embodiments, R^2 is $-C(O)OH$. In some embodiments, R^2 is a 5-6 membered monocyclic heteroaromatic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur). In some embodiments R^2 is an oxazolyl group. In some embodiments, R^2 is a pyrimidinyl group.

[0058] In some embodiments, R^2 is selected from those depicted in the compounds of **Table 1**, below.

[0059] As defined generally above, each instance of R^3 is independently hydrogen or an optionally substituted C_{1-6} aliphatic group. In some embodiments, each instance of R^3 is hydrogen.

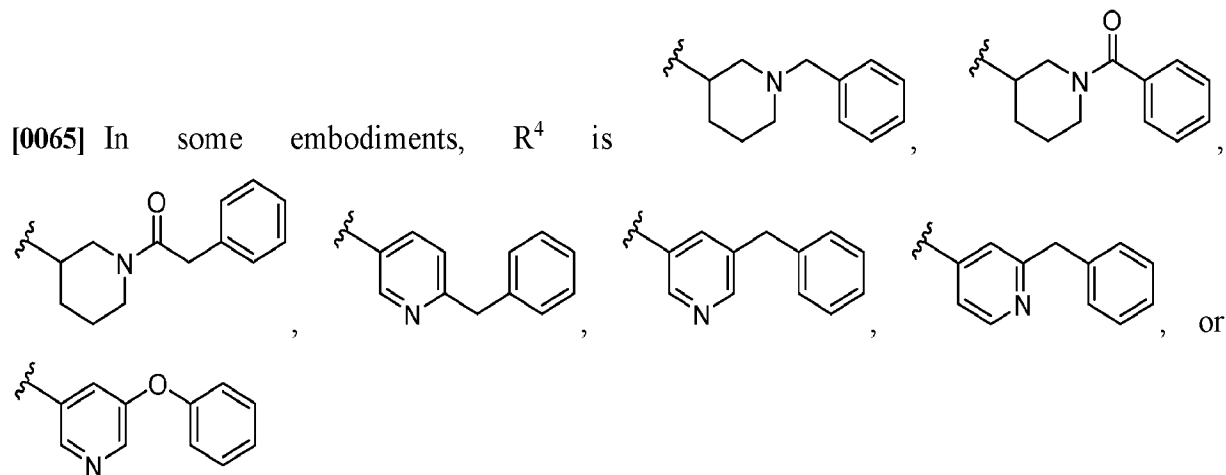
[0060] As defined generally above, R^4 is a cyclic group selected from a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, a 7-12 membered saturated or partially unsaturated bicyclic carbocyclic ring, phenyl, an 8-10 membered bicyclic aromatic carbocyclic ring, a 3-8 membered saturated or partially unsaturated monocyclic heterocyclic ring (having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur), a 7-12 membered saturated or partially unsaturated bicyclic heterocyclic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), a 5-6 membered monocyclic heteroaromatic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), and an 8-10 membered bicyclic heteroaromatic ring (having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur), wherein the cyclic group is optionally substituted with one or more instances of R^5 .

[0061] In some embodiments, R^4 is a cyclic group selected from a 3-8 membered saturated or partially unsaturated monocyclic heterocyclic ring (having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur), and a 5-6 membered monocyclic heteroaromatic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), wherein the cyclic group is optionally substituted with one or more instances of R^5 . In some embodiments, R^4 is a 3-8 membered saturated or partially unsaturated monocyclic heterocyclic ring (having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur), optionally substituted with one or more instances of R^5 . In some embodiments, R^4 is a 5-6 membered monocyclic heteroaromatic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), optionally substituted with one or more instances of R^5 . In some embodiments, R^4 is a cyclic group selected from phenyl, pyridine, and piperidine, wherein the cyclic group is optionally substituted with one or more instances of R^5 . In some embodiments, R^4 is phenyl, optionally substituted with one or more instances of R^5 . In some embodiments, R^4 is pyridine, optionally substituted with one or more instances of R^5 . In some embodiments, R^4 is piperidine, optionally substituted with one or more instances of R^5 . In some embodiments, R^4 is selected from those depicted in the compounds of **Table 1**, below.

[0062] In some embodiments, R^4 is substituted with 0, 1, or 2 instances of R^5 . In some embodiments, R^4 is substituted with 1 instance of R^5 . R^3 is substituted with 2 instances of R^5 . R^4 is substituted with 3 instances of R^5 . In some embodiments, R^4 is unsubstituted.

[0063] As defined generally above, each instance of R^5 is independently halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{OR}$, $-\text{SR}$, $-\text{NR}_2$, $-\text{S(O)}_2\text{R}$, $-\text{S(O)}_2\text{NR}_2$, $-\text{S(O)R}$, $-\text{S(O)NR}_2$, $-\text{C(O)R}$, $-\text{C(O)OR}$, $-\text{C(O)NR}_2$, $-\text{C(O)N(R)OR}$, $-\text{OC(O)R}$, $-\text{OC(O)NR}_2$, $-\text{N(R)C(O)OR}$, $-\text{N(R)C(O)R}$, $-\text{N(R)C(O)NR}_2$, $-\text{N(R)C(NR)NR}_2$, $-\text{N(R)S(O)}_2\text{NR}_2$, $-\text{N(R)S(O)}_2\text{R}$, an optionally substituted C_{1-6} aliphatic group, or an optionally substituted $-\text{C}_{1-6}$ aliphatic-Cy group.

[0064] In some embodiments, R^5 is $-\text{OR}$, $-\text{C(O)R}$, an optionally substituted C_{1-6} aliphatic group, or an optionally substituted $-\text{C}_{1-6}$ aliphatic-Cy group. In some embodiments, R^5 is $-\text{OR}$. In some embodiments, R^5 is $-\text{C(O)R}$. In some embodiments, R^5 is an optionally substituted C_{1-6} aliphatic group. In some embodiments, R^5 is an optionally substituted $-\text{C}_{1-6}$ aliphatic-Cy group. In some embodiments, R^5 is an optionally substituted benzyl group, an optionally substituted benzoyl group, an optionally substituted phenoxy group, or an optionally substituted phenylacetyl group. In some embodiments R^5 is an optionally substituted benzyl group. In some embodiments R^5 is an optionally substituted benzoyl group. In some embodiments R^5 is an optionally substituted phenoxy group. In some embodiments R^5 is an optionally substituted phenylacetyl group. In some embodiments, R^5 is selected from those depicted in the compounds of **Table 1**, below.



[0066] In some embodiments, R^A is a substituent of **Table A1** or **Table A2**:

Table A1: Exemplary R^A substituents

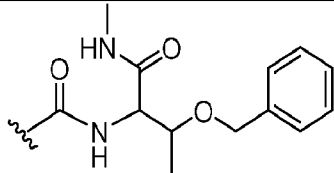
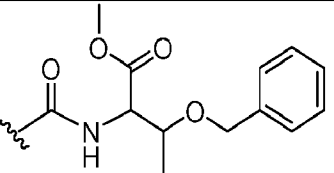
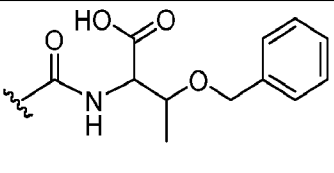
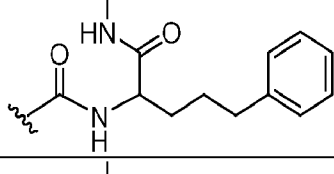
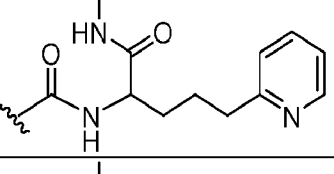
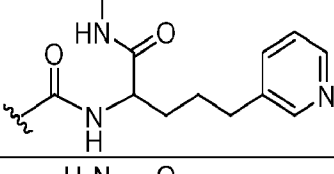
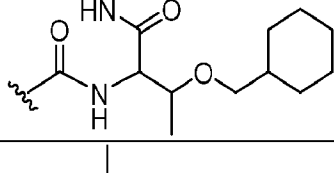
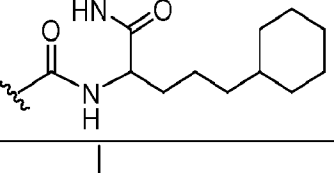
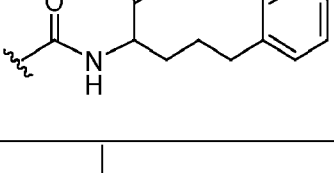
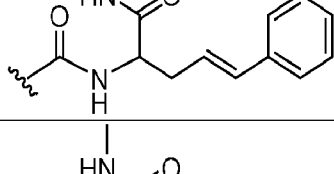
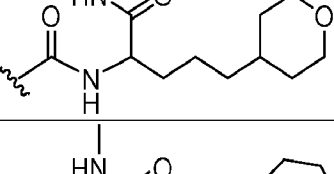
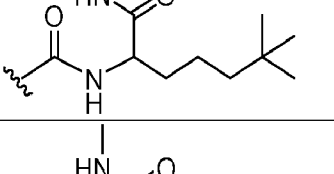
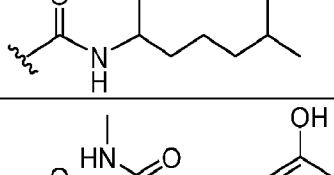
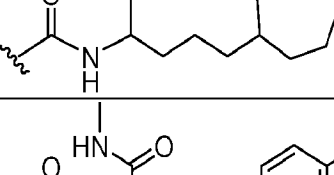
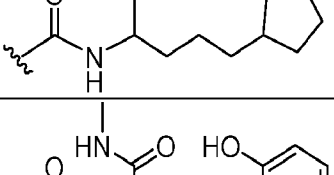
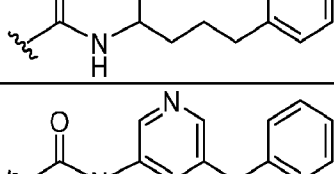
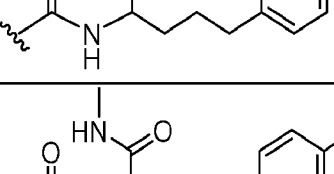
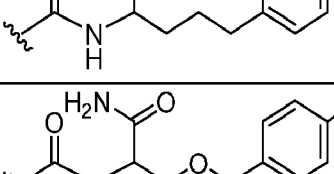
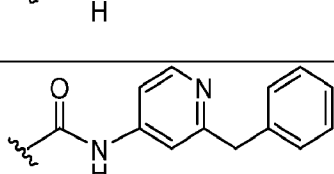
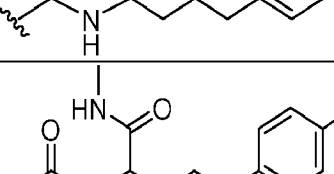
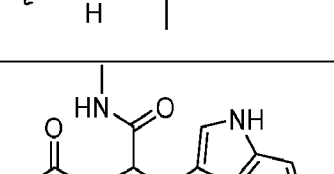
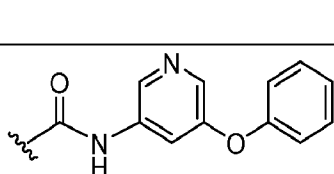
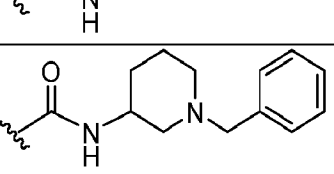
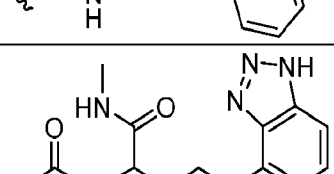
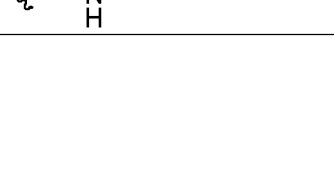
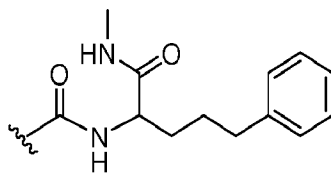
		
		
		
		
		
		
		
		
		

Table A2: Additional Exemplary R^A substituents

[0067] In some embodiments, R^A is a substituent of **Table A1** or **Table A2**. In some embodiments, R^A is a substituent of **Table A1**. In some embodiments, R^A is a substituent of **Table A2**.



[0068] In some embodiments, R^A is

[0069] As defined generally above, L^2 is a saturated or unsaturated, straight or branched, optionally substituted bivalent C_{1-4} hydrocarbon chain, wherein 0-2 methylene units of L^2 are independently replaced by -O-, -NR-, -S-, -OC(O)-, -C(O)O-, -C(O)-, -S(O)-, -S(O)₂-, -C(S)-, -NRS(O)₂-, -S(O)₂NR-, -NRC(O)-, -C(O)NR-, -OC(O)NR-, -NRC(O)O-, or -NRC(O)NR-. In some embodiments, L^2 is a saturated, straight, optionally substituted bivalent C_{1-4} hydrocarbon chain, wherein 0-2 methylene units of L^2 are independently replaced by -O-, -NR-, -OC(O)-, -C(O)O-, -C(O)-, -NRC(O)-, or -C(O)NR-. In some embodiments, L^2 is a saturated, straight, optionally substituted bivalent C_{1-4} hydrocarbon chain. In some embodiments, L^2 is a saturated, straight, optionally substituted bivalent C_{1-4} hydrocarbon chain, wherein 1 methylene unit of L^2 is replaced by -O-, -NR-, -OC(O)-, -C(O)O-, -C(O)-, -NRC(O)-, or -C(O)NR-. In some embodiments, L^2 is a saturated, straight, optionally substituted bivalent C_{1-4} hydrocarbon chain, wherein 1 methylene unit of L^2 is replaced by -C(O)-. In some embodiments, L^2 is -CH₂- or -C(O)-. In some embodiments, L^2 is -CH₂-. In some embodiments, L^2 is -C(O)-. In some embodiments, L^2 is selected from those depicted in the compounds of **Table 1**, below.

[0070] As generally defined above, R^6 is an optionally substituted C_{1-6} aliphatic group, or a cyclic group selected from a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, a 7-12 membered saturated or partially unsaturated bicyclic carbocyclic ring, phenyl, an 8-10 membered bicyclic aromatic carbocyclic ring, a 3-8 membered saturated or partially unsaturated monocyclic heterocyclic ring (having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur), a 7-12 membered saturated or partially unsaturated bicyclic heterocyclic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), a 5-6 membered monocyclic heteroaromatic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), and an 8-10 membered bicyclic heteroaromatic ring (having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur), wherein the cyclic group is optionally substituted with one or more instances of R^7 .

[0071] In some embodiments, R^6 is an optionally substituted C_{1-6} aliphatic group. In some embodiments, R^6 is a cyclic group selected from a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, a 7-12 membered saturated or partially unsaturated bicyclic

carbocyclic ring, phenyl, an 8-10 membered bicyclic aromatic carbocyclic ring, a 3-8 membered saturated or partially unsaturated monocyclic heterocyclic ring (having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur), a 7-12 membered saturated or partially unsaturated bicyclic heterocyclic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), a 5-6 membered monocyclic heteroaromatic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), and an 8-10 membered bicyclic heteroaromatic ring (having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur), wherein the cyclic group is optionally substituted with one or more instances of R^7 . In some embodiments, R^6 is a cyclic group selected from phenyl, an 8-10 membered bicyclic aromatic carbocyclic ring, a 5-6 membered monocyclic heteroaromatic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), and an 8-10 membered bicyclic heteroaromatic ring (having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur), wherein the cyclic group is optionally substituted with one or more instances of R^7 .

[0072] In some embodiments, R^6 is a cyclic group selected from cyclohexyl, phenyl, quinolinyl, isoquinolinyl, quinoxaliny, 2,3-dihydrobenzo[b][1,4]dioxinyl, pyrazolyl, isoxazolyl, imidazolyl, thiazolyl, pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, 2,3-dihydrobenzo[d]furanyl, benzofuranyl, indolyl, benzo[1,2,3]triazole, benzimidazolyl, imidazo[1,2-a]pyrimidinyl, imidazo[1,2-a]pyrazinyl, indazolyl, indolinyl, indoliziny, isoindolinyl, and 2,3-dihydrobenzo[d]oxazolyl, wherein the cyclic group is optionally substituted with one or more instances of R^7 .

[0073] In some embodiments, R^6 is cyclohexyl, optionally substituted with one or more instances of R^7 . In some embodiments, R^6 is phenyl, optionally substituted with one or more instances of R^7 . In some embodiments, R^6 is quinolinyl, optionally substituted with one or more instances of R^7 . In some embodiments, R^6 is isoquinolinyl, optionally substituted with one or more instances of R^7 . In some embodiments, R^6 is quinoxaliny, optionally substituted with one or more instances of R^7 . In some embodiments, R^6 is 2,3-dihydrobenzo[b][1,4]dioxinyl, optionally substituted with one or more instances of R^7 . In some embodiments, R^6 is pyrazolyl, optionally substituted with one or more instances of R^7 . In some embodiments, R^6 is isoxazolyl, optionally substituted with one or more instances of R^7 . In some embodiments, R^6 is imidazolyl, optionally substituted with one or more instances of R^7 . In some embodiments, R^6 is thiazolyl, optionally substituted with one

or more instances of R^7 . In some embodiments, R^6 is pyridinyl, optionally substituted with one or more instances of R^7 . In some embodiments, R^6 is pyrazinyl, optionally substituted with one or more instances of R^7 . In some embodiments, R^6 is pyridazinyl, optionally substituted with one or more instances of R^7 . In some embodiments, R^6 is pyrimidinyl, optionally substituted with one or more instances of R^7 . In some embodiments, R^6 is 2,3-dihydrobenzo[d]furanyl, optionally substituted with one or more instances of R^7 . In some embodiments, R^6 is benzofuranyl, optionally substituted with one or more instances of R^7 . In some embodiments, R^5 is indolyl, optionally substituted with one or more instances of R^7 . In some embodiments, R^6 is benzo[1,2,3]triazole, optionally substituted with one or more instances of R^7 . In some embodiments, R^6 is benzimidazolyl, optionally substituted with one or more instances of R^7 . In some embodiments, R^6 is imidazo[1,2-a]pyrimidinyl, optionally substituted with one or more instances of R^7 . In some embodiments, R^6 is imidazo[1,2-a]pyrazinyl, optionally substituted with one or more instances of R^7 . In some embodiments, R^6 is indazolyl, optionally substituted with one or more instances of R^7 . In some embodiments, R^6 is indolinyl, optionally substituted with one or more instances of R^7 . In some embodiments, R^6 is indoliziny, optionally substituted with one or more instances of R^7 . In some embodiments, R^6 is isoindolinyl, optionally substituted with one or more instances of R^7 . In some embodiments, R^6 is 2,3,-dihydrobenzo[d]oxazolyl, optionally substituted with one or more instances of R^7 . In some embodiments, R^6 is selected from those depicted in the compounds of **Table 1**, below.

[0074] In some embodiments, R^6 is substituted with 0, 1, 2 or 3 instances of R^7 . In some embodiments, R^6 is substituted with 1 instance of R^7 . R^6 is substituted with 2 instances of R^7 . R^6 is substituted with 3 instances of R^7 . In some embodiments, R^6 is unsubstituted.

[0075] As defined generally above, each R^7 is independently halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{OR}$, $-\text{SR}$, $-\text{NR}_2$, $-\text{S}(\text{O})_2\text{R}$, $-\text{S}(\text{O})_2\text{NR}_2$, $-\text{S}(\text{O})\text{R}$, $-\text{S}(\text{O})\text{NR}_2$, $-\text{C}(\text{O})\text{R}$, $-\text{C}(\text{O})\text{OR}$, $-\text{C}(\text{O})\text{NR}_2$, $-\text{C}(\text{O})\text{N}(\text{R})\text{OR}$, $-\text{OC}(\text{O})\text{R}$, $-\text{OC}(\text{O})\text{NR}_2$, $-\text{N}(\text{R})\text{C}(\text{O})\text{OR}$, $-\text{N}(\text{R})\text{C}(\text{O})\text{R}$, $-\text{N}(\text{R})\text{C}(\text{O})\text{NR}_2$, $-\text{N}(\text{R})\text{C}(\text{O})\text{S}(\text{O})_2\text{R}$, $-\text{N}(\text{R})\text{C}(\text{NR})\text{NR}_2$, $-\text{N}(\text{R})\text{S}(\text{O})_2\text{NR}_2$, $-\text{N}(\text{R})\text{S}(\text{O})_2\text{R}$, an optionally substituted C_{1-6} aliphatic group, or Cy, or two instances of R^6 on the same carbon atom are taken together to form an oxo group.

[0076] In some embodiments, each R^7 is independently halogen, $-\text{CN}$, $-\text{OR}$, $-\text{NR}_2$, $-\text{S}(\text{O})_2\text{NR}_2$, $-\text{N}(\text{R})\text{C}(\text{O})\text{R}$, $-\text{N}(\text{R})\text{C}(\text{O})\text{S}(\text{O})_2\text{R}$, an optionally substituted C_{1-6} aliphatic group, or Cy, or two instances of R^7 on the same carbon atom are taken together to form an oxo group. In some

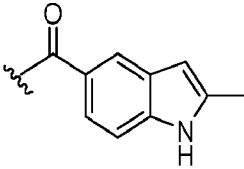
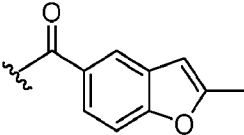
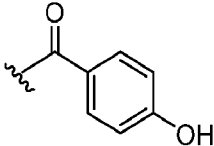
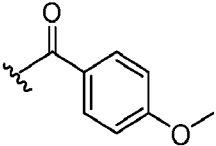
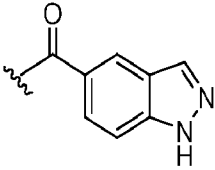
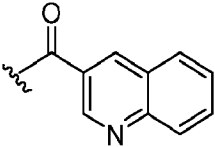
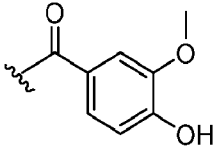
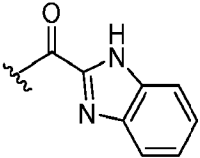
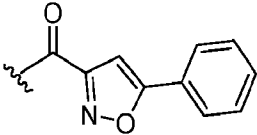
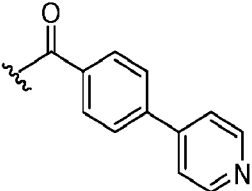
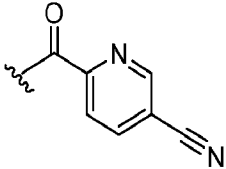
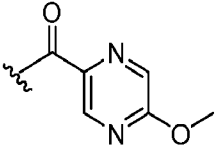
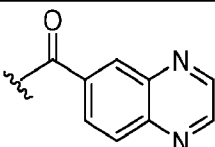
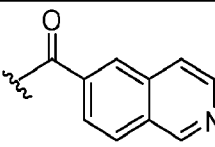
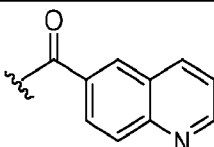
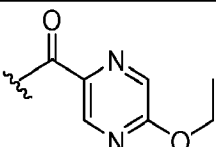
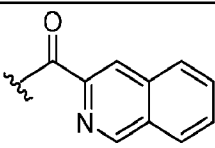
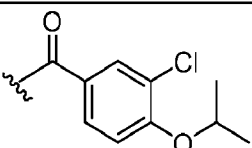
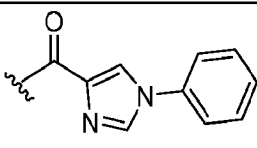
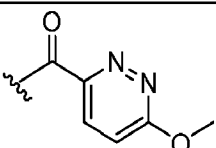
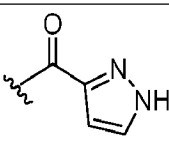
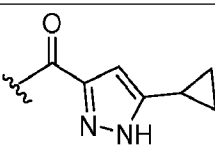
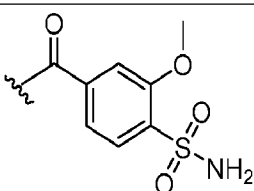
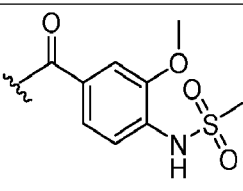
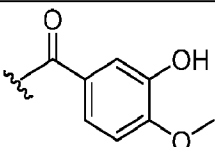
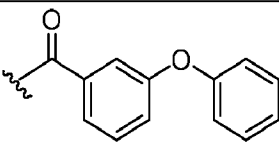
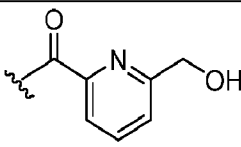
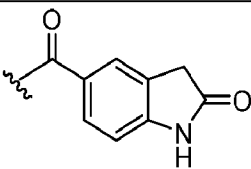
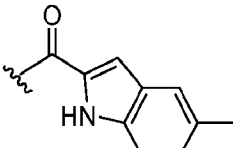
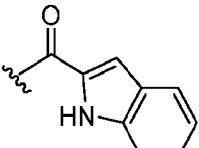
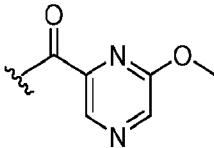
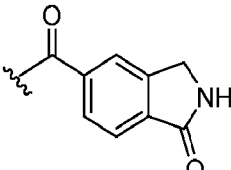
embodiments, each R^7 is independently -OR, an optionally substituted C_{1-6} aliphatic group, Cy or two instances of R^7 on the same carbon atom are taken together to form an oxo group.

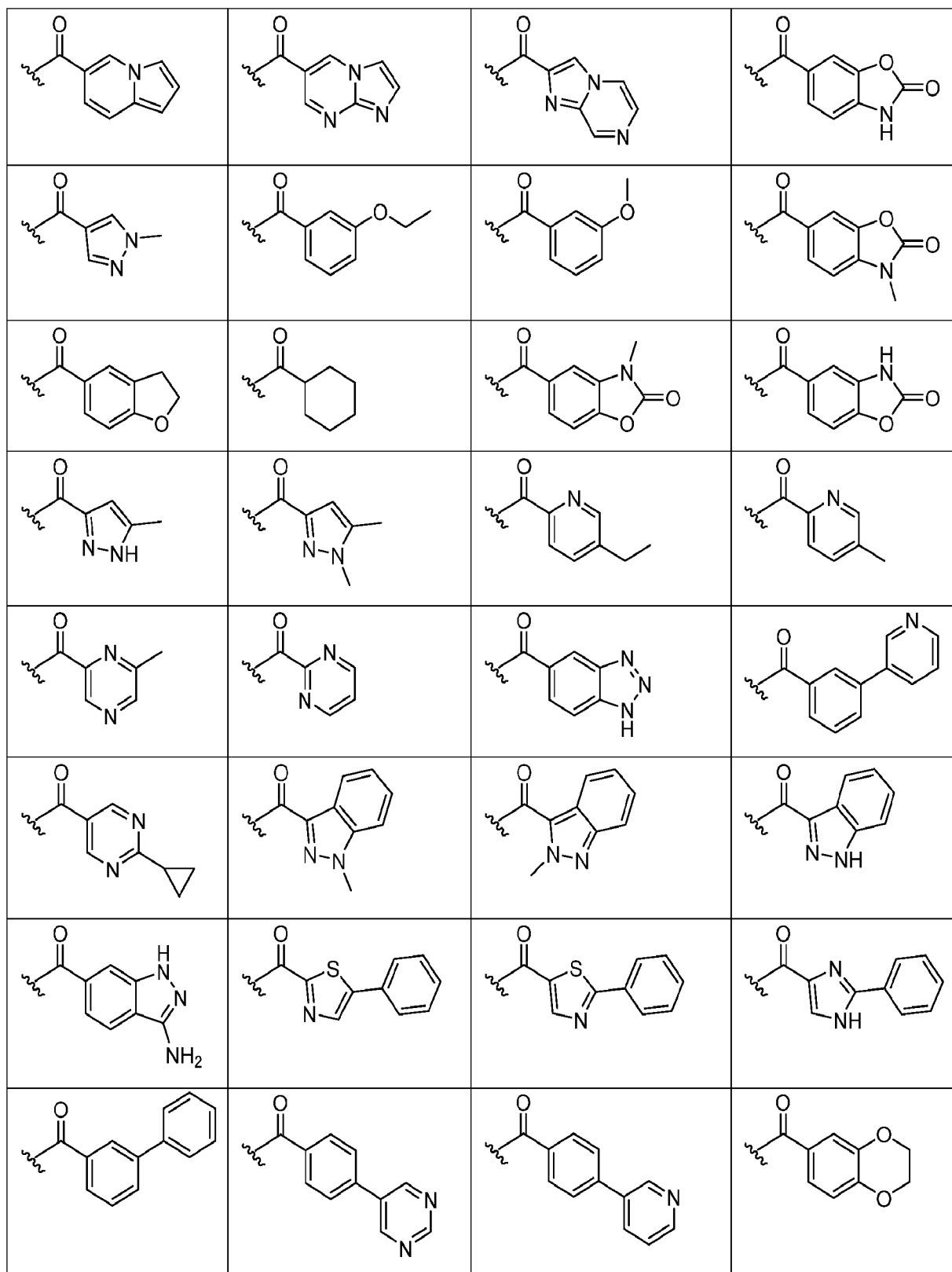
[0077] In some embodiments, each R^7 is independently fluoro, chloro, methoxy, ethoxy, isopropoxy, cyclopropoxy, isobutoxy, phenoxy, 2-cyclopropylethoxy, methyl, ethyl, cyclopropyl, isobutyl, phenyl, pyridinyl, pyrimidinyl, cyclopropanecarboxamido, 2-cyclopropylacetamido, (methylsulfonyl)methanamido, cyano, hydroxymethyl, trifluoromethoxy, trifluoromethyl, sulfamoyl, or amino, or two instances of R^7 on the same carbon atom are taken together to form an oxo group. In some embodiments, each R^7 is independently -OR. In some embodiments, each R^7 is independently selected from those depicted in the compounds of **Table 1**, below.

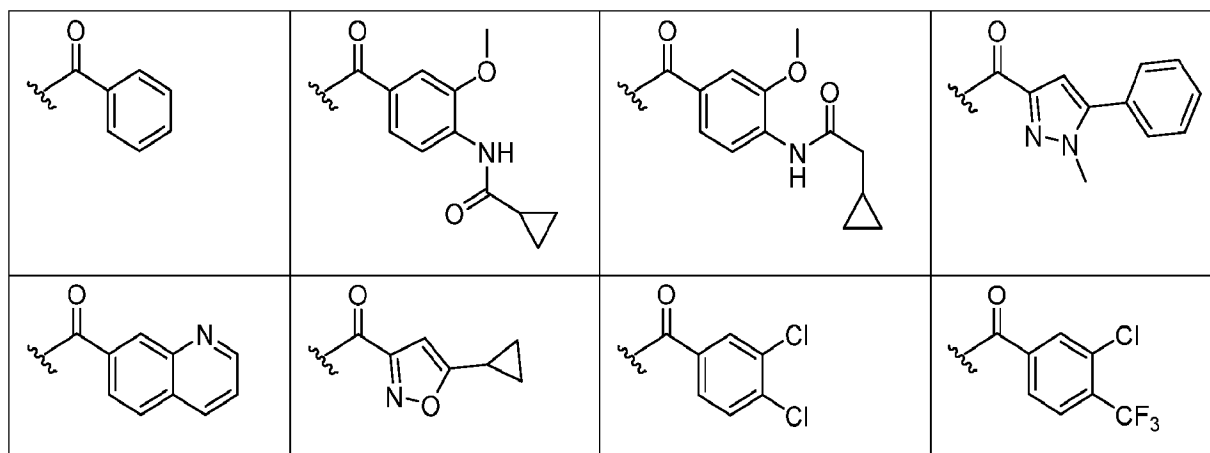
[0078] In some embodiments, $-L^2-R^6$ is a substituent of **Table B1** or **Table B2**:

Table B1: Exemplary $-L^2-R^6$ substituents

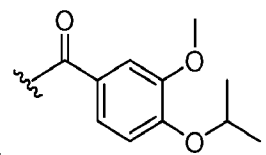
Table B2: Additional Exemplary -L²-R⁶ substituents





[0079] In some embodiments, $-L^2-R^6$ is a substituent of **Table B1**. In some embodiments, $-L^2-R^6$

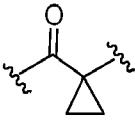


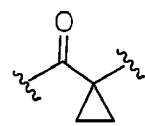
is a substituent of **Table B2**. In some embodiments, $-L^2-R^6$ is

[0080] As defined generally above, L^3 is a saturated or unsaturated, straight or branched, optionally substituted bivalent C_{1-4} hydrocarbon chain, wherein 0-2 methylene units of L^3 are independently replaced by $-O-$, $-NR-$, $-S-$, $-OC(O)-$, $-C(O)O-$, $-C(O)-$, $-S(O)-$, $-S(O)_2-$, $-C(S)-$, $-NRS(O)_2-$, $-S(O)_2NR-$, $-NRC(O)-$, $-C(O)NR-$, $-OC(O)NR-$, $-NRC(O)O-$, or $-NRC(O)NR-$. In some embodiments, L^3 is a saturated, straight, optionally substituted bivalent C_{1-4} hydrocarbon chain, wherein 0-2 methylene units of L^3 are independently replaced by $-O-$, $-NR-$, $-OC(O)-$, $-C(O)O-$, $-C(O)-$, $-NRC(O)-$, or $-C(O)NR$. In some embodiments, L^3 is a saturated, straight, optionally substituted bivalent C_{1-4} hydrocarbon chain. In some embodiments, L^3 is a saturated, straight, optionally substituted bivalent C_{1-4} hydrocarbon chain, wherein 1 methylene unit of L^3 is replaced by $-O-$, $-NR-$, $-OC(O)-$, $-C(O)O-$, $-C(O)-$, $-NRC(O)-$, or $-C(O)NR$. In some embodiments, L^3 is a saturated, straight, optionally substituted bivalent C_{1-4} hydrocarbon chain, wherein 1 methylene unit of L^3 is replaced by $-C(O)-$. In some embodiments, L^3 is a saturated, straight, substituted bivalent C_{1-4} hydrocarbon chain, wherein 1 methylene unit of L^3 is replaced by $-C(O)-$, and wherein the C_{1-4} hydrocarbon chain is substituted twice on the same carbon atom and forms a 3-6 membered saturated or partially unsaturated monocyclic carbocyclic ring. In some embodiments, L^3 is $-C(O)CH_2-$, $-C(O)C(CH_3)H-$, $-C(O)C(CH_3)_2-$, $-C(O)CH_2CH_2-$, $-$

$C(O)CH_2CH_2CH_2-$, or $-C(O)-$. In some embodiments, L^3 is $-C(O)CH_2-$, or $-$

C(O)C(CH₃)H-. In some embodiments, L³ is -C(O)CH₂-. In some embodiments, L³ is -C(O)C(CH₃)H-. In some embodiments, L³ is -C(O)C(CH₃)₂-. In some embodiments, L³ is -C(O)CH₂CH₂-. In some embodiments, L³ is -

C(O)-. In some embodiments, L³ is . In some embodiments, L³ is -C(O)CH₂-,



or -C(O)C(CH₃)H-. In some embodiments, L³ is selected from those depicted in the compounds of **Table 1**, below.

[0081] As defined generally above, R⁸ is a cyclic group selected from a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, a 7-12 membered saturated or partially unsaturated bicyclic carbocyclic ring, phenyl, an 8-10 membered bicyclic aromatic carbocyclic ring, a 3-8 membered saturated or partially unsaturated monocyclic heterocyclic ring (having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur), a 7-12 membered saturated or partially unsaturated bicyclic heterocyclic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), a 5-6 membered monocyclic heteroaromatic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), and an 8-10 membered bicyclic heteroaromatic ring (having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur), wherein the cyclic group is optionally substituted with one or more instances of R⁹.

[0082] In some embodiments, R⁸ is a cyclic group selected from phenyl, a 3-8 membered saturated or partially unsaturated monocyclic heterocyclic ring (having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur), a 7-12 membered saturated or partially unsaturated bicyclic heterocyclic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), a 5-6 membered monocyclic heteroaromatic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), and an 8-10 membered bicyclic heteroaromatic ring (having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur), wherein the cyclic group is optionally substituted with one or more instances of R⁹. In some embodiments, R⁸ is an 8-10 membered bicyclic heteroaromatic ring (having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur), optionally substituted with one or more instances of R⁹. In some embodiments, R⁸ a cyclic group selected from indolyl, indazolyl,

benzimidazolyl, benzofuranyl, phenyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, quinolinyl, isoquinolinyl, pyrazolyl, tetrazolyl, quinoxalinyl, indolizinyl, thiazolyl, oxazolyl, pyrrolyl, imidazo[1,2-a]pyrazinyl, and tetrahydropyranyl wherein the cyclic group is optionally substituted with one or more instances of R^9 . In some embodiments, R^8 is a cyclic group selected from indolyl, indazolyl, benzofuranyl, and benzimidazolyl, wherein the cyclic group is optionally substituted with one or more instances of R^9 .

[0083] In some embodiments, R^8 is indolyl optionally substituted with one or more instances of R^9 . In some embodiments, R^8 is indazolyl, optionally substituted with one or more instances of R^9 . In some embodiments, R^8 is benzimidazolyl, optionally substituted with one or more instances of R^9 . In some embodiments, R^8 is benzofuranyl, optionally substituted with one or more instances of R^9 . In some embodiments, R^8 is phenyl, optionally substituted with one or more instances of R^9 . In some embodiments, R^8 is pyridinyl, optionally substituted with one or more instances of R^9 . In some embodiments, R^8 is pyrimidinyl, optionally substituted with one or more instances of R^9 . In some embodiments, R^8 is pyridazinyl, optionally substituted with one or more instances of R^9 . In some embodiments, R^8 is pyrazinyl, optionally substituted with one or more instances of R^9 . In some embodiments, R^8 is quinolinyl, optionally substituted with one or more instances of R^9 . In some embodiments, R^8 is isoquinolinyl, optionally substituted with one or more instances of R^9 . In some embodiments, R^8 is pyrazolyl, optionally substituted with one or more instances of R^9 . In some embodiments, R^8 is tetrazolyl, optionally substituted with one or more instances of R^9 . In some embodiments, R^8 is quinoxalinyl, optionally substituted with one or more instances of R^9 . In some embodiments, R^8 is indolizinyl, optionally substituted with one or more instances of R^9 . In some embodiments, R^8 is thiazolyl, optionally substituted with one or more instances of R^9 . In some embodiments, R^8 is oxazolyl, optionally substituted with one or more instances of R^9 . In some embodiments, R^8 is pyrrolyl, optionally substituted with one or more instances of R^9 . In some embodiments, R^8 is imidazo[1,2-a]pyrazinyl, optionally substituted with one or more instances of R^9 . In some embodiments, R^8 is tetrahydropyranyl, optionally substituted with one or more instances of R^9 . In some embodiments, R^8 is selected from those depicted in the compounds of **Table 1**, below.

[0084] In some embodiments, R^8 is substituted with 0, 1 or 2 instances of R^9 . In some embodiments, R^8 is substituted with 1 instance of R^9 . R^8 is substituted with 2 instances of R^9 . In some embodiments, R^8 is unsubstituted.

[0085] As defined generally above, each instance of R^9 is independently halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{OR}$, $-\text{SR}$, $-\text{NR}_2$, $-\text{S(O)}_2\text{R}$, $-\text{S(O)}_2\text{NR}_2$, $-\text{S(O)R}$, $-\text{S(O)NR}_2$, $-\text{C(O)R}$, $-\text{C(O)OR}$, $-\text{C(O)NR}_2$, $-\text{C(O)N(R)OR}$, $-\text{OC(O)R}$, $-\text{OC(O)NR}_2$, $-\text{N(R)C(O)OR}$, $-\text{N(R)C(O)R}$, $-\text{N(R)C(O)NR}_2$, $-\text{N(R)C(NR)NR}_2$, $-\text{N(R)S(O)}_2\text{NR}_2$, $-\text{N(R)S(O)}_2\text{R}$, an optionally substituted C_{1-6} aliphatic group, an optionally substituted C_{1-6} aliphatic-Cy group, or Cy.

[0086] In some embodiments, each instance of R^9 is independently halogen, $-\text{CN}$, $-\text{OR}$, an optionally substituted C_{1-6} aliphatic group, or Cy. In some embodiments, each instance of R^9 is independently halogen, $-\text{CN}$, $-\text{OR}$, or a C_{1-6} aliphatic group. In some embodiments, each instance of R^9 is independently fluoro, chloro, bromo, $-\text{CN}$, methyl, ethyl methoxy, hydroxymethyl, cyclopropylmethoxy, 2-methoxyethyl, phenyl or pyridinyl. In some embodiments, each instance of R^9 is independently chloro, bromo, $-\text{CN}$, methyl, or methoxy. In some embodiments, each R^9 is independently selected from those depicted in the compounds of **Table 1**, below.

[0087] In some embodiments, $-\text{L}^3\text{-R}^8$ is a substituent of **Table C1** or **Table C2**:

Table C1: Exemplary $-\text{L}^3\text{-R}^8$ substituents

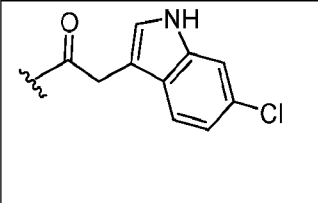
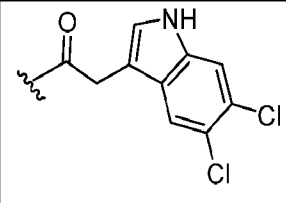
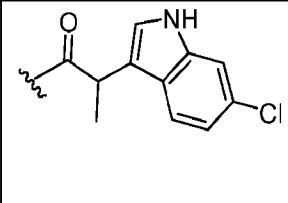
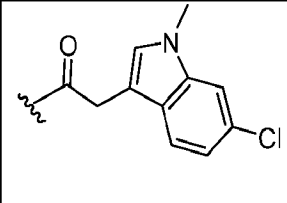
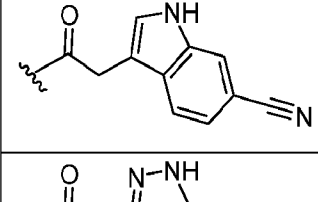
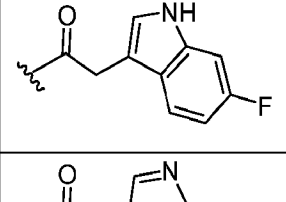
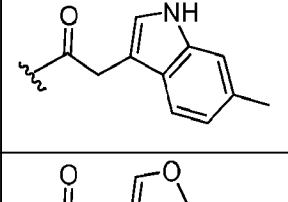
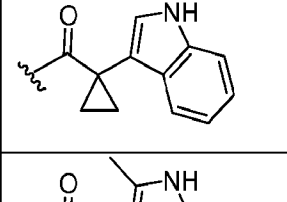
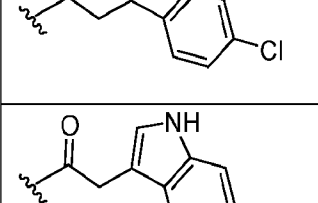
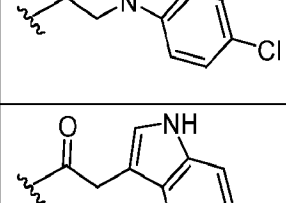
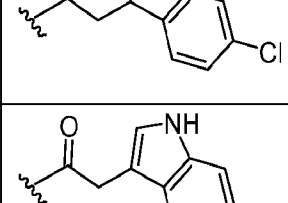
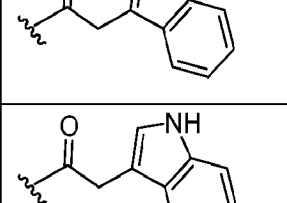
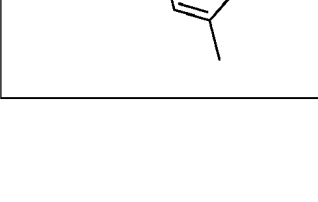
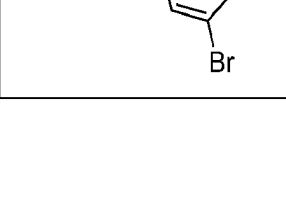
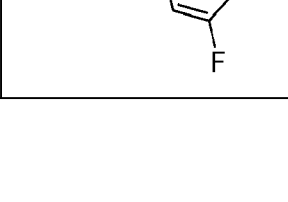
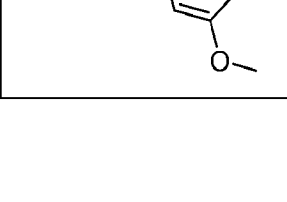
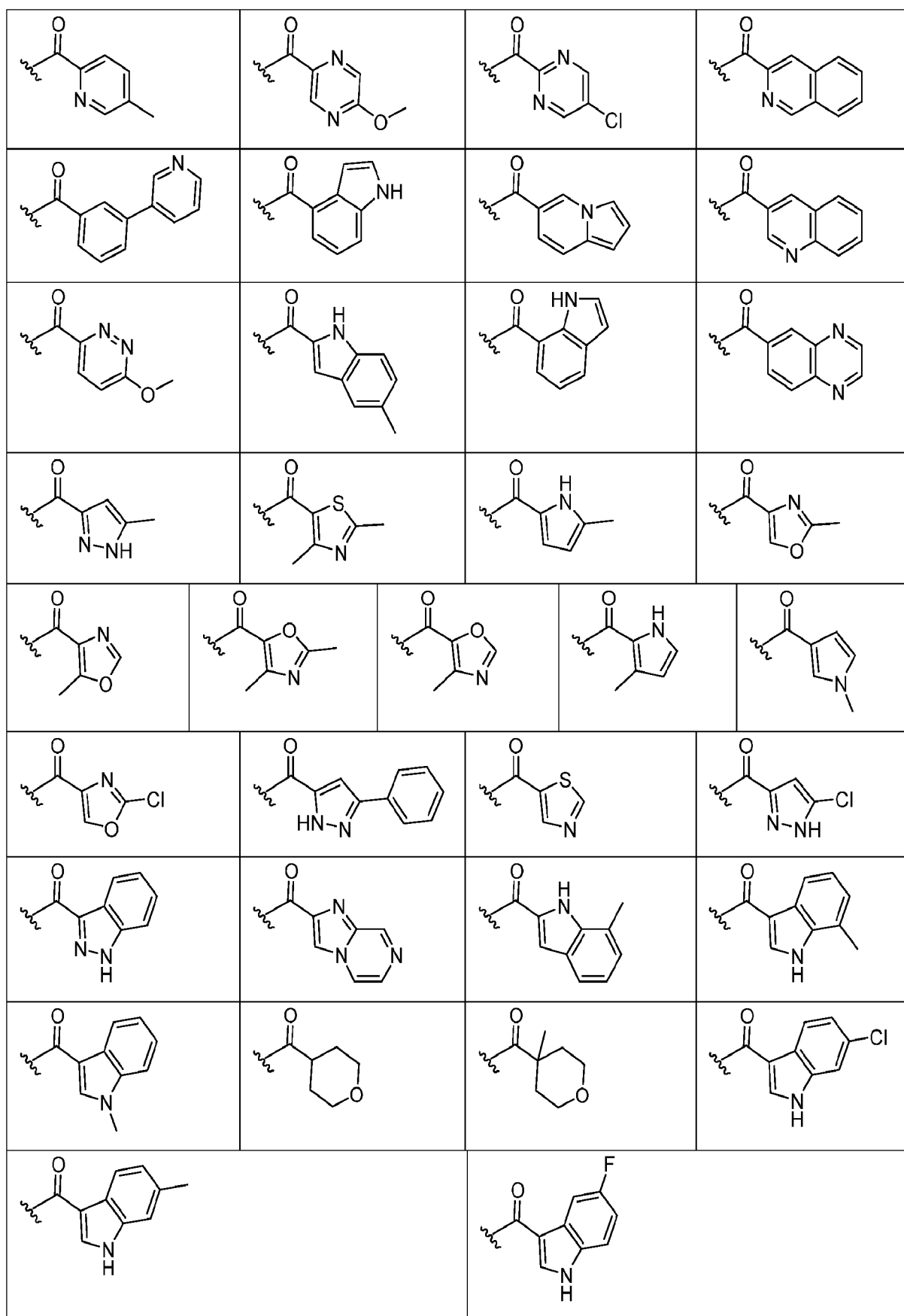
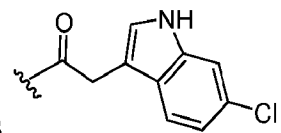
			
			
			
			

Table C2: Additional Exemplary -L³-R⁸ substituents



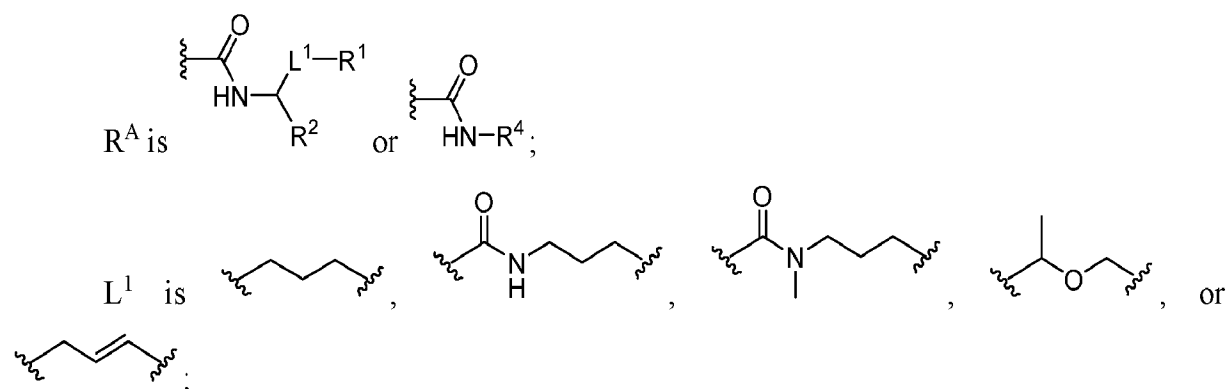
[0088] In some embodiments, $-L^3-R^8$ is a substituent of **Table C1**. In some embodiments, $-L^3-R^8$

is a substituent of **Table C2**. In some embodiments, $-L^3-R^8$ is



[0089] In some embodiments, each instance of Cy is independently phenyl or a 5-6 membered monocyclic heteroaromatic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur).

[0090] In some embodiments:



R^1 is a C_{1-4} aliphatic group or an optionally substituted cyclic group selected from a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, phenyl, a 3-8 membered saturated or partially unsaturated monocyclic heterocyclic ring (having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur), a 5-6 membered monocyclic heteroaromatic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), and an 8-10 membered bicyclic heteroaromatic ring (having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur);

R^2 is hydrogen, methyl, $-C(O)NHCH_3$, $-C(O)NH_2$, $-C(O)OCH_3$, $-C(O)OH$, or an optionally substituted 5-6 membered monocyclic heteroaromatic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur);

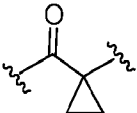
R^4 is a cyclic group selected from a 3-8 membered saturated or partially unsaturated monocyclic heterocyclic ring (having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur), and a 5-6 membered monocyclic heteroaromatic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), wherein the cyclic group is optionally substituted with one or more instances of R^5 ;

each R^5 is independently $-OR$, $-C(O)R$, an optionally substituted C_{1-6} aliphatic group, or an optionally substituted $-C_{1-6}$ aliphatic-Cy group;

L^2 is $-C(O)-$;

R^6 is a cyclic group selected from phenyl, an 8-10 membered bicyclic aromatic carbocyclic ring, a 5-6 membered monocyclic heteroaromatic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), and an 8-10 membered bicyclic heteroaromatic ring (having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur), wherein the cyclic group is optionally substituted with one or more instances of R^7 ;

each R^7 is independently $-OR$, an optionally substituted C_{1-6} aliphatic group, Cy or two instances of R^7 on the same carbon atom are taken together to form an oxo group;

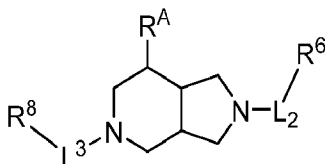
L^3 is $-C(O)CH_2-$,  or $-C(O)C(CH_3)H-$;

R^8 is an 8-10 membered bicyclic heteroaromatic ring (having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur), optionally substituted with one or more instances of R^9 ;

each instance of R^9 is independently halogen, $-CN$, $-OR$, or a C_{1-6} aliphatic group; and

each instance of Cy is independently phenyl or a 5-6 membered monocyclic heteroaromatic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur).

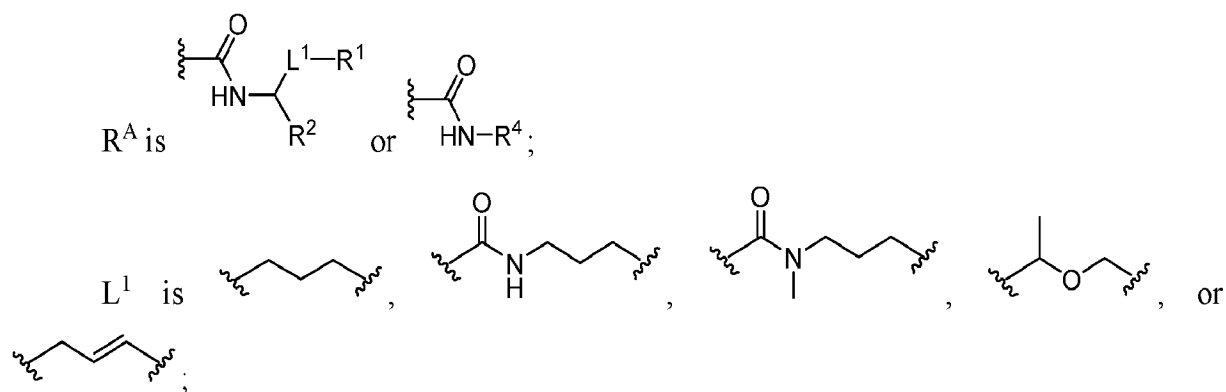
[0091] In some embodiments, the present disclosure provides a compound of Formula **I**, which is a compound of Formula **II**:



II

or a pharmaceutically acceptable salt thereof, wherein R^A , L^2 , R^6 , L^3 and R^8 , and their constituent groups, are each as defined and described herein. In some embodiments, R^A is a substituent from **Table A1**. In some embodiments, $-L^2-R^6$ is a substituent from **Table B1**. In some embodiments, $-L^3-R^8$ is a substituent from **Table C1**. In some embodiments, R^A is a substituent from **Table A1**,

and $-L^2-R^6$ is a substituent from **Table B1**. In some embodiments, R^A is a substituent from **Table A1**, and $-L^3-R^8$ is a substituent from **Table C1**. In some embodiments, $-L^2-R^6$ is a substituent from **Table B1**, and $-L^3-R^8$ is a substituent from **Table C1**. And in some embodiments, R^A is a substituent from **Table A1**, $-L^2-R^6$ is a substituent from **Table B1**, and $-L^3-R^8$ is a substituent from **Table C1**. In some embodiments:



R^1 is a C_{1-4} aliphatic group or an optionally substituted cyclic group selected from a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, phenyl, a 3-8 membered saturated or partially unsaturated monocyclic heterocyclic ring (having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur), a 5-6 membered monocyclic heteroaromatic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), and an 8-10 membered bicyclic heteroaromatic ring (having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur);

R^2 is hydrogen, methyl, $-C(O)NHCH_3$, $-C(O)NH_2$, $-C(O)OCH_3$, $-C(O)OH$, or a 5-6 membered monocyclic heteroaromatic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur);

R^4 is a 3-8 membered saturated or partially unsaturated monocyclic heterocyclic ring (having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur), optionally substituted with one or more instances of R^5 ;

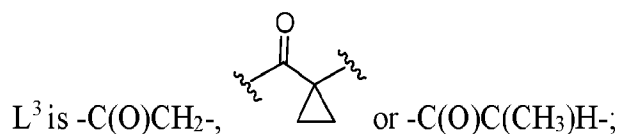
each R^5 is independently $-OR$, $-C(O)R$, an optionally substituted C_{1-6} aliphatic group, or an optionally substituted $-C_{1-6}$ aliphatic-Cy group;

L^2 is $-C(O)-$;

R^6 is a cyclic group selected from phenyl, an 8-10 membered bicyclic aromatic carbocyclic ring, a 5-6 membered monocyclic heteroaromatic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), and an 8-10 membered bicyclic heteroaromatic ring

(having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur), wherein the cyclic group is optionally substituted with one or more instances of R^7 ;

each R^7 is independently -OR, an optionally substituted C_{1-6} aliphatic group, Cy or two instances of R^7 on the same carbon atom are taken together to form an oxo group;

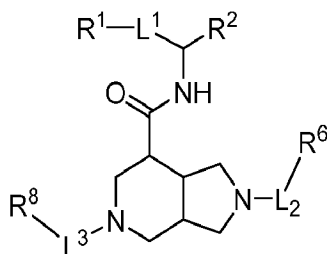


R^8 is an 8-10 membered bicyclic heteroaromatic ring (having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur), optionally substituted with one or more instances of R^9 ;

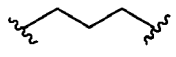
each instance of R^9 is independently halogen, $-CN$, $-OR$, or a C_{1-6} aliphatic group; and

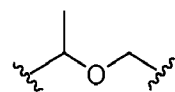
each instance of Cy is independently phenyl or a 5-6 membered monocyclic heteroaromatic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur).

[0092] In some embodiments, the present disclosure provides a compound of Formula **I**, which is a compound of Formula **III**:



III

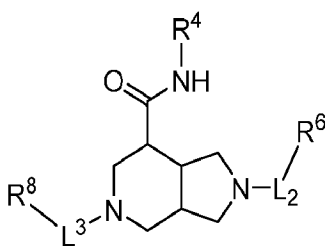
or a pharmaceutically acceptable salt thereof, wherein R^1 , R^2 , L^1 , L^2 , R^6 , L^3 and R^8 , and their constituent groups, are each as defined and described herein. In some embodiments, $-L^2-R^6$ is a substituent from **Table B1**. In some embodiments, $-L^3-R^8$ is a substituent from **Table C1**. In some embodiments, $-L^2-R^6$ is a substituent from **Table B1**, and $-L^3-R^8$ is a substituent from **Table C1**. In some embodiments, R^1 is optionally substituted phenyl. In some embodiments, R^1 is optionally substituted cyclohexyl. In some embodiments, L^1 is . In some embodiments, L^1 is



In some embodiments, R^2 is $-C(O)NHCH_3$. In some embodiments, L^2 is $-C(O)-$.

In some embodiments, R^6 is phenyl optionally substituted with one or more instances of R^7 . In some embodiments, R^6 is pyrazolyl optionally substituted with one or more instances of R^7 . In some embodiments, L^3 is $-C(O)CH_2-$. In some embodiments, L^3 is $-C(O)C(CH_3)H-$. In some embodiments, R^8 is a cyclic group selected from indolyl, indazolyl, benzofuranyl, and benzimidazolyl, wherein the cyclic group is optionally substituted with one or more instances of R^9 . In some embodiments, R^8 is indolyl optionally substituted with one or more instances of R^9 .

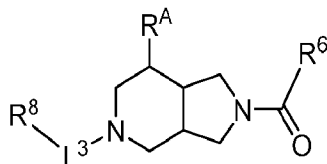
[0093] In some embodiments, the present disclosure provides a compound of Formula I, which is a compound of Formula IV:



IV

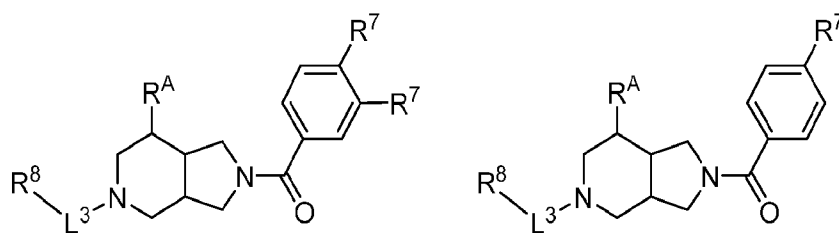
[0094] or a pharmaceutically acceptable salt thereof, wherein R^4 , L^2 , R^6 , L^3 and R^8 , and their constituent groups, are each as defined and described herein. In some embodiments, $-L^2-R^6$ is a substituent from **Table B1**. In some embodiments, $-L^3-R^8$ is a substituent from **Table C1**. In some embodiments, $-L^2-R^6$ is a substituent from **Table B1**, and $-L^3-R^8$ is a substituent from **Table C1**. In some embodiments, R^4 is pyridinyl, optionally substituted with one or more instances of R^5 . In some embodiments, R^4 is piperidinyl, optionally substituted with one or more instances of R^5 . In some embodiments, L^2 is $-C(O)-$. In some embodiments, R^6 is phenyl optionally substituted with one or more instances of R^7 . In some embodiments, R^6 is pyrazolyl optionally substituted with one or more instances of R^7 . In some embodiments, L^3 is $-C(O)CH_2-$. In some embodiments, L^3 is $-C(O)C(CH_3)H-$. In some embodiments, R^8 is a cyclic group selected from indolyl, indazolyl, benzofuranyl, and benzimidazolyl, wherein the cyclic group is optionally substituted with one or more instances of R^9 . In some embodiments, R^8 is indolyl optionally substituted with one or more instances of R^9 .

[0095] In some embodiments, the present disclosure provides a compound of Formula I, which is a compound of Formula V:

**V**

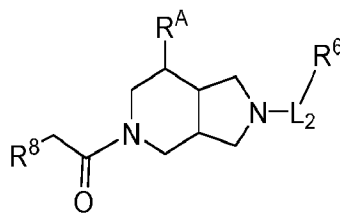
or a pharmaceutically acceptable salt thereof, wherein R^A , R^6 , L^3 and R^8 , and their constituent groups, are each as defined and described herein. In some embodiments, R^A is a substituent from **Table A1**. In some embodiments, $-L^3-R^8$ is a substituent from **Table C1**. In some embodiments, R^A is a substituent from **Table A1**, and $-L^3-R^8$ is a substituent from **Table C1**. In some embodiments, R^6 is phenyl optionally substituted with one or more instances of R^7 . In some embodiments, R^6 is pyrazolyl optionally substituted with one or more instances of R^7 .

[0096] In some embodiments, the present disclosure provides a compound of Formula **I**, which is a compound of Formula **Va** or **Vb**:

**Va****Vb**

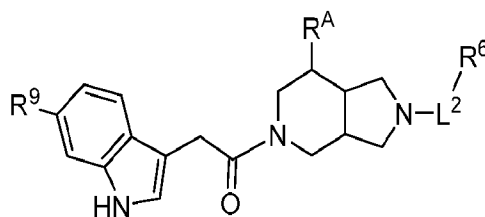
or a pharmaceutically acceptable salt thereof, wherein R^A , R^7 , L^3 and R^8 , and their constituent groups, are each as defined and described herein. In some embodiments, R^A is a substituent from **Table A1**. In some embodiments, $-L^3-R^8$ is a substituent from **Table C1**. In some embodiments, R^A is a substituent from **Table A1**, and $-L^3-R^8$ is a substituent from **Table C1**. In some embodiments, each instance of R^7 is $-OR$ or a halogen. In some embodiments, each instance of R^7 is $-OR$. In some embodiments, L^3 is $-C(O)CH_2-$. In some embodiments, L^3 is $-C(O)C(CH_3)H-$. In some embodiments, R^8 is a cyclic group selected from indolyl, indazolyl, benzofuranyl, and benzimidazolyl, wherein the cyclic group is optionally substituted with one or more instances of R^9 . In some embodiments, R^8 is indolyl optionally substituted with one or more instances of R^9 .

[0097] In some embodiments, the present disclosure provides a compound of Formula **I**, which is a compound of Formula **VI**:

**VI**

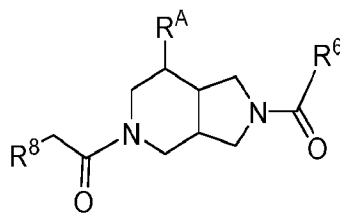
or a pharmaceutically acceptable salt thereof, wherein R^A , L^2 , R^6 , and R^8 , and their constituent groups, are each as defined and described herein. In some embodiments, R^A is a substituent from **Table A1**. In some embodiments, $-L^2-R^6$ is a substituent from **Table B1**. In some embodiments, R^A is a substituent from **Table A1**, and $-L^2-R^6$ is a substituent from **Table B1**. In some embodiments, R^8 is a cyclic group selected from indolyl, indazolyl, benzofuranyl, and benzimidazolyl, wherein the cyclic group is optionally substituted with one or more instances of R^9 . In some embodiments, R^8 is indolyl optionally substituted with one or more instances of R^9 .

[0098] In some embodiments, the present disclosure provides a compound of Formula **I**, which is a compound of Formula **VIa**:

**VIa**

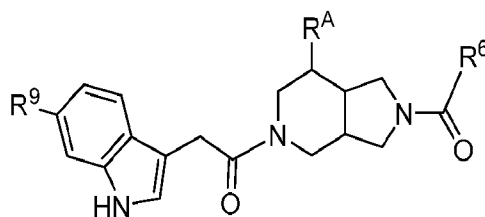
or a pharmaceutically acceptable salt thereof, wherein R^A , L^2 , R^6 , and R^9 , and their constituent groups, are each as defined and described herein. In some embodiments, R^A is a substituent from **Table A1**. In some embodiments, $-L^2-R^6$ is a substituent from **Table B1**. In some embodiments, R^A is a substituent from **Table A1**, and $-L^2-R^6$ is a substituent from **Table B1**. In some embodiments, R^9 is a halogen, methyl or $-CN$. In some embodiments, R^9 is chloro.

[0099] In some embodiments, the present disclosure provides a compound of Formula **I**, which is a compound of Formula **VIIa**:

**VIIa**

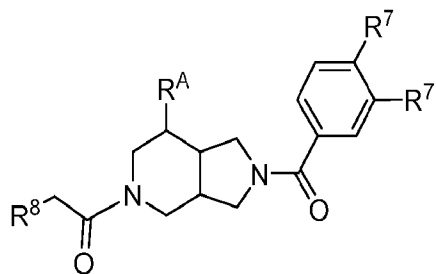
or a pharmaceutically acceptable salt thereof, wherein R^A , R^6 , and R^8 , and their constituent groups, are each as defined and described herein. In some embodiments, R^A is a substituent from **Table A1**. In some embodiments, R^6 is phenyl optionally substituted with one or more instances of R^7 . In some embodiments, R^6 is pyrazolyl optionally substituted with one or more instances of R^7 . In some embodiments, R^8 is a cyclic group selected from indolyl, indazolyl, benzofuranyl, and benzimidazolyl, wherein the cyclic group is optionally substituted with one or more instances of R^9 . In some embodiments, R^8 is indolyl optionally substituted with one or more instances of R^9 .

[00100] In some embodiments, the present disclosure provides a compound of Formula **I**, which is a compound of Formula **VIIb**:

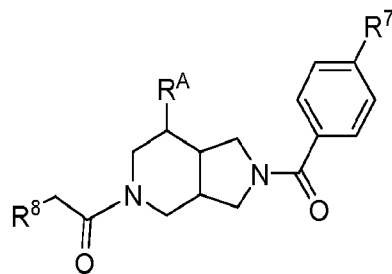
**VIIb**

or a pharmaceutically acceptable salt thereof, wherein R^A , R^6 , and R^9 , and their constituent groups, are each as defined and described herein. In some embodiments, R^A is a substituent from **Table A1**. In some embodiments, R^6 is phenyl optionally substituted with one or more instances of R^7 . In some embodiments, R^6 is pyrazolyl optionally substituted with one or more instances of R^7 . In some embodiments, R^9 is a halogen, methyl or $-CN$. In some embodiments, R^9 is chloro.

[00101] In some embodiments, the present disclosure provides a compound of Formula **I**, which is a compound of Formula **VIIc**:



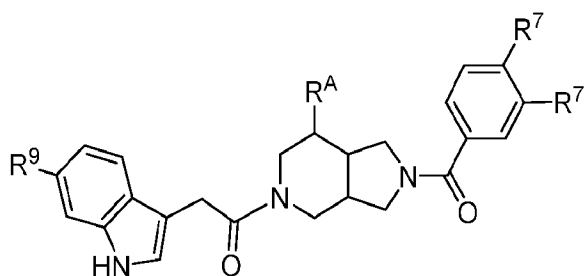
VIIc



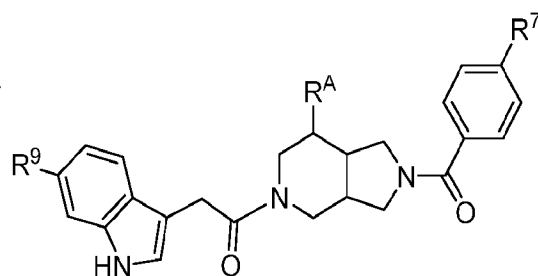
VIIId

or a pharmaceutically acceptable salt thereof, wherein R^A , R^7 , and R^8 , and their constituent groups, are each as defined and described herein. In some embodiments, R^A is a substituent from **Table A1**. In some embodiments, each instance of R^7 is $-OR$ or a halogen. In some embodiments, each instance of R^7 is $-OR$. In some embodiments, L^3 is $-C(O)CH_2-$. In some embodiments, L^3 is $-C(O)C(CH_3)H-$. In some embodiments, R^8 is a cyclic group selected from indolyl, indazolyl, benzofuranyl, and benzimidazolyl, wherein the cyclic group is optionally substituted with one or more instances of R^9 . In some embodiments, R^8 is indolyl optionally substituted with one or more instances of R^9 .

[00102] In some embodiments, the present disclosure provides a compound of Formula **I**, which is a compound of Formula **VIIe** or **VIIIf**:



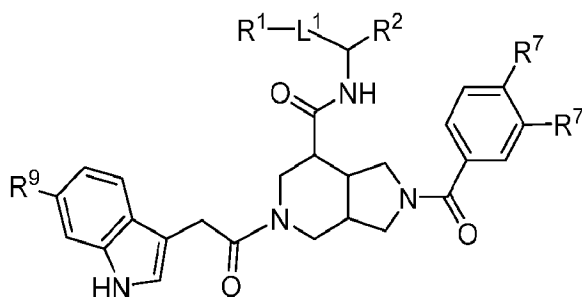
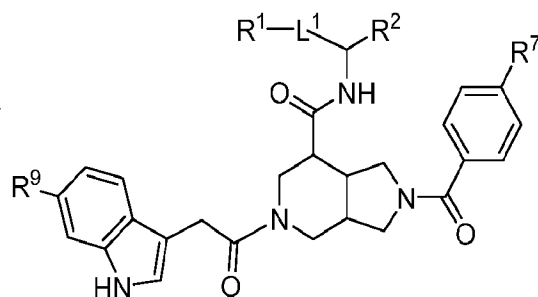
VIIe



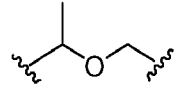
VIIIf

or a pharmaceutically acceptable salt thereof, wherein R^A , R^7 , and R^9 , and their constituent groups, are each as defined and described herein. In some embodiments, R^A is a substituent from **Table A1**. In some embodiments, each instance of R^7 is $-OR$ or a halogen. In some embodiments, each instance of R^7 is $-OR$. In some embodiments, R^9 is a halogen, methyl or $-CN$. In some embodiments, R^9 is chloro.

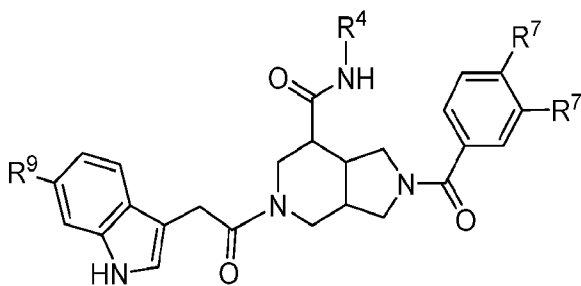
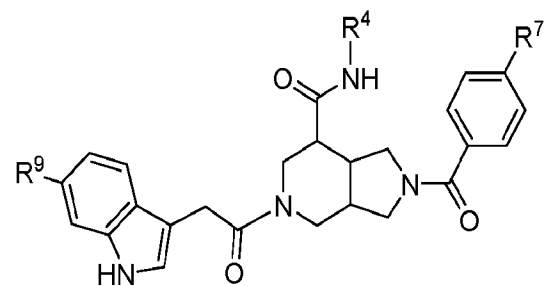
[00103] In some embodiments, the present disclosure provides a compound of Formula **I**, which is a compound of Formula **VIIIa** or **VIIIb**:

**VIIIa****VIIIb**

or a pharmaceutically acceptable salt thereof, wherein R^1 , R^2 , R^7 , and R^9 , and their constituent groups, are each as defined and described herein. In some embodiments, R^1 is optionally substituted phenyl. In some embodiments, R^1 is optionally substituted cyclohexyl. In some

embodiments, L^1 is . In some embodiments, L^1 is . In some embodiments, R^2 is $-C(O)NHCH_3$. In some embodiments, each instance of R^7 is $-OR$ or a halogen. In some embodiments, each instance of R^7 is $-OR$. In some embodiments, R^9 is a halogen, methyl or $-CN$. In some embodiments, R^9 is chloro.

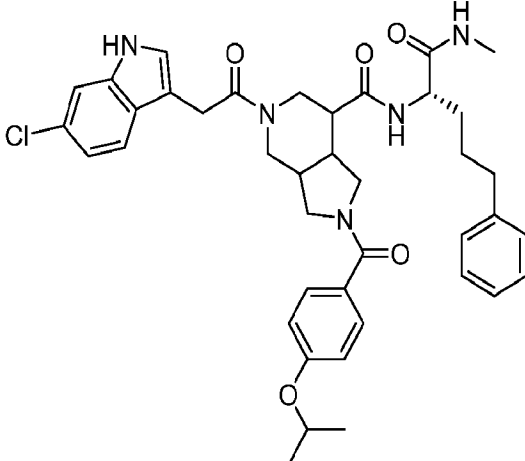
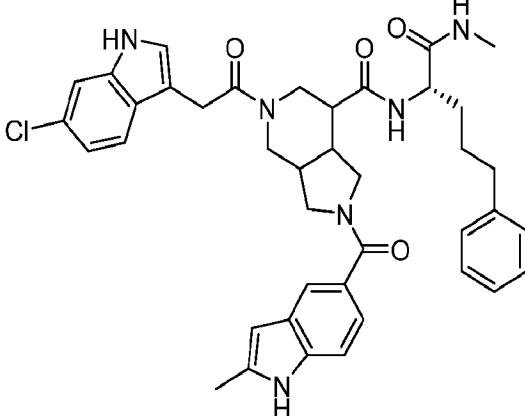
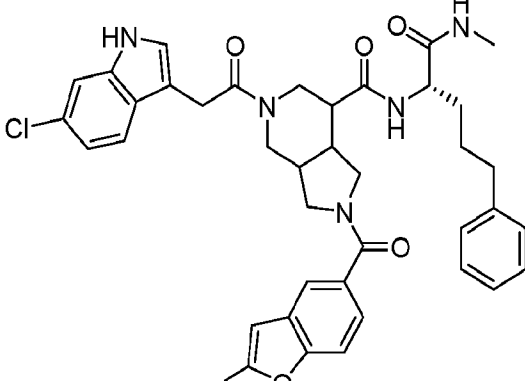
[00104] In some embodiments, the present disclosure provides a compound of Formula **I**, which is a compound of Formula **VIIIc** or **VIIIb**:

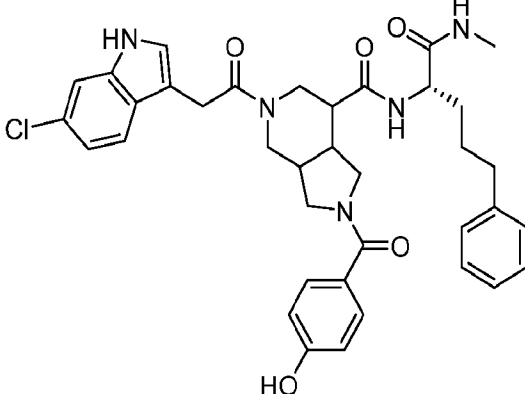
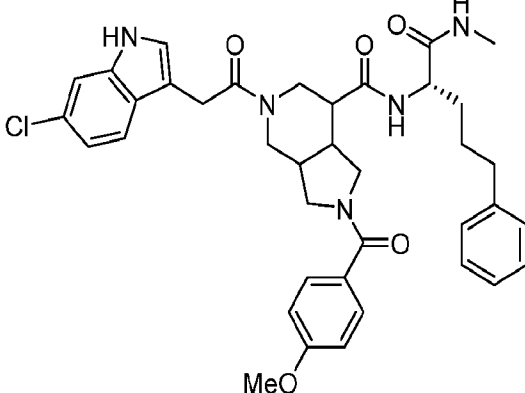
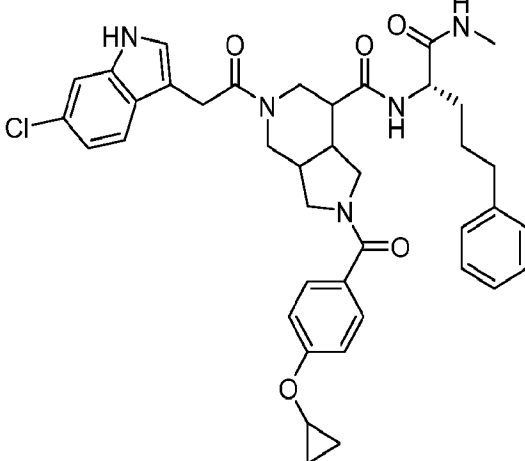
**VIIIc****VIIIb**

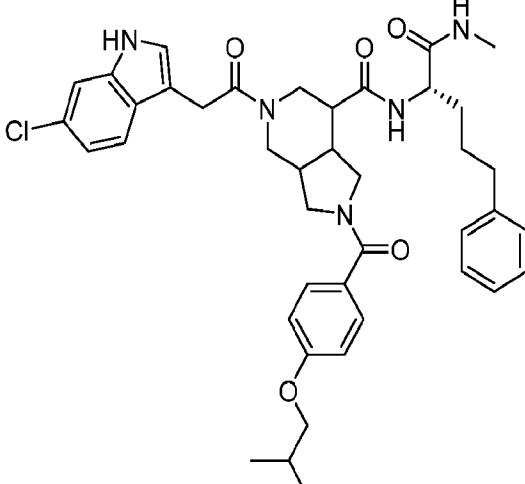
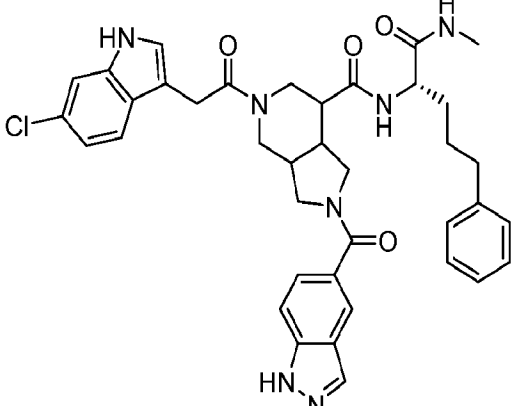
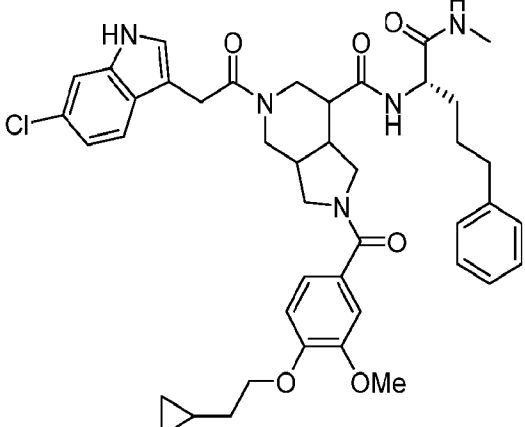
or a pharmaceutically acceptable salt thereof, wherein R^4 , R^7 , and R^9 , and their constituent groups, are each as defined and described herein. In some embodiments, R^4 is pyridinyl, optionally substituted with one or more instances of R^5 . In some embodiments, R^4 is piperidinyl, optionally substituted with one or more instances of R^5 . In some embodiments, each instance of R^7 is $-OR$ or a halogen. In some embodiments, each instance of R^7 is $-OR$. In some embodiments, R^9 is a halogen, methyl or $-CN$. In some embodiments, R^9 is chloro.

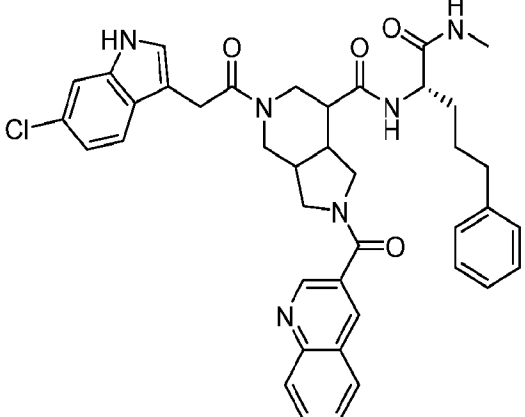
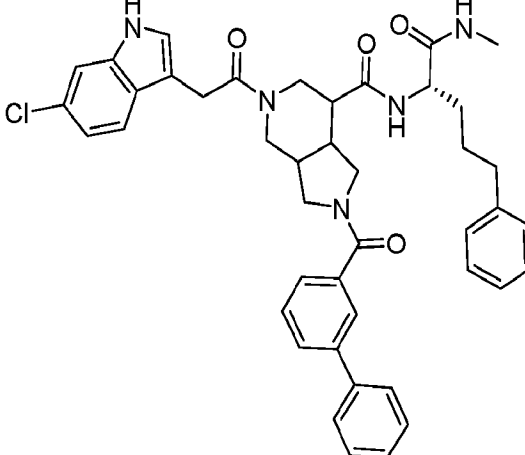
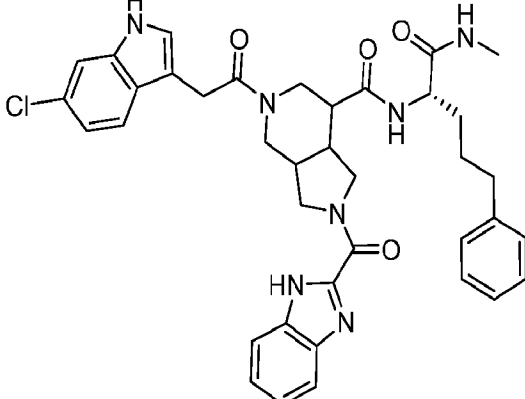
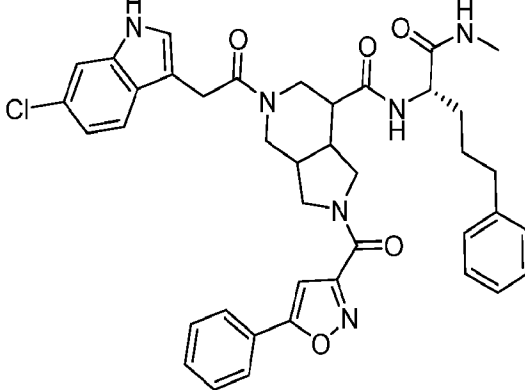
[00105] Exemplary compounds of the present disclosure are set forth in **Table 1**, below.

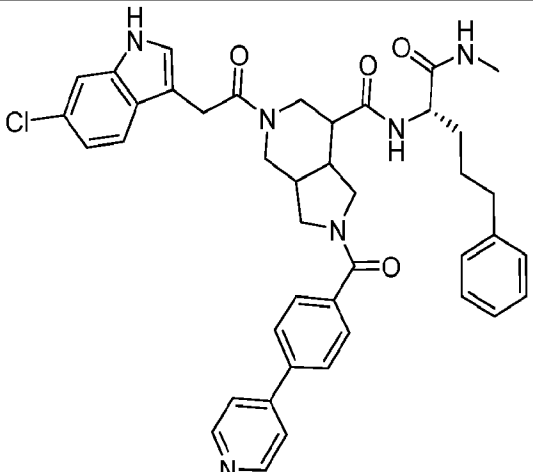
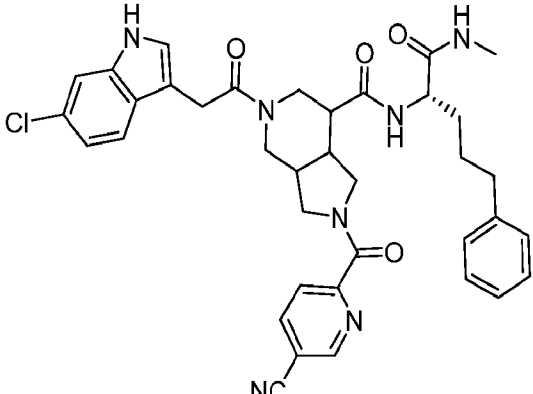
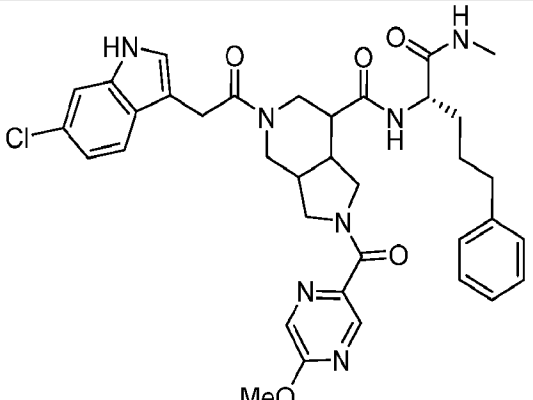
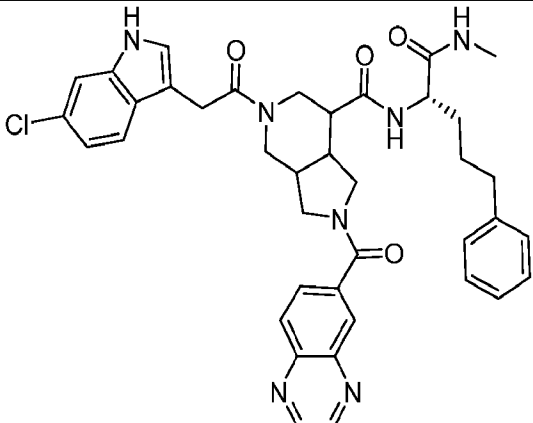
Table 1. Exemplary Compounds

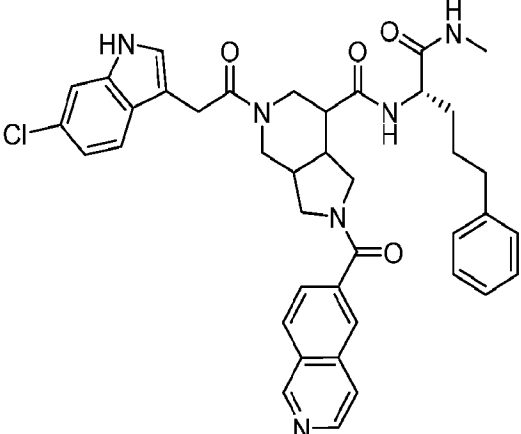
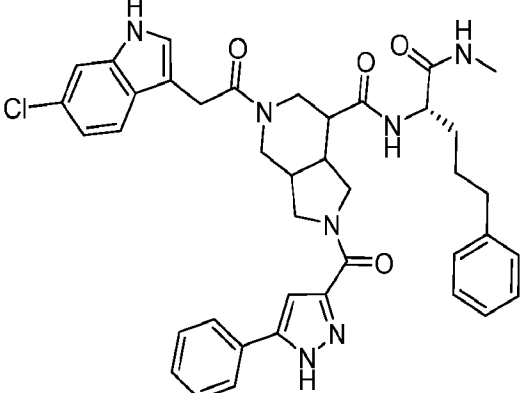
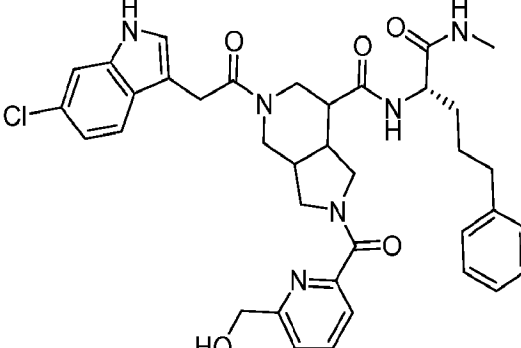
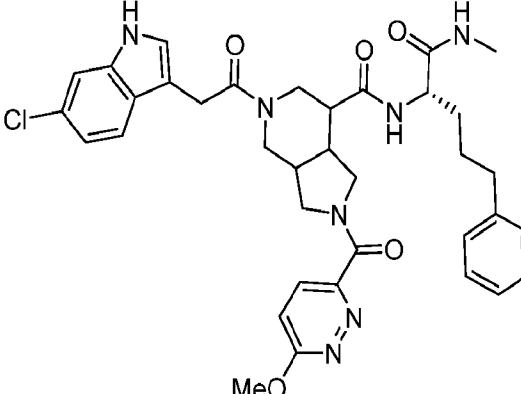
#	Structure
I-1	 Chemical structure of compound I-1: A complex molecule featuring a 5-chloro-1H-indol-3-yl group connected via a methylene group to a carbonyl group. This carbonyl is part of a bicyclic system (a 6-membered ring fused to a 5-membered ring, both containing nitrogen atoms). The 6-membered ring is also connected to another carbonyl group, which is further connected to a chiral center (marked with a dashed bond). This chiral center is part of a side chain that includes a benzyl group and a methylamino group.
I-2	 Chemical structure of compound I-2: Similar to I-1, but the side chain is connected to a different aromatic system, specifically a 4-methyl-1H-indol-3-yl group.
I-3	 Chemical structure of compound I-3: Similar to I-1, but the side chain is connected to a different aromatic system, specifically a 4-methoxy-1H-indol-3-yl group.

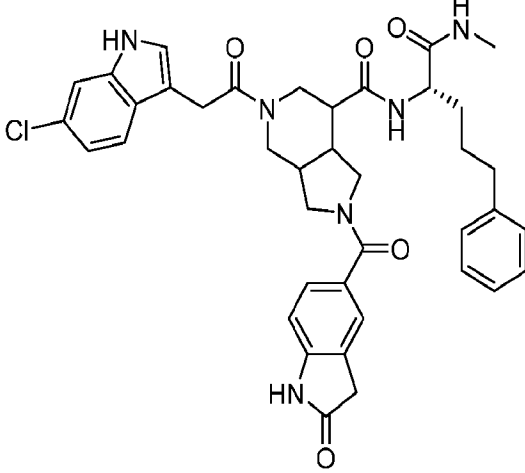
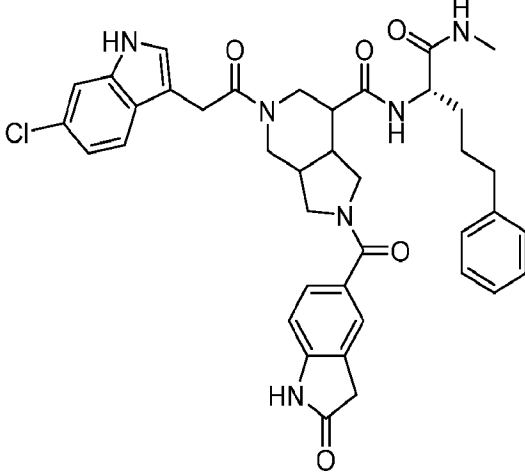
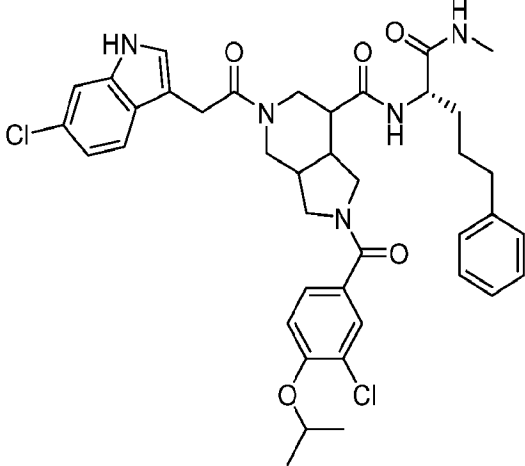
#	Structure
I-4	
I-5	
I-6	

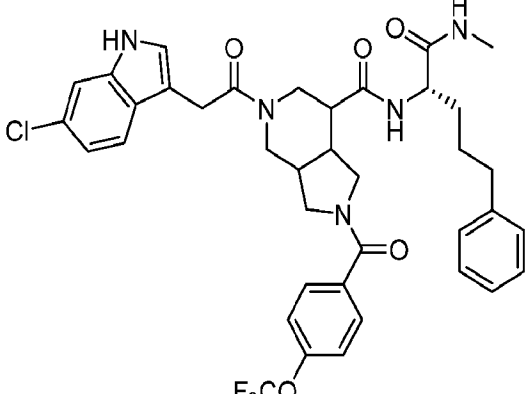
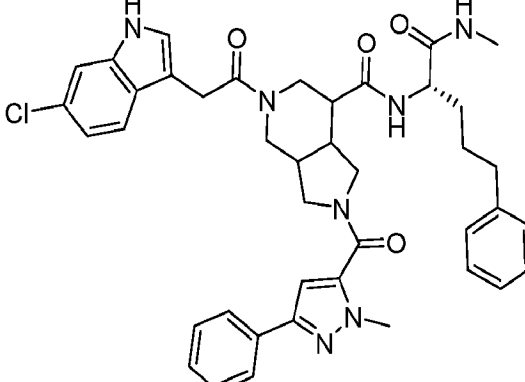
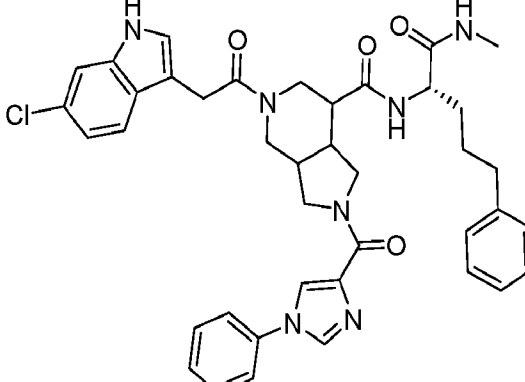
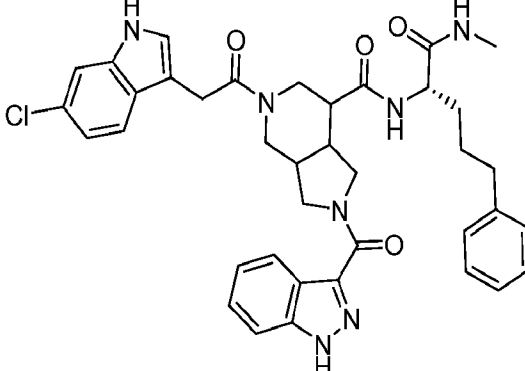
#	Structure
I-7	 <chem>CN(C)C(=O)N[C@@H](Cc1ccccc1)C(=O)N2CC[C@H](C(=O)N3C[C@@H](C2)CC[C@H]3C(=O)Cc4c[nH]c5ccc(Cl)cc45)CC[C@H](N2)C(=O)c6ccc(OCC(C)C)cc6</chem>
I-8	 <chem>CN(C)C(=O)N[C@@H](Cc1ccccc1)C(=O)N2CC[C@H](C(=O)N3C[C@@H](C2)CC[C@H]3C(=O)Cc4c[nH]c5ccc(Cl)cc45)CC[C@H](N2)C(=O)c6ccc7c(c6)c[nH]7</chem>
I-9	 <chem>CN(C)C(=O)N[C@@H](Cc1ccccc1)C(=O)N2CC[C@H](C(=O)N3C[C@@H](C2)CC[C@H]3C(=O)Cc4c[nH]c5ccc(Cl)cc45)CC[C@H](N2)C(=O)c6ccc(OC)c(OC[C@H]7CC8CC8O7)c6</chem>

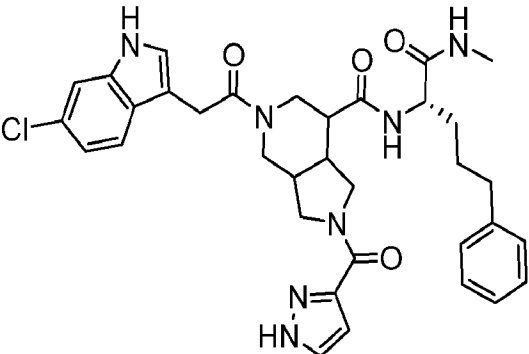
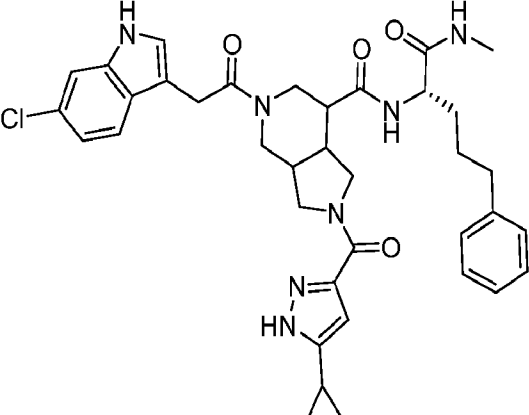
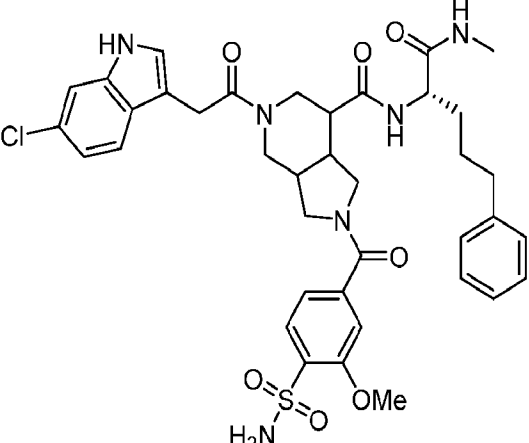
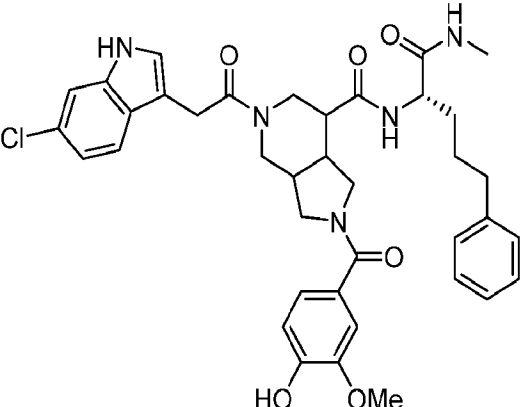
#	Structure
I-10	 <chem>CNC(=O)[C@H](Cc1ccccc1)NC(=O)C2CCN(C2Cc3ccccc3C(=O)c4ccc5ccccc5n4)c5cc6ccccc6n5CCc7c[nH]c8ccc(Cl)cc78</chem>
I-11	 <chem>CNC(=O)[C@H](Cc1ccccc1)NC(=O)C2CCN(C2Cc3ccccc3C(=O)c4ccc(cc4)-c5ccccc5)c6c[nH]c7ccc(Cl)cc67</chem>
I-12	 <chem>CNC(=O)[C@H](Cc1ccccc1)NC(=O)C2CCN(C2Cc3ccccc3C(=O)c4c[nH]c5ccccc45)c6c[nH]c7ccc(Cl)cc67</chem>
I-13	 <chem>CNC(=O)[C@H](Cc1ccccc1)NC(=O)C2CCN(C2Cc3ccccc3C(=O)c4oc5ccccc5n4)c6c[nH]c7ccc(Cl)cc67</chem>

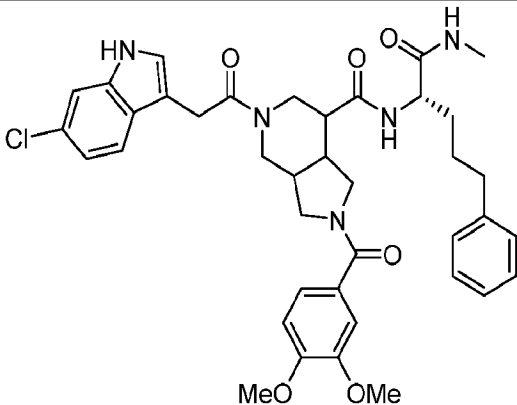
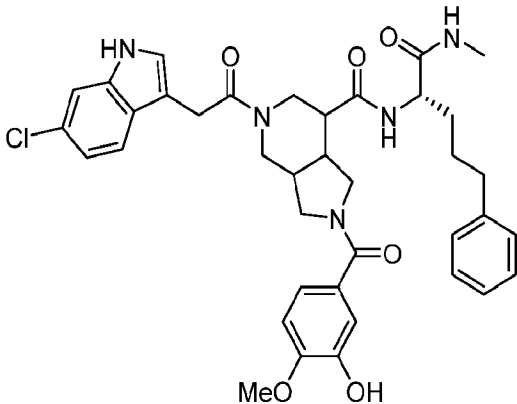
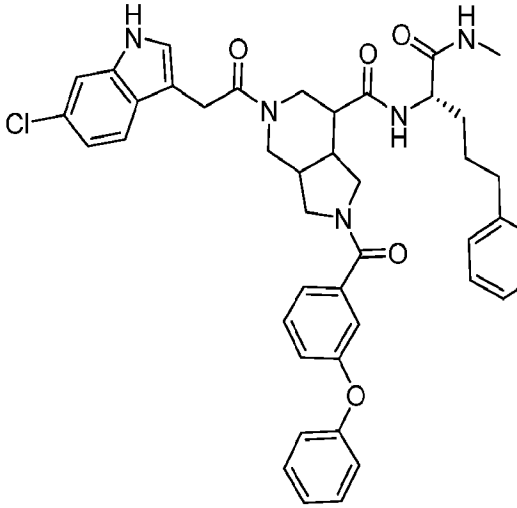
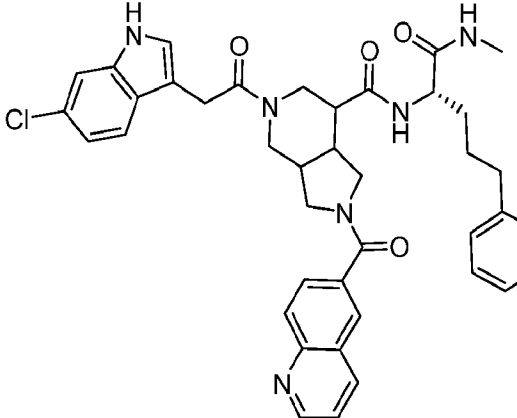
#	Structure
I-14	 Chemical structure of compound I-14. It features a 4-chloro-1H-indol-3-yl group connected via a methylene group to a carbonyl group. This carbonyl is part of a bicyclic system (a 6-membered ring fused to a 5-membered ring, both containing nitrogen). The 5-membered ring nitrogen is also part of a carbonyl group, which is connected to a 4-pyridyl group. The 6-membered ring nitrogen is connected to a carbonyl group, which is further connected to a chiral center. This chiral center is also connected to a 3-phenylpropyl group and a methylamino group.
I-15	 Chemical structure of compound I-15. It is similar to I-14, but the 4-pyridyl group is replaced by a 4-cyanopyridyl group.
I-16	 Chemical structure of compound I-16. It is similar to I-14, but the 4-pyridyl group is replaced by a 4-methoxy-2-pyridyl group.
I-17	 Chemical structure of compound I-17. It is similar to I-14, but the 4-pyridyl group is replaced by a 4-quinolyl group.

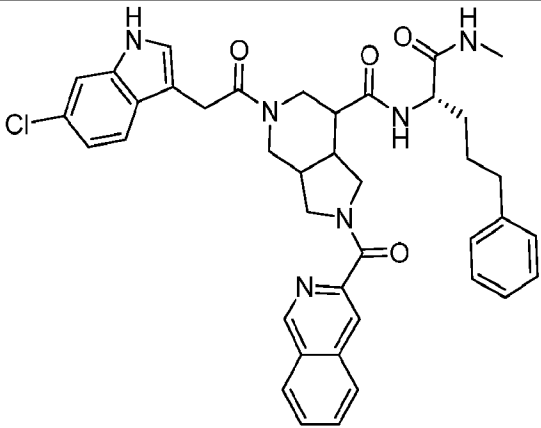
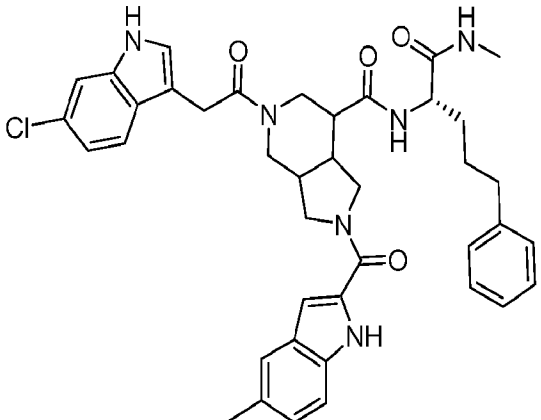
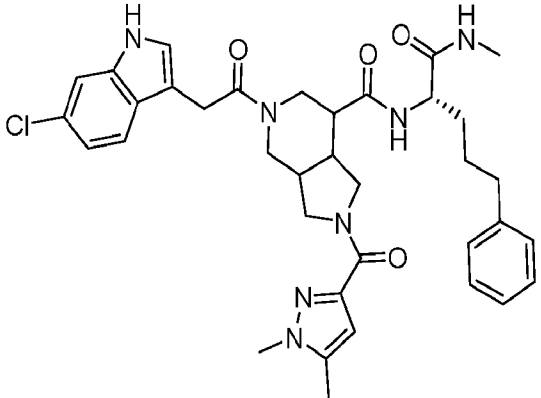
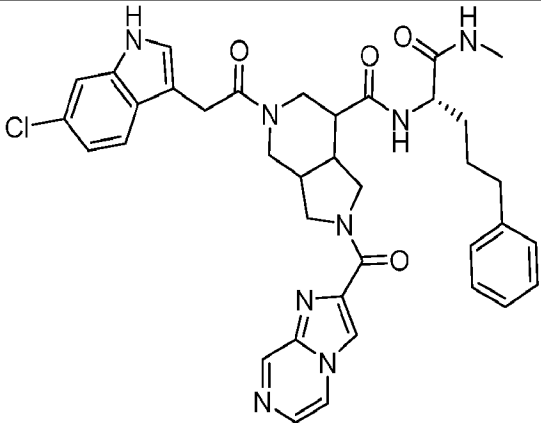
#	Structure
I-18	
I-19	
I-20	
I-21	

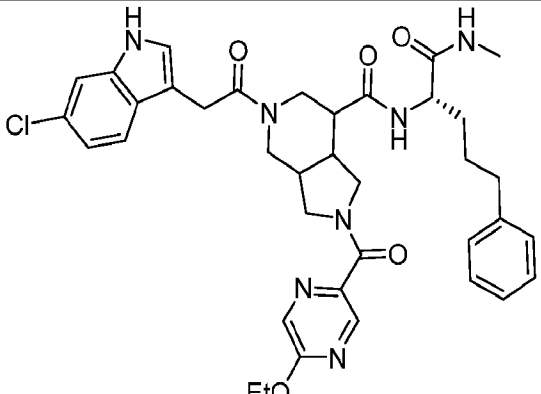
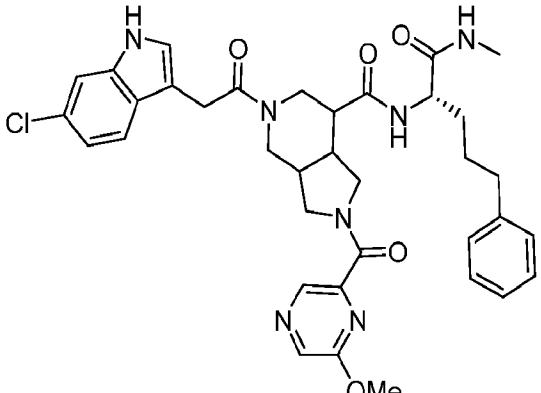
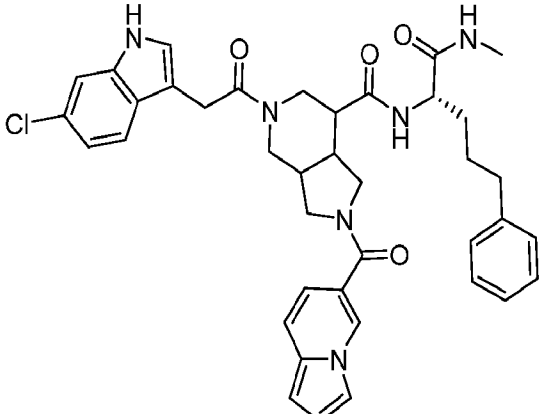
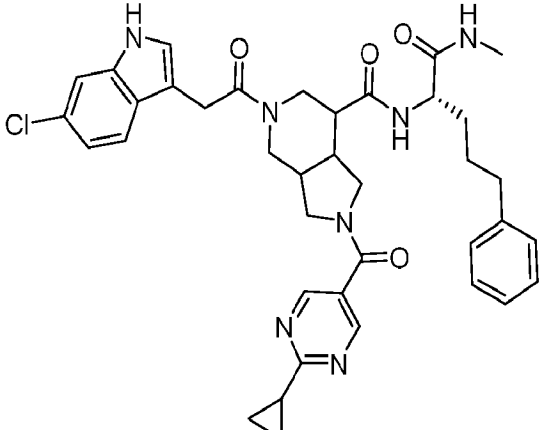
#	Structure
I-22	 Chemical structure of I-22: A complex molecule featuring a 4-chlorophenyl group attached to an indole ring, which is linked via a carbonyl group to a bicyclic amine system. The bicyclic amine is further substituted with a carbonyl group connected to a benzamide derivative, and another carbonyl group connected to a benzamide derivative. The structure is labeled as the "First eluting diastereomer".
I-23	 Chemical structure of I-23: A complex molecule featuring a 4-chlorophenyl group attached to an indole ring, which is linked via a carbonyl group to a bicyclic amine system. The bicyclic amine is further substituted with a carbonyl group connected to a benzamide derivative, and another carbonyl group connected to a benzamide derivative. The structure is labeled as the "Second eluting diastereomer".
I-24	 Chemical structure of I-24: A complex molecule featuring a 4-chlorophenyl group attached to an indole ring, which is linked via a carbonyl group to a bicyclic amine system. The bicyclic amine is further substituted with a carbonyl group connected to a benzamide derivative, and another carbonyl group connected to a benzamide derivative. The structure is labeled as the "Second eluting diastereomer".

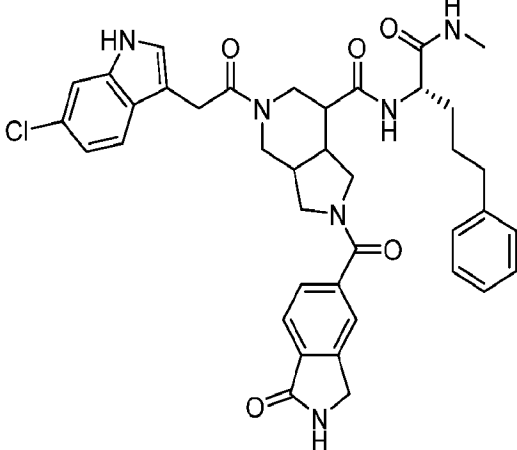
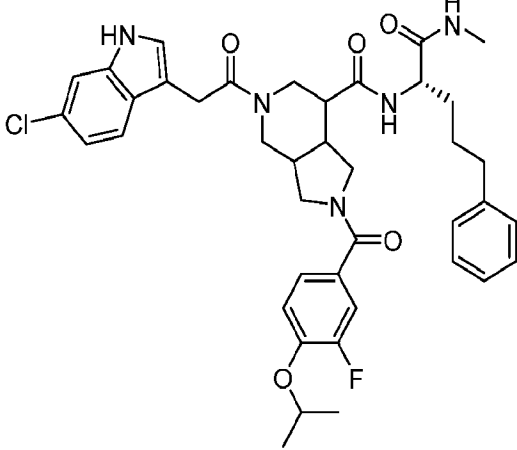
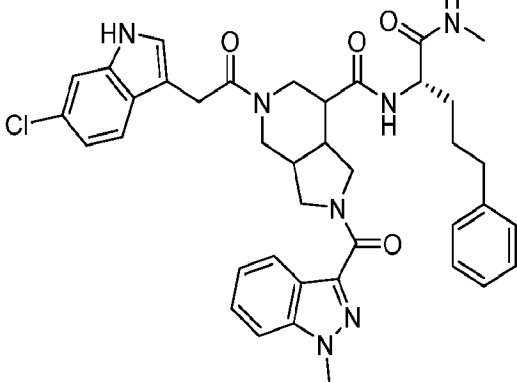
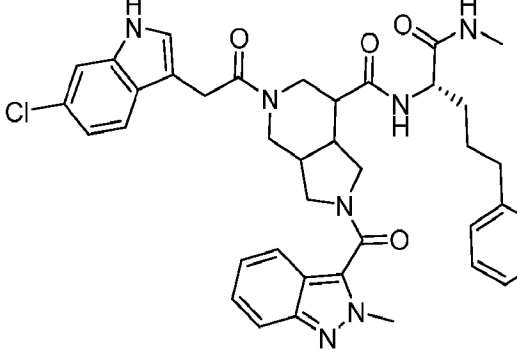
#	Structure
I-25	 Chemical structure of compound I-25: A bicyclic core consisting of a 6-membered ring fused to a 5-membered ring, both containing a nitrogen atom. The 6-membered ring is substituted with a (4-chlorophenyl)-1H-indol-3-ylmethyl group at position 1 and a (4-(trifluoromethoxy)phenyl) group at position 3. The 5-membered ring is substituted with a (4-phenylbutyl) group at position 2 and a (4-methyl-1H-imidazol-2-yl) group at position 4. The core is also substituted with a (4-chlorophenyl)-1H-indol-3-ylmethyl group at position 1 and a (4-(trifluoromethoxy)phenyl) group at position 3.
I-26	 Chemical structure of compound I-26: A bicyclic core consisting of a 6-membered ring fused to a 5-membered ring, both containing a nitrogen atom. The 6-membered ring is substituted with a (4-chlorophenyl)-1H-indol-3-ylmethyl group at position 1 and a (4-(trifluoromethoxy)phenyl) group at position 3. The 5-membered ring is substituted with a (4-phenylbutyl) group at position 2 and a (4-methyl-1H-imidazol-2-yl) group at position 4. The core is also substituted with a (4-chlorophenyl)-1H-indol-3-ylmethyl group at position 1 and a (4-(trifluoromethoxy)phenyl) group at position 3.
I-27	 Chemical structure of compound I-27: A bicyclic core consisting of a 6-membered ring fused to a 5-membered ring, both containing a nitrogen atom. The 6-membered ring is substituted with a (4-chlorophenyl)-1H-indol-3-ylmethyl group at position 1 and a (4-(trifluoromethoxy)phenyl) group at position 3. The 5-membered ring is substituted with a (4-phenylbutyl) group at position 2 and a (4-methyl-1H-imidazol-2-yl) group at position 4. The core is also substituted with a (4-chlorophenyl)-1H-indol-3-ylmethyl group at position 1 and a (4-(trifluoromethoxy)phenyl) group at position 3.
I-28	 Chemical structure of compound I-28: A bicyclic core consisting of a 6-membered ring fused to a 5-membered ring, both containing a nitrogen atom. The 6-membered ring is substituted with a (4-chlorophenyl)-1H-indol-3-ylmethyl group at position 1 and a (4-(trifluoromethoxy)phenyl) group at position 3. The 5-membered ring is substituted with a (4-phenylbutyl) group at position 2 and a (4-methyl-1H-imidazol-2-yl) group at position 4. The core is also substituted with a (4-chlorophenyl)-1H-indol-3-ylmethyl group at position 1 and a (4-(trifluoromethoxy)phenyl) group at position 3.

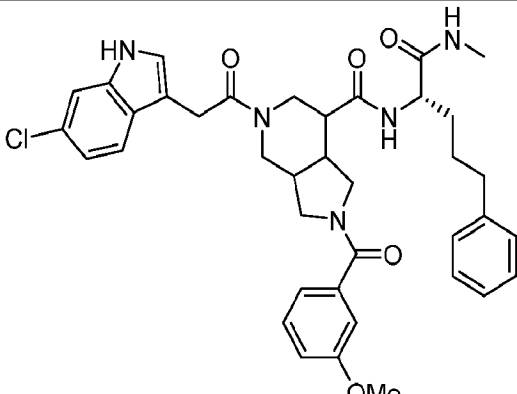
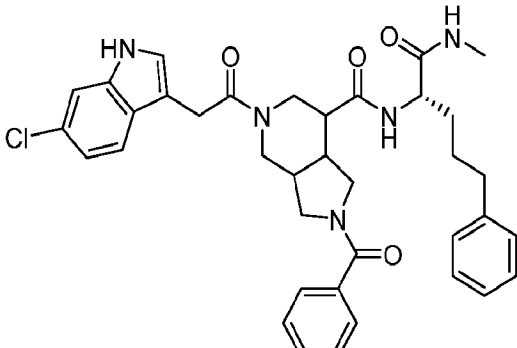
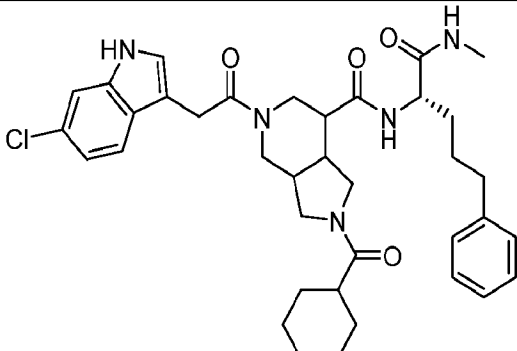
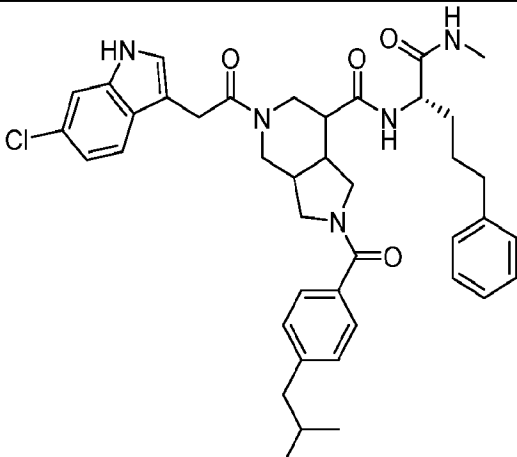
#	Structure
I-29	 Chemical structure of compound I-29: A bicyclic core consisting of a 6-membered ring fused to a 5-membered ring, both containing nitrogen atoms. The 6-membered ring is substituted with a 5-chloro-1H-indol-3-ylmethyl group and a (2-methylamino-3-phenylpropyl)carbamoyl group. The 5-membered ring is substituted with a (2-(1H-imidazol-2-yl)ethyl)carbamoyl group.
I-30	 Chemical structure of compound I-30: A bicyclic core consisting of a 6-membered ring fused to a 5-membered ring, both containing nitrogen atoms. The 6-membered ring is substituted with a 5-chloro-1H-indol-3-ylmethyl group and a (2-methylamino-3-phenylpropyl)carbamoyl group. The 5-membered ring is substituted with a (2-(1H-imidazol-2-yl)ethyl)carbamoyl group.
I-31	 Chemical structure of compound I-31: A bicyclic core consisting of a 6-membered ring fused to a 5-membered ring, both containing nitrogen atoms. The 6-membered ring is substituted with a 5-chloro-1H-indol-3-ylmethyl group and a (2-methylamino-3-phenylpropyl)carbamoyl group. The 5-membered ring is substituted with a (2-(4-methoxy-3-sulfamoylphenyl)ethyl)carbamoyl group.
I-32	 Chemical structure of compound I-32: A bicyclic core consisting of a 6-membered ring fused to a 5-membered ring, both containing nitrogen atoms. The 6-membered ring is substituted with a 5-chloro-1H-indol-3-ylmethyl group and a (2-methylamino-3-phenylpropyl)carbamoyl group. The 5-membered ring is substituted with a (2-(4-methoxy-3-hydroxyphenyl)ethyl)carbamoyl group.

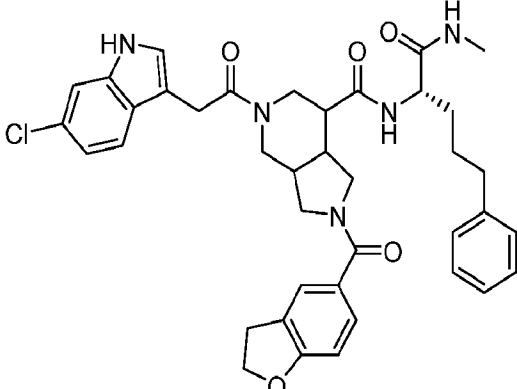
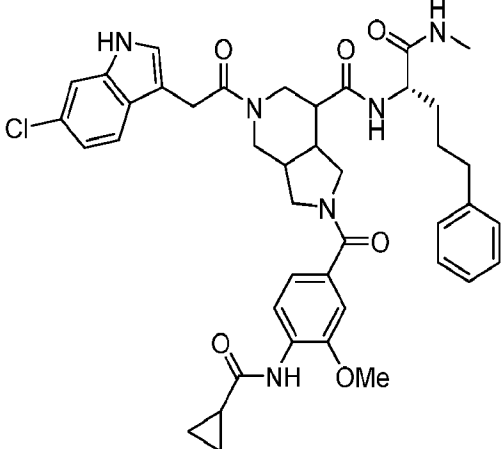
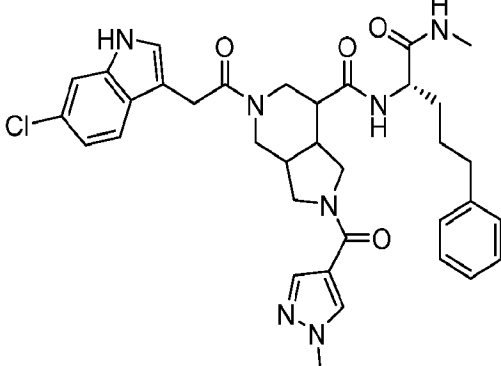
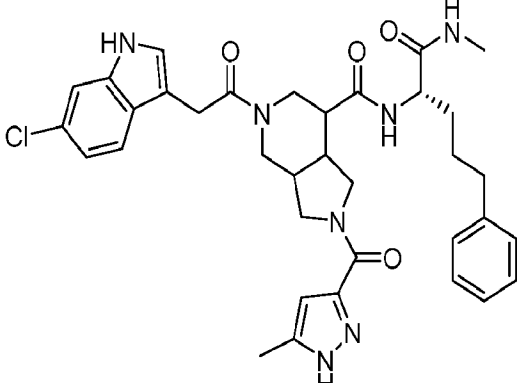
#	Structure
I-33	
I-34	
I-35	
I-36	

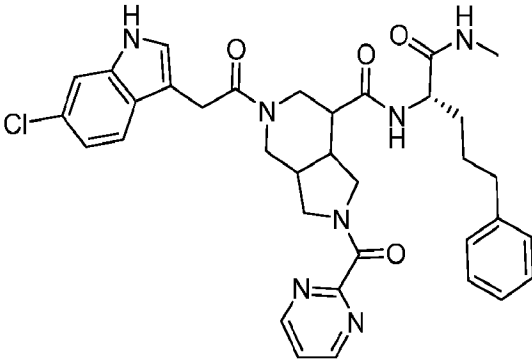
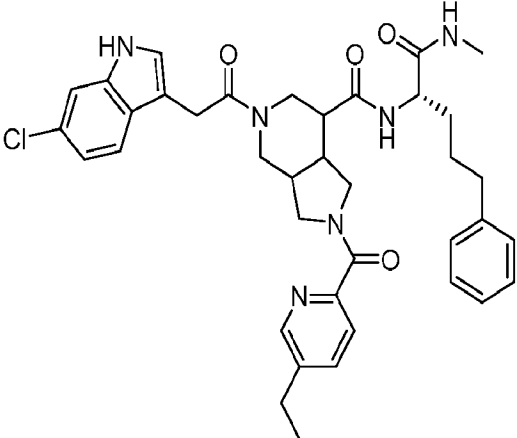
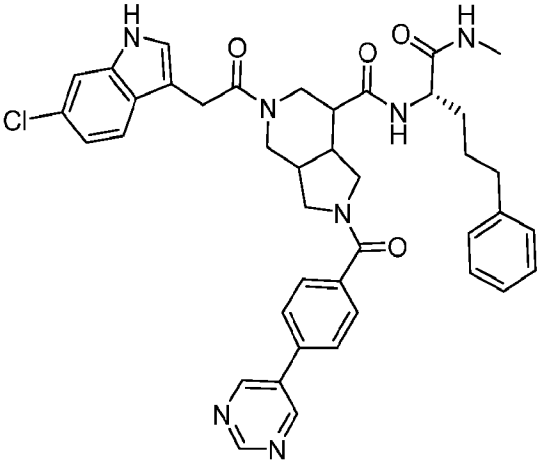
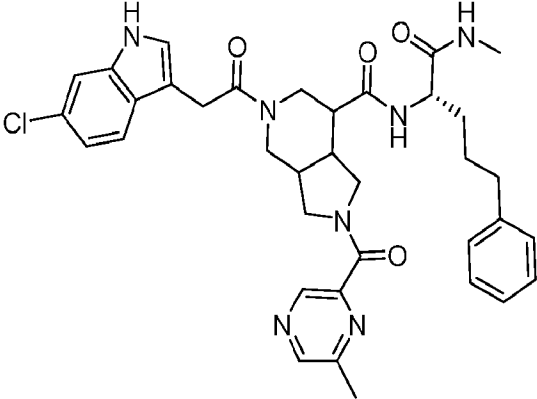
#	Structure
I-37	 Chemical structure of I-37: A complex molecule featuring a 4-chloro-1H-indol-3-yl group connected via a methylene group to a carbonyl group. This carbonyl is part of a bicyclic system (a 6-membered ring fused to a 5-membered ring) which also contains a carbonyl group and a methylamino group. The 5-membered ring is further substituted with a carbonyl group connected to a quinoline ring system.
I-38	 Chemical structure of I-38: Similar to I-37, but the quinoline ring system is replaced by an indole ring system.
I-39	 Chemical structure of I-39: Similar to I-37, but the quinoline ring system is replaced by a pyrazole ring system.
I-40	 Chemical structure of I-40: Similar to I-37, but the quinoline ring system is replaced by a pyrimidine ring system.

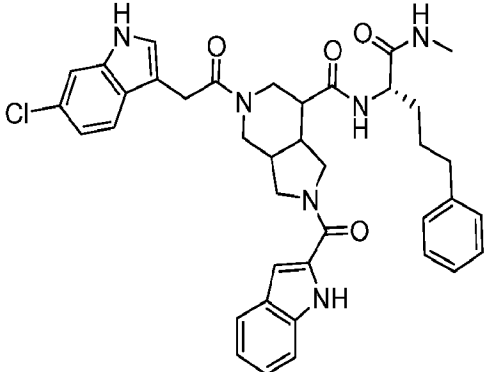
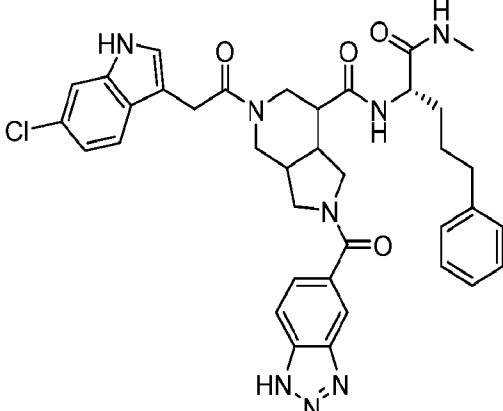
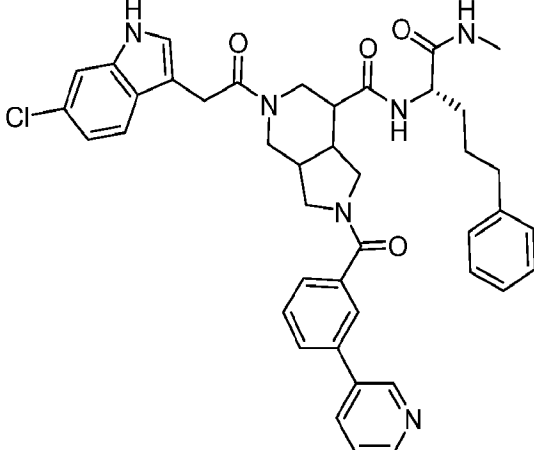
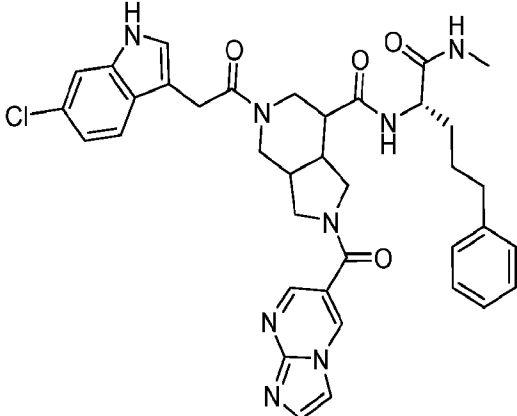
#	Structure
I-41	 Chemical structure of compound I-41: A complex molecule featuring a 4-chloro-1H-indol-3-yl group connected via a methylene group to a carbonyl group. This carbonyl is part of a bicyclic system (a 6-membered ring fused to a 5-membered ring, both containing nitrogen). The 6-membered ring is also connected to another carbonyl group, which is further connected to a chiral center. This chiral center is bonded to a methylamino group (NHMe) and a (2-ethoxy-6-methylpyrimidin-4-yl)methyl group. The 5-membered ring of the bicyclic system is connected to a carbonyl group, which is further connected to a chiral center. This chiral center is bonded to a methylamino group (NHMe) and a (2-ethoxy-6-methylpyrimidin-4-yl)methyl group.
I-42	 Chemical structure of compound I-42: A complex molecule featuring a 4-chloro-1H-indol-3-yl group connected via a methylene group to a carbonyl group. This carbonyl is part of a bicyclic system (a 6-membered ring fused to a 5-membered ring, both containing nitrogen). The 6-membered ring is also connected to another carbonyl group, which is further connected to a chiral center. This chiral center is bonded to a methylamino group (NHMe) and a (2-methoxy-6-methylpyrimidin-4-yl)methyl group. The 5-membered ring of the bicyclic system is connected to a carbonyl group, which is further connected to a chiral center. This chiral center is bonded to a methylamino group (NHMe) and a (2-methoxy-6-methylpyrimidin-4-yl)methyl group.
I-43	 Chemical structure of compound I-43: A complex molecule featuring a 4-chloro-1H-indol-3-yl group connected via a methylene group to a carbonyl group. This carbonyl is part of a bicyclic system (a 6-membered ring fused to a 5-membered ring, both containing nitrogen). The 6-membered ring is also connected to another carbonyl group, which is further connected to a chiral center. This chiral center is bonded to a methylamino group (NHMe) and a (2-methyl-6-methylpyridin-4-yl)methyl group. The 5-membered ring of the bicyclic system is connected to a carbonyl group, which is further connected to a chiral center. This chiral center is bonded to a methylamino group (NHMe) and a (2-methyl-6-methylpyridin-4-yl)methyl group.
I-44	 Chemical structure of compound I-44: A complex molecule featuring a 4-chloro-1H-indol-3-yl group connected via a methylene group to a carbonyl group. This carbonyl is part of a bicyclic system (a 6-membered ring fused to a 5-membered ring, both containing nitrogen). The 6-membered ring is also connected to another carbonyl group, which is further connected to a chiral center. This chiral center is bonded to a methylamino group (NHMe) and a (2-methyl-6-methylpyridin-4-yl)methyl group. The 5-membered ring of the bicyclic system is connected to a carbonyl group, which is further connected to a chiral center. This chiral center is bonded to a methylamino group (NHMe) and a (2-methyl-6-methylpyridin-4-yl)methyl group.

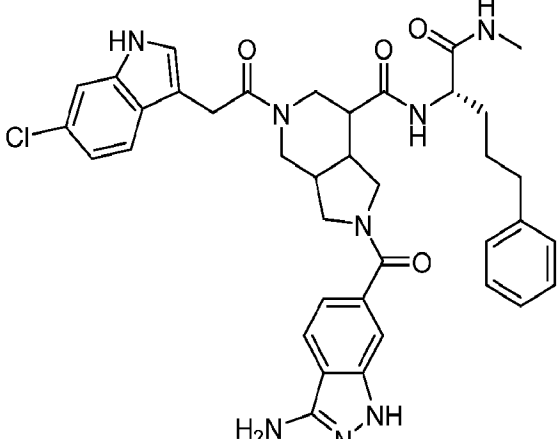
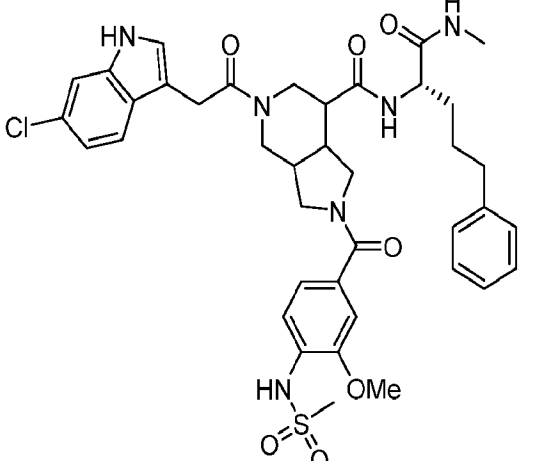
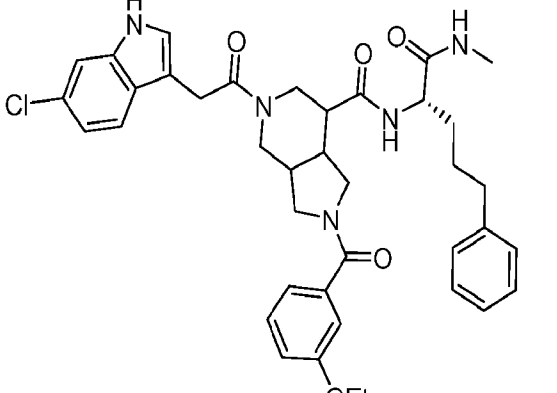
#	Structure
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I-46	
I-47	
I-48	

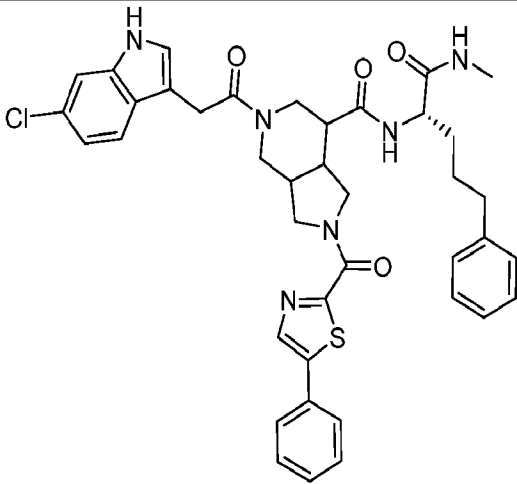
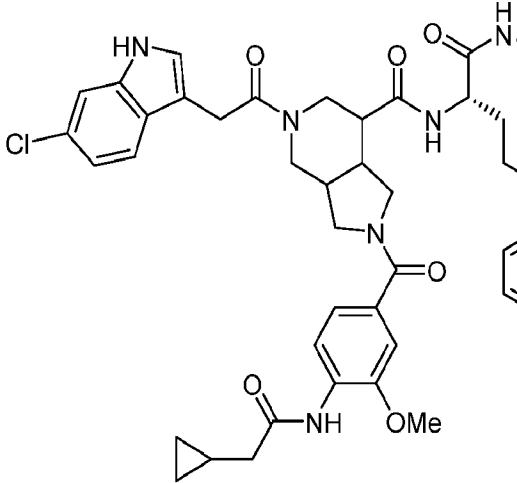
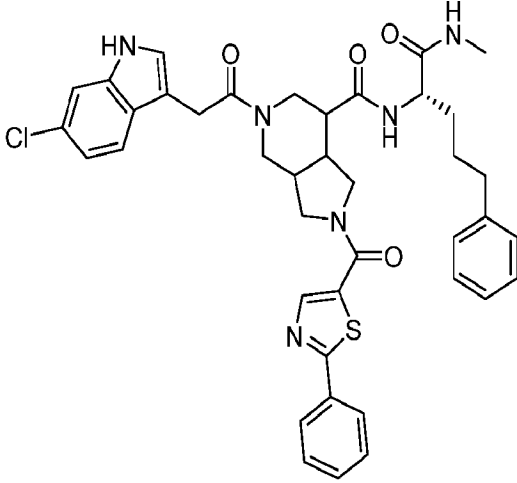
#	Structure
I-49	
I-50	
I-51	
I-52	

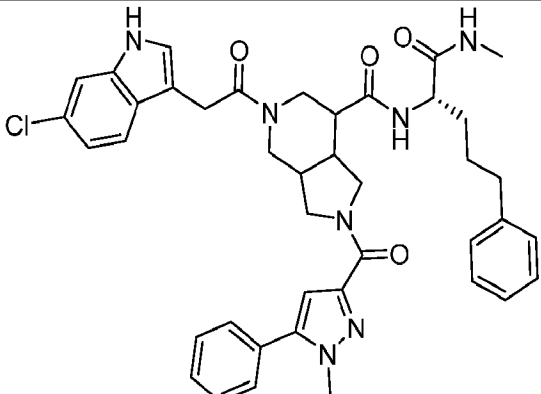
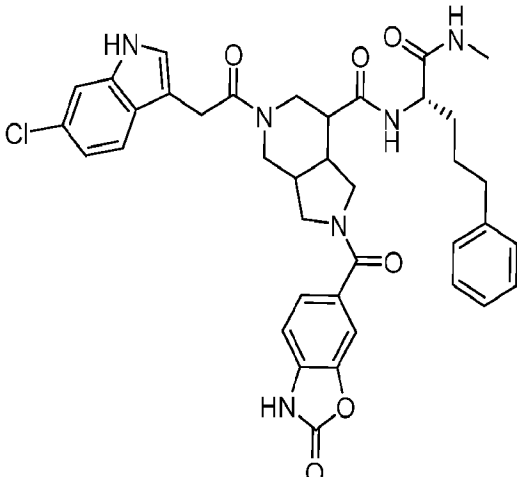
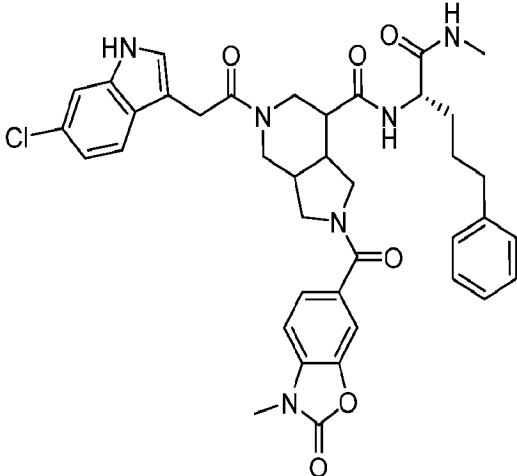
#	Structure
I-53	
I-54	
I-55	
I-56	

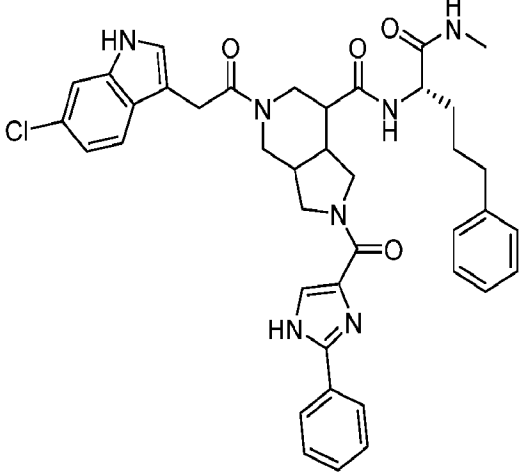
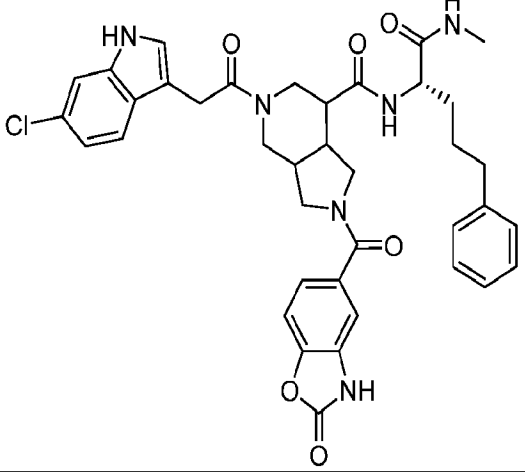
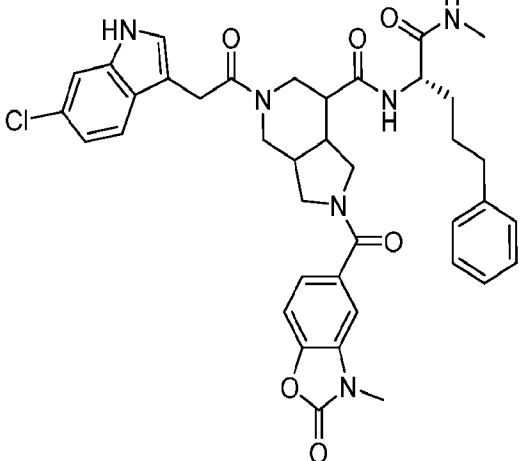
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I-57	
I-58	
I-59	
I-60	

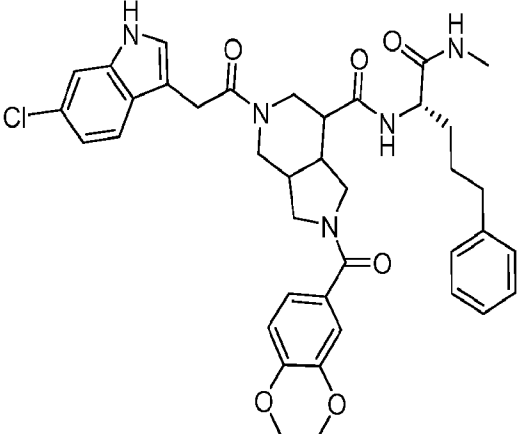
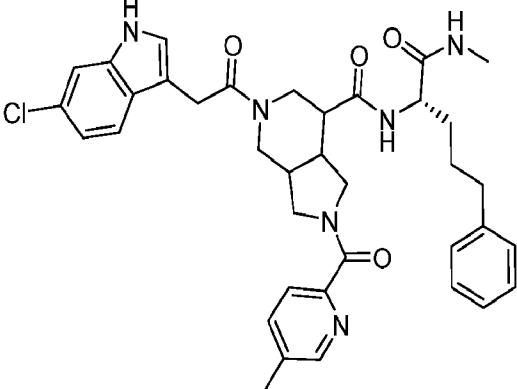
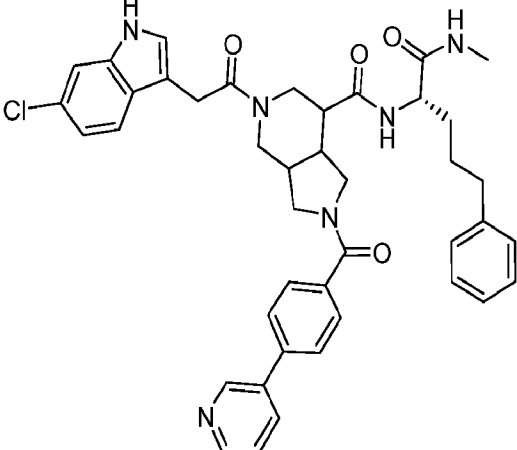
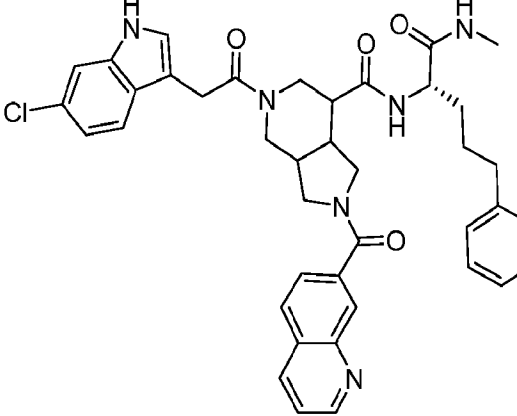
#	Structure
I-61	
I-62	
I-63	
I-64	

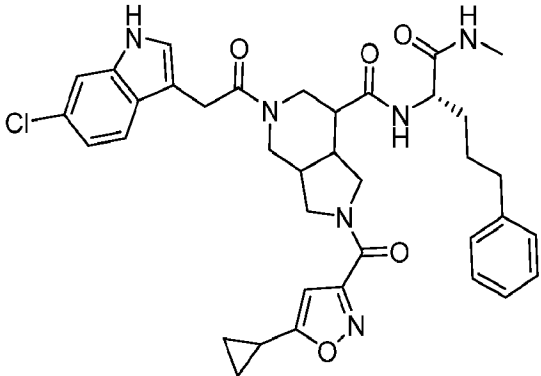
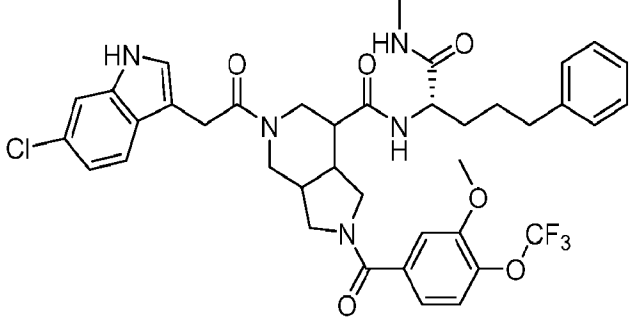
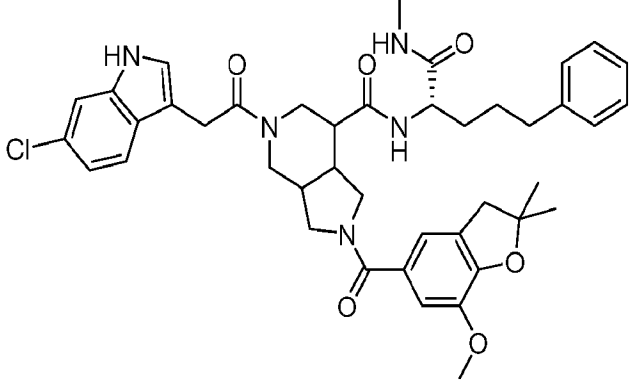
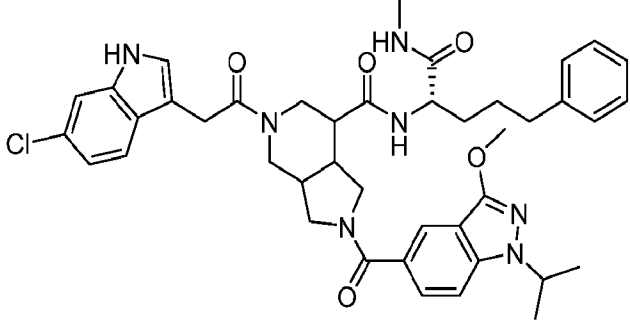
#	Structure
I-65	 Chemical structure of compound I-65. It features a 4-chloro-1H-indol-3-yl group connected via a methylene group to a carbonyl group. This carbonyl is part of a bicyclic system (a 6-membered ring fused to a 5-membered ring) where the nitrogen of the 5-membered ring is substituted with a benzyl group. The 6-membered ring also has a carbonyl group substituted with a (S)-1-methyl-2-phenylpropan-1-yl group. The 5-membered ring is further substituted with a 4-amino-1H-indazol-2-yl group.
I-66	 Chemical structure of compound I-66. It is similar to I-65, but the 4-amino-1H-indazol-2-yl group is replaced by a 4-methoxy-N-methylsulfamoyl-1H-indazol-2-yl group.
I-67	 Chemical structure of compound I-67. It is similar to I-65, but the 4-amino-1H-indazol-2-yl group is replaced by a 4-ethoxy-1H-indazol-2-yl group.

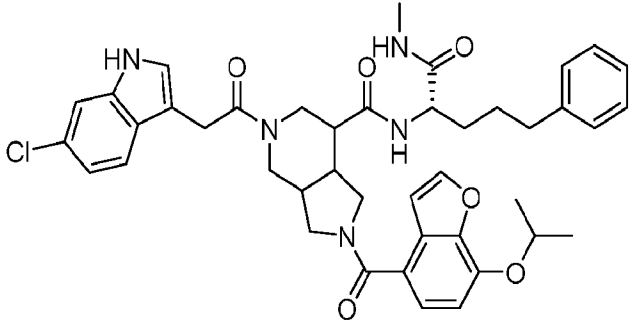
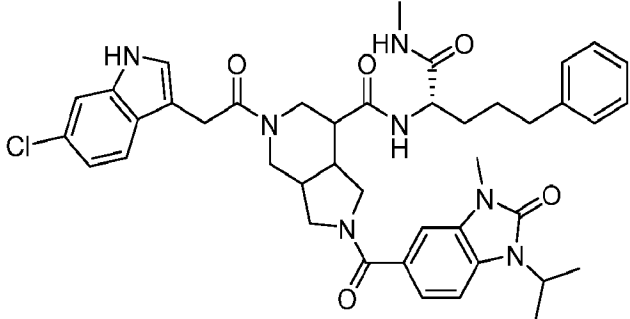
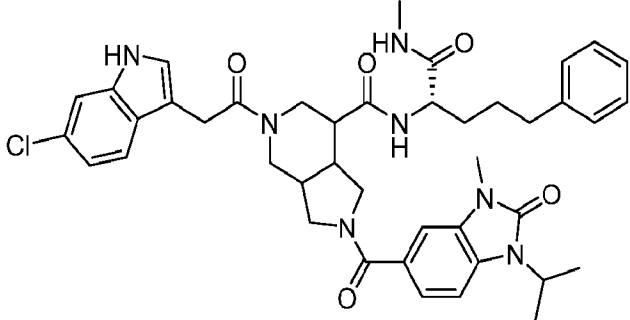
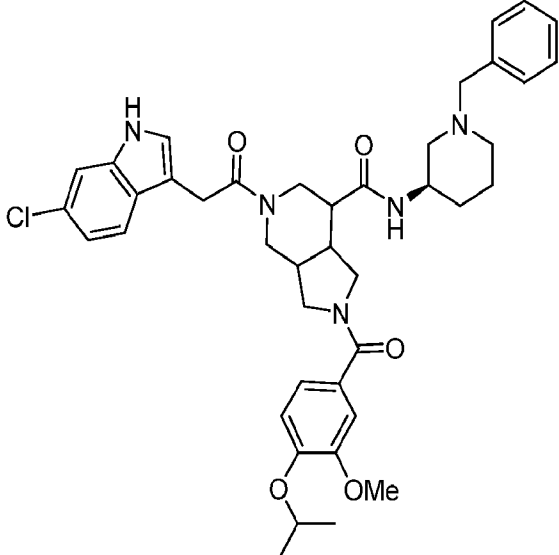
#	Structure
I-68	 Chemical structure of I-68: A complex molecule featuring a 4-chloro-1H-indol-3-yl group connected via a methylene group to a carbonyl group. This carbonyl is part of a bicyclic system (a 6-membered ring fused to a 5-membered ring, both containing nitrogen atoms). The 6-membered ring is also connected to a carbonyl group, which is further connected to a chiral center. This chiral center is bonded to a methylamino group (NHMe) and a (2-phenyl)ethyl group. The 5-membered ring is connected to a carbonyl group, which is further connected to a thiazole ring, which is in turn connected to a phenyl group.
I-69	 Chemical structure of I-69: A complex molecule featuring a 4-chloro-1H-indol-3-yl group connected via a methylene group to a carbonyl group. This carbonyl is part of a bicyclic system (a 6-membered ring fused to a 5-membered ring, both containing nitrogen atoms). The 6-membered ring is also connected to a carbonyl group, which is further connected to a chiral center. This chiral center is bonded to a methylamino group (NHMe) and a (2-phenyl)ethyl group. The 5-membered ring is connected to a carbonyl group, which is further connected to a 4-methoxyphenyl group, which is in turn connected to a cyclopropylmethyl group.
I-70	 Chemical structure of I-70: A complex molecule featuring a 4-chloro-1H-indol-3-yl group connected via a methylene group to a carbonyl group. This carbonyl is part of a bicyclic system (a 6-membered ring fused to a 5-membered ring, both containing nitrogen atoms). The 6-membered ring is also connected to a carbonyl group, which is further connected to a chiral center. This chiral center is bonded to a methylamino group (NHMe) and a (2-phenyl)ethyl group. The 5-membered ring is connected to a carbonyl group, which is further connected to a thiazole ring, which is in turn connected to a phenyl group.

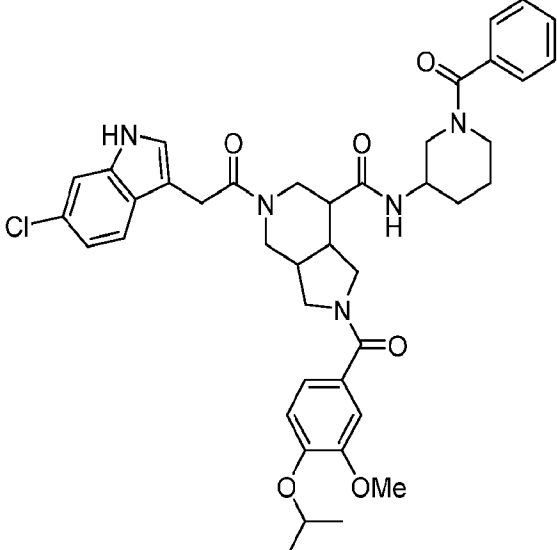
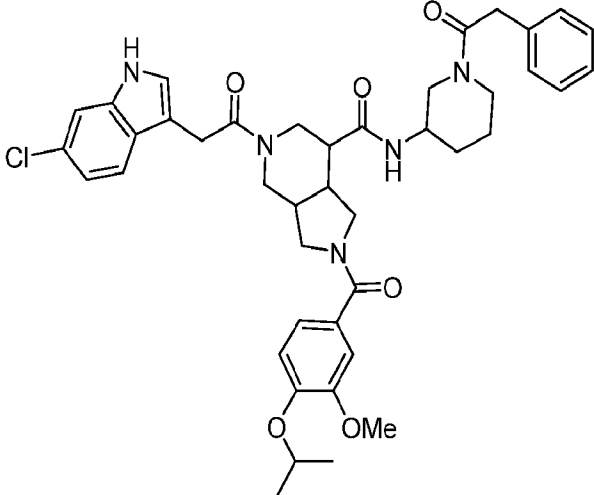
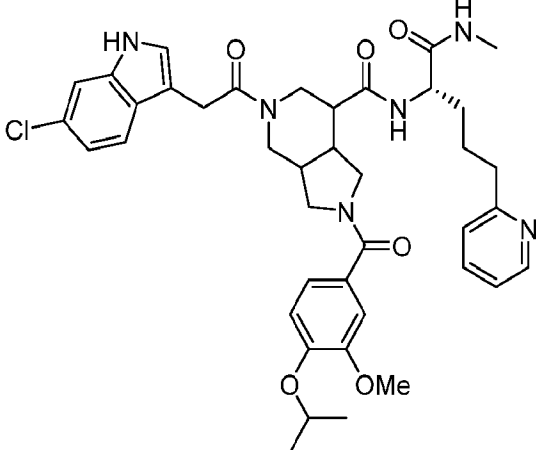
#	Structure
I-71	 Chemical structure of compound I-71. It features a 4-chloro-1H-indol-3-yl group connected via a methylene group to a carbonyl group. This carbonyl is part of a bicyclic system (a 6-membered ring fused to a 5-membered ring) where the nitrogen of the 5-membered ring is substituted with a 1-methyl-1H-pyrazol-4-yl group. The 6-membered ring also has a carbonyl group attached to a chiral center, which is further substituted with a (2-methylamino-2-phenylethyl) group and a methyl group.
I-72	 Chemical structure of compound I-72. It features a 4-chloro-1H-indol-3-yl group connected via a methylene group to a carbonyl group. This carbonyl is part of a bicyclic system (a 6-membered ring fused to a 5-membered ring) where the nitrogen of the 5-membered ring is substituted with a 1,3-dioxo-4,5-dihydro-1H-benzodioxole-2-yl group. The 6-membered ring also has a carbonyl group attached to a chiral center, which is further substituted with a (2-methylamino-2-phenylethyl) group and a methyl group.
I-73	 Chemical structure of compound I-73. It features a 4-chloro-1H-indol-3-yl group connected via a methylene group to a carbonyl group. This carbonyl is part of a bicyclic system (a 6-membered ring fused to a 5-membered ring) where the nitrogen of the 5-membered ring is substituted with a 1,3-dioxo-4,5-dihydro-1H-benzodioxole-2-yl group. The 6-membered ring also has a carbonyl group attached to a chiral center, which is further substituted with a (2-methylamino-2-phenylethyl) group and a methyl group.

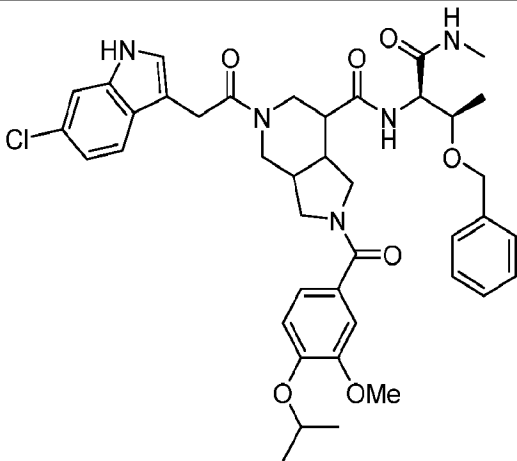
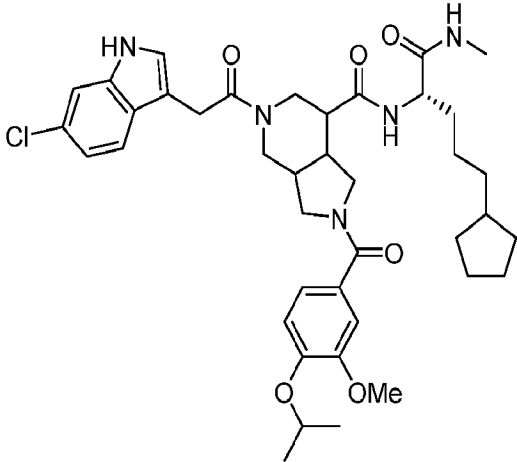
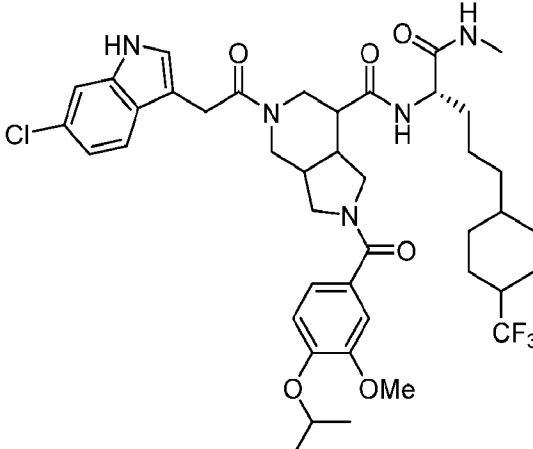
#	Structure
I-74	 Chemical structure of compound I-74. It features a 4-chloro-1H-indol-3-ylmethyl group connected via a carbonyl to a bicyclic amine system (a 6-membered ring fused to a 5-membered ring). The 6-membered ring is also connected via a carbonyl to a side chain containing a benzyl group and a methylamino group. The 5-membered ring is connected via a carbonyl to a 1-phenyl-1H-imidazol-2-yl group.
I-75	 Chemical structure of compound I-75. It is similar to I-74, but the 1-phenyl-1H-imidazol-2-yl group is replaced by a 1-methyl-5-oxo-1,3-dihydroisobenzofuran-2-yl group.
I-76	 Chemical structure of compound I-76. It is similar to I-75, but the 1-methyl-5-oxo-1,3-dihydroisobenzofuran-2-yl group is replaced by a 1-methyl-5-oxo-1,3-dihydroisobenzofuran-2-yl group where the nitrogen is methylated.

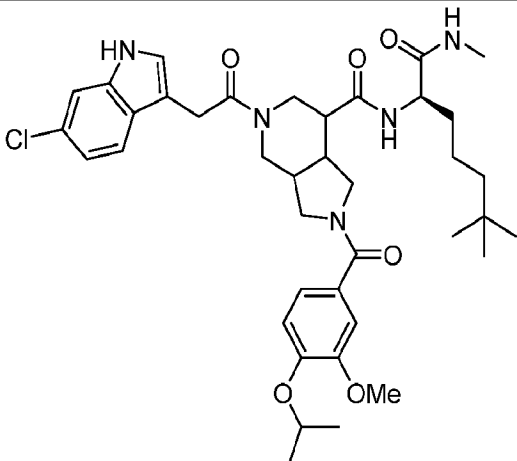
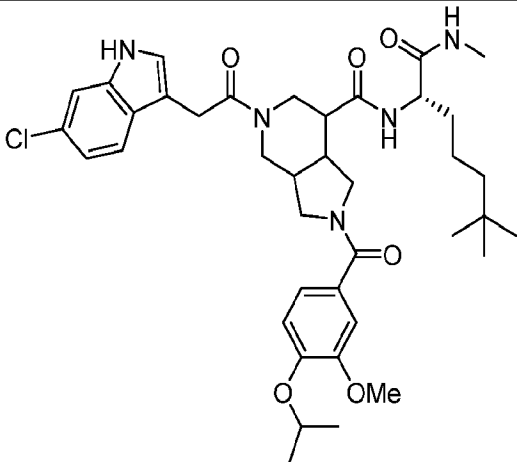
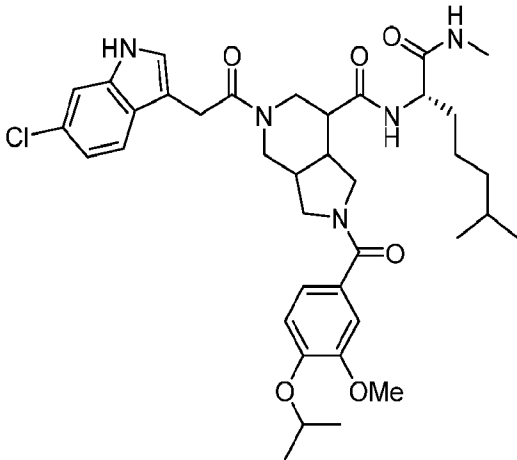
#	Structure
I-77	
I-78	
I-79	
I-80	

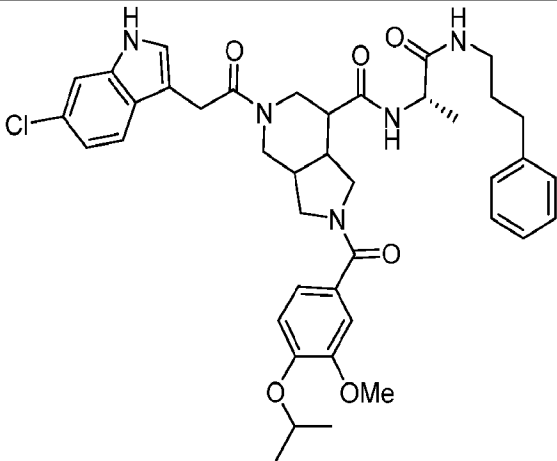
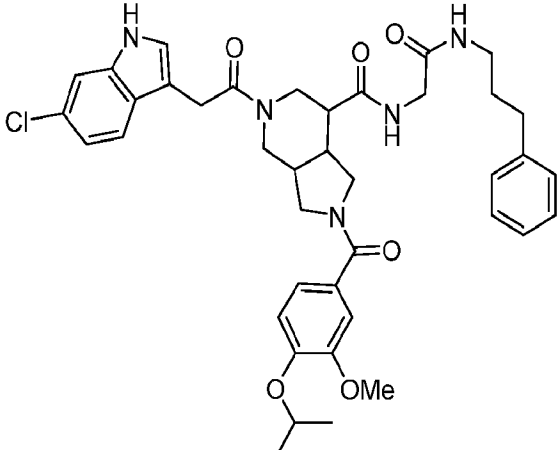
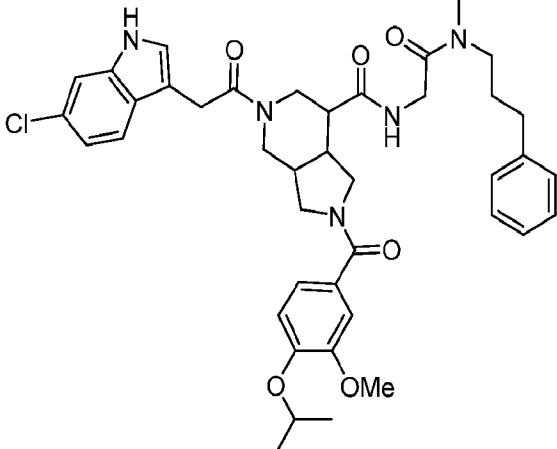
#	Structure
I-81	
I-82	
I-83	
I-84	

#	Structure
I-85	
I-86	 First eluting diastereomer
I-87	 Second eluting diastereomer
I-88	

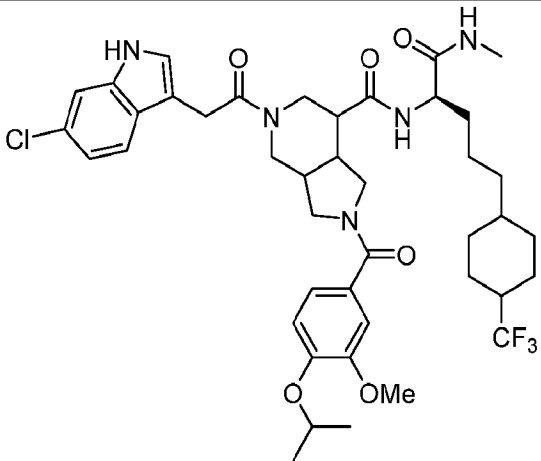
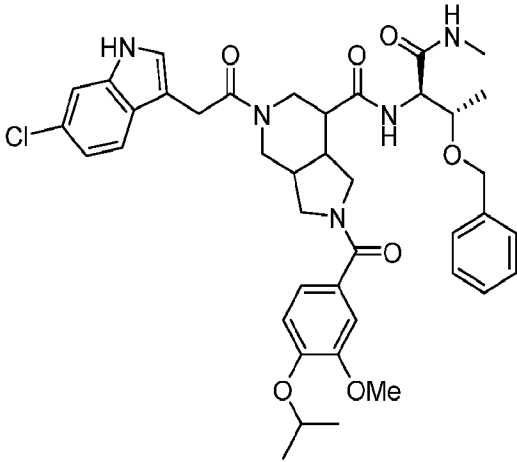
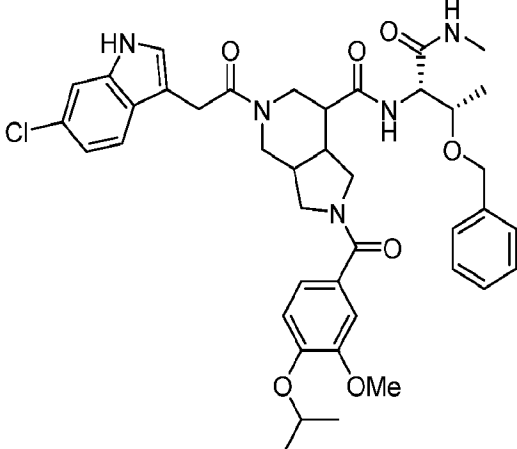
#	Structure
I-89	 Chemical structure of compound I-89: A bicyclic core (a 6,7-dihydro-5H-benzodiazepine derivative) substituted with a 4-chloro-1H-indol-3-ylmethyl group, a benzoyl group, and a 4-(4-methoxy-2-isopropoxyphenyl) group. The core is also substituted with a 4-phenylpiperidin-1-yl group.
I-90	 Chemical structure of compound I-90: A bicyclic core (a 6,7-dihydro-5H-benzodiazepine derivative) substituted with a 4-chloro-1H-indol-3-ylmethyl group, a benzoyl group, and a 4-(4-methoxy-2-isopropoxyphenyl) group. The core is also substituted with a 4-benzylpiperidin-1-yl group.
I-91	 Chemical structure of compound I-91: A bicyclic core (a 6,7-dihydro-5H-benzodiazepine derivative) substituted with a 4-chloro-1H-indol-3-ylmethyl group, a benzoyl group, and a 4-(4-methoxy-2-isopropoxyphenyl) group. The core is also substituted with a 4-(4-pyridin-2-ylbutyl)amino group.

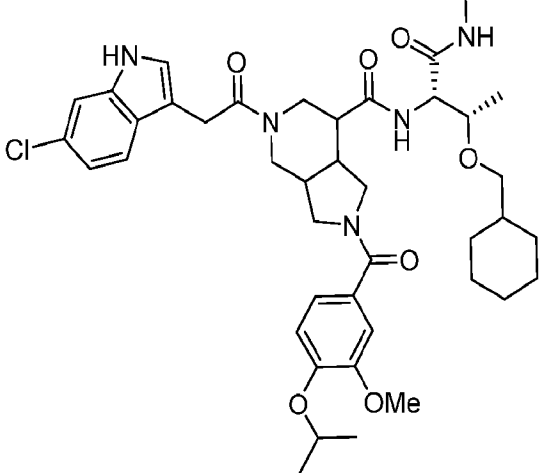
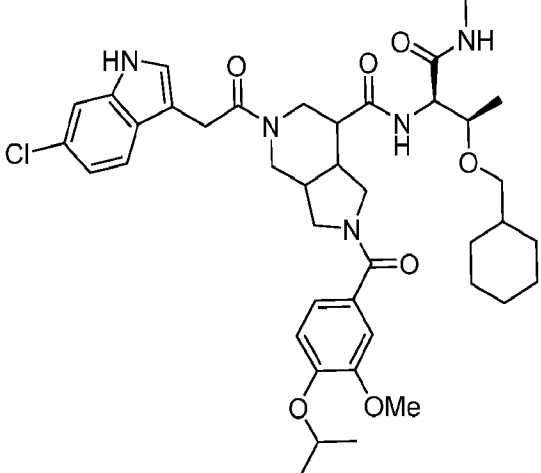
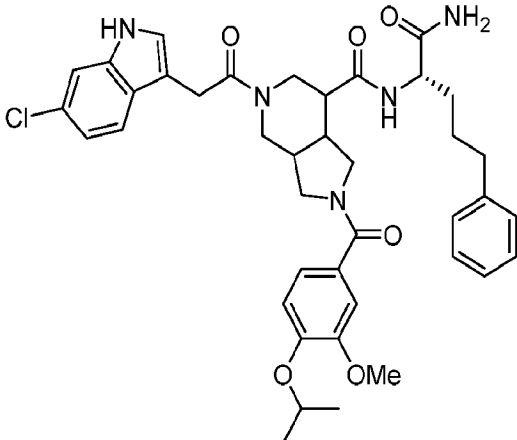
#	Structure
I-92	 Chemical structure of I-92: A complex molecule featuring a 4-chloro-1H-indol-3-yl group connected via a methylene group to a carbonyl group. This carbonyl is part of a piperidine ring system. The piperidine ring is substituted with a 4-(4-methoxy-2-isopropoxyphenyl) group and a 1-(4-methoxy-2-isopropoxyphenyl) group. The piperidine ring is also connected to a carbonyl group, which is part of a side chain containing a methyl group, a methoxy group, and a benzyl group.
I-93	 Chemical structure of I-93: A complex molecule featuring a 4-chloro-1H-indol-3-yl group connected via a methylene group to a carbonyl group. This carbonyl is part of a piperidine ring system. The piperidine ring is substituted with a 4-(4-methoxy-2-isopropoxyphenyl) group and a 1-(4-methoxy-2-isopropoxyphenyl) group. The piperidine ring is also connected to a carbonyl group, which is part of a side chain containing a methyl group, a methoxy group, and a cyclopentyl group.
I-94	 Chemical structure of I-94: A complex molecule featuring a 4-chloro-1H-indol-3-yl group connected via a methylene group to a carbonyl group. This carbonyl is part of a piperidine ring system. The piperidine ring is substituted with a 4-(4-methoxy-2-isopropoxyphenyl) group and a 1-(4-methoxy-2-isopropoxyphenyl) group. The piperidine ring is also connected to a carbonyl group, which is part of a side chain containing a methyl group, a methoxy group, and a 4-(trifluoromethyl)cyclohexyl group.

#	Structure
I-95	 Chemical structure of compound I-95. It features a 4-chloro-1H-indol-3-yl group connected via a methylene group to a carbonyl group. This carbonyl is part of a bicyclic system (a 6,7-dihydro-1,2,3,4-tetrahydropyrido[2,1-b]pyrazine derivative). The nitrogen at position 1 of the bicyclic system is substituted with a carbonyl group, which is further substituted with a 4-isopropoxy-2-methoxyphenyl group. The nitrogen at position 4 of the bicyclic system is substituted with a carbonyl group, which is further substituted with a (S)-1-(tert-butyl)pyrrolidine-2-carboxamide group.
I-96	 Chemical structure of compound I-96. It is identical to I-95, except for the stereochemistry of the chiral center in the pyrrolidine ring, which is (R).
I-97	 Chemical structure of compound I-97. It is identical to I-96, except for the stereochemistry of the chiral center in the pyrrolidine ring, which is (S).

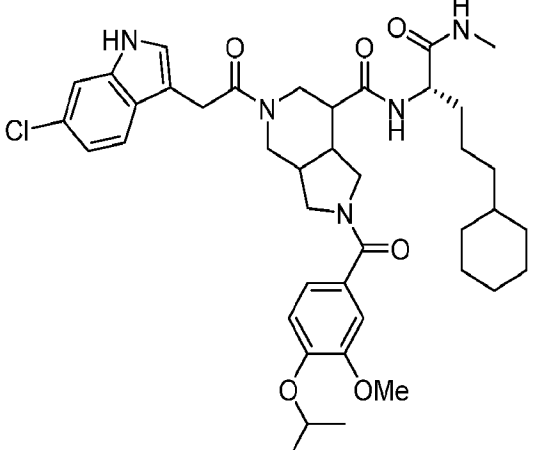
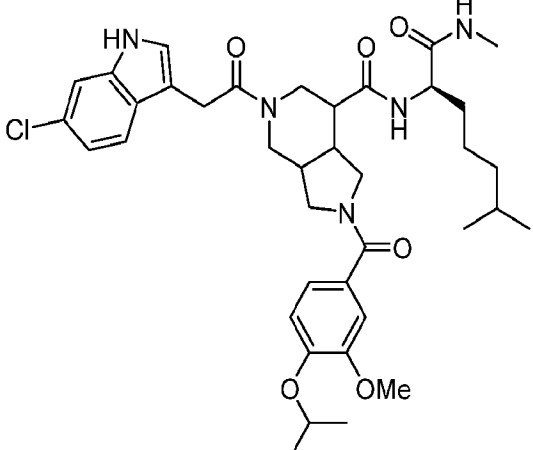
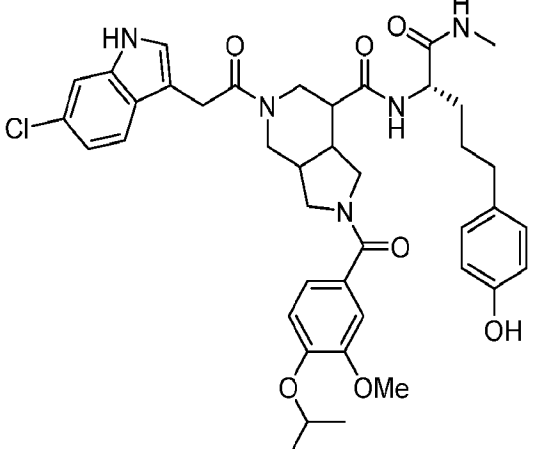
#	Structure
I-98	 Chemical structure of compound I-98. It features a 5-chloro-1H-indol-3-yl group connected via a methylene group to a carbonyl group. This carbonyl is part of a bicyclic system (a 6-membered ring fused to a 5-membered ring) where the nitrogen is also connected to a carbonyl group. This second carbonyl is further connected to a 4-methoxy-2-isopropoxyphenyl group. The nitrogen of the 5-membered ring is also connected to a carbonyl group, which is part of a side chain containing a chiral center (indicated by a wedge bond) and a benzyl group.
I-99	 Chemical structure of compound I-99. It is similar to I-98, but the side chain is a 2-phenylethan-1-yl group, and there is no chiral center indicated.
I-100	 Chemical structure of compound I-100. It is similar to I-99, but the side chain is a 1-phenylethyl group, with a methyl group attached to the nitrogen atom. First eluting diastereomer

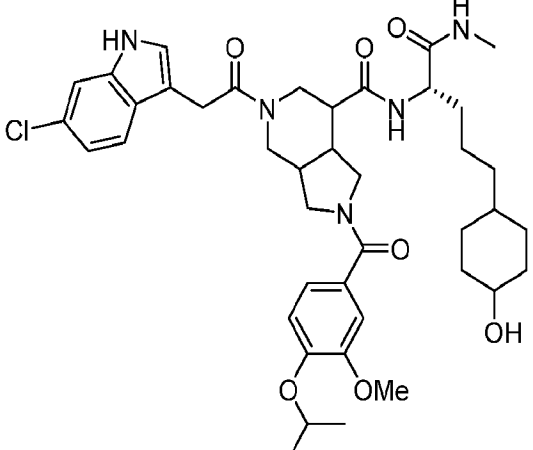
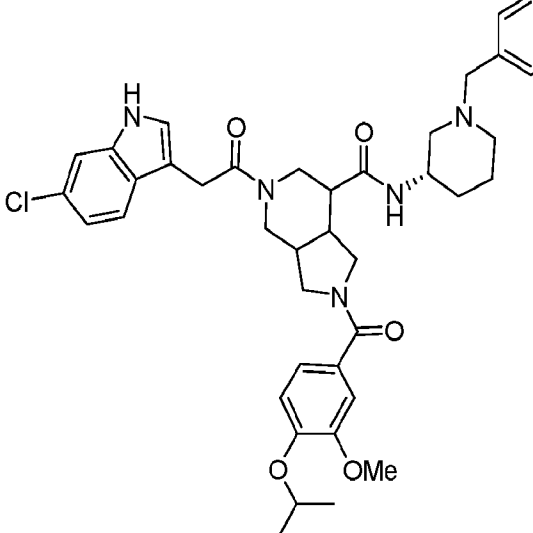
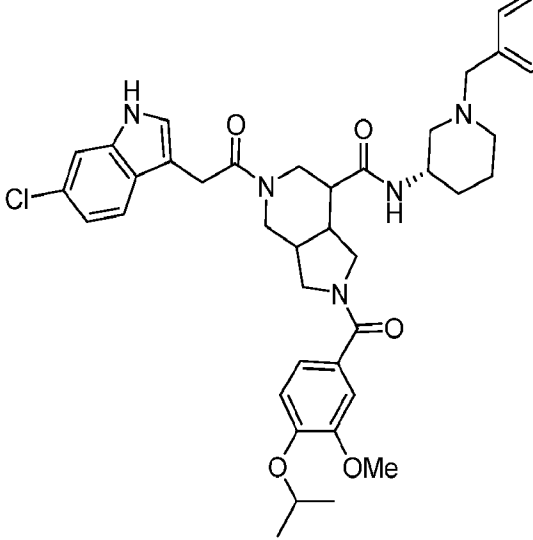
#	Structure
I-101	Second eluting diastereomer
I-102	
I-103	

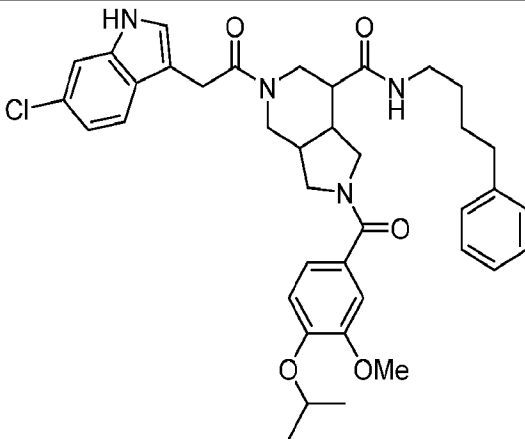
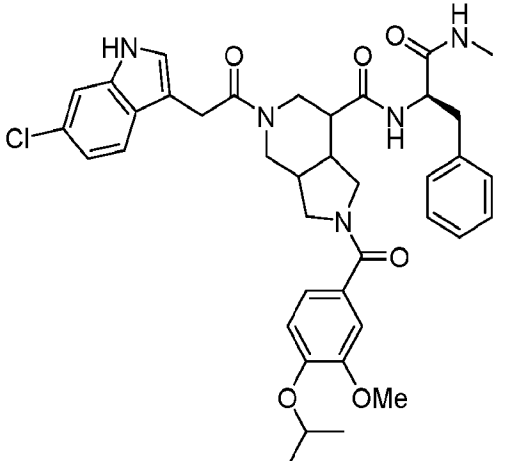
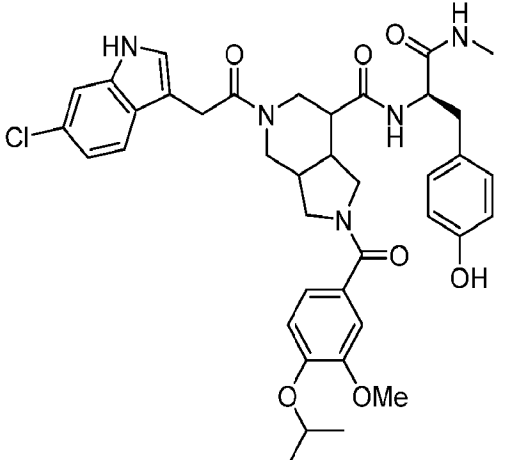
#	Structure
I-104	 Chemical structure of compound I-104. It features a 4-chloro-1H-indol-3-yl group connected via a methylene group to a carbonyl group. This carbonyl is part of a bicyclic system (a 6-membered ring fused to a 5-membered ring, both containing nitrogen). The 6-membered ring is also connected to another carbonyl group, which is further connected to a chiral center. This chiral center is bonded to a methyl group, a hydrogen atom, and a 4-(trifluoromethyl)cyclohexyl group. The 5-membered ring of the bicyclic system is connected to a carbonyl group, which is further connected to a 4-isopropoxy-2-methoxyphenyl group.
I-105	 Chemical structure of compound I-105. It features a 4-chloro-1H-indol-3-yl group connected via a methylene group to a carbonyl group. This carbonyl is part of a bicyclic system (a 6-membered ring fused to a 5-membered ring, both containing nitrogen). The 6-membered ring is also connected to another carbonyl group, which is further connected to a chiral center. This chiral center is bonded to a methyl group, a hydrogen atom, and a 4-benzyloxyphenyl group. The 5-membered ring of the bicyclic system is connected to a carbonyl group, which is further connected to a 4-isopropoxy-2-methoxyphenyl group.
I-106	 Chemical structure of compound I-106. It features a 4-chloro-1H-indol-3-yl group connected via a methylene group to a carbonyl group. This carbonyl is part of a bicyclic system (a 6-membered ring fused to a 5-membered ring, both containing nitrogen). The 6-membered ring is also connected to another carbonyl group, which is further connected to a chiral center. This chiral center is bonded to a methyl group, a hydrogen atom, and a 4-benzyloxyphenyl group. The 5-membered ring of the bicyclic system is connected to a carbonyl group, which is further connected to a 4-isopropoxy-2-methoxyphenyl group.

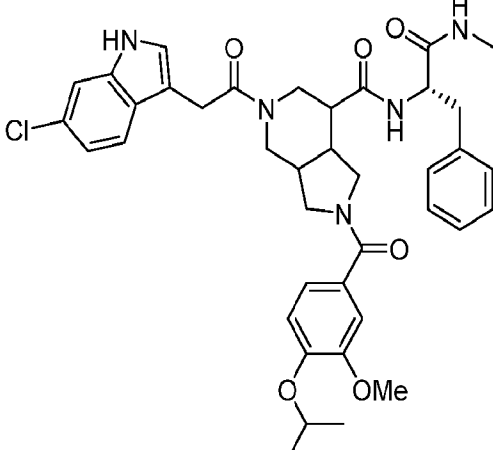
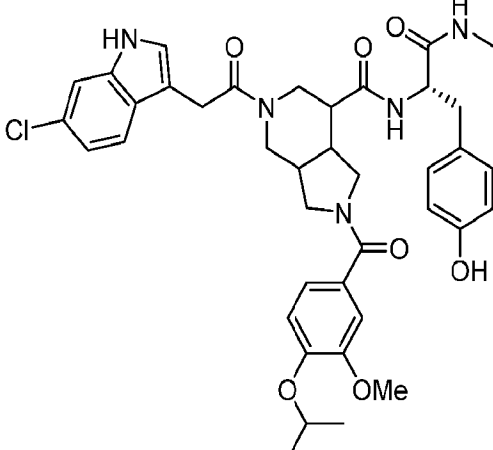
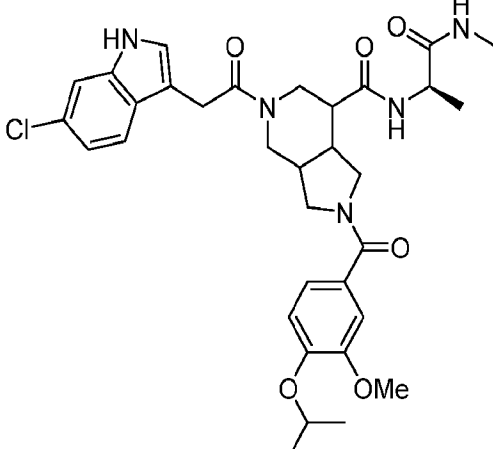
#	Structure
I-107	 Chemical structure of I-107: A complex molecule featuring a 4-chloro-1H-indol-3-yl group connected via a methylene group to a carbonyl group. This carbonyl is part of a bicyclic system (a 6-membered ring fused to a 5-membered ring, both containing nitrogen). The 5-membered ring nitrogen is also part of a carbonyl group, which is connected to a 4-isopropoxyphenyl group. The 6-membered ring nitrogen is connected to a carbonyl group, which is further connected to a chiral center. This chiral center is also connected to a cyclohexylmethoxy group and a methylamino group.
I-108	 Chemical structure of I-108: Similar to I-107, but the chiral center is connected to a methyl group instead of a methylamino group.
I-109	 Chemical structure of I-109: Similar to I-107, but the chiral center is connected to a benzyl group instead of a cyclohexylmethoxy group, and the methylamino group is replaced by an amino group (NH₂).

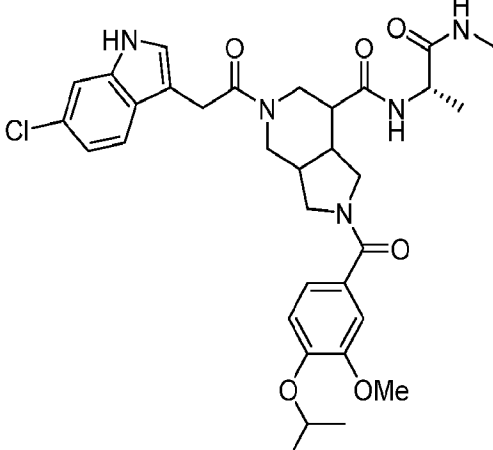
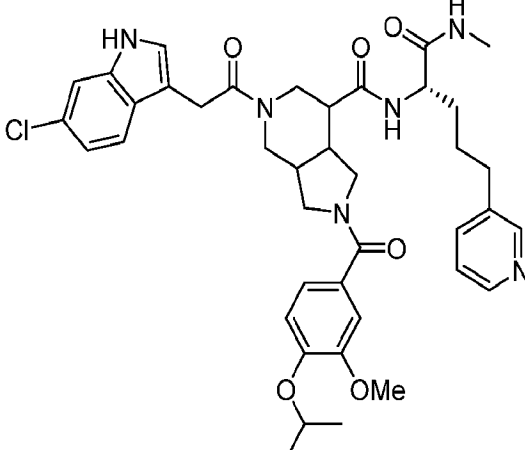
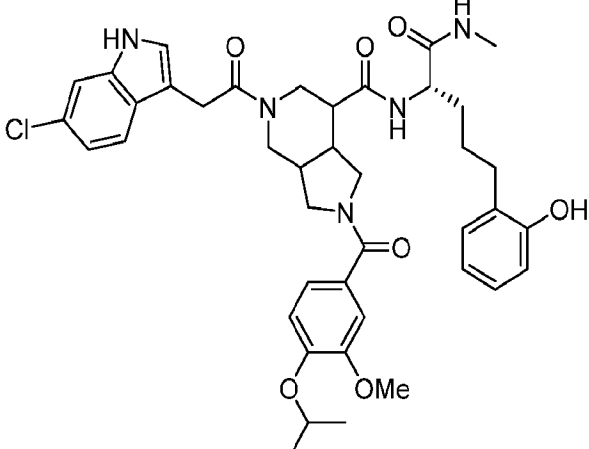
#	Structure
I-110	First eluting diastereomer
I-111	Second eluting diastereomer
I-112	

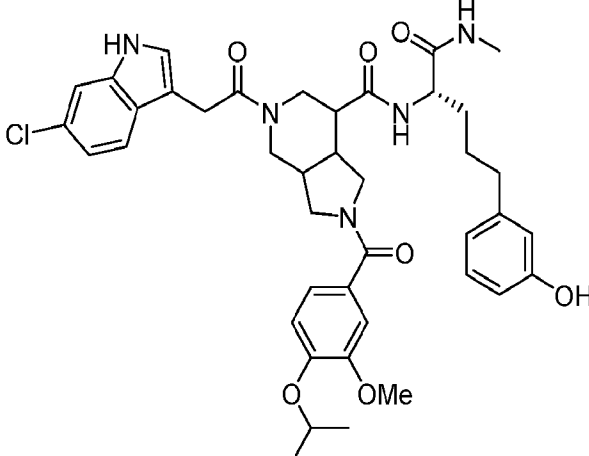
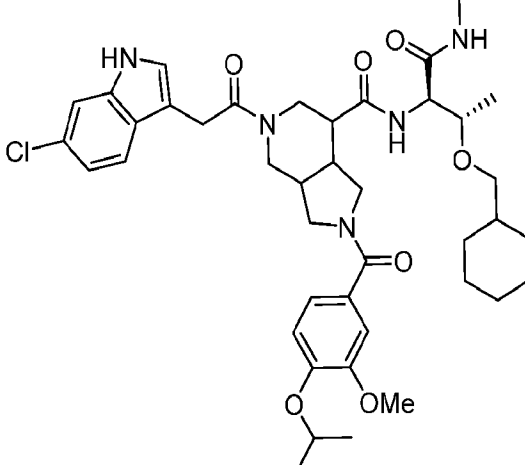
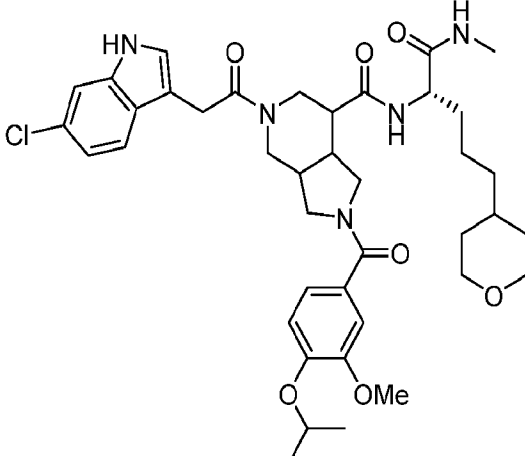
#	Structure
I-113	 Chemical structure of compound I-113. It features a 4-chlorophenyl group attached to an indole ring, which is linked via a methylene group to a carbonyl group. This carbonyl is part of a bicyclic system (a 6-membered ring fused to a 5-membered ring, both containing nitrogen). The 5-membered ring is substituted with a carbonyl group and a methoxy group. The 6-membered ring is substituted with a carbonyl group and a methoxy group. The carbonyl group on the 6-membered ring is linked to a side chain containing a carbonyl group, a methoxy group, and a cyclohexyl group.
I-114	 Chemical structure of compound I-114. It features a 4-chlorophenyl group attached to an indole ring, which is linked via a methylene group to a carbonyl group. This carbonyl is part of a bicyclic system (a 6-membered ring fused to a 5-membered ring, both containing nitrogen). The 5-membered ring is substituted with a carbonyl group and a methoxy group. The 6-membered ring is substituted with a carbonyl group and a methoxy group. The carbonyl group on the 6-membered ring is linked to a side chain containing a carbonyl group, a methoxy group, and an isobutyl group.
I-115	 Chemical structure of compound I-115. It features a 4-chlorophenyl group attached to an indole ring, which is linked via a methylene group to a carbonyl group. This carbonyl is part of a bicyclic system (a 6-membered ring fused to a 5-membered ring, both containing nitrogen). The 5-membered ring is substituted with a carbonyl group and a methoxy group. The 6-membered ring is substituted with a carbonyl group and a methoxy group. The carbonyl group on the 6-membered ring is linked to a side chain containing a carbonyl group, a methoxy group, and a 4-hydroxyphenyl group.

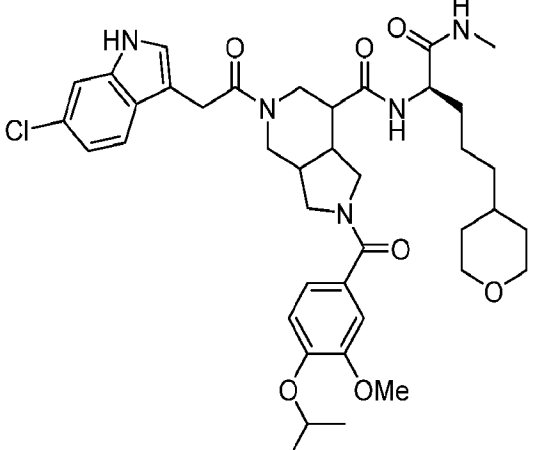
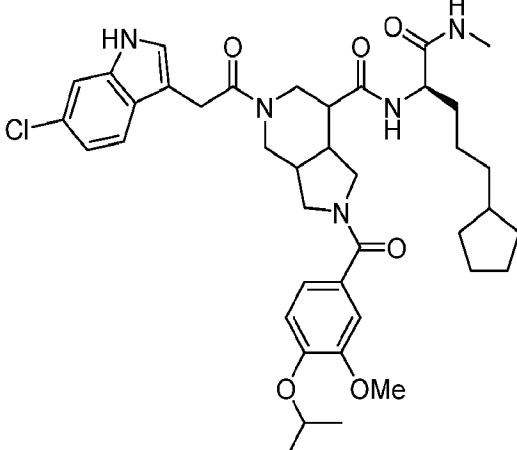
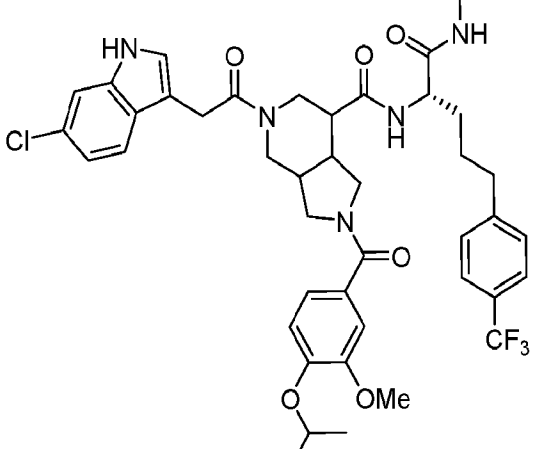
#	Structure
I-116	 Chemical structure of I-116: A complex molecule featuring a 5-chloro-1H-indol-3-yl group connected via a methylene group to a carbonyl group. This carbonyl is part of a bicyclic system (a 6-membered ring fused to a 5-membered ring, both containing nitrogen). The 6-membered ring is also connected to another carbonyl group, which is further connected to a 4-(4-methoxy-3-isopropoxyphenyl) group. The 5-membered ring is connected to a carbonyl group, which is further connected to a 4-(4-hydroxyphenyl) group. The molecule also contains a methyl group and a hydroxyl group.
I-117	 Chemical structure of I-117: A complex molecule featuring a 5-chloro-1H-indol-3-yl group connected via a methylene group to a carbonyl group. This carbonyl is part of a bicyclic system (a 6-membered ring fused to a 5-membered ring, both containing nitrogen). The 6-membered ring is also connected to another carbonyl group, which is further connected to a 4-(4-methoxy-3-isopropoxyphenyl) group. The 5-membered ring is connected to a carbonyl group, which is further connected to a 4-(4-phenylpiperidin-1-yl) group. The molecule also contains a methyl group and a hydroxyl group. First eluting diastereomer
I-118	 Chemical structure of I-118: A complex molecule featuring a 5-chloro-1H-indol-3-yl group connected via a methylene group to a carbonyl group. This carbonyl is part of a bicyclic system (a 6-membered ring fused to a 5-membered ring, both containing nitrogen). The 6-membered ring is also connected to another carbonyl group, which is further connected to a 4-(4-methoxy-3-isopropoxyphenyl) group. The 5-membered ring is connected to a carbonyl group, which is further connected to a 4-(4-phenylpiperidin-1-yl) group. The molecule also contains a methyl group and a hydroxyl group. Second eluting diastereomer

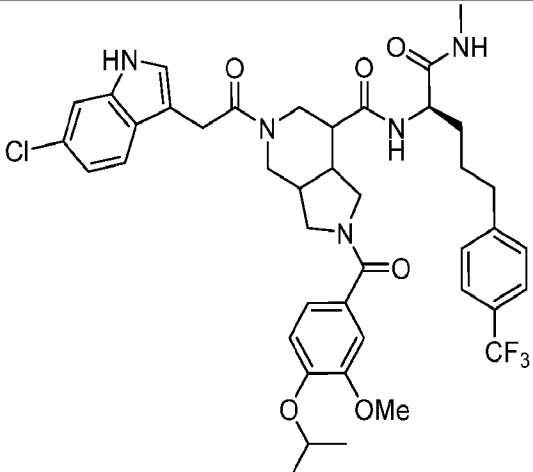
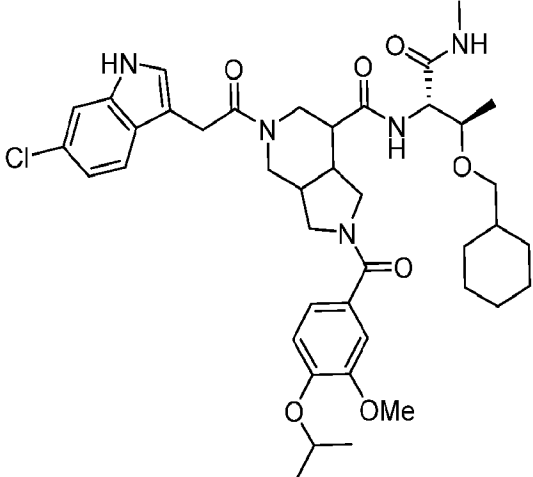
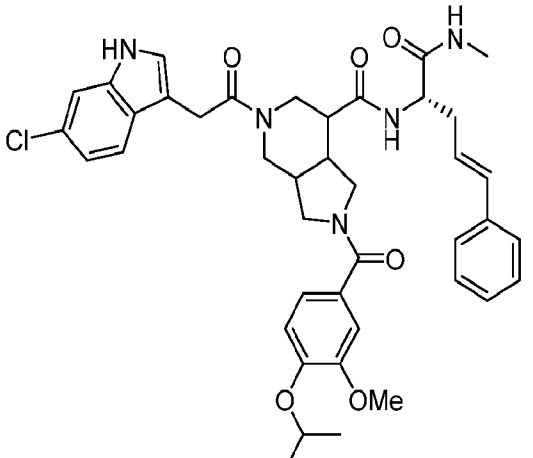
#	Structure
I-119	 Chemical structure of I-119: A complex molecule featuring a 4-chlorophenyl group attached to an indole ring. The indole ring is connected via a methylene group to a carbonyl group, which is part of a bicyclic system (a 6-membered ring fused to a 5-membered ring). The 6-membered ring contains a nitrogen atom. The 5-membered ring is connected to a carbonyl group, which is further connected to a benzyl group. The benzyl group is attached to a carbonyl group, which is connected to a 4-methoxyphenyl group. The 4-methoxyphenyl group is connected to a carbonyl group, which is connected to a 4-methoxyphenyl group. The 4-methoxyphenyl group is connected to a carbonyl group, which is connected to a 4-methoxyphenyl group.
I-120	 Chemical structure of I-120: A complex molecule featuring a 4-chlorophenyl group attached to an indole ring. The indole ring is connected via a methylene group to a carbonyl group, which is part of a bicyclic system (a 6-membered ring fused to a 5-membered ring). The 6-membered ring contains a nitrogen atom. The 5-membered ring is connected to a carbonyl group, which is further connected to a benzyl group. The benzyl group is attached to a carbonyl group, which is connected to a 4-methoxyphenyl group. The 4-methoxyphenyl group is connected to a carbonyl group, which is connected to a 4-methoxyphenyl group. The 4-methoxyphenyl group is connected to a carbonyl group, which is connected to a 4-methoxyphenyl group.
I-121	 Chemical structure of I-121: A complex molecule featuring a 4-chlorophenyl group attached to an indole ring. The indole ring is connected via a methylene group to a carbonyl group, which is part of a bicyclic system (a 6-membered ring fused to a 5-membered ring). The 6-membered ring contains a nitrogen atom. The 5-membered ring is connected to a carbonyl group, which is further connected to a benzyl group. The benzyl group is attached to a carbonyl group, which is connected to a 4-methoxyphenyl group. The 4-methoxyphenyl group is connected to a carbonyl group, which is connected to a 4-methoxyphenyl group. The 4-methoxyphenyl group is connected to a carbonyl group, which is connected to a 4-methoxyphenyl group.

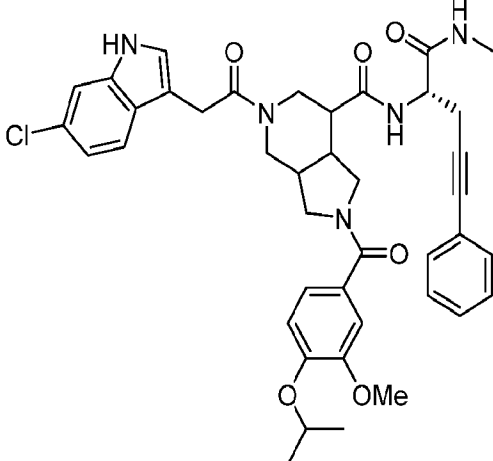
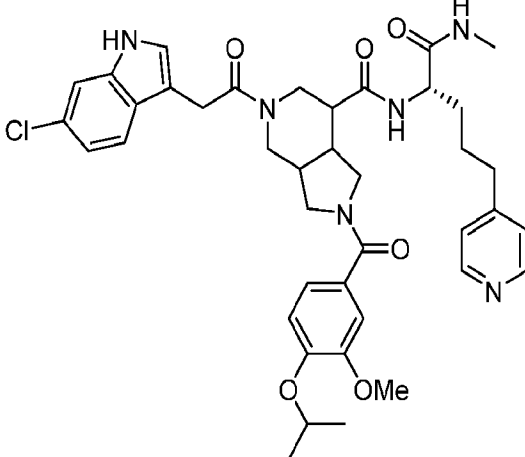
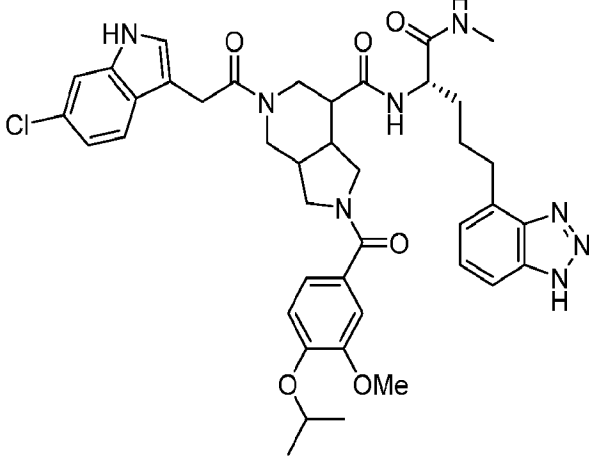
#	Structure
I-122	 Chemical structure of I-122: A complex molecule featuring a 4-chlorophenyl group attached to an indole ring. The indole ring is connected via a methylene group to a carbonyl group, which is part of a bicyclic system (a 6-membered ring fused to a 5-membered ring). The 6-membered ring is substituted with a carbonyl group and a methylene group. The 5-membered ring is substituted with a carbonyl group and a methylene group. The carbonyl group on the 5-membered ring is connected to a chiral center (a carbon atom bonded to a hydrogen atom, a methyl group, and a phenyl group). The carbonyl group on the 6-membered ring is connected to a carbonyl group, which is part of a 4-methoxyphenyl group. The 4-methoxyphenyl group is substituted with a methoxy group and an isopropoxy group.
I-123	 Chemical structure of I-123: A complex molecule featuring a 4-chlorophenyl group attached to an indole ring. The indole ring is connected via a methylene group to a carbonyl group, which is part of a bicyclic system (a 6-membered ring fused to a 5-membered ring). The 6-membered ring is substituted with a carbonyl group and a methylene group. The 5-membered ring is substituted with a carbonyl group and a methylene group. The carbonyl group on the 5-membered ring is connected to a chiral center (a carbon atom bonded to a hydrogen atom, a hydroxyl group, and a phenyl group). The carbonyl group on the 6-membered ring is connected to a carbonyl group, which is part of a 4-methoxyphenyl group. The 4-methoxyphenyl group is substituted with a methoxy group and an isopropoxy group.
I-124	 Chemical structure of I-124: A complex molecule featuring a 4-chlorophenyl group attached to an indole ring. The indole ring is connected via a methylene group to a carbonyl group, which is part of a bicyclic system (a 6-membered ring fused to a 5-membered ring). The 6-membered ring is substituted with a carbonyl group and a methylene group. The 5-membered ring is substituted with a carbonyl group and a methylene group. The carbonyl group on the 5-membered ring is connected to a chiral center (a carbon atom bonded to a hydrogen atom, a methyl group, and a phenyl group). The carbonyl group on the 6-membered ring is connected to a carbonyl group, which is part of a 4-methoxyphenyl group. The 4-methoxyphenyl group is substituted with a methoxy group and an isopropoxy group.

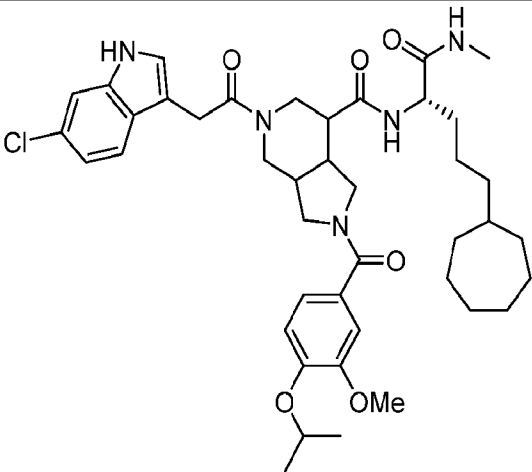
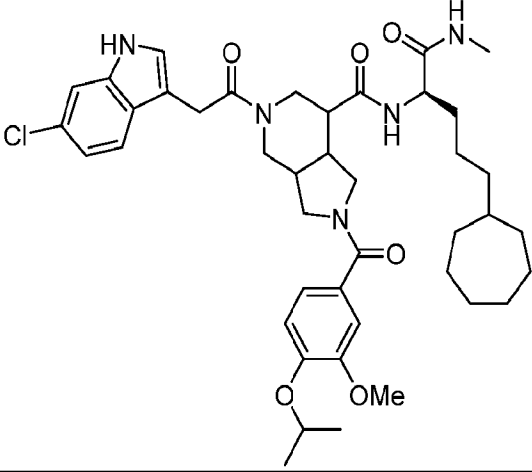
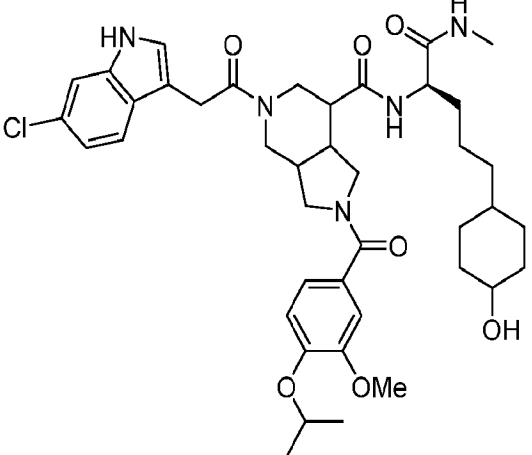
#	Structure
I-125	 Chemical structure of I-125: A complex molecule featuring a 4-chlorophenyl group connected to an indole ring. The indole ring is linked via a methylene group to a carbonyl group, which is part of a bicyclic system (a 6-membered ring fused to a 5-membered ring). The 6-membered ring is substituted with a carbonyl group and a methylene group. The 5-membered ring is substituted with a carbonyl group and a methylene group. The carbonyl group on the 5-membered ring is linked to a 4-methoxyphenyl group. The carbonyl group on the 6-membered ring is linked to a carbonyl group, which is further linked to a carbonyl group, which is finally linked to a carbonyl group. The carbonyl group on the 6-membered ring is linked to a carbonyl group, which is further linked to a carbonyl group, which is finally linked to a carbonyl group. The carbonyl group on the 6-membered ring is linked to a carbonyl group, which is further linked to a carbonyl group, which is finally linked to a carbonyl group.
I-126	 Chemical structure of I-126: Similar to I-125, but the carbonyl group on the 5-membered ring is linked to a carbonyl group, which is further linked to a carbonyl group, which is finally linked to a carbonyl group. The carbonyl group on the 6-membered ring is linked to a carbonyl group, which is further linked to a carbonyl group, which is finally linked to a carbonyl group. The carbonyl group on the 6-membered ring is linked to a carbonyl group, which is further linked to a carbonyl group, which is finally linked to a carbonyl group.
I-127	 Chemical structure of I-127: Similar to I-125, but the carbonyl group on the 5-membered ring is linked to a carbonyl group, which is further linked to a carbonyl group, which is finally linked to a carbonyl group. The carbonyl group on the 6-membered ring is linked to a carbonyl group, which is further linked to a carbonyl group, which is finally linked to a carbonyl group. The carbonyl group on the 6-membered ring is linked to a carbonyl group, which is further linked to a carbonyl group, which is finally linked to a carbonyl group.

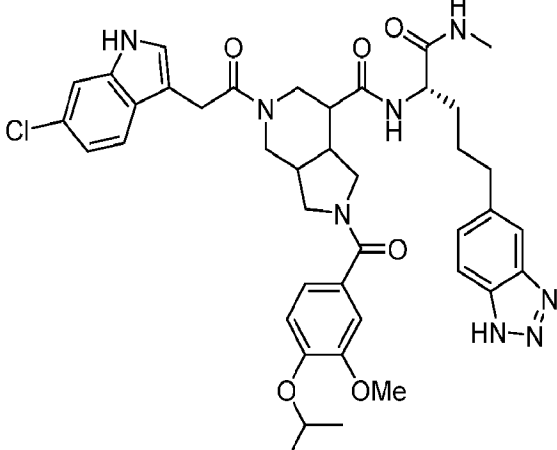
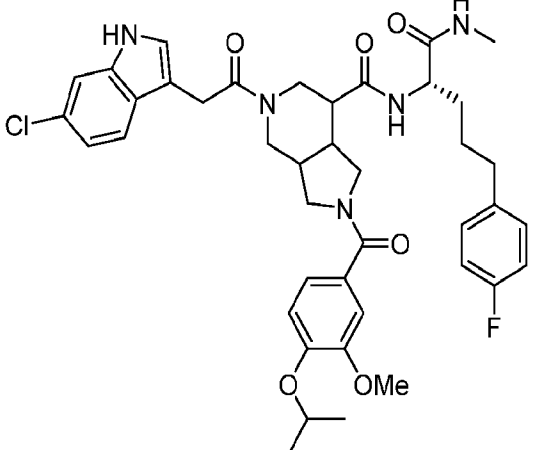
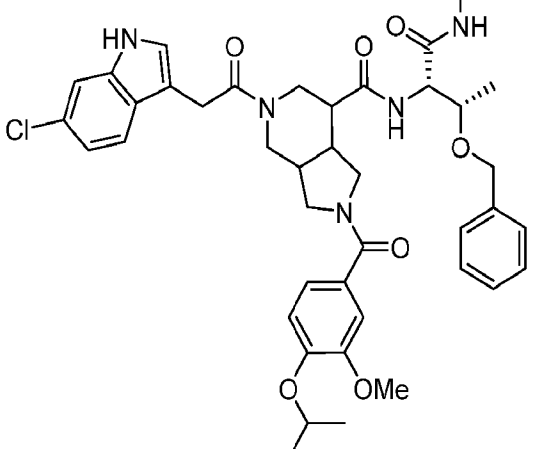
#	Structure
I-128	 Chemical structure of compound I-128. It features a central bicyclic core consisting of a 6-membered ring fused to a 5-membered ring, both containing nitrogen atoms. The 6-membered ring is substituted with a 4-chlorophenyl group and a 2-methoxy-4-isopropoxyphenyl group. The 5-membered ring is substituted with a 2-methoxy-4-isopropoxyphenyl group and a 4-hydroxyphenyl group. The 6-membered ring is also substituted with a 2-methoxy-4-isopropoxyphenyl group and a 4-hydroxyphenyl group. The 5-membered ring is substituted with a 2-methoxy-4-isopropoxyphenyl group and a 4-hydroxyphenyl group.
I-129	 Chemical structure of compound I-129. It features a central bicyclic core consisting of a 6-membered ring fused to a 5-membered ring, both containing nitrogen atoms. The 6-membered ring is substituted with a 4-chlorophenyl group and a 2-methoxy-4-isopropoxyphenyl group. The 5-membered ring is substituted with a 2-methoxy-4-isopropoxyphenyl group and a 4-hydroxyphenyl group. The 6-membered ring is also substituted with a 2-methoxy-4-isopropoxyphenyl group and a 4-hydroxyphenyl group. The 5-membered ring is substituted with a 2-methoxy-4-isopropoxyphenyl group and a 4-hydroxyphenyl group.
I-130	 Chemical structure of compound I-130. It features a central bicyclic core consisting of a 6-membered ring fused to a 5-membered ring, both containing nitrogen atoms. The 6-membered ring is substituted with a 4-chlorophenyl group and a 2-methoxy-4-isopropoxyphenyl group. The 5-membered ring is substituted with a 2-methoxy-4-isopropoxyphenyl group and a 4-hydroxyphenyl group. The 6-membered ring is also substituted with a 2-methoxy-4-isopropoxyphenyl group and a 4-hydroxyphenyl group. The 5-membered ring is substituted with a 2-methoxy-4-isopropoxyphenyl group and a 4-hydroxyphenyl group.

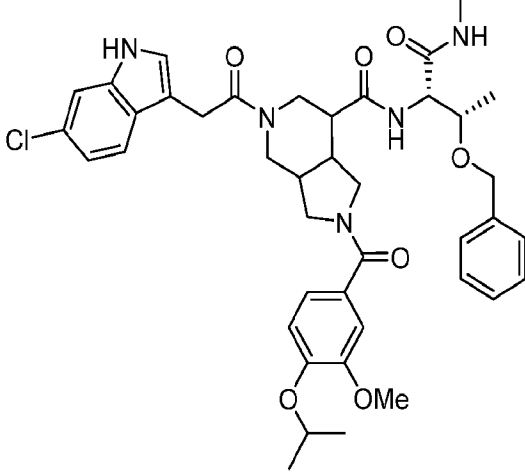
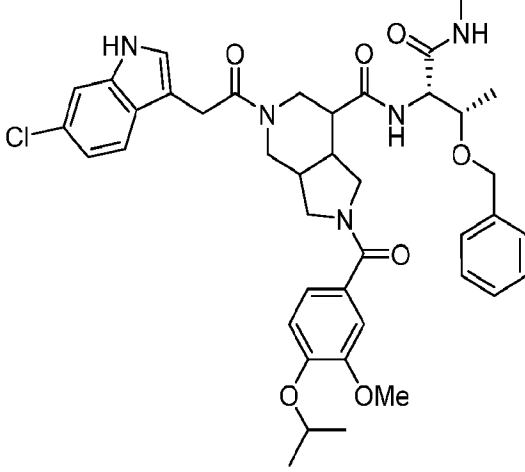
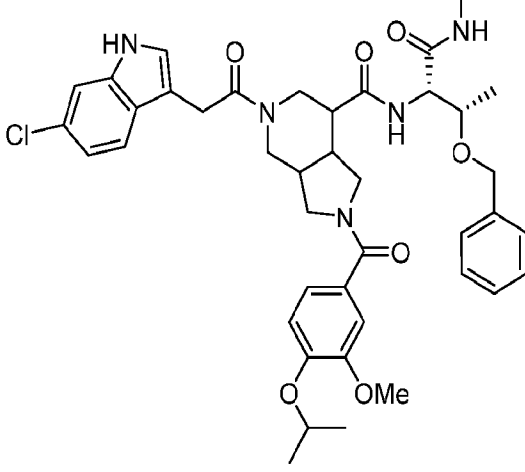
#	Structure
I-131	 Chemical structure of I-131: A complex molecule featuring a 4-chloro-1H-indol-3-yl group connected via a methylene group to a carbonyl group. This carbonyl is part of a bicyclic system (a 6-membered ring fused to a 5-membered ring, both containing nitrogen). The 5-membered ring is substituted with a carbonyl group linked to a 4-isopropoxy-2-methoxyphenyl group. The 6-membered ring is substituted with a carbonyl group linked to a chiral center. This chiral center is also substituted with a methyl group and a (4-(4-methoxy-2-isopropoxyphenyl)-1-methyl-1H-pyrazol-5-yl)methyl group.
I-132	 Chemical structure of I-132: Similar to I-131, but the chiral center is substituted with a methyl group and a cyclopentylmethyl group instead of the pyrazolylmethyl group.
I-133	 Chemical structure of I-133: Similar to I-131, but the chiral center is substituted with a methyl group and a (4-(4-methoxy-2-isopropoxyphenyl)-1H-pyrazol-5-yl)methyl group. The stereochemistry at the chiral center is indicated by a wedge bond to the methyl group and a dashed bond to the pyrazolylmethyl group.

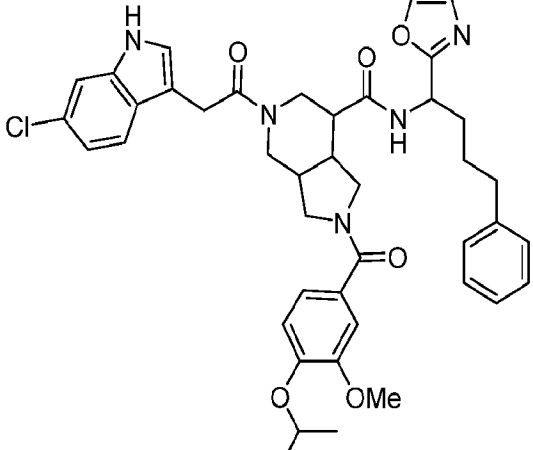
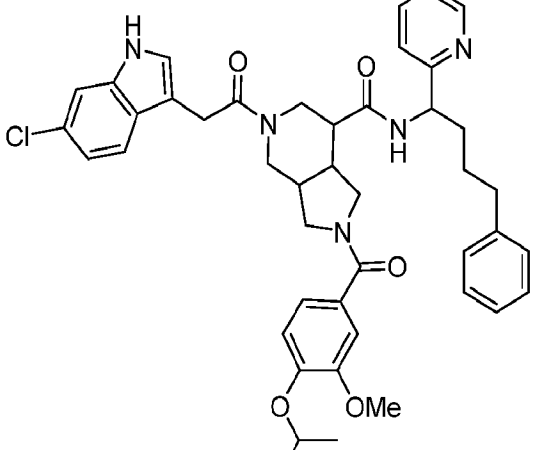
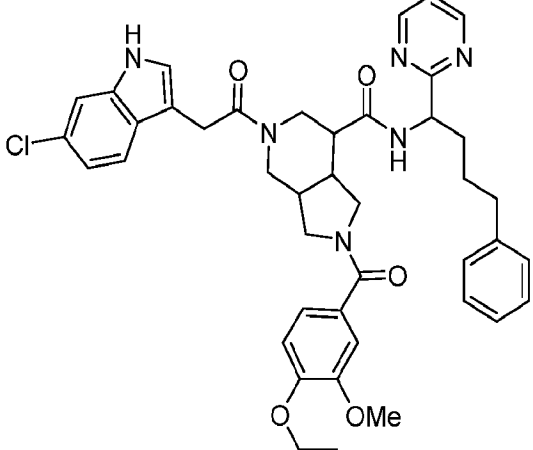
#	Structure
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I-135	
I-136	

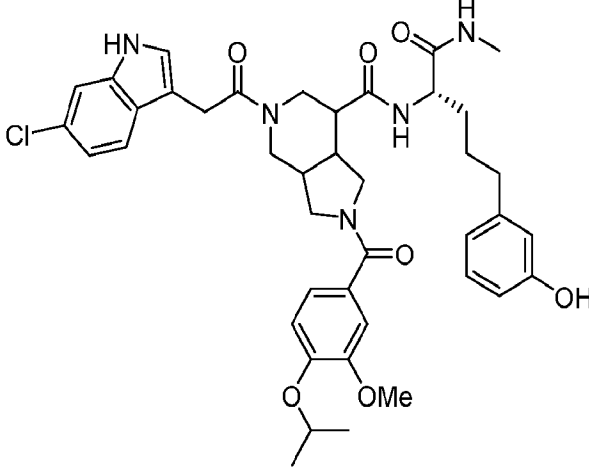
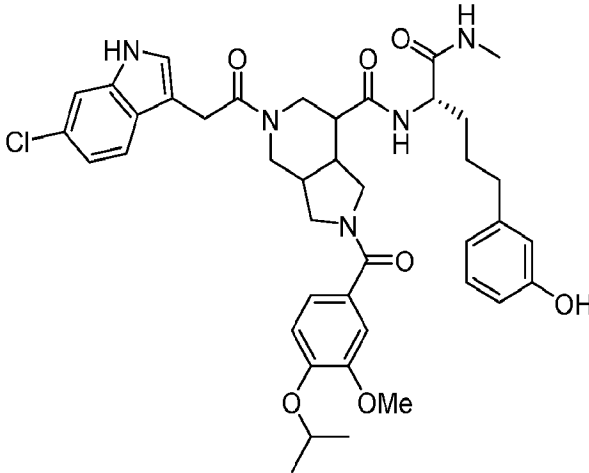
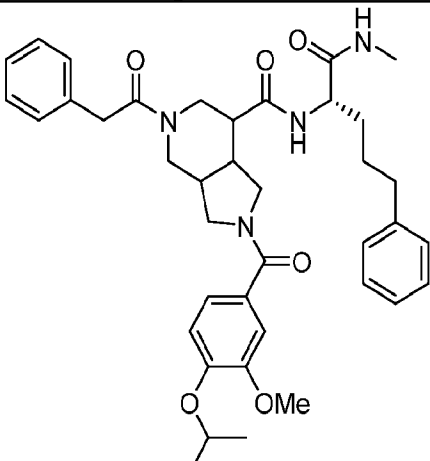
#	Structure
I-137	 Chemical structure of I-137: A complex molecule featuring a 4-chlorophenyl group attached to an indole ring. The indole ring is connected via a methylene group to a carbonyl group, which is part of a bicyclic system (a 6-membered ring fused to a 5-membered ring). The 6-membered ring is substituted with a carbonyl group and a methylene group. The 5-membered ring is substituted with a carbonyl group and a methylene group. The carbonyl group on the 5-membered ring is connected to a phenyl ring, which is further substituted with a methoxy group and an isopropoxy group. The carbonyl group on the 6-membered ring is connected to a methylene group, which is further substituted with a carbonyl group and a methylene group. The carbonyl group on the 6-membered ring is connected to a methylene group, which is further substituted with a carbonyl group and a methylene group. The carbonyl group on the 6-membered ring is connected to a methylene group, which is further substituted with a carbonyl group and a methylene group.
I-138	 Chemical structure of I-138: A complex molecule featuring a 4-chlorophenyl group attached to an indole ring. The indole ring is connected via a methylene group to a carbonyl group, which is part of a bicyclic system (a 6-membered ring fused to a 5-membered ring). The 6-membered ring is substituted with a carbonyl group and a methylene group. The 5-membered ring is substituted with a carbonyl group and a methylene group. The carbonyl group on the 5-membered ring is connected to a phenyl ring, which is further substituted with a methoxy group and an isopropoxy group. The carbonyl group on the 6-membered ring is connected to a methylene group, which is further substituted with a carbonyl group and a methylene group. The carbonyl group on the 6-membered ring is connected to a methylene group, which is further substituted with a carbonyl group and a methylene group. The carbonyl group on the 6-membered ring is connected to a methylene group, which is further substituted with a carbonyl group and a methylene group.
I-139	 Chemical structure of I-139: A complex molecule featuring a 4-chlorophenyl group attached to an indole ring. The indole ring is connected via a methylene group to a carbonyl group, which is part of a bicyclic system (a 6-membered ring fused to a 5-membered ring). The 6-membered ring is substituted with a carbonyl group and a methylene group. The 5-membered ring is substituted with a carbonyl group and a methylene group. The carbonyl group on the 5-membered ring is connected to a phenyl ring, which is further substituted with a methoxy group and an isopropoxy group. The carbonyl group on the 6-membered ring is connected to a methylene group, which is further substituted with a carbonyl group and a methylene group. The carbonyl group on the 6-membered ring is connected to a methylene group, which is further substituted with a carbonyl group and a methylene group. The carbonyl group on the 6-membered ring is connected to a methylene group, which is further substituted with a carbonyl group and a methylene group.

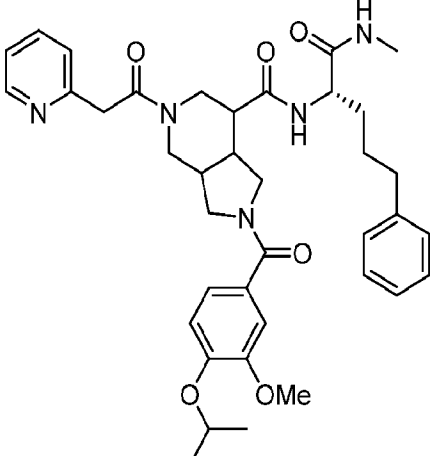
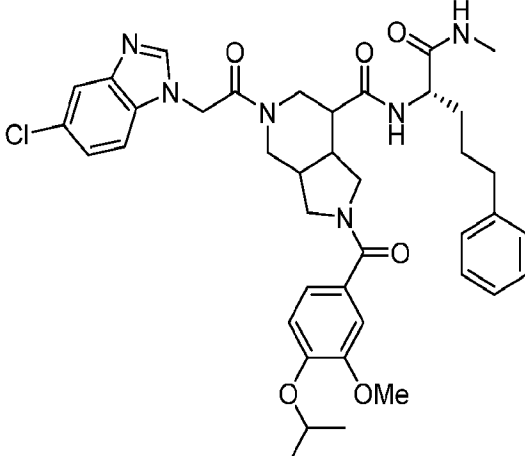
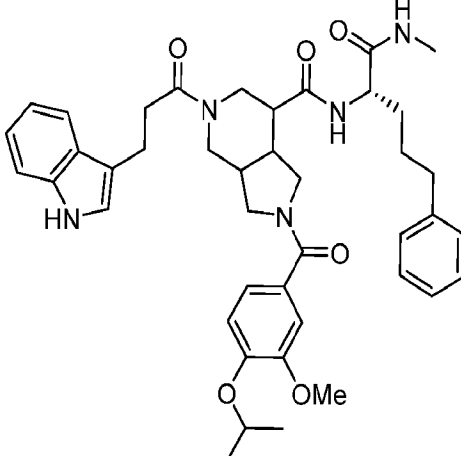
#	Structure
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I-141	
I-142	

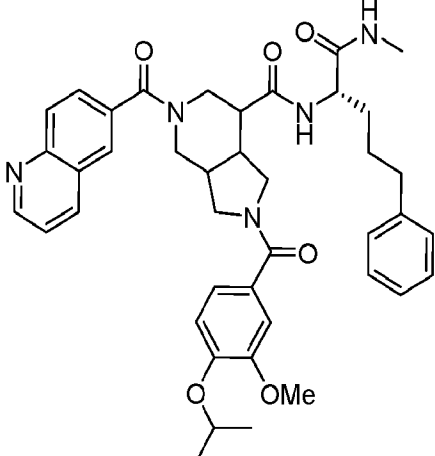
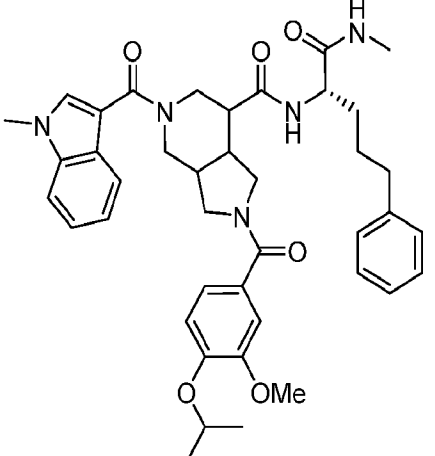
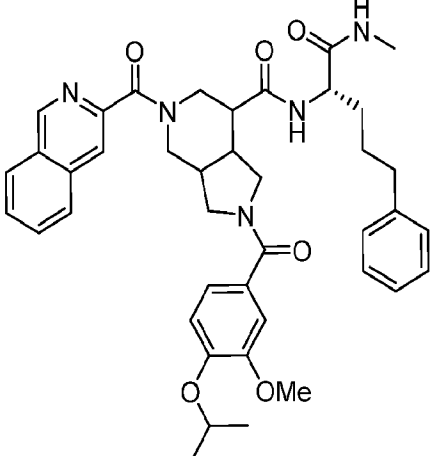
#	Structure
I-143	 Chemical structure of I-143: A complex molecule featuring a central bicyclic core (a 6-membered ring fused to a 5-membered ring, both containing nitrogen atoms). The 6-membered ring is substituted with a 4-chlorophenyl group and a 2-methoxy-4-isopropylphenyl group. The 5-membered ring is substituted with a 2-methoxy-4-isopropylphenyl group and a 4-fluorophenyl group. The 6-membered ring is also substituted with a 2-methoxy-4-isopropylphenyl group and a 4-fluorophenyl group. The 5-membered ring is substituted with a 2-methoxy-4-isopropylphenyl group and a 4-fluorophenyl group.
I-144	 Chemical structure of I-144: A complex molecule featuring a central bicyclic core (a 6-membered ring fused to a 5-membered ring, both containing nitrogen atoms). The 6-membered ring is substituted with a 4-chlorophenyl group and a 2-methoxy-4-isopropylphenyl group. The 5-membered ring is substituted with a 2-methoxy-4-isopropylphenyl group and a 4-fluorophenyl group. The 6-membered ring is also substituted with a 2-methoxy-4-isopropylphenyl group and a 4-fluorophenyl group. The 5-membered ring is substituted with a 2-methoxy-4-isopropylphenyl group and a 4-fluorophenyl group.
I-145	 Chemical structure of I-145: A complex molecule featuring a central bicyclic core (a 6-membered ring fused to a 5-membered ring, both containing nitrogen atoms). The 6-membered ring is substituted with a 4-chlorophenyl group and a 2-methoxy-4-isopropylphenyl group. The 5-membered ring is substituted with a 2-methoxy-4-isopropylphenyl group and a 4-fluorophenyl group. The 6-membered ring is also substituted with a 2-methoxy-4-isopropylphenyl group and a 4-fluorophenyl group. The 5-membered ring is substituted with a 2-methoxy-4-isopropylphenyl group and a 4-fluorophenyl group. First eluting diastereomer – n-Hexane / EtOH

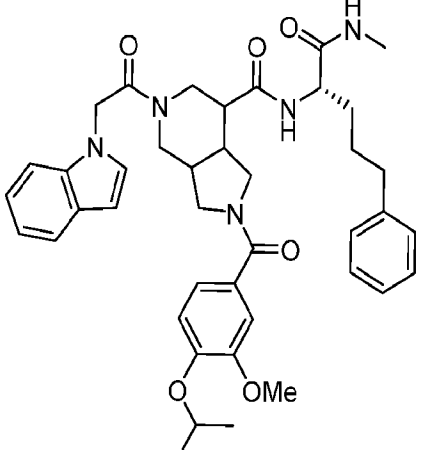
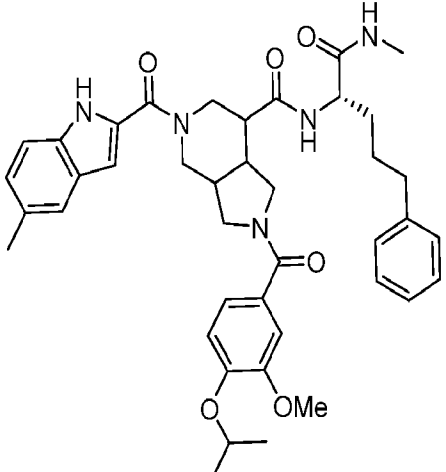
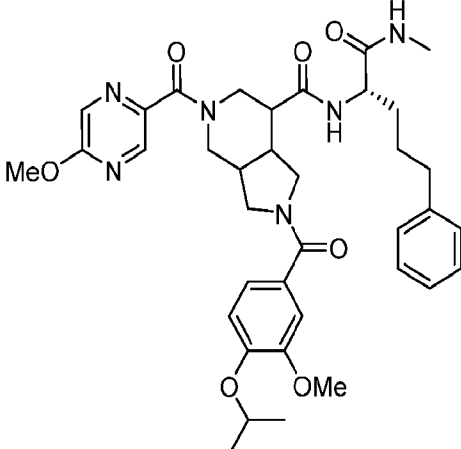
#	Structure
I-146	 Chemical structure of I-146: A complex molecule featuring a 4-chlorophenyl group attached to an indole ring, which is linked via a carbonyl group to a bicyclic amine system. The bicyclic amine is further substituted with a carbonyl group connected to a 4-methoxyphenyl group and another carbonyl group connected to a chiral center. The chiral center is also substituted with a benzyl group and a methyl group. The molecule is identified as the second eluting diastereomer - n-Hexane / EtOH.
I-147	 Chemical structure of I-147: A complex molecule featuring a 4-chlorophenyl group attached to an indole ring, which is linked via a carbonyl group to a bicyclic amine system. The bicyclic amine is further substituted with a carbonyl group connected to a 4-methoxyphenyl group and another carbonyl group connected to a chiral center. The chiral center is also substituted with a benzyl group and a methyl group. The molecule is identified as the first eluting diastereomer - H₂O / Acetonitrile.
I-148	 Chemical structure of I-148: A complex molecule featuring a 4-chlorophenyl group attached to an indole ring, which is linked via a carbonyl group to a bicyclic amine system. The bicyclic amine is further substituted with a carbonyl group connected to a 4-methoxyphenyl group and another carbonyl group connected to a chiral center. The chiral center is also substituted with a benzyl group and a methyl group. The molecule is identified as the second eluting diastereomer - H₂O / Acetonitrile.

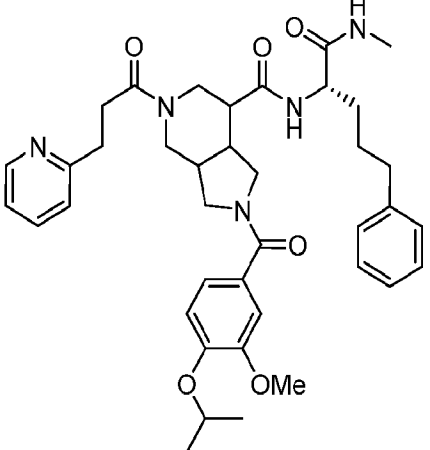
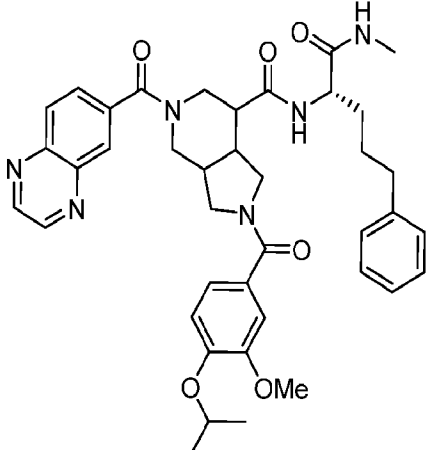
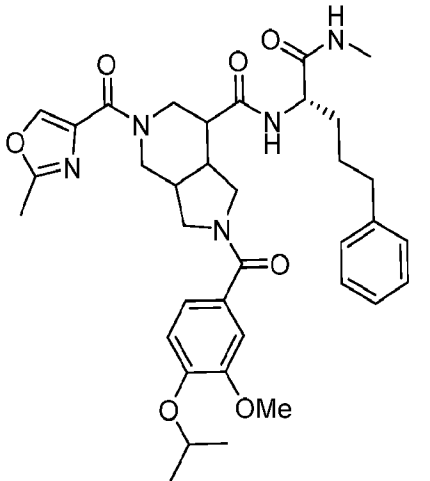
#	Structure
I-149	 Chemical structure of compound I-149. It features a central bicyclic core consisting of a 6-membered ring and a 5-membered ring, both containing nitrogen atoms. The 6-membered ring is substituted with a 5-chloro-1H-indol-3-ylmethyl group and a 2-methoxy-4-(4-methoxyphenyl)-1,3-dioxane group. The 5-membered ring is substituted with a 2-methoxy-4-(4-methoxyphenyl)-1,3-dioxane group and a 2-methoxy-4-(4-methoxyphenyl)-1,3-dioxane group. The 6-membered ring is also substituted with a 2-methoxy-4-(4-methoxyphenyl)-1,3-dioxane group.
I-150	 Chemical structure of compound I-150. It features a central bicyclic core consisting of a 6-membered ring and a 5-membered ring, both containing nitrogen atoms. The 6-membered ring is substituted with a 5-chloro-1H-indol-3-ylmethyl group and a 2-methoxy-4-(4-methoxyphenyl)-1,3-dioxane group. The 5-membered ring is substituted with a 2-methoxy-4-(4-methoxyphenyl)-1,3-dioxane group and a 2-methoxy-4-(4-methoxyphenyl)-1,3-dioxane group. The 6-membered ring is also substituted with a 2-methoxy-4-(4-methoxyphenyl)-1,3-dioxane group.
I-151	 Chemical structure of compound I-151. It features a central bicyclic core consisting of a 6-membered ring and a 5-membered ring, both containing nitrogen atoms. The 6-membered ring is substituted with a 5-chloro-1H-indol-3-ylmethyl group and a 2-methoxy-4-(4-methoxyphenyl)-1,3-dioxane group. The 5-membered ring is substituted with a 2-methoxy-4-(4-methoxyphenyl)-1,3-dioxane group and a 2-methoxy-4-(4-methoxyphenyl)-1,3-dioxane group. The 6-membered ring is also substituted with a 2-methoxy-4-(4-methoxyphenyl)-1,3-dioxane group.

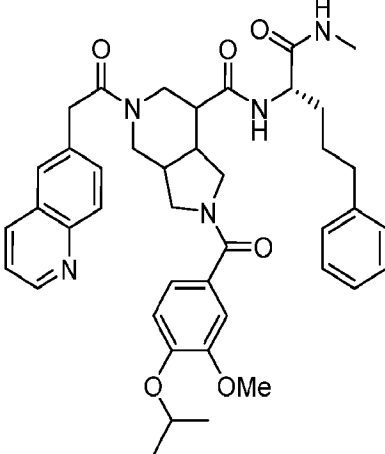
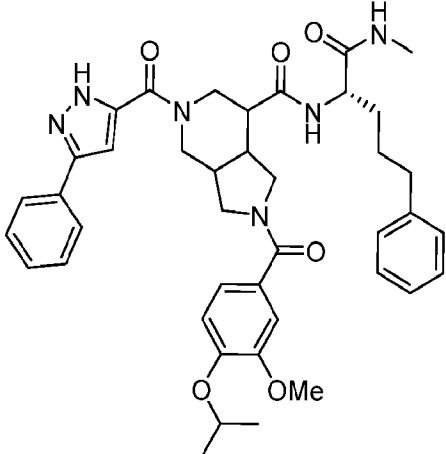
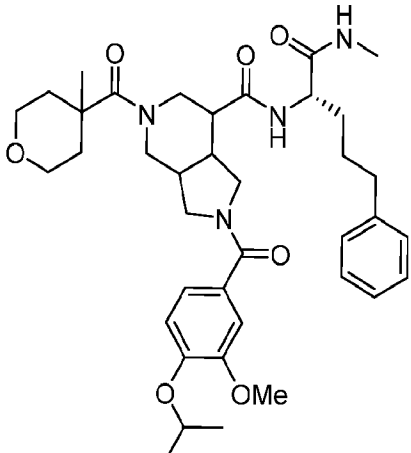
#	Structure
I-152	 Chemical structure of I-152: A complex molecule featuring a 4-chloro-1H-indol-3-yl group connected via a methylene group to a carbonyl group. This carbonyl is part of a bicyclic system (a 6-membered ring fused to a 5-membered ring, both containing nitrogen). The 6-membered ring is also connected to another carbonyl group, which is part of a side chain containing a chiral center (indicated by a wedge bond) and a 4-hydroxyphenyl group. The 5-membered ring is connected to a carbonyl group, which is part of a side chain containing a 4-(4-methoxy-2-isopropoxyphenyl) group. First eluting diastereomer
I-153	 Chemical structure of I-153: A complex molecule featuring a 4-chloro-1H-indol-3-yl group connected via a methylene group to a carbonyl group. This carbonyl is part of a bicyclic system (a 6-membered ring fused to a 5-membered ring, both containing nitrogen). The 6-membered ring is also connected to another carbonyl group, which is part of a side chain containing a chiral center (indicated by a wedge bond) and a 4-hydroxyphenyl group. The 5-membered ring is connected to a carbonyl group, which is part of a side chain containing a 4-(4-methoxy-2-isopropoxyphenyl) group. Second eluting diastereomer
I-154	 Chemical structure of I-154: A complex molecule featuring a benzyl group connected via a carbonyl group to a bicyclic system (a 6-membered ring fused to a 5-membered ring, both containing nitrogen). The 6-membered ring is also connected to another carbonyl group, which is part of a side chain containing a chiral center (indicated by a wedge bond) and a phenyl group. The 5-membered ring is connected to a carbonyl group, which is part of a side chain containing a 4-(4-methoxy-2-isopropoxyphenyl) group.

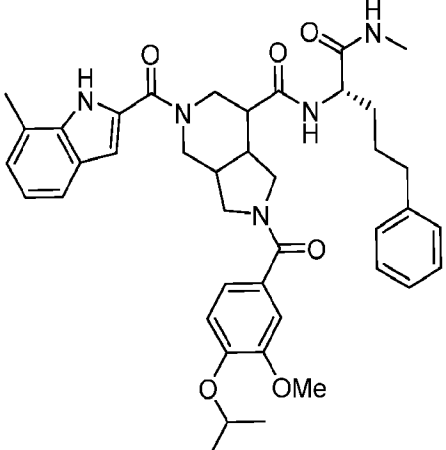
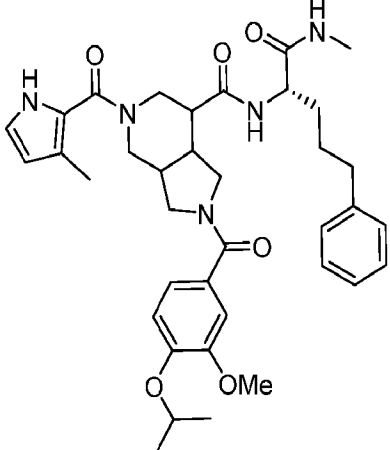
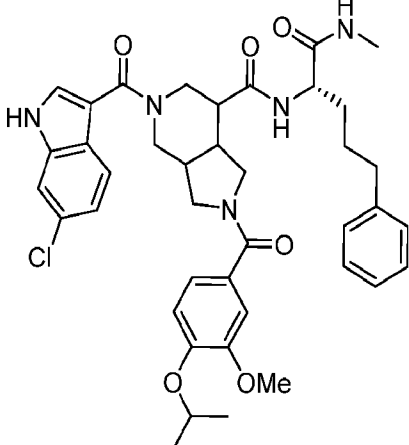
#	Structure
I-155	 Chemical structure of compound I-155. It features a bicyclic core consisting of a piperidine ring fused to a pyrrolidine ring. The piperidine nitrogen is substituted with a (2-pyridyl)methyl ketone group. The pyrrolidine nitrogen is substituted with a 4-(4-methoxy-2-isopropoxyphenyl)carbonyl group. A side chain is attached to the piperidine ring, consisting of a (1-methylamino)propan-2-yl group linked via a chiral center to a 3-phenylpropyl group.
I-156	 Chemical structure of compound I-156. It features a bicyclic core consisting of a piperidine ring fused to a pyrrolidine ring. The piperidine nitrogen is substituted with a (1-(4-chlorophenyl)-1H-imidazol-2-yl)methyl ketone group. The pyrrolidine nitrogen is substituted with a 4-(4-methoxy-2-isopropoxyphenyl)carbonyl group. A side chain is attached to the piperidine ring, consisting of a (1-methylamino)propan-2-yl group linked via a chiral center to a 3-phenylpropyl group.
I-157	 Chemical structure of compound I-157. It features a bicyclic core consisting of a piperidine ring fused to a pyrrolidine ring. The piperidine nitrogen is substituted with a (3-(1H-indol-3-yl)propyl) ketone group. The pyrrolidine nitrogen is substituted with a 4-(4-methoxy-2-isopropoxyphenyl)carbonyl group. A side chain is attached to the piperidine ring, consisting of a (1-methylamino)propan-2-yl group linked via a chiral center to a 3-phenylpropyl group.

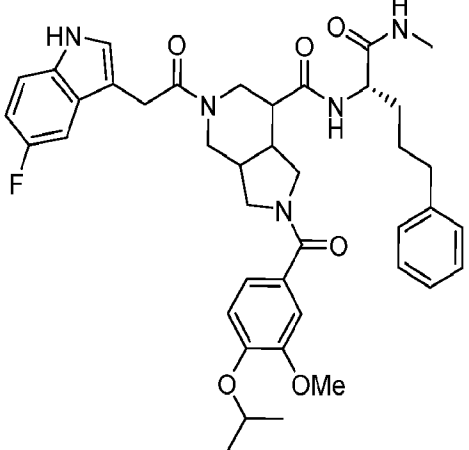
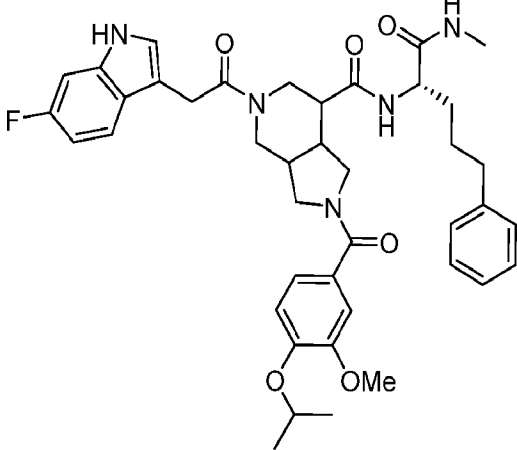
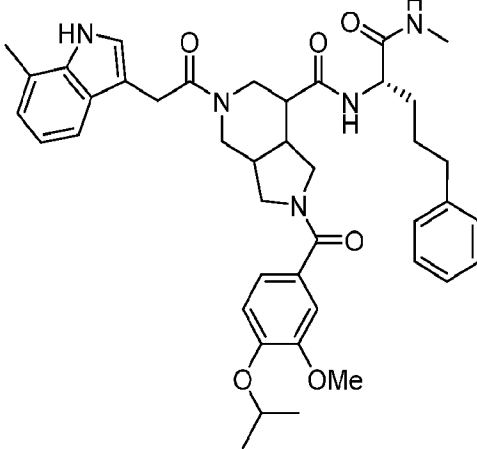
#	Structure
I-158	 Chemical structure of I-158: A complex molecule featuring a bicyclic core (a 6-membered ring fused to a 5-membered ring). The 6-membered ring is substituted with a quinoline-2-carbonyl group (via an amide linkage) and a 2-methoxy-4-isopropoxyphenyl group (via an amide linkage). The 5-membered ring is substituted with a 2-methoxy-4-isopropoxyphenyl group (via an amide linkage) and a 2-methoxy-4-isopropoxyphenyl group (via an amide linkage). The 2-methoxy-4-isopropoxyphenyl group is further substituted with a 2-methoxy-4-isopropoxyphenyl group (via an amide linkage).
I-159	 Chemical structure of I-159: A complex molecule featuring a bicyclic core (a 6-membered ring fused to a 5-membered ring). The 6-membered ring is substituted with a 2-methoxy-4-isopropoxyphenyl group (via an amide linkage) and a 2-methoxy-4-isopropoxyphenyl group (via an amide linkage). The 5-membered ring is substituted with a 2-methoxy-4-isopropoxyphenyl group (via an amide linkage) and a 2-methoxy-4-isopropoxyphenyl group (via an amide linkage). The 2-methoxy-4-isopropoxyphenyl group is further substituted with a 2-methoxy-4-isopropoxyphenyl group (via an amide linkage).
I-160	 Chemical structure of I-160: A complex molecule featuring a bicyclic core (a 6-membered ring fused to a 5-membered ring). The 6-membered ring is substituted with a 2-methoxy-4-isopropoxyphenyl group (via an amide linkage) and a 2-methoxy-4-isopropoxyphenyl group (via an amide linkage). The 5-membered ring is substituted with a 2-methoxy-4-isopropoxyphenyl group (via an amide linkage) and a 2-methoxy-4-isopropoxyphenyl group (via an amide linkage). The 2-methoxy-4-isopropoxyphenyl group is further substituted with a 2-methoxy-4-isopropoxyphenyl group (via an amide linkage).

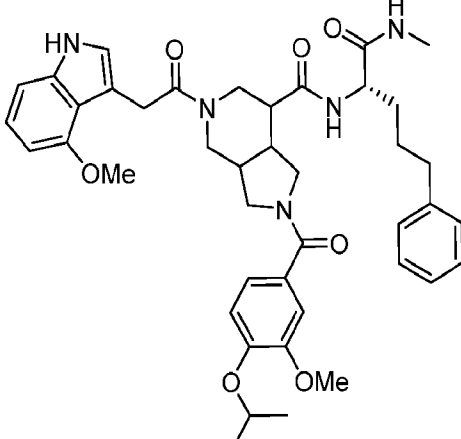
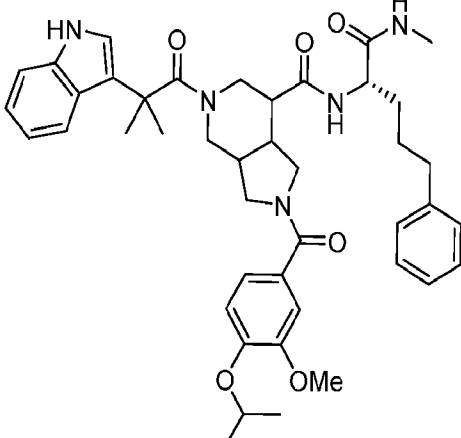
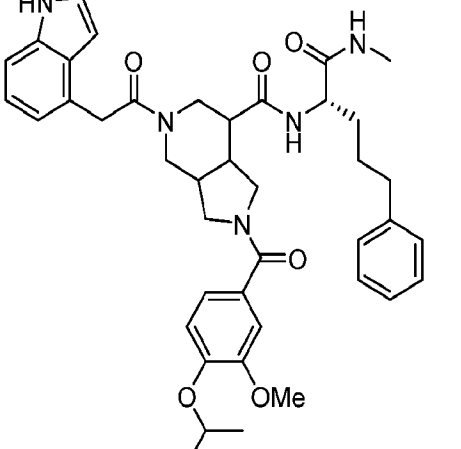
#	Structure
I-161	 Chemical structure of compound I-161. It features a bicyclic core consisting of a 6-membered ring and a 5-membered ring, both containing nitrogen atoms. The 6-membered ring is substituted with a carbonyl group linked to an indole ring, and another carbonyl group linked to a dimethylamino group. The 5-membered ring is substituted with a carbonyl group linked to a benzyl group and another carbonyl group linked to a 4-isopropoxyphenyl group. The stereochemistry at the chiral center is indicated by a wedge bond.
I-162	 Chemical structure of compound I-162. It features a bicyclic core consisting of a 6-membered ring and a 5-membered ring, both containing nitrogen atoms. The 6-membered ring is substituted with a carbonyl group linked to a 4-methyl-1H-indol-3-yl group, and another carbonyl group linked to a dimethylamino group. The 5-membered ring is substituted with a carbonyl group linked to a benzyl group and another carbonyl group linked to a 4-isopropoxyphenyl group. The stereochemistry at the chiral center is indicated by a wedge bond.
I-163	 Chemical structure of compound I-163. It features a bicyclic core consisting of a 6-membered ring and a 5-membered ring, both containing nitrogen atoms. The 6-membered ring is substituted with a carbonyl group linked to a 4-methoxy-2-pyridyl group, and another carbonyl group linked to a dimethylamino group. The 5-membered ring is substituted with a carbonyl group linked to a benzyl group and another carbonyl group linked to a 4-isopropoxyphenyl group. The stereochemistry at the chiral center is indicated by a wedge bond.

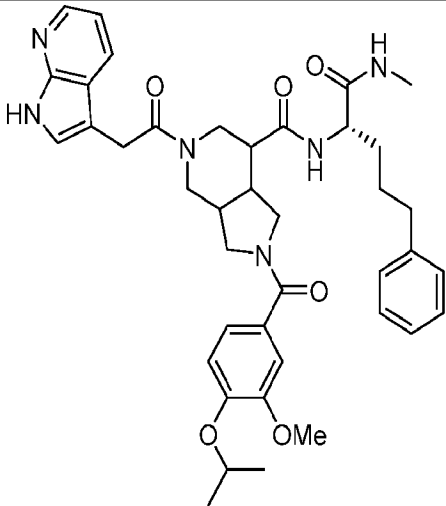
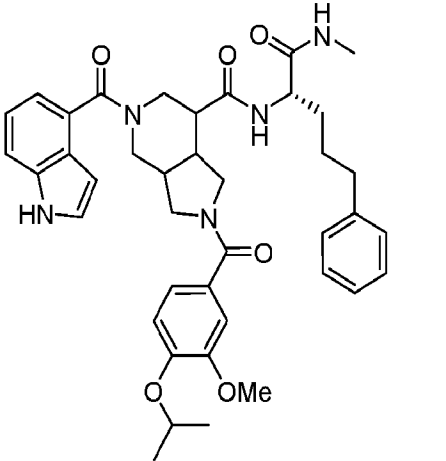
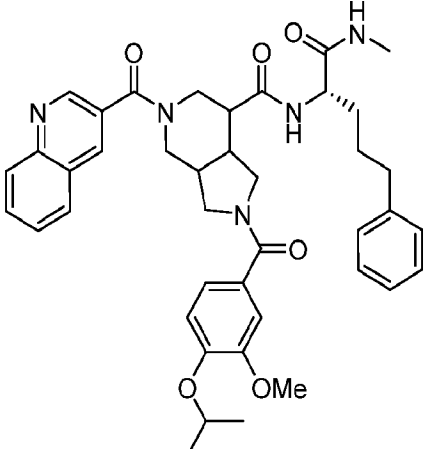
#	Structure
I-164	 Chemical structure of I-164: A complex molecule featuring a central bicyclic core (a 6-membered ring fused to a 5-membered ring, both containing nitrogen atoms). The 6-membered ring is substituted with a pyridine-3-ylmethyl group via a carbonyl linkage. The 5-membered ring is substituted with a 4-(3-methoxy-4-isopropoxyphenyl) group via a carbonyl linkage. A side chain on the 6-membered ring includes a carbonyl group linked to a 1-methyl-2-phenylpropyl group.
I-165	 Chemical structure of I-165: Similar to I-164, but the pyridine ring is replaced by a quinoline ring system, specifically a 6-quinoline-2-ylmethyl group.
I-166	 Chemical structure of I-166: Similar to I-164, but the pyridine ring is replaced by a 2-methyl-1,3,4-oxadiazole ring system, specifically a 2-methyl-1,3,4-oxadiazol-5-ylmethyl group.

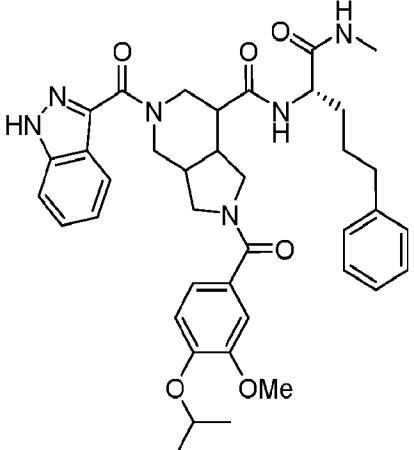
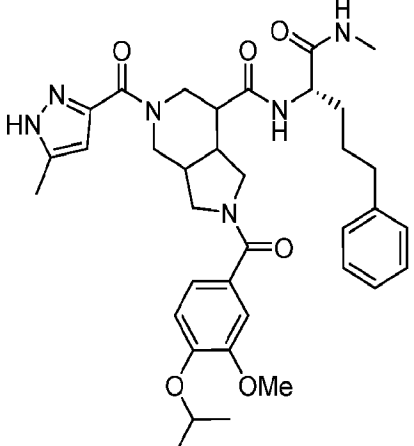
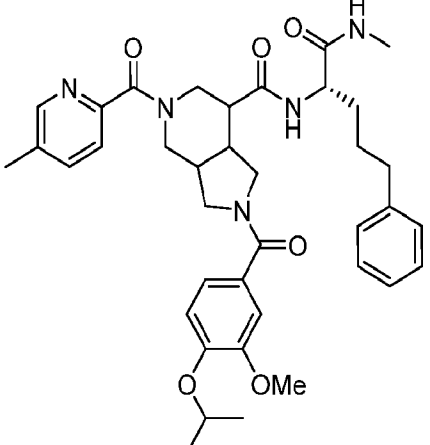
#	Structure
I-167	
I-168	
I-169	

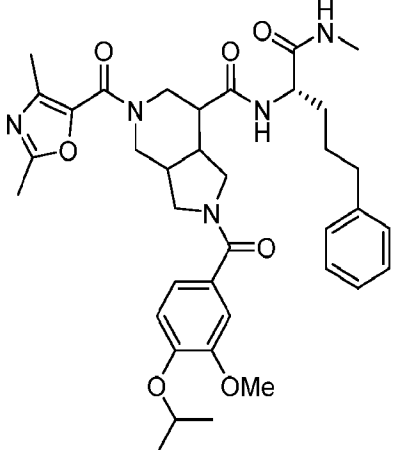
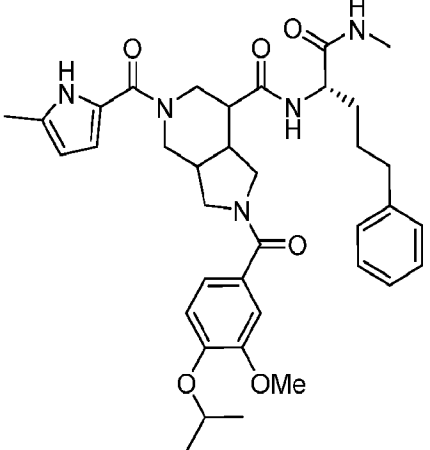
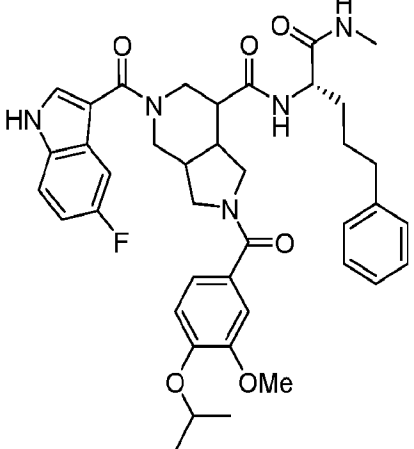
#	Structure
I-170	 Chemical structure of I-170: A complex molecule featuring a central bicyclic core (a 6-membered ring fused to a 5-membered ring, both containing nitrogen atoms). The 6-membered ring is substituted with a 2-methyl-1H-indol-3-yl group via a carbonyl linkage. The 5-membered ring is substituted with a 4-(4-methoxy-2-(propan-2-yloxy)phenyl)phenyl group via a carbonyl linkage. A side chain is attached to the 6-membered ring, consisting of a 2-(benzyloxy)ethyl group linked to a 2-methyl-2-oxoethyl group.
I-171	 Chemical structure of I-171: A complex molecule featuring a central bicyclic core (a 6-membered ring fused to a 5-membered ring, both containing nitrogen atoms). The 6-membered ring is substituted with a 2-methyl-1H-imidazol-5-yl group via a carbonyl linkage. The 5-membered ring is substituted with a 4-(4-methoxy-2-(propan-2-yloxy)phenyl)phenyl group via a carbonyl linkage. A side chain is attached to the 6-membered ring, consisting of a 2-(benzyloxy)ethyl group linked to a 2-methyl-2-oxoethyl group.
I-172	 Chemical structure of I-172: A complex molecule featuring a central bicyclic core (a 6-membered ring fused to a 5-membered ring, both containing nitrogen atoms). The 6-membered ring is substituted with a 4-chloro-1H-indol-3-yl group via a carbonyl linkage. The 5-membered ring is substituted with a 4-(4-methoxy-2-(propan-2-yloxy)phenyl)phenyl group via a carbonyl linkage. A side chain is attached to the 6-membered ring, consisting of a 2-(benzyloxy)ethyl group linked to a 2-methyl-2-oxoethyl group.

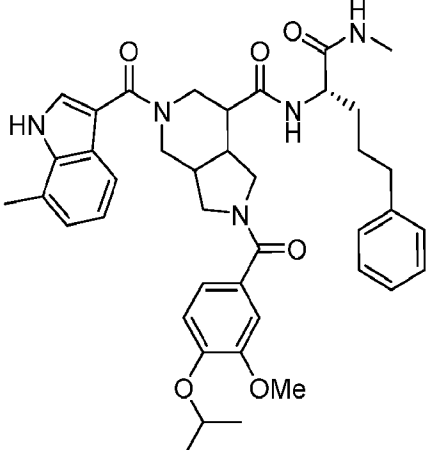
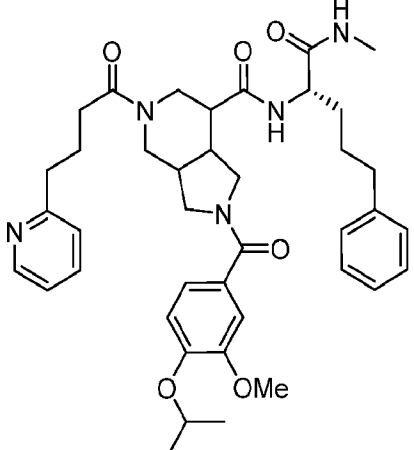
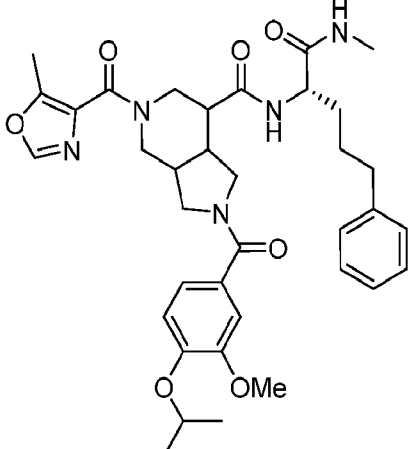
#	Structure
I-173	 Chemical structure of I-173: A complex molecule featuring a 4-fluorophenyl group attached to an indole ring, which is linked via a carbonyl group to a piperidine ring. The piperidine ring is further substituted with a carbonyl group connected to a benzyl group, and another carbonyl group connected to a chiral center. The chiral center is also linked to a benzyl group and a carbonyl group connected to a dimethylamino group.
I-174	 Chemical structure of I-174: A complex molecule featuring a 4-fluorophenyl group attached to an indole ring, which is linked via a carbonyl group to a piperidine ring. The piperidine ring is further substituted with a carbonyl group connected to a benzyl group, and another carbonyl group connected to a chiral center. The chiral center is also linked to a benzyl group and a carbonyl group connected to a dimethylamino group.
I-175	 Chemical structure of I-175: A complex molecule featuring a 4-methylphenyl group attached to an indole ring, which is linked via a carbonyl group to a piperidine ring. The piperidine ring is further substituted with a carbonyl group connected to a benzyl group, and another carbonyl group connected to a chiral center. The chiral center is also linked to a benzyl group and a carbonyl group connected to a dimethylamino group.

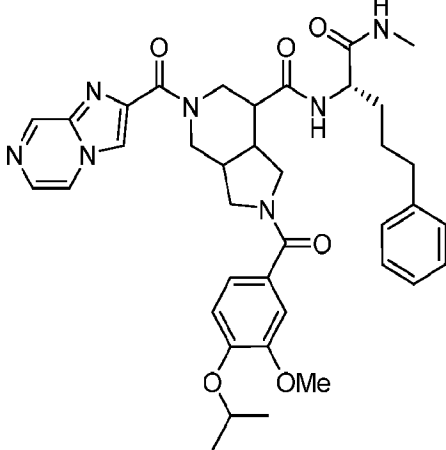
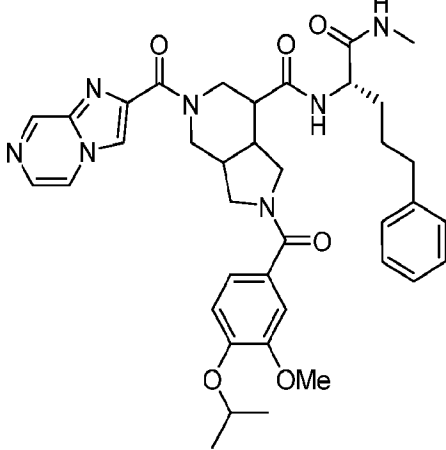
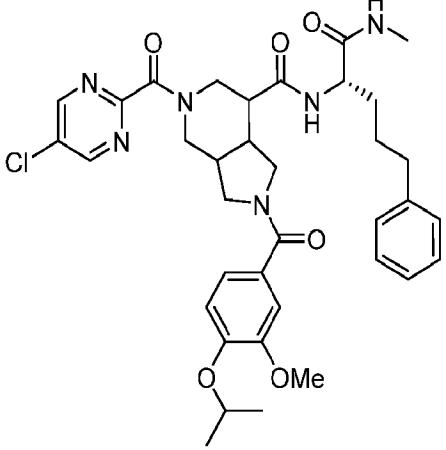
#	Structure
I-176	 Chemical structure of compound I-176. It features a 5-methoxy-1H-indol-3-yl group connected via a methylene group to a carbonyl group. This carbonyl is part of a bicyclic system (a 6,7-dihydro-1,2,4-triazolo[4,5-c]pyridine derivative) where the nitrogen is also connected to a carbonyl group. This carbonyl is further connected to a 4-isopropoxyphenyl group. The other nitrogen of the bicyclic system is connected to a carbonyl group, which is part of a side chain containing a chiral center (marked with a wedge bond) and a benzyl group. The side chain also includes a methylamino group.
I-177	 Chemical structure of compound I-177. It is similar to I-176, but the 5-methoxy-1H-indol-3-yl group is connected via a quaternary carbon atom (a tert-butyl group) to the carbonyl group of the bicyclic system.
I-178	 Chemical structure of compound I-178. It is similar to I-176, but the 5-methoxy-1H-indol-3-yl group is connected via a methylene group to the carbonyl group of the bicyclic system, and the nitrogen of the bicyclic system is connected to a carbonyl group that is part of a side chain containing a chiral center (marked with a wedge bond) and a benzyl group. The side chain also includes a methylamino group.

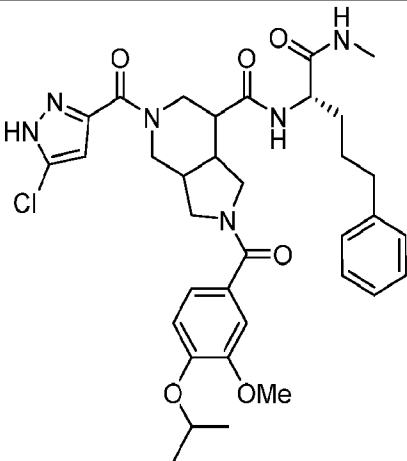
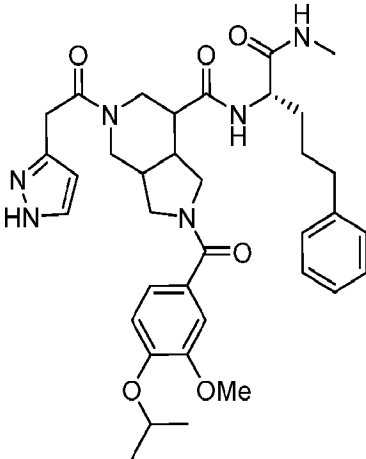
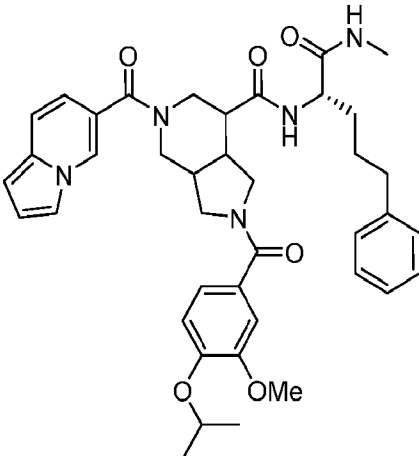
#	Structure
I-179	 Chemical structure of compound I-179. It features a bicyclic core consisting of a piperidine ring fused to a pyrrolidine ring. The piperidine ring is substituted with a 5-oxo-1H-indol-3-ylmethyl group at the 2-position and a (2-methoxy-4-(propan-2-yloxy)phenyl)carbonyl group at the 4-position. The pyrrolidine ring is substituted with a (2-methoxy-4-(propan-2-yloxy)phenyl)carbonyl group at the 2-position and a (2-methoxy-4-(propan-2-yloxy)phenyl)carbonyl group at the 4-position. Additionally, the piperidine ring is substituted with a (2-methoxy-4-(propan-2-yloxy)phenyl)carbonyl group at the 6-position. The pyrrolidine ring is substituted with a (2-methoxy-4-(propan-2-yloxy)phenyl)carbonyl group at the 2-position and a (2-methoxy-4-(propan-2-yloxy)phenyl)carbonyl group at the 4-position.
I-180	 Chemical structure of compound I-180. It features a bicyclic core consisting of a piperidine ring fused to a pyrrolidine ring. The piperidine ring is substituted with a 5-oxo-1H-indol-3-ylmethyl group at the 2-position and a (2-methoxy-4-(propan-2-yloxy)phenyl)carbonyl group at the 4-position. The pyrrolidine ring is substituted with a (2-methoxy-4-(propan-2-yloxy)phenyl)carbonyl group at the 2-position and a (2-methoxy-4-(propan-2-yloxy)phenyl)carbonyl group at the 4-position. Additionally, the piperidine ring is substituted with a (2-methoxy-4-(propan-2-yloxy)phenyl)carbonyl group at the 6-position. The pyrrolidine ring is substituted with a (2-methoxy-4-(propan-2-yloxy)phenyl)carbonyl group at the 2-position and a (2-methoxy-4-(propan-2-yloxy)phenyl)carbonyl group at the 4-position.
I-181	 Chemical structure of compound I-181. It features a bicyclic core consisting of a piperidine ring fused to a pyrrolidine ring. The piperidine ring is substituted with a 5-oxo-1H-indol-3-ylmethyl group at the 2-position and a (2-methoxy-4-(propan-2-yloxy)phenyl)carbonyl group at the 4-position. The pyrrolidine ring is substituted with a (2-methoxy-4-(propan-2-yloxy)phenyl)carbonyl group at the 2-position and a (2-methoxy-4-(propan-2-yloxy)phenyl)carbonyl group at the 4-position. Additionally, the piperidine ring is substituted with a (2-methoxy-4-(propan-2-yloxy)phenyl)carbonyl group at the 6-position. The pyrrolidine ring is substituted with a (2-methoxy-4-(propan-2-yloxy)phenyl)carbonyl group at the 2-position and a (2-methoxy-4-(propan-2-yloxy)phenyl)carbonyl group at the 4-position.

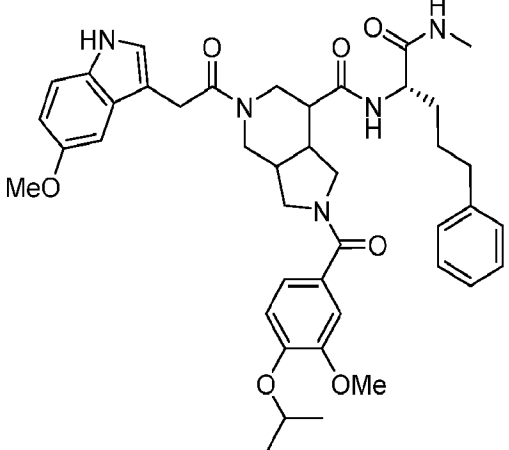
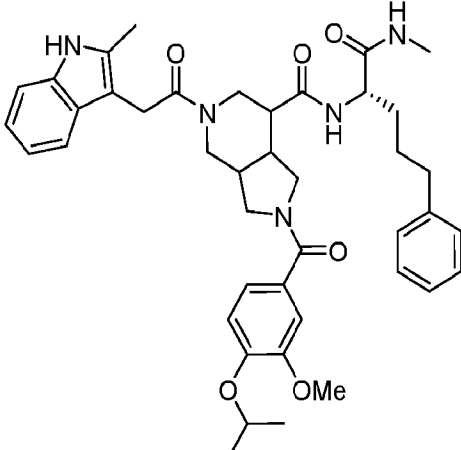
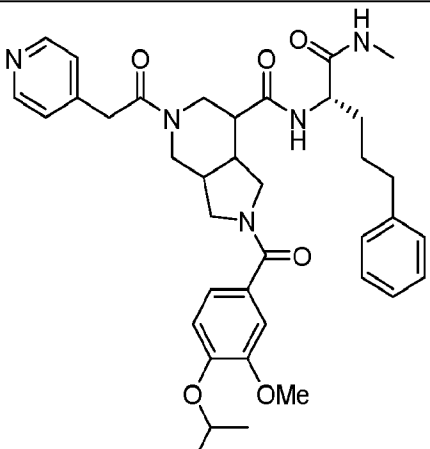
#	Structure
I-182	 Chemical structure of compound I-182. It features a bicyclic core consisting of a 6-membered ring and a 5-membered ring. The 6-membered ring is substituted with a benzimidazole-2-carbonyl group at position 1 and a (1-methyl-2-phenylpropyl)carbamoyl group at position 3. The 5-membered ring is substituted with a (4-isopropoxyphenyl)carbamoyl group at position 2. The stereochemistry at the chiral center is (S).
I-183	 Chemical structure of compound I-183. It features a bicyclic core consisting of a 6-membered ring and a 5-membered ring. The 6-membered ring is substituted with a 4-methyl-1H-imidazole-2-carbonyl group at position 1 and a (1-methyl-2-phenylpropyl)carbamoyl group at position 3. The 5-membered ring is substituted with a (4-isopropoxyphenyl)carbamoyl group at position 2. The stereochemistry at the chiral center is (S).
I-184	 Chemical structure of compound I-184. It features a bicyclic core consisting of a 6-membered ring and a 5-membered ring. The 6-membered ring is substituted with a 4-methylpyridine-2-carbonyl group at position 1 and a (1-methyl-2-phenylpropyl)carbamoyl group at position 3. The 5-membered ring is substituted with a (4-isopropoxyphenyl)carbamoyl group at position 2. The stereochemistry at the chiral center is (S).

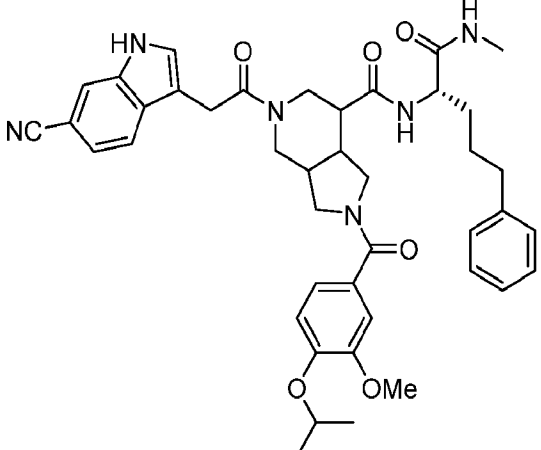
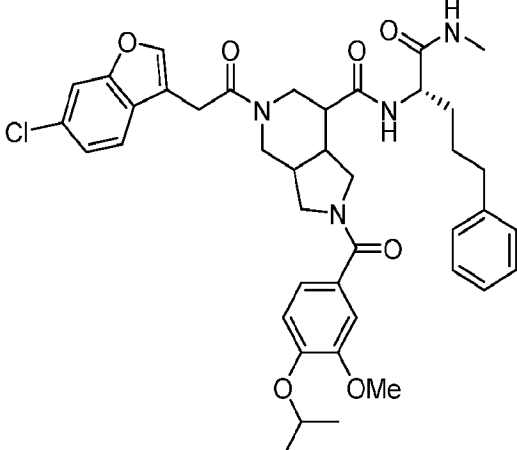
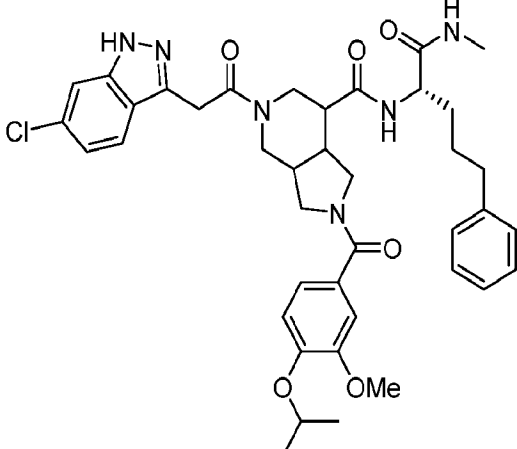
#	Structure
I-188	 Chemical structure of I-188: A complex molecule featuring a central bicyclic core (a 6-membered ring fused to a 5-membered ring, both containing nitrogen atoms). The 6-membered ring is substituted with a 2-methyl-1,3,4-oxadiazol-5-yl group via a carbonyl linkage. The 5-membered ring is substituted with a 4-(4-methoxy-2-isopropoxyphenyl) group via a carbonyl linkage. A side chain is attached to the 6-membered ring, consisting of a carbonyl group linked to a chiral center (marked with a dashed bond) which is further linked to a 3-phenylpropyl group. The side chain also includes a methylamino group (NHMe) at the end.
I-189	 Chemical structure of I-189: Similar to I-188, but the 2-methyl-1,3,4-oxadiazol-5-yl group is replaced by a 2-methyl-1H-imidazol-5-yl group.
I-190	 Chemical structure of I-190: Similar to I-188, but the 2-methyl-1,3,4-oxadiazol-5-yl group is replaced by a 2-fluoro-1H-indol-3-yl group.

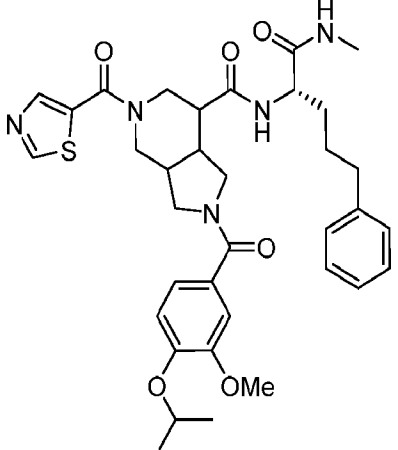
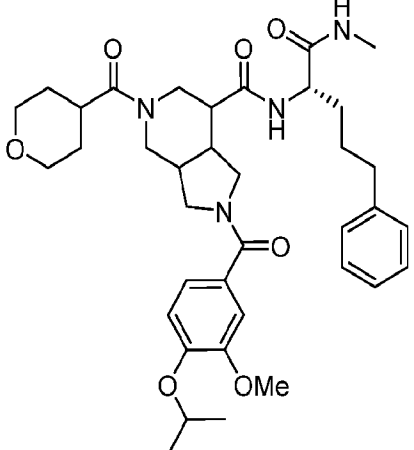
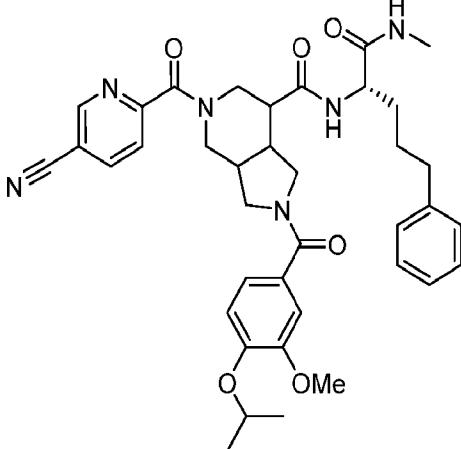
#	Structure
I-191	 Chemical structure of I-191: A complex molecule featuring a central bicyclic core (a 6-membered ring fused to a 5-membered ring, both containing nitrogen atoms). The 6-membered ring is substituted with a 4-methoxyphenyl group (via a carbonyl linkage) and a 4-methoxyphenyl group (via a carbonyl linkage). The 5-membered ring is substituted with a 4-methoxyphenyl group (via a carbonyl linkage) and a 4-methoxyphenyl group (via a carbonyl linkage). The 6-membered ring is also substituted with a 4-methoxyphenyl group (via a carbonyl linkage) and a 4-methoxyphenyl group (via a carbonyl linkage). The 5-membered ring is substituted with a 4-methoxyphenyl group (via a carbonyl linkage) and a 4-methoxyphenyl group (via a carbonyl linkage).
I-192	 Chemical structure of I-192: A complex molecule featuring a central bicyclic core (a 6-membered ring fused to a 5-membered ring, both containing nitrogen atoms). The 6-membered ring is substituted with a 4-methoxyphenyl group (via a carbonyl linkage) and a 4-methoxyphenyl group (via a carbonyl linkage). The 5-membered ring is substituted with a 4-methoxyphenyl group (via a carbonyl linkage) and a 4-methoxyphenyl group (via a carbonyl linkage). The 6-membered ring is also substituted with a 4-methoxyphenyl group (via a carbonyl linkage) and a 4-methoxyphenyl group (via a carbonyl linkage). The 5-membered ring is substituted with a 4-methoxyphenyl group (via a carbonyl linkage) and a 4-methoxyphenyl group (via a carbonyl linkage).
I-193	 Chemical structure of I-193: A complex molecule featuring a central bicyclic core (a 6-membered ring fused to a 5-membered ring, both containing nitrogen atoms). The 6-membered ring is substituted with a 4-methoxyphenyl group (via a carbonyl linkage) and a 4-methoxyphenyl group (via a carbonyl linkage). The 5-membered ring is substituted with a 4-methoxyphenyl group (via a carbonyl linkage) and a 4-methoxyphenyl group (via a carbonyl linkage). The 6-membered ring is also substituted with a 4-methoxyphenyl group (via a carbonyl linkage) and a 4-methoxyphenyl group (via a carbonyl linkage). The 5-membered ring is substituted with a 4-methoxyphenyl group (via a carbonyl linkage) and a 4-methoxyphenyl group (via a carbonyl linkage).

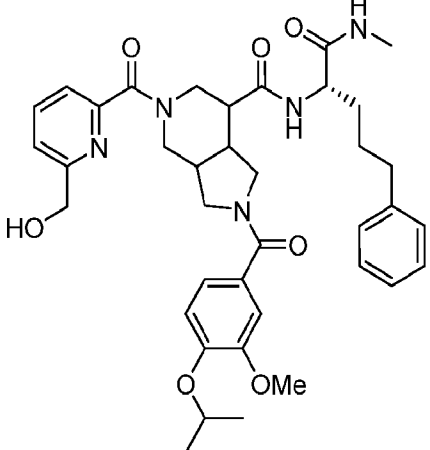
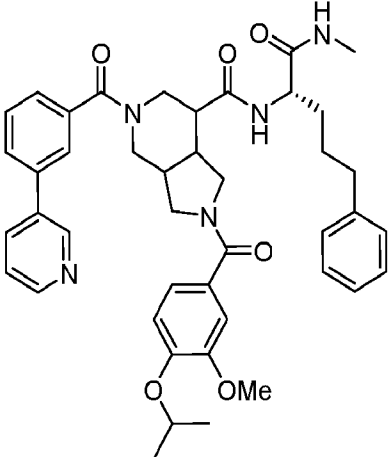
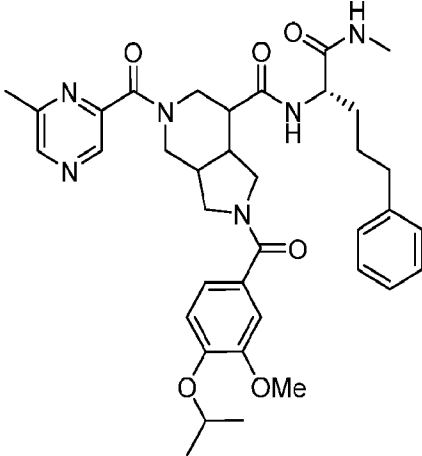
#	Structure
I-194	 Chemical structure of I-194: A complex molecule featuring a pyrimidine ring system connected via a carbonyl group to a piperidine ring. The piperidine ring is further substituted with a carbonyl group linked to a pyrrolidine ring, which is in turn connected to a carbonyl group linked to a benzene ring. The benzene ring has a methoxy group (OMe) and an isopropoxy group. The piperidine ring is also substituted with a carbonyl group linked to a chiral center, which is further substituted with a benzyl group and a methyl group. First eluting diastereomer
I-195	 Chemical structure of I-195: A complex molecule featuring a pyrimidine ring system connected via a carbonyl group to a piperidine ring. The piperidine ring is further substituted with a carbonyl group linked to a pyrrolidine ring, which is in turn connected to a carbonyl group linked to a benzene ring. The benzene ring has a methoxy group (OMe) and an isopropoxy group. The piperidine ring is also substituted with a carbonyl group linked to a chiral center, which is further substituted with a benzyl group and a methyl group. Second eluting diastereomer
I-196	 Chemical structure of I-196: A complex molecule featuring a pyrimidine ring system connected via a carbonyl group to a piperidine ring. The piperidine ring is further substituted with a carbonyl group linked to a pyrrolidine ring, which is in turn connected to a carbonyl group linked to a benzene ring. The benzene ring has a methoxy group (OMe) and an isopropoxy group. The piperidine ring is also substituted with a carbonyl group linked to a chiral center, which is further substituted with a benzyl group and a methyl group.

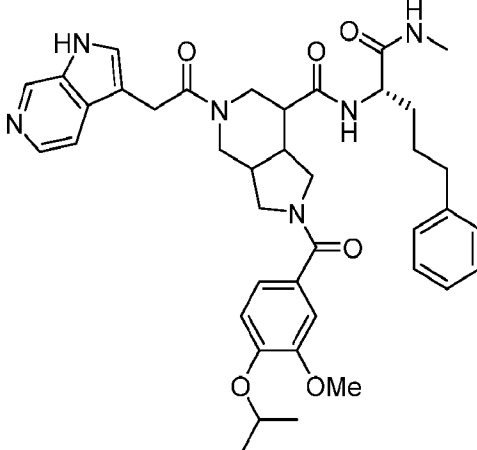
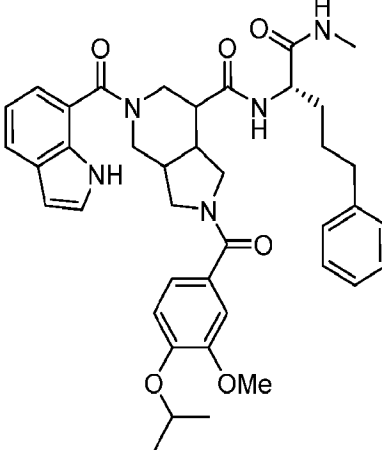
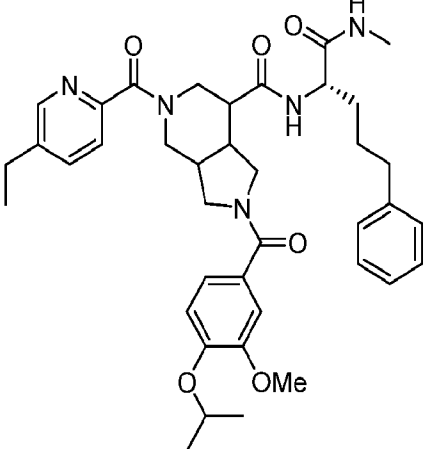
#	Structure
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I-198	
I-199	

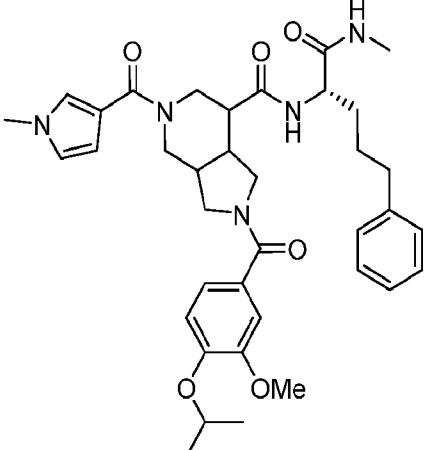
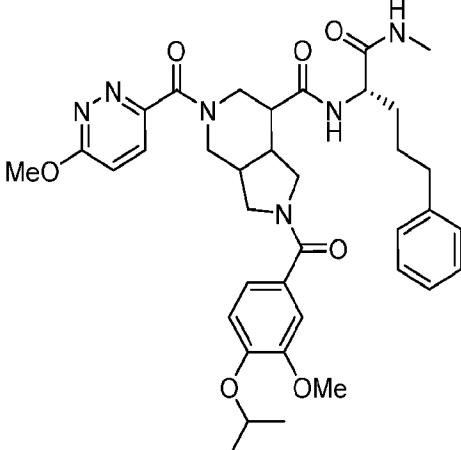
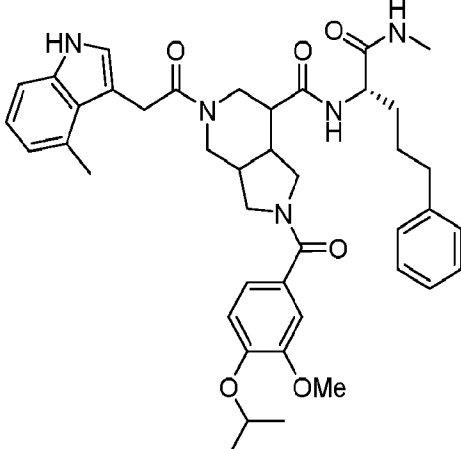
#	Structure
I-200	 Chemical structure of compound I-200. It features a 4-methoxyphenyl group attached to a 1,2,3,4-tetrahydropyridine ring. The tetrahydropyridine ring is substituted with a 4-methoxyphenyl group, a 4-methoxyphenyl group, and a 4-methoxyphenyl group. The structure also includes a 4-methoxyphenyl group, a 4-methoxyphenyl group, and a 4-methoxyphenyl group.
I-201	 Chemical structure of compound I-201. It features a 4-methoxyphenyl group attached to a 1,2,3,4-tetrahydropyridine ring. The tetrahydropyridine ring is substituted with a 4-methoxyphenyl group, a 4-methoxyphenyl group, and a 4-methoxyphenyl group. The structure also includes a 4-methoxyphenyl group, a 4-methoxyphenyl group, and a 4-methoxyphenyl group.
I-202	 Chemical structure of compound I-202. It features a 4-methoxyphenyl group attached to a 1,2,3,4-tetrahydropyridine ring. The tetrahydropyridine ring is substituted with a 4-methoxyphenyl group, a 4-methoxyphenyl group, and a 4-methoxyphenyl group. The structure also includes a 4-methoxyphenyl group, a 4-methoxyphenyl group, and a 4-methoxyphenyl group.

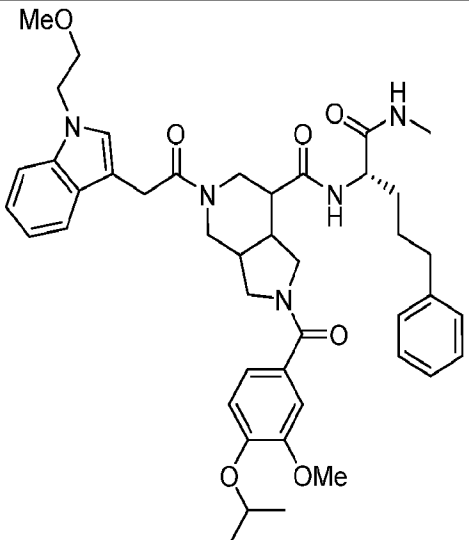
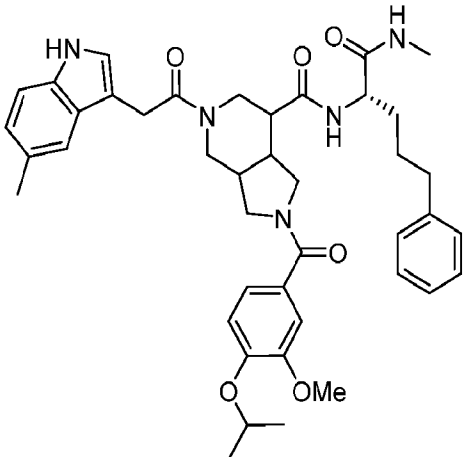
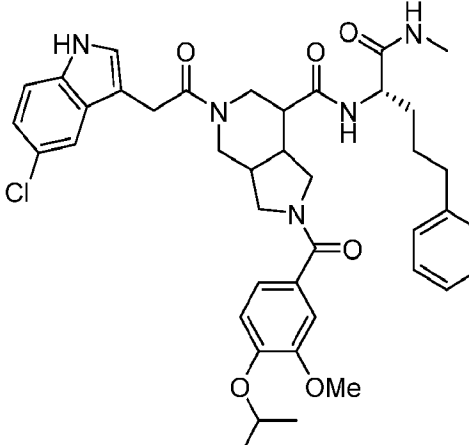
#	Structure
I-203	 Chemical structure of compound I-203. It features a bicyclic core consisting of a 6-membered ring fused to a 5-membered ring, both containing nitrogen atoms. The 6-membered ring is substituted with a 4-cyano-1H-indol-3-ylmethyl group and a 2-methoxy-4-(isopropoxy)phenyl group. The 5-membered ring is substituted with a 2-methoxy-4-(isopropoxy)phenyl group and a 2-methoxy-4-(isopropoxy)phenyl group. The 6-membered ring is also substituted with a 2-methoxy-4-(isopropoxy)phenyl group. The 5-membered ring is substituted with a 2-methoxy-4-(isopropoxy)phenyl group.
I-204	 Chemical structure of compound I-204. It features a bicyclic core consisting of a 6-membered ring fused to a 5-membered ring, both containing nitrogen atoms. The 6-membered ring is substituted with a 4-chloro-2-furylmethyl group and a 2-methoxy-4-(isopropoxy)phenyl group. The 5-membered ring is substituted with a 2-methoxy-4-(isopropoxy)phenyl group and a 2-methoxy-4-(isopropoxy)phenyl group. The 6-membered ring is also substituted with a 2-methoxy-4-(isopropoxy)phenyl group. The 5-membered ring is substituted with a 2-methoxy-4-(isopropoxy)phenyl group.
I-205	 Chemical structure of compound I-205. It features a bicyclic core consisting of a 6-membered ring fused to a 5-membered ring, both containing nitrogen atoms. The 6-membered ring is substituted with a 4-chloro-1H-indol-3-ylmethyl group and a 2-methoxy-4-(isopropoxy)phenyl group. The 5-membered ring is substituted with a 2-methoxy-4-(isopropoxy)phenyl group and a 2-methoxy-4-(isopropoxy)phenyl group. The 6-membered ring is also substituted with a 2-methoxy-4-(isopropoxy)phenyl group. The 5-membered ring is substituted with a 2-methoxy-4-(isopropoxy)phenyl group.

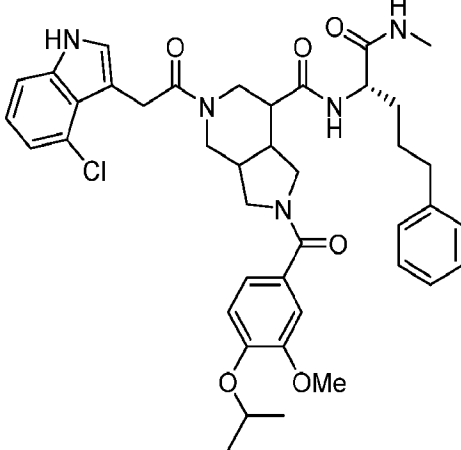
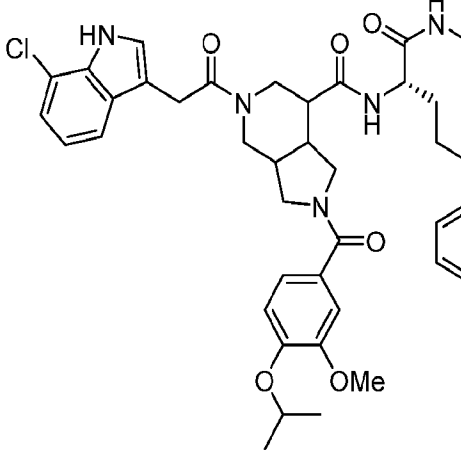
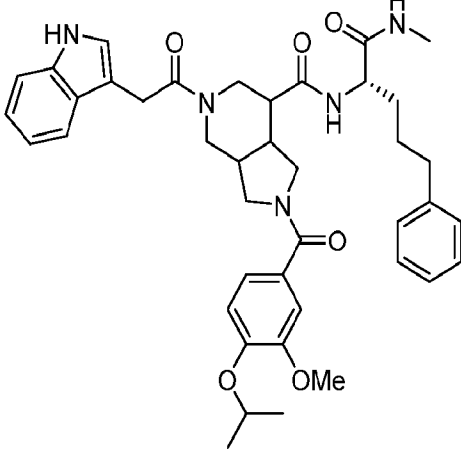
#	Structure
I-206	 Chemical structure of I-206: A bicyclic core (6,7,8,9-tetrahydro-5H-benz[5,6]cyclohepta[1,2-b]pyridine) substituted with a thiazole-2-carbonyl group at position 2, a (4-methoxy-2-isopropoxyphenyl)carbonyl group at position 4, and a (1-methyl-2-phenylethyl)carbamoyl group at position 5. The stereochemistry at the chiral center is (S).
I-207	 Chemical structure of I-207: A bicyclic core (6,7,8,9-tetrahydro-5H-benz[5,6]cyclohepta[1,2-b]pyridine) substituted with a (4-methoxy-2-isopropoxyphenyl)carbonyl group at position 4, a (4-methoxy-2-isopropoxyphenyl)carbonyl group at position 5, and a (1-methyl-2-phenylethyl)carbamoyl group at position 6. The stereochemistry at the chiral center is (S).
I-208	 Chemical structure of I-208: A bicyclic core (6,7,8,9-tetrahydro-5H-benz[5,6]cyclohepta[1,2-b]pyridine) substituted with a (4-methoxy-2-isopropoxyphenyl)carbonyl group at position 4, a (4-methoxy-2-isopropoxyphenyl)carbonyl group at position 5, and a (1-methyl-2-phenylethyl)carbamoyl group at position 6. The stereochemistry at the chiral center is (S).

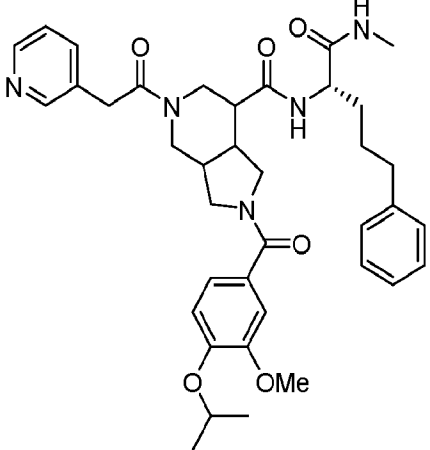
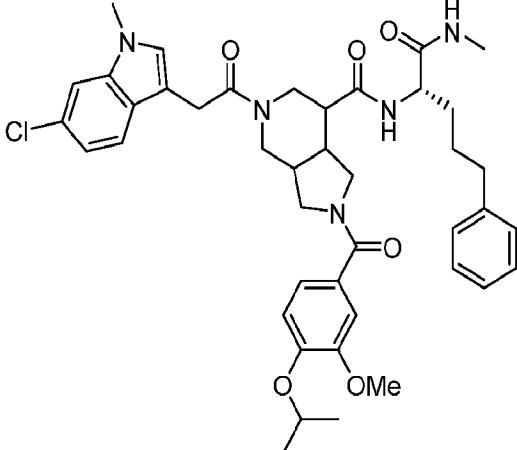
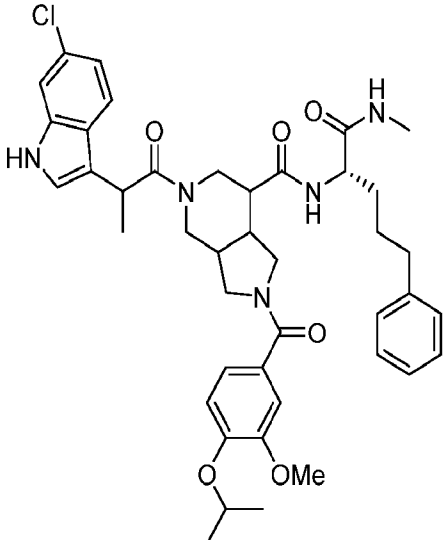
#	Structure
I-209	 Chemical structure of compound I-209. It features a bicyclic core consisting of a 6-membered ring fused to a 5-membered ring, both containing nitrogen atoms. The 6-membered ring is substituted with a pyridine-2-ylmethyl group (HO-CH₂-C₅H₄N) and a (3-methoxy-4-isopropoxyphenyl)carbamoyl group (-C(=O)-NH-CH(CH₃)-CH₂-CH₂-C₆H₅). The 5-membered ring is substituted with a (3-methoxy-4-isopropoxyphenyl)carbamoyl group (-C(=O)-NH-CH(CH₃)-CH₂-CH₂-C₆H₅) and a (3-methoxy-4-isopropoxyphenyl)carbamoyl group (-C(=O)-NH-CH(CH₃)-CH₂-CH₂-C₆H₅).
I-210	 Chemical structure of compound I-210. It features a bicyclic core consisting of a 6-membered ring fused to a 5-membered ring, both containing nitrogen atoms. The 6-membered ring is substituted with a (3-methoxy-4-isopropoxyphenyl)carbamoyl group (-C(=O)-NH-CH(CH₃)-CH₂-CH₂-C₆H₅) and a (3-methoxy-4-isopropoxyphenyl)carbamoyl group (-C(=O)-NH-CH(CH₃)-CH₂-CH₂-C₆H₅). The 5-membered ring is substituted with a (3-methoxy-4-isopropoxyphenyl)carbamoyl group (-C(=O)-NH-CH(CH₃)-CH₂-CH₂-C₆H₅) and a (3-methoxy-4-isopropoxyphenyl)carbamoyl group (-C(=O)-NH-CH(CH₃)-CH₂-CH₂-C₆H₅).
I-211	 Chemical structure of compound I-211. It features a bicyclic core consisting of a 6-membered ring fused to a 5-membered ring, both containing nitrogen atoms. The 6-membered ring is substituted with a (3-methoxy-4-isopropoxyphenyl)carbamoyl group (-C(=O)-NH-CH(CH₃)-CH₂-CH₂-C₆H₅) and a (3-methoxy-4-isopropoxyphenyl)carbamoyl group (-C(=O)-NH-CH(CH₃)-CH₂-CH₂-C₆H₅). The 5-membered ring is substituted with a (3-methoxy-4-isopropoxyphenyl)carbamoyl group (-C(=O)-NH-CH(CH₃)-CH₂-CH₂-C₆H₅) and a (3-methoxy-4-isopropoxyphenyl)carbamoyl group (-C(=O)-NH-CH(CH₃)-CH₂-CH₂-C₆H₅).

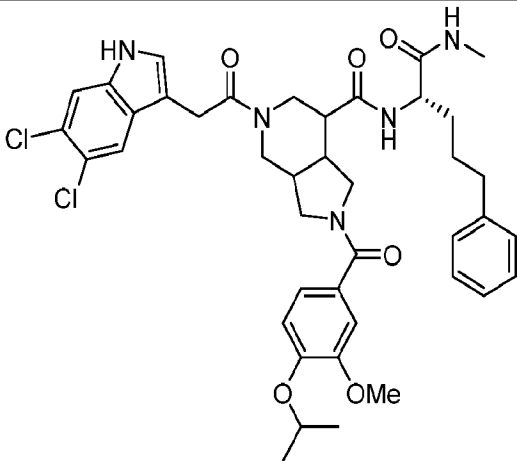
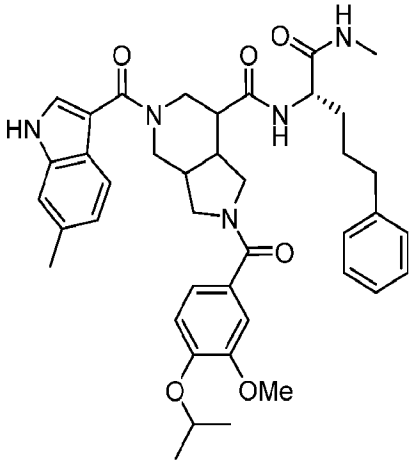
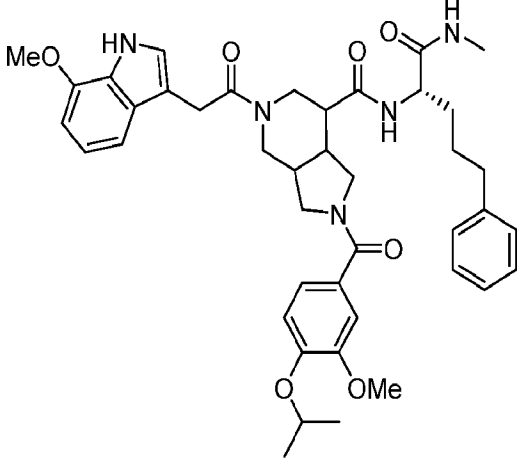
#	Structure
I-212	 Chemical structure of compound I-212. It features a bicyclic core consisting of a 6-membered ring and a 5-membered ring, both containing nitrogen atoms. The 6-membered ring is substituted with a 2-pyridylmethyl group via a carbonyl linkage and a 2-(4-methoxyphenyl)-2-methylpropanoyl group via a nitrogen atom. The 5-membered ring is substituted with a 2-(4-methoxyphenyl)-2-methylpropanoyl group via a nitrogen atom and a 2-(4-methoxyphenyl)-2-methylpropanoyl group via a carbonyl linkage. A 2-(4-methoxyphenyl)-2-methylpropanoyl group is also attached to the 5-membered ring via a carbonyl linkage. A 2-(4-methoxyphenyl)-2-methylpropanoyl group is attached to the 6-membered ring via a carbonyl linkage. A 2-(4-methoxyphenyl)-2-methylpropanoyl group is attached to the 5-membered ring via a carbonyl linkage. A 2-(4-methoxyphenyl)-2-methylpropanoyl group is attached to the 6-membered ring via a carbonyl linkage.
I-213	 Chemical structure of compound I-213. It features a bicyclic core consisting of a 6-membered ring and a 5-membered ring, both containing nitrogen atoms. The 6-membered ring is substituted with a 2-pyridylmethyl group via a carbonyl linkage and a 2-(4-methoxyphenyl)-2-methylpropanoyl group via a nitrogen atom. The 5-membered ring is substituted with a 2-(4-methoxyphenyl)-2-methylpropanoyl group via a nitrogen atom and a 2-(4-methoxyphenyl)-2-methylpropanoyl group via a carbonyl linkage. A 2-(4-methoxyphenyl)-2-methylpropanoyl group is also attached to the 5-membered ring via a carbonyl linkage. A 2-(4-methoxyphenyl)-2-methylpropanoyl group is attached to the 6-membered ring via a carbonyl linkage. A 2-(4-methoxyphenyl)-2-methylpropanoyl group is attached to the 5-membered ring via a carbonyl linkage. A 2-(4-methoxyphenyl)-2-methylpropanoyl group is attached to the 6-membered ring via a carbonyl linkage.
I-214	 Chemical structure of compound I-214. It features a bicyclic core consisting of a 6-membered ring and a 5-membered ring, both containing nitrogen atoms. The 6-membered ring is substituted with a 2-pyridylmethyl group via a carbonyl linkage and a 2-(4-methoxyphenyl)-2-methylpropanoyl group via a nitrogen atom. The 5-membered ring is substituted with a 2-(4-methoxyphenyl)-2-methylpropanoyl group via a nitrogen atom and a 2-(4-methoxyphenyl)-2-methylpropanoyl group via a carbonyl linkage. A 2-(4-methoxyphenyl)-2-methylpropanoyl group is also attached to the 5-membered ring via a carbonyl linkage. A 2-(4-methoxyphenyl)-2-methylpropanoyl group is attached to the 6-membered ring via a carbonyl linkage. A 2-(4-methoxyphenyl)-2-methylpropanoyl group is attached to the 5-membered ring via a carbonyl linkage. A 2-(4-methoxyphenyl)-2-methylpropanoyl group is attached to the 6-membered ring via a carbonyl linkage.

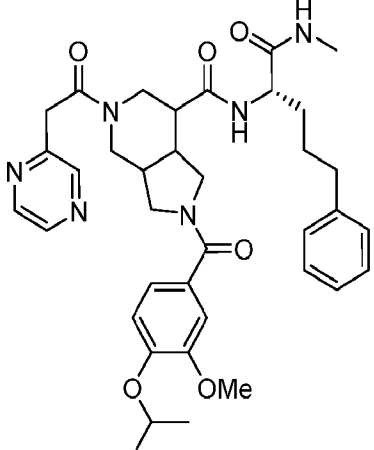
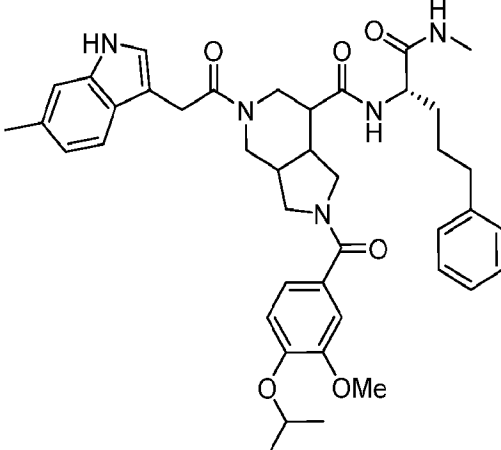
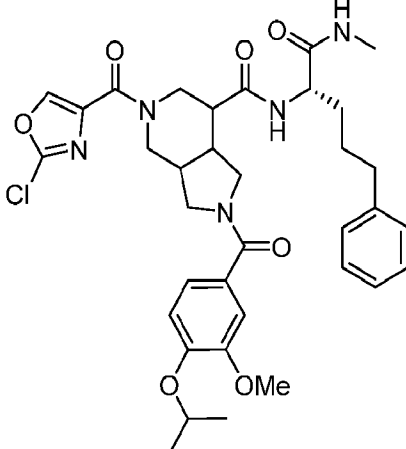
#	Structure
I-215	 Chemical structure of compound I-215. It features a bicyclic core consisting of a 6-membered ring fused to a 5-membered ring, both containing nitrogen atoms. The 6-membered ring is substituted with a 4-methyl-1H-pyridine-2-carbonyl group and a (2-methoxy-4-isopropoxyphenyl)carbonyl group. The 5-membered ring is substituted with a (2-methoxy-4-isopropoxyphenyl)carbonyl group and a (2-methoxy-4-isopropoxyphenyl)carbonyl group. A side chain is attached to the 6-membered ring, consisting of a (2-methoxy-4-isopropoxyphenyl)carbonyl group and a (2-methoxy-4-isopropoxyphenyl)carbonyl group.
I-216	 Chemical structure of compound I-216. It features a bicyclic core consisting of a 6-membered ring fused to a 5-membered ring, both containing nitrogen atoms. The 6-membered ring is substituted with a 4-methoxy-2-pyridyl group and a (2-methoxy-4-isopropoxyphenyl)carbonyl group. The 5-membered ring is substituted with a (2-methoxy-4-isopropoxyphenyl)carbonyl group and a (2-methoxy-4-isopropoxyphenyl)carbonyl group. A side chain is attached to the 6-membered ring, consisting of a (2-methoxy-4-isopropoxyphenyl)carbonyl group and a (2-methoxy-4-isopropoxyphenyl)carbonyl group.
I-217	 Chemical structure of compound I-217. It features a bicyclic core consisting of a 6-membered ring fused to a 5-membered ring, both containing nitrogen atoms. The 6-membered ring is substituted with a 4-methyl-1H-indol-3-ylmethyl group and a (2-methoxy-4-isopropoxyphenyl)carbonyl group. The 5-membered ring is substituted with a (2-methoxy-4-isopropoxyphenyl)carbonyl group and a (2-methoxy-4-isopropoxyphenyl)carbonyl group. A side chain is attached to the 6-membered ring, consisting of a (2-methoxy-4-isopropoxyphenyl)carbonyl group and a (2-methoxy-4-isopropoxyphenyl)carbonyl group.

#	Structure
I-218	 Chemical structure of compound I-218. It features a 2-methoxyethyl group attached to an indole ring. The indole ring is connected via a methylene group to a carbonyl group, which is part of a piperidine ring system. The piperidine ring is further substituted with a carbonyl group linked to a benzyl group, and another carbonyl group linked to a chiral center. The chiral center is also substituted with a methyl group and a benzyl group. The piperidine ring is also substituted with a carbonyl group linked to a benzyl group.
I-219	 Chemical structure of compound I-219. It features a 2-methoxyethyl group attached to an indole ring. The indole ring is connected via a methylene group to a carbonyl group, which is part of a piperidine ring system. The piperidine ring is further substituted with a carbonyl group linked to a benzyl group, and another carbonyl group linked to a chiral center. The chiral center is also substituted with a methyl group and a benzyl group. The piperidine ring is also substituted with a carbonyl group linked to a benzyl group.
I-220	 Chemical structure of compound I-220. It features a 2-methoxyethyl group attached to an indole ring. The indole ring is connected via a methylene group to a carbonyl group, which is part of a piperidine ring system. The piperidine ring is further substituted with a carbonyl group linked to a benzyl group, and another carbonyl group linked to a chiral center. The chiral center is also substituted with a methyl group and a benzyl group. The piperidine ring is also substituted with a carbonyl group linked to a benzyl group.

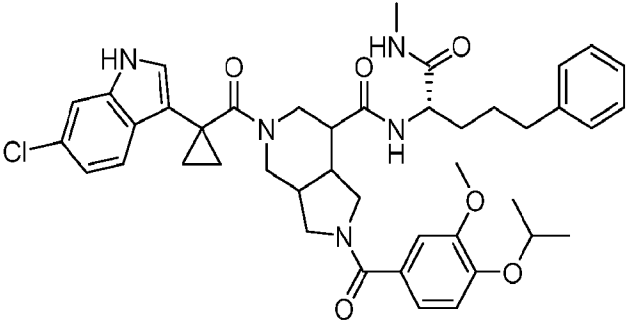
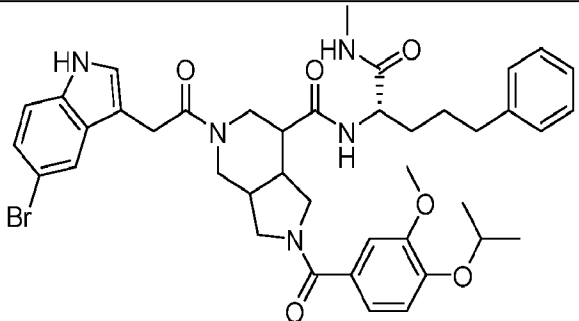
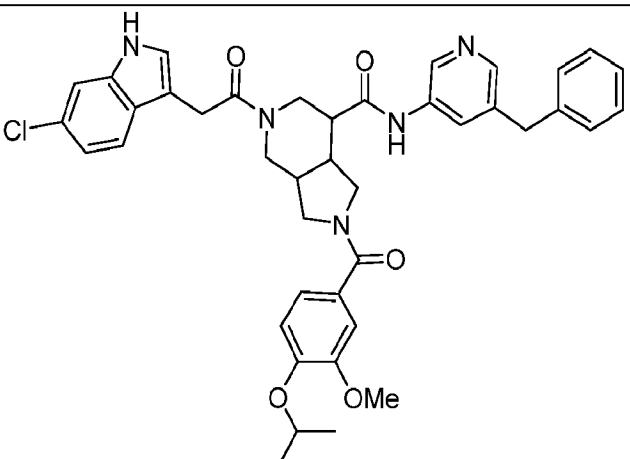
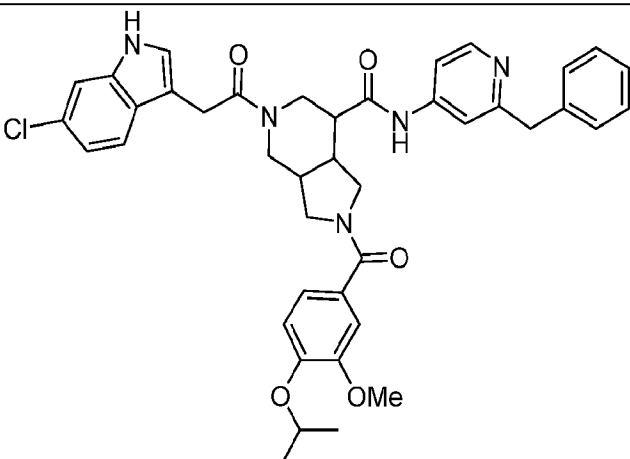
#	Structure
I-221	 Chemical structure of compound I-221. It features a 5-chloro-1H-indol-3-yl group connected via a methylene group to a carbonyl group. This carbonyl is part of a piperidine ring system. The piperidine ring is substituted with a 4-(4-methoxy-2-isopropoxyphenyl) group and a 2-(4-methoxy-2-isopropoxyphenyl) group. The piperidine ring is also connected to a carbonyl group, which is part of a side chain containing a benzyl group and a dimethylamino group.
I-222	 Chemical structure of compound I-222. It is similar to I-221, but the chlorine atom is at the 6-position of the indole ring.
I-223	 Chemical structure of compound I-223. It is similar to I-221, but the chlorine atom is at the 7-position of the indole ring.

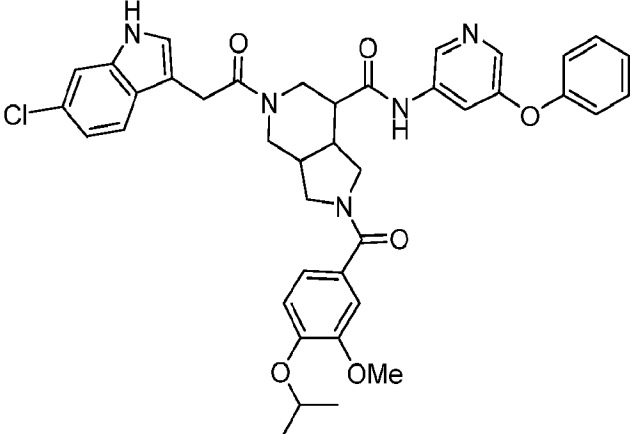
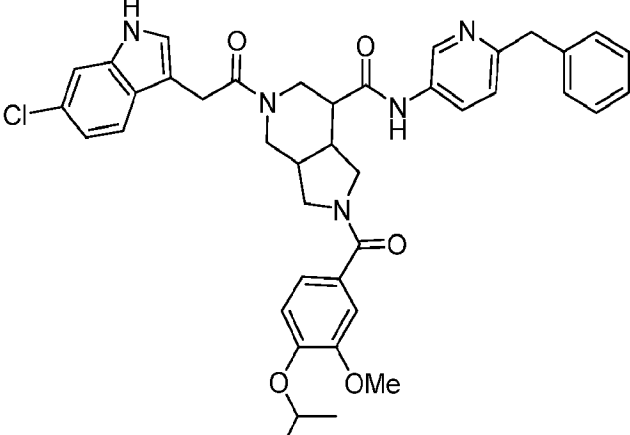
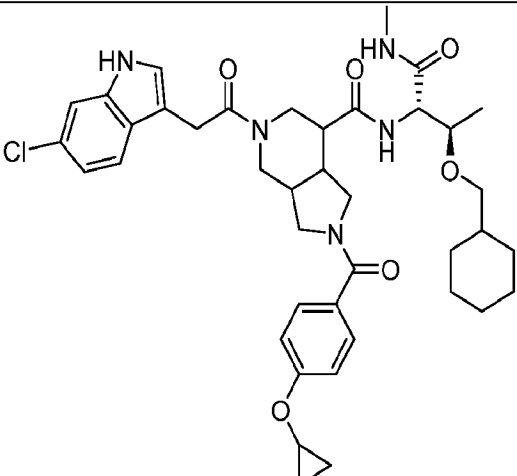
#	Structure
I-224	 Chemical structure of I-224: A bicyclic core (a 6-membered ring fused to a 5-membered ring, both containing a nitrogen atom) is substituted with a 4-pyridylmethyl ketone group on the 6-membered ring, a 3-(4-methoxyphenyl)propanoyl group on the 5-membered ring, and a 2-methyl-3-phenylpropanamide group on the 6-membered ring. The amide group is shown with a dashed bond to the chiral center.
I-225	 Chemical structure of I-225: A bicyclic core (a 6-membered ring fused to a 5-membered ring, both containing a nitrogen atom) is substituted with a 2-(4-chlorophenyl)-1-methyl-1H-indol-3-ylmethyl ketone group on the 6-membered ring, a 3-(4-methoxyphenyl)propanoyl group on the 5-membered ring, and a 2-methyl-3-phenylpropanamide group on the 6-membered ring. The amide group is shown with a dashed bond to the chiral center.
I-226	 Chemical structure of I-226: A bicyclic core (a 6-membered ring fused to a 5-membered ring, both containing a nitrogen atom) is substituted with a 2-(4-chlorophenyl)-1H-indol-3-ylmethyl ketone group on the 6-membered ring, a 3-(4-methoxyphenyl)propanoyl group on the 5-membered ring, and a 2-methyl-3-phenylpropanamide group on the 6-membered ring. The amide group is shown with a dashed bond to the chiral center.

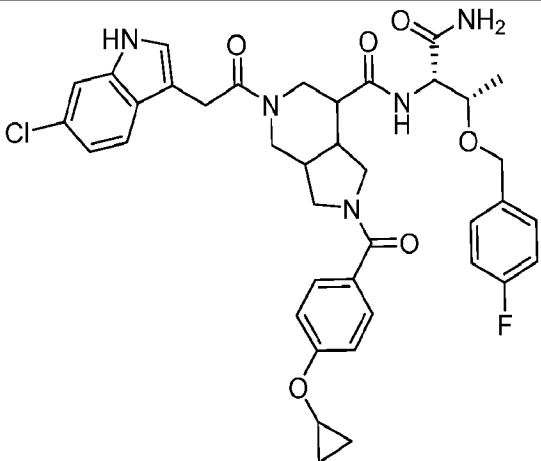
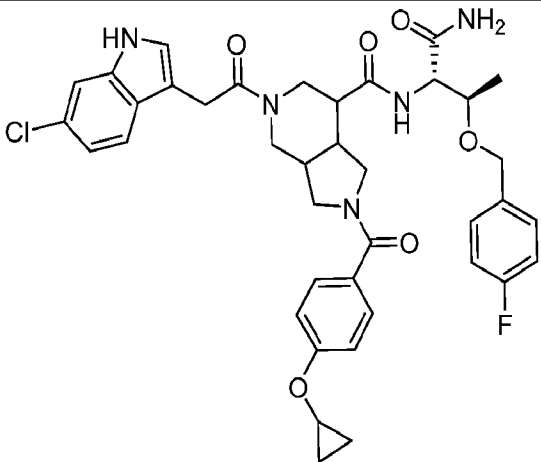
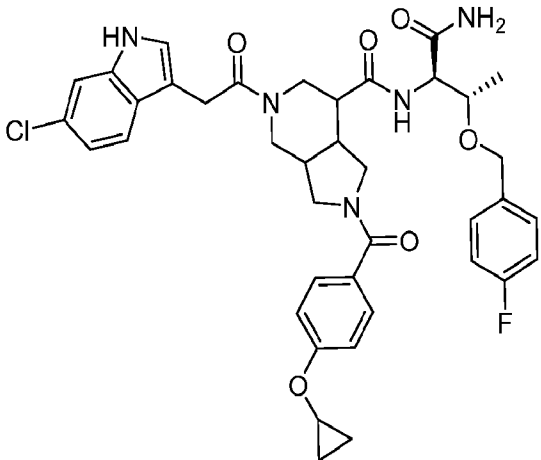
#	Structure
I-227	 Chemical structure of I-227: A complex molecule featuring a 2,6-dichlorophenyl group attached to an indole ring, which is linked via a methylene group to a carbonyl group. This carbonyl is part of a bicyclic system (a 6-membered ring fused to a 5-membered ring) containing a nitrogen atom. The nitrogen is also part of a carbamate group, which is further substituted with a 4-methoxyphenyl group and a 2-methoxyphenyl group. The carbamate group is also linked to a 2-phenylethyl group via a chiral center.
I-228	 Chemical structure of I-228: A complex molecule featuring a 4-methylphenyl group attached to an indole ring, which is linked via a methylene group to a carbonyl group. This carbonyl is part of a bicyclic system (a 6-membered ring fused to a 5-membered ring) containing a nitrogen atom. The nitrogen is also part of a carbamate group, which is further substituted with a 4-methoxyphenyl group and a 2-methoxyphenyl group. The carbamate group is also linked to a 2-phenylethyl group via a chiral center.
I-229	 Chemical structure of I-229: A complex molecule featuring a 4-methoxyphenyl group attached to an indole ring, which is linked via a methylene group to a carbonyl group. This carbonyl is part of a bicyclic system (a 6-membered ring fused to a 5-membered ring) containing a nitrogen atom. The nitrogen is also part of a carbamate group, which is further substituted with a 4-methoxyphenyl group and a 2-methoxyphenyl group. The carbamate group is also linked to a 2-phenylethyl group via a chiral center.

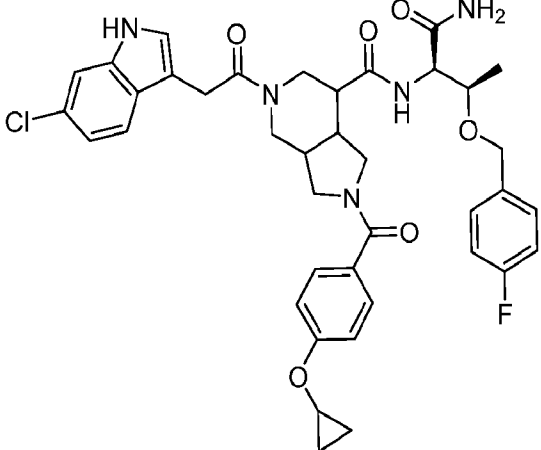
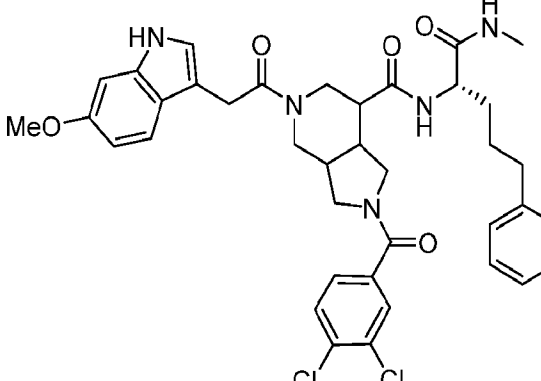
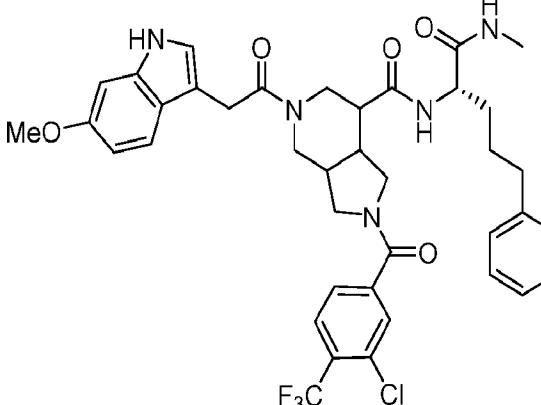
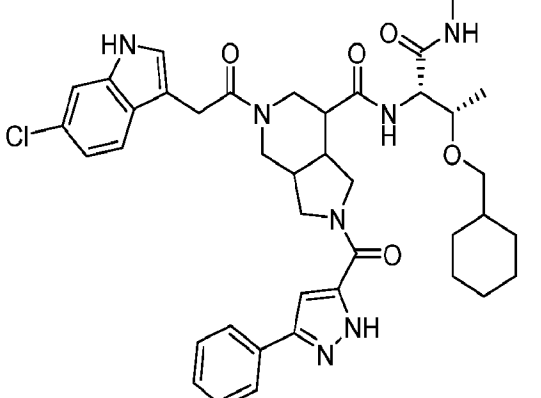
#	Structure
I-230	
I-231	
I-232	 First eluting diastereomer

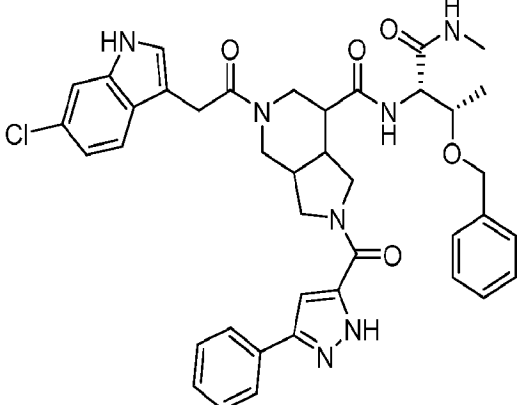
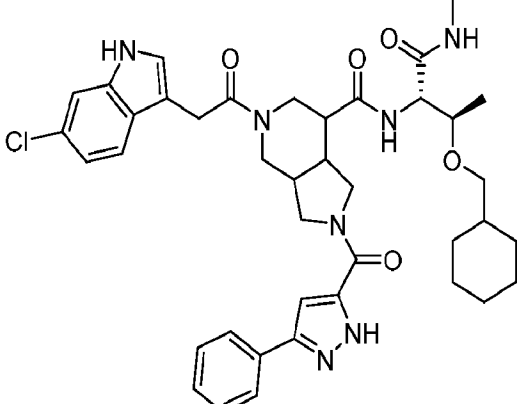
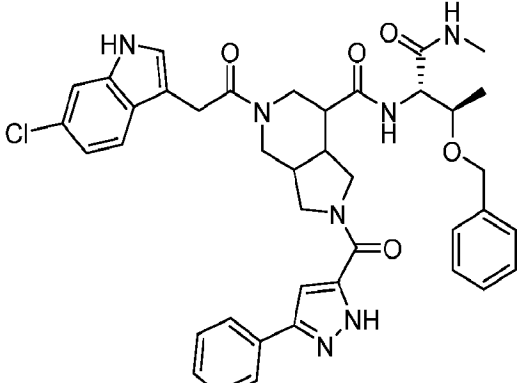
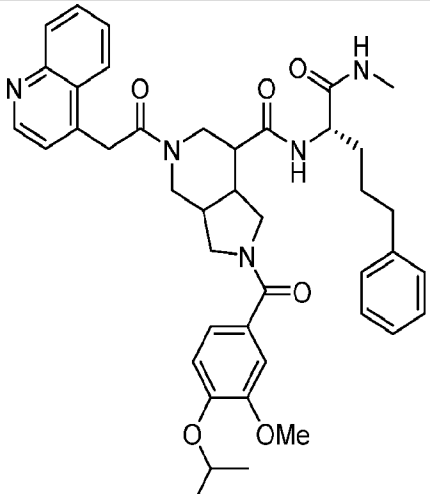
#	Structure
I-233	Second eluting diastereomer
I-234	Second eluting diastereomer
I-235	Second eluting diastereomer

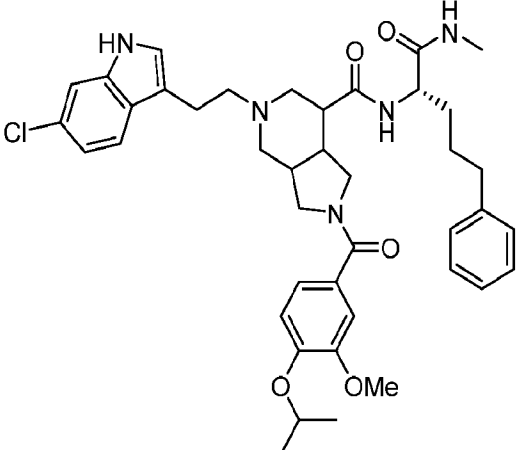
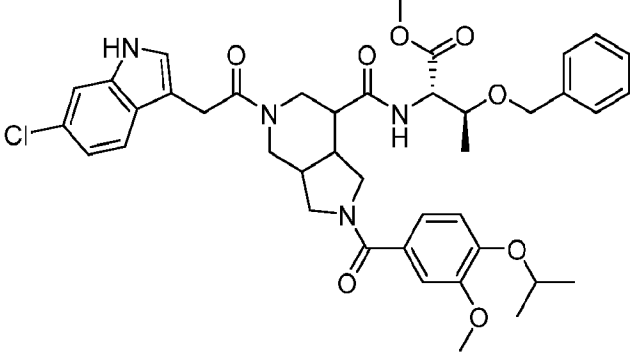
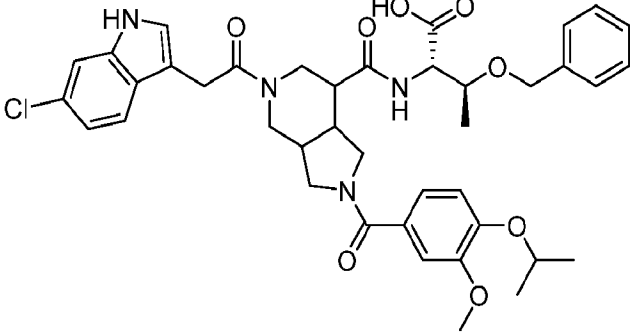
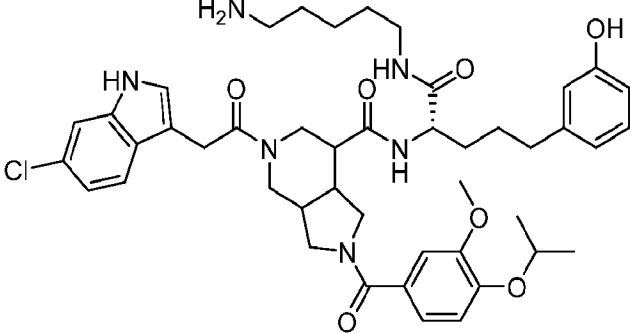
#	Structure
I-236	 Chemical structure of I-236: A complex molecule featuring a 4-chloro-1H-indol-3-yl group connected via a carbonyl to a bicyclic amine system. The bicyclic amine is further substituted with a 4-((4-methoxy-2-isopropoxyphenyl)carbamoyl)pyrrolidine-1-carboxamide group and a 4-((4-methoxy-2-isopropoxyphenyl)carbamoyl)pyrrolidine-1-carboxamide group. The molecule also contains a 4-((4-methoxy-2-isopropoxyphenyl)carbamoyl)pyrrolidine-1-carboxamide group.
I-237	 Chemical structure of I-237: A complex molecule featuring a 4-bromo-1H-indol-3-yl group connected via a carbonyl to a bicyclic amine system. The bicyclic amine is further substituted with a 4-((4-methoxy-2-isopropoxyphenyl)carbamoyl)pyrrolidine-1-carboxamide group and a 4-((4-methoxy-2-isopropoxyphenyl)carbamoyl)pyrrolidine-1-carboxamide group. The molecule also contains a 4-((4-methoxy-2-isopropoxyphenyl)carbamoyl)pyrrolidine-1-carboxamide group.
I-238	 Chemical structure of I-238: A complex molecule featuring a 4-chloro-1H-indol-3-yl group connected via a carbonyl to a bicyclic amine system. The bicyclic amine is further substituted with a 4-((4-methoxy-2-isopropoxyphenyl)carbamoyl)pyrrolidine-1-carboxamide group and a 4-((4-methoxy-2-isopropoxyphenyl)carbamoyl)pyrrolidine-1-carboxamide group. The molecule also contains a 4-((4-methoxy-2-isopropoxyphenyl)carbamoyl)pyrrolidine-1-carboxamide group.
I-239	 Chemical structure of I-239: A complex molecule featuring a 4-chloro-1H-indol-3-yl group connected via a carbonyl to a bicyclic amine system. The bicyclic amine is further substituted with a 4-((4-methoxy-2-isopropoxyphenyl)carbamoyl)pyrrolidine-1-carboxamide group and a 4-((4-methoxy-2-isopropoxyphenyl)carbamoyl)pyrrolidine-1-carboxamide group. The molecule also contains a 4-((4-methoxy-2-isopropoxyphenyl)carbamoyl)pyrrolidine-1-carboxamide group.

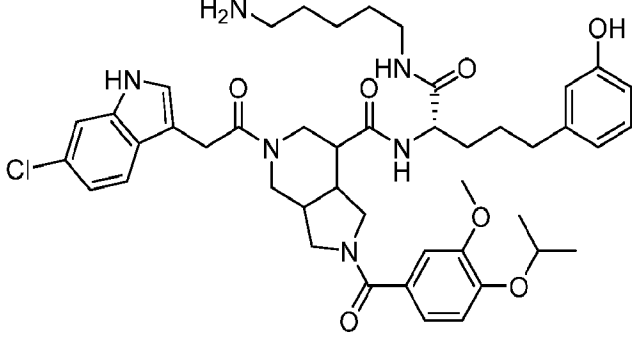
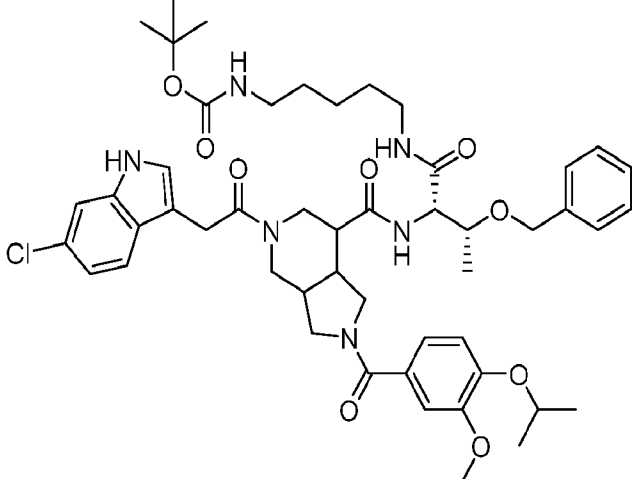
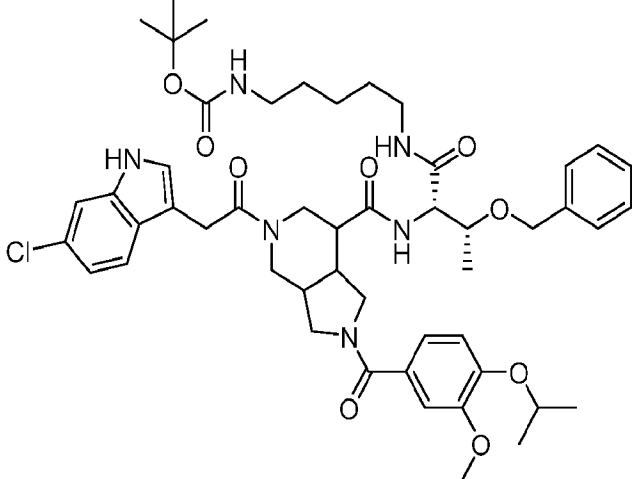
#	Structure
I-240	
I-241	
I-242	

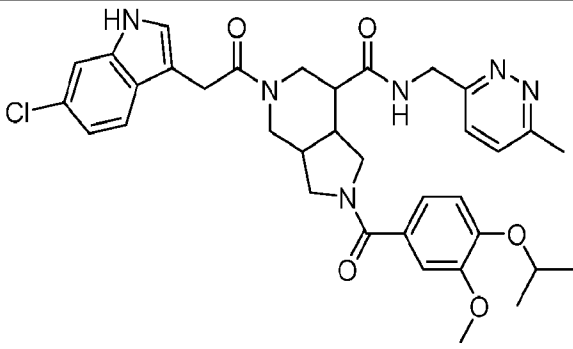
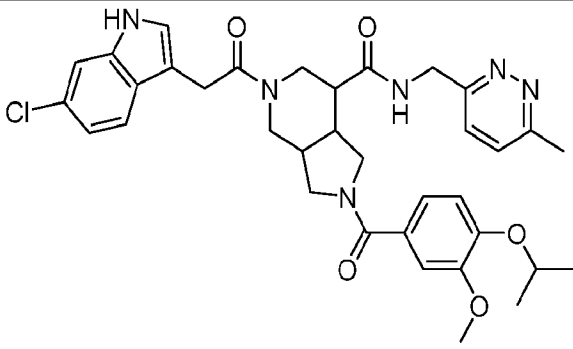
#	Structure
I-243	 Chemical structure of I-243: A complex molecule featuring a 4-chloro-1H-indol-3-yl group connected via a methylene group to a carbonyl group. This carbonyl is part of a bicyclic system (a 6-membered ring fused to a 5-membered ring, both containing nitrogen). The 6-membered ring is also connected to another carbonyl group, which is further connected to a chiral center. This chiral center has a methyl group (wedge), a 4-fluorophenylmethoxy group (dash), and an amide group (-NH-C(=O)-NH₂). The 5-membered ring of the bicyclic system is connected to a carbonyl group, which is further connected to a 4-(cyclopropyloxy)phenyl group.
I-244	 Chemical structure of I-244: Similar to I-243, but the chiral center has a methyl group (wedge) and a 4-fluorophenylmethoxy group (wedge) instead of a dash.
I-245	 Chemical structure of I-245: Similar to I-243, but the chiral center has a methyl group (dash) and a 4-fluorophenylmethoxy group (dash) instead of a wedge.

#	Structure
I-246	 Chemical structure of I-246: A complex molecule featuring a 4-chloro-1H-indol-3-yl group connected via a methylene group to a carbonyl group. This carbonyl is part of a bicyclic system (a 6-membered ring fused to a 5-membered ring, both containing nitrogen). The 6-membered ring is also connected to another carbonyl group, which is further connected to a chiral center. This chiral center has a methyl group, an amino group (NH₂), and a 4-fluorobenzyl group. The 5-membered ring of the bicyclic system is connected to a carbonyl group, which is further connected to a 4-(cyclopropyloxy)phenyl group.
I-247	 Chemical structure of I-247: A complex molecule featuring a 4-methoxy-1H-indol-3-yl group connected via a methylene group to a carbonyl group. This carbonyl is part of a bicyclic system (a 6-membered ring fused to a 5-membered ring, both containing nitrogen). The 6-membered ring is also connected to another carbonyl group, which is further connected to a chiral center. This chiral center has a methyl group, a dimethylamino group (NHMe₂), and a 3-phenylpropyl group. The 5-membered ring of the bicyclic system is connected to a carbonyl group, which is further connected to a 2,4-dichlorophenyl group.
I-248	 Chemical structure of I-248: A complex molecule featuring a 4-methoxy-1H-indol-3-yl group connected via a methylene group to a carbonyl group. This carbonyl is part of a bicyclic system (a 6-membered ring fused to a 5-membered ring, both containing nitrogen). The 6-membered ring is also connected to another carbonyl group, which is further connected to a chiral center. This chiral center has a methyl group, a dimethylamino group (NHMe₂), and a 3-phenylpropyl group. The 5-membered ring of the bicyclic system is connected to a carbonyl group, which is further connected to a 2-chloro-4-(trifluoromethyl)phenyl group.
I-249	 Chemical structure of I-249: A complex molecule featuring a 4-chloro-1H-indol-3-yl group connected via a methylene group to a carbonyl group. This carbonyl is part of a bicyclic system (a 6-membered ring fused to a 5-membered ring, both containing nitrogen). The 6-membered ring is also connected to another carbonyl group, which is further connected to a chiral center. This chiral center has a methyl group, a dimethylamino group (NHMe₂), and a 4-cyclohexylmethoxy group. The 5-membered ring of the bicyclic system is connected to a carbonyl group, which is further connected to a 1-phenyl-1H-tetrazol-5-yl group.

#	Structure
I-250	 Chemical structure of I-250: A complex molecule featuring a 5-chloro-1H-indol-3-yl group connected via a methylene chain to a piperidine ring. The piperidine ring is substituted with a benzyl group and a 1H-tetrazol-5-yl group. The piperidine ring is also connected via a methylene chain to a carbonyl group, which is further connected to a chiral center. The chiral center is substituted with a methyl group, a benzyl group, and a methoxy group.
I-251	 Chemical structure of I-251: A complex molecule featuring a 5-chloro-1H-indol-3-yl group connected via a methylene chain to a piperidine ring. The piperidine ring is substituted with a benzyl group and a 1H-tetrazol-5-yl group. The piperidine ring is also connected via a methylene chain to a carbonyl group, which is further connected to a chiral center. The chiral center is substituted with a methyl group, a benzyl group, and a methoxy group.
I-252	 Chemical structure of I-252: A complex molecule featuring a 5-chloro-1H-indol-3-yl group connected via a methylene chain to a piperidine ring. The piperidine ring is substituted with a benzyl group and a 1H-tetrazol-5-yl group. The piperidine ring is also connected via a methylene chain to a carbonyl group, which is further connected to a chiral center. The chiral center is substituted with a methyl group, a benzyl group, and a methoxy group.
I-253	 Chemical structure of I-253: A complex molecule featuring a 1H-indol-3-yl group connected via a methylene chain to a piperidine ring. The piperidine ring is substituted with a benzyl group and a 1H-tetrazol-5-yl group. The piperidine ring is also connected via a methylene chain to a carbonyl group, which is further connected to a chiral center. The chiral center is substituted with a methyl group, a benzyl group, and a methoxy group.

#	Structure
I-254	 Chemical structure of I-254: A complex molecule featuring a 4-chloro-1H-indol-3-yl group connected via a 2-(2-((4-methoxy-3-(propan-2-yloxy)phenyl)carbamoyl)pyrrolidin-1-yl)ethyl linker to a 2-((4-methoxy-3-(propan-2-yloxy)phenyl)carbamoyl)pyrrolidine ring. This pyrrolidine ring is further substituted with a 2-((4-methoxy-3-(propan-2-yloxy)phenyl)carbamoyl)pyrrolidine-1-yl group and a 2-((4-methoxy-3-(propan-2-yloxy)phenyl)carbamoyl)pyrrolidine-1-yl group. The molecule also contains a 2-((4-methoxy-3-(propan-2-yloxy)phenyl)carbamoyl)pyrrolidine-1-yl group and a 2-((4-methoxy-3-(propan-2-yloxy)phenyl)carbamoyl)pyrrolidine-1-yl group.
I-255	 Chemical structure of I-255: A complex molecule featuring a 4-chloro-1H-indol-3-yl group connected via a 2-(2-((4-methoxy-3-(propan-2-yloxy)phenyl)carbamoyl)pyrrolidin-1-yl)ethyl linker to a 2-((4-methoxy-3-(propan-2-yloxy)phenyl)carbamoyl)pyrrolidine ring. This pyrrolidine ring is further substituted with a 2-((4-methoxy-3-(propan-2-yloxy)phenyl)carbamoyl)pyrrolidine-1-yl group and a 2-((4-methoxy-3-(propan-2-yloxy)phenyl)carbamoyl)pyrrolidine-1-yl group. The molecule also contains a 2-((4-methoxy-3-(propan-2-yloxy)phenyl)carbamoyl)pyrrolidine-1-yl group and a 2-((4-methoxy-3-(propan-2-yloxy)phenyl)carbamoyl)pyrrolidine-1-yl group.
I-256	 Chemical structure of I-256: A complex molecule featuring a 4-chloro-1H-indol-3-yl group connected via a 2-(2-((4-methoxy-3-(propan-2-yloxy)phenyl)carbamoyl)pyrrolidin-1-yl)ethyl linker to a 2-((4-methoxy-3-(propan-2-yloxy)phenyl)carbamoyl)pyrrolidine ring. This pyrrolidine ring is further substituted with a 2-((4-methoxy-3-(propan-2-yloxy)phenyl)carbamoyl)pyrrolidine-1-yl group and a 2-((4-methoxy-3-(propan-2-yloxy)phenyl)carbamoyl)pyrrolidine-1-yl group. The molecule also contains a 2-((4-methoxy-3-(propan-2-yloxy)phenyl)carbamoyl)pyrrolidine-1-yl group and a 2-((4-methoxy-3-(propan-2-yloxy)phenyl)carbamoyl)pyrrolidine-1-yl group.
I-257	 Chemical structure of I-257: A complex molecule featuring a 4-chloro-1H-indol-3-yl group connected via a 2-(2-((4-methoxy-3-(propan-2-yloxy)phenyl)carbamoyl)pyrrolidin-1-yl)ethyl linker to a 2-((4-methoxy-3-(propan-2-yloxy)phenyl)carbamoyl)pyrrolidine ring. This pyrrolidine ring is further substituted with a 2-((4-methoxy-3-(propan-2-yloxy)phenyl)carbamoyl)pyrrolidine-1-yl group and a 2-((4-methoxy-3-(propan-2-yloxy)phenyl)carbamoyl)pyrrolidine-1-yl group. The molecule also contains a 2-((4-methoxy-3-(propan-2-yloxy)phenyl)carbamoyl)pyrrolidine-1-yl group and a 2-((4-methoxy-3-(propan-2-yloxy)phenyl)carbamoyl)pyrrolidine-1-yl group. Synthesized from first eluting intermediate

#	Structure
I-258	 Chemical structure of I-258: A complex molecule featuring a 4-chloro-1H-indol-3-yl group connected via a methylene group to a carbonyl group. This carbonyl is part of a bicyclic system (a 6-membered ring fused to a 5-membered ring containing a nitrogen atom). The nitrogen atom is also connected to a carbonyl group, which is further connected to a chiral center. This chiral center is also connected to a 4-hydroxyphenyl group and a 4-(4-methoxy-2-isopropoxyphenyl) group. The molecule also contains a long alkyl chain with a terminal amino group (H₂N). Synthesized from second eluting intermediate
I-259	 Chemical structure of I-259: A complex molecule featuring a 4-chloro-1H-indol-3-yl group connected via a methylene group to a carbonyl group. This carbonyl is part of a bicyclic system (a 6-membered ring fused to a 5-membered ring containing a nitrogen atom). The nitrogen atom is also connected to a carbonyl group, which is further connected to a chiral center. This chiral center is also connected to a 4-(4-methoxy-2-isopropoxyphenyl) group and a 4-(benzyloxy)phenyl group. The molecule also contains a long alkyl chain with a terminal amino group (H₂N). First eluting diastereomer
I-260	 Chemical structure of I-260: A complex molecule featuring a 4-chloro-1H-indol-3-yl group connected via a methylene group to a carbonyl group. This carbonyl is part of a bicyclic system (a 6-membered ring fused to a 5-membered ring containing a nitrogen atom). The nitrogen atom is also connected to a carbonyl group, which is further connected to a chiral center. This chiral center is also connected to a 4-(4-methoxy-2-isopropoxyphenyl) group and a 4-(benzyloxy)phenyl group. The molecule also contains a long alkyl chain with a terminal amino group (H₂N). Second eluting diastereomer

#	Structure
I-261	 First eluting enantiomer
I-262	 Second eluting enantiomer

[00106] In some embodiments, the present disclosure provides a compound set forth in **Table 1**, above, or a pharmaceutically acceptable salt thereof. In some embodiments, the disclosure provides a compound set forth in **Table 1**, above, or a pharmaceutically acceptable salt thereof, and any enantiomers, diastereomers, or conformation isomers thereof.

[00107] In some embodiments, the present disclosure provides a pharmaceutical composition comprising a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier, excipient, vehicle, adjuvant or diluent. In some embodiments, the present disclosure provides a pharmaceutical composition comprising a compound set forth in **Table 1** above, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier, excipient, vehicle, adjuvant or diluent. In some embodiments, the pharmaceutical composition further comprises an additional therapeutic agent.

[00108] In some embodiments, the present disclosure provides a complex comprising a CDK2 protein and a compound of the present disclosure.

[00109] In some embodiments, the present disclosure provides a method of inhibiting the activity of a cyclin-dependent kinase (CDK). In some embodiments, the method comprises contacting a

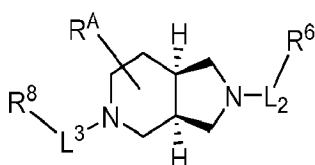
compound of the present disclosure with a CDK. In some embodiments, the compound and the CDK are contacted *in vivo*. In some embodiments, the compound and the CDK are contacted *in vitro*.

[00110] In some embodiments, the present disclosure provides compounds that selectively inhibit CDK2 over other cyclin-dependent kinases (CDKs). In some embodiments, the compounds of the present disclosure selectively inhibit CDK2 over one or more other CDKs, selected from CDK1, CDK3, CDK4, CDK5, CDK6, CDK7, CDK8, CDK9, CDK10, CDK11, CDK12 and CDK13. In some embodiments, the compounds of the present disclosure selectively inhibit CDK2 over CDK4. In some embodiments, the compounds of the present disclosure selectively inhibit CDK2 over CDK6. In some embodiments, the compounds of the present disclosure selectively inhibit CDK2 over CDK4 and CDK6.

[00111] In some embodiments, the present disclosure provides compounds that selectively inhibit CDK2/cyclin E complexes over other CDK complexes.

[00112] In any of the preceding embodiments, the central bicyclic core of any of the compounds or formulas described herein can be in one of a number of stereochemical configurations, or a mixture of two or more stereochemical configurations.

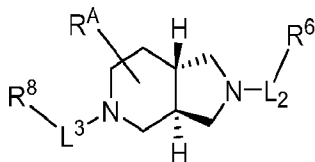
[00113] In some embodiments, the present disclosure provides a compound of Formula **I**, which is a compound of Formula **Ia**:



Ia

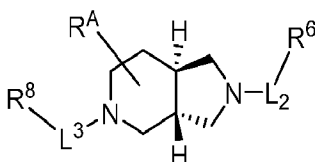
or a pharmaceutically acceptable salt thereof, wherein R^A , L^2 , R^6 , L^3 and R^8 , and their constituent groups, are each as defined and described herein.

[00114] In some embodiments, the present disclosure provides a compound of Formula **I**, which is a compound of Formula **Ib**:

**Ib**

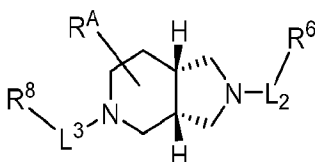
or a pharmaceutically acceptable salt thereof, wherein R^A , L^2 , R^6 , L^3 and R^8 , and their constituent groups, are each as defined and described herein.

[00115] In some embodiments, the present disclosure provides a compound of Formula **I**, which is a compound of Formula **Ic**:

**Ic**

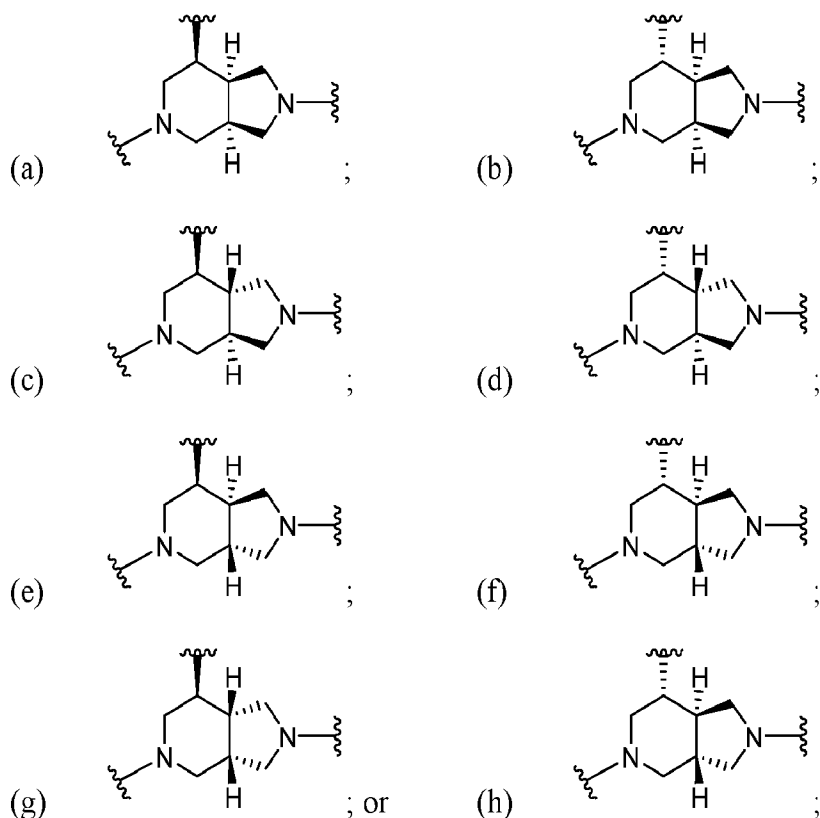
or a pharmaceutically acceptable salt thereof, wherein R^A , L^2 , R^6 , L^3 and R^8 , and their constituent groups, are each as defined and described herein.

[00116] In some embodiments, the present disclosure provides a compound of Formula **I**, which is a compound of Formula **Id**:

**Id**

or a pharmaceutically acceptable salt thereof, wherein R^A , L^2 , R^6 , L^3 and R^8 , and their constituent groups, are each as defined and described herein.

[00117] In some embodiments, the present disclosure provides a compound of any one of Formulas **II**, **III**, **IV**, **V**, **Va**, **Vb**, **VI**, **VIa**, **VIIa**, **VIIb**, **VIIc**, **VIIId**, **VIIe**, **VIIIf**, **VIIIa**, **VIIIb**, **VIIIc**, or **VIIId**, or a compound of Table 1, or a pharmaceutically acceptable salt thereof, wherein the central bicyclic core of said Formula or compound has a stereochemical configuration as shown below:



or a combination of two or more of the aforementioned stereochemical configurations. In some embodiments, the compound has stereochemical configuration “(a)”. In some embodiments, the compound has stereochemical configuration “(b)”. In some embodiments, the compound has stereochemical configuration “(c)”. In some embodiments, the compound has stereochemical configuration “(d)”. In some embodiments, the compound has stereochemical configuration “(e)”. In some embodiments, the compound has stereochemical configuration “(f)”. In some embodiments, the compound has stereochemical configuration “(g)”. In some embodiments, the compound has stereochemical configuration “(h)”.

4. General Methods of Providing the Present Compounds

[00118] The compounds of this disclosure may be prepared or isolated in general by synthetic and/or semi-synthetic methods known to those skilled in the art for analogous compounds and by methods described in detail in the Examples, herein.

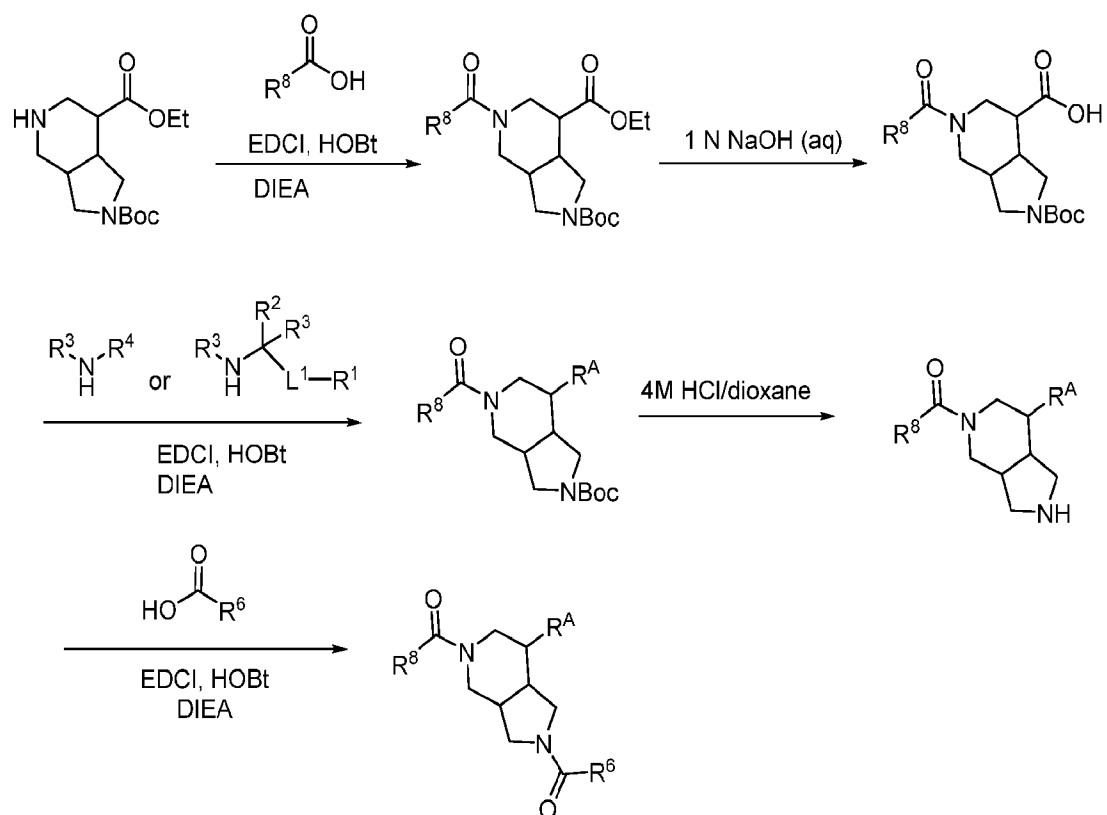
[00119] In the Schemes below, where a particular protecting group (“PG”), leaving group (“LG”), or transformation condition is depicted, one of ordinary skill in the art will appreciate that other protecting groups, leaving groups, and transformation conditions are also suitable and are

contemplated. Such groups and transformations are described in detail in *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, M. B. Smith and J. March, 5th Edition, John Wiley & Sons, 2001, *Comprehensive Organic Transformations*, R. C. Larock, 2nd Edition, John Wiley & Sons, 1999, and *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, the entirety of each of which is hereby incorporated herein by reference.

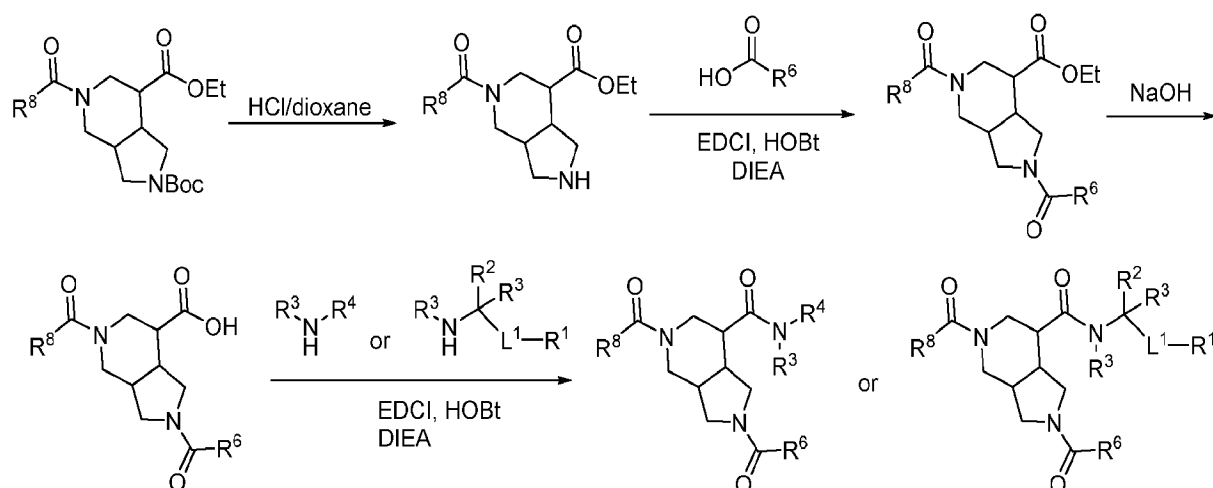
[00120] As used herein, the phrase “leaving group” (LG) includes, but is not limited to, halogens (e.g. fluoride, chloride, bromide, iodide), sulfonates (e.g. mesylate, tosylate, benzenesulfonate, brosylate, nosylate, triflate), diazonium, and the like.

[00121] Amino protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, the entirety of which is incorporated herein by reference. Suitable amino protecting groups include, but are not limited to, aralkylamines, carbamates, cyclic imides, allyl amines, amides, and the like. Examples of such groups include t-butyloxycarbonyl (BOC), ethyloxycarbonyl, methyloxycarbonyl, trichloroethyloxycarbonyl, allyloxycarbonyl (Alloc), benzyloxycarbonyl (CBZ), allyl, phthalimide, benzyl (Bn), fluorenylmethylcarbonyl (Fmoc), formyl, acetyl, chloroacetyl, dichloroacetyl, trichloroacetyl, phenylacetyl, trifluoroacetyl, benzoyl, and the like.

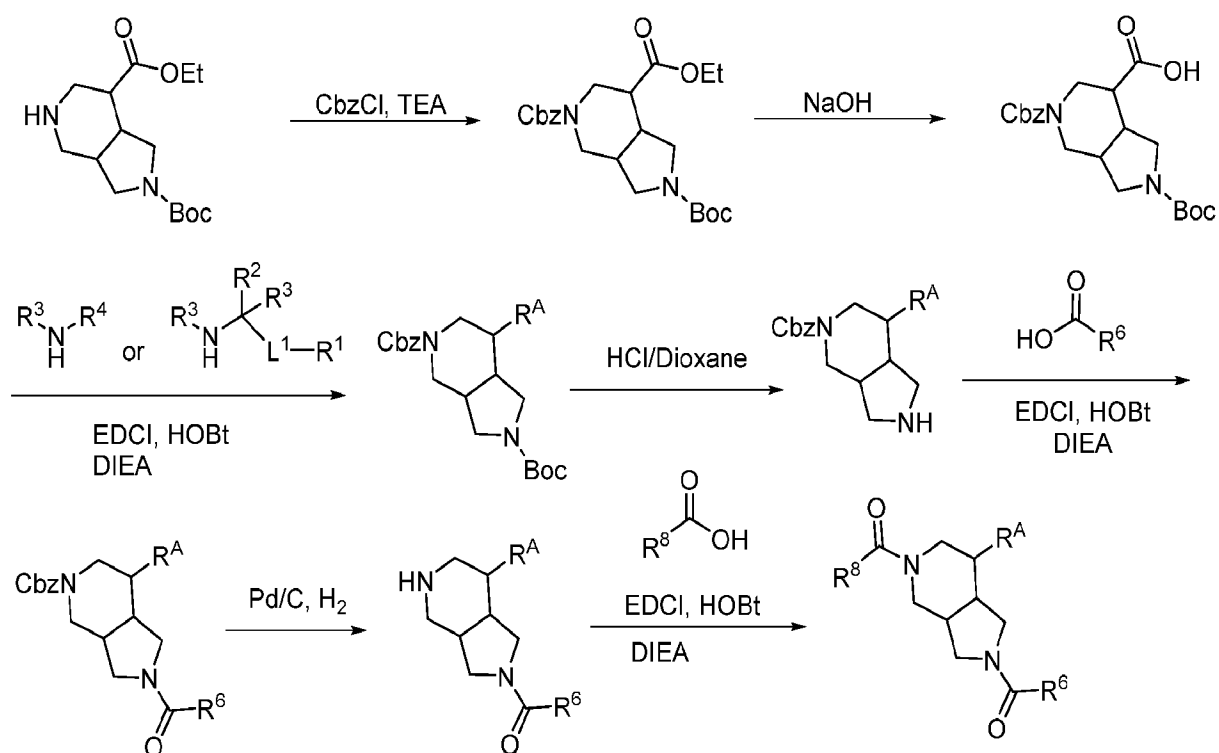
[00122] Compounds of the present disclosure, including those of Formula I and the compounds of **Table 1**, can generally be prepared according the methods described below. Reagents and conditions can be modified and substituted using knowledge common to one of ordinary skill in the art, as needed, in order to arrive at the compounds of the present disclosure.

Scheme 1: General Synthesis Method 1

Scheme 2: General Synthesis Method 2



Scheme 3: General Synthesis Method 3



5. Uses, Formulation and Administration

Pharmaceutically acceptable compositions

[00123] According to another embodiment, the disclosure provides a composition comprising a compound of this disclosure or a pharmaceutically acceptable derivative thereof and a

pharmaceutically acceptable carrier, adjuvant, or vehicle. The amount of compound in compositions of this disclosure is such that it is effective to measurably inhibit a CDK2 protein, or a mutant thereof, in a biological sample or in a patient. In certain embodiments, the amount of compound in compositions of this disclosure is such that it is effective to measurably inhibit a CDK2 protein, or a mutant thereof, in a biological sample or in a patient. In certain embodiments, a composition of this disclosure is formulated for administration to a patient in need of such composition. In some embodiments, a composition of this disclosure is formulated for oral administration to a patient.

[00124] Compositions of the present disclosure may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques. Preferably, the compositions are administered orally, intraperitoneally or intravenously. Sterile injectable forms of the compositions of this disclosure may be aqueous or oleaginous suspension. These suspensions may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium.

[00125] For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant, such as carboxymethyl cellulose or similar dispersing agents that are commonly used in the formulation of pharmaceutically acceptable dosage forms including emulsions and suspensions. Other commonly used surfactants, such as Tweens, Spans and other emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms may also be used for the purposes of formulation.

[00126] Pharmaceutically acceptable compositions of this disclosure may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, aqueous suspensions or solutions. In the case of tablets for oral use, carriers commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried cornstarch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening, flavoring or coloring agents may also be added.

[00127] Alternatively, pharmaceutically acceptable compositions of this disclosure may be administered in the form of suppositories for rectal administration. These can be prepared by mixing the agent with a suitable non-irritating excipient that is solid at room temperature but liquid at rectal temperature and therefore will melt in the rectum to release the drug. Such materials include cocoa butter, beeswax and polyethylene glycols.

[00128] Pharmaceutically acceptable compositions of this disclosure may also be administered topically, especially when the target of treatment includes areas or organs readily accessible by topical application, including diseases of the eye, the skin, or the lower intestinal tract. Suitable topical formulations are readily prepared for each of these areas or organs.

[00129] Topical application for the lower intestinal tract can be effected in a rectal suppository formulation (see above) or in a suitable enema formulation. Topically-transdermal patches may also be used.

[00130] For topical applications, provided pharmaceutically acceptable compositions may be formulated in a suitable ointment containing the active component suspended or dissolved in one or more carriers. Carriers for topical administration of compounds of this disclosure include, but are not limited to, mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene, polyoxypropylene compound, emulsifying wax and water. Alternatively, provided pharmaceutically acceptable compositions can be formulated in a suitable lotion or cream containing the active components suspended or dissolved in one or more pharmaceutically acceptable carriers. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

[00131] For ophthalmic use, provided pharmaceutically acceptable compositions may be formulated as micronized suspensions in isotonic, pH adjusted sterile saline, or, preferably, as solutions in isotonic, pH adjusted sterile saline, either with or without a preservative such as benzylalkonium chloride. Alternatively, for ophthalmic uses, the pharmaceutically acceptable compositions may be formulated in an ointment such as petrolatum.

[00132] Pharmaceutically acceptable compositions of this disclosure may also be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other conventional solubilizing or dispersing agents.

[00133] Most preferably, pharmaceutically acceptable compositions of this disclosure are formulated for oral administration. Such formulations may be administered with or without food. In some embodiments, pharmaceutically acceptable compositions of this disclosure are administered without food. In other embodiments, pharmaceutically acceptable compositions of this disclosure are administered with food.

[00134] The amount of compounds of the present disclosure that may be combined with the carrier materials to produce a composition in a single dosage form will vary depending upon the host treated, the particular mode of administration. Preferably, provided compositions should be formulated so that a dosage of between 0.01 - 100 mg/kg body weight/day of the compound can be administered to a patient receiving these compositions.

[00135] It should also be understood that a specific dosage and treatment regimen for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, and the judgment of the treating physician and the severity of the particular disease being treated. The amount of a compound of the present disclosure in the composition will also depend upon the particular compound in the composition.

Uses of Compounds and Pharmaceutically Acceptable Compositions

[00136] Compounds and compositions described herein are generally useful for the modulation of the activity CDK2. In some embodiments, the compounds and compositions described herein are CDK2 inhibitors.

[00137] In some embodiments, the compounds and compositions of the present disclosure are useful for treating diseases and disorders associated with CDK2 activity, including, but not limited to cancers, myeloproliferative disorders, autoimmune disorders, inflammatory disorders, viral infections, fibrotic disorders, and neurodegenerative disorders.

[00138] In some embodiments, the disclosure provides a method of inhibiting the activity of a CDK2, the method comprising contacting a compound of the present disclosure, or a pharmaceutically acceptable salt thereof with the CDK2. In some embodiments, the contacting takes place *in vitro*. In some embodiments, the contacting takes place *in vivo*.

[00139] In some embodiments, the disclosure provides a method of treating, preventing or lessening the severity of a disease or disorder associated with CDK2 activity in a patient, including, but not limited to cancers, myeloproliferative disorders, autoimmune disorders, inflammatory disorders, fibrotic disorders, and neurodegenerative disorders, said method comprising administering to a patient in need thereof, a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising an effective amount of a compound of the present disclosure, or a pharmaceutically acceptable salt thereof.

[00140] The disclosure further provides a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising an effective amount of a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, for use in the treatment of a disease or disorder associated with CDK2 activity.

[00141] The disclosure further provides a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising an effective amount of a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, for use in the manufacture of a medicament for treating a disease or disorder associated with CDK2 activity.

[00142] In some embodiments, the disease or disorder associated with CDK2 activity is a CDK2-mediated disease or disorder. In some embodiments, the disease or disorder associated with CDK2 activity is a disease or disorder caused by CDK2 over-activity.

[00143] In some embodiments, the disease or disorder associated with CDK2 activity is cancer.

[00144] In some embodiments, the cancer is selected from breast cancer, ovarian cancer, bladder cancer, uterine cancer, prostate cancer, lung cancer, esophageal cancer, head and neck cancer, colorectal cancer, kidney cancer, liver cancer, pancreatic cancer, stomach cancer, melanoma and thyroid cancer.

[00145] In some embodiments, the cancer is characterized by amplification or overexpression of CCNE1 and/or CCNE2.

[00146] In some embodiments, the cancer is breast cancer. In some embodiments, the breast cancer is a breast cancer selected from ER-positive/HR-positive breast cancer, HER2-negative breast cancer, ER-positive/HR-positive breast cancer, HER2-positive breast cancer, triple negative breast cancer (TNBC), inflammatory breast cancer, endocrine resistant breast cancer, trastuzumab resistant breast cancer, breast cancer with primary or acquired resistance to CDK4/CDK6 inhibition, advanced breast cancer and metastatic breast cancer. In some embodiments the breast cancer is characterized by amplification or overexpression of CCNE1 and/or CCNE2.

[00147] In some embodiments, the cancer is ovarian cancer. In some embodiments, the ovarian cancer is high-grade serous ovarian cancer (HGSOC). In some embodiments the ovarian cancer is characterized by amplification or overexpression of CCNE1 and/or CCNE2.

[00148] In some embodiments, the cancer is bladder cancer. In some embodiments, the bladder cancer is characterized by amplification or overexpression of CCNE1 and/or CCNE2.

[00149] In some embodiments, the cancer is uterine cancer. In some embodiments, the uterine cancer is characterized by amplification or overexpression of CCNE1 and/or CCNE2.

[00150] In some embodiments, the cancer is prostate cancer. In some embodiments, the prostate cancer is characterized by amplification or overexpression of CCNE1 and/or CCNE2.

[00151] In some embodiments, the cancer is lung cancer. In some embodiments, the lung cancer is a lung cancer selected from non-small cell lung cancer, small cell lung cancer, squamous cell carcinoma, adenocarcinoma, and mesothelioma. In some embodiments, the lung cancer is

characterized by amplification or overexpression of CCNE1 and/or CCNE2. In some embodiments, the lung cancer is CCNE1 amplified squamous cell carcinoma or CCNE1 amplified adenocarcinoma.

[00152] In some embodiments, the cancer is head and neck cancer. In some embodiments, the head and neck cancer is characterized by amplification or overexpression of CCNE1 and/or CCNE2.

[00153] In some embodiments, the cancer is colorectal cancer. In some embodiments, the colorectal cancer is characterized by amplification or overexpression of CCNE1 and/or CCNE2.

[00154] In some embodiments, the cancer is kidney cancer. In some embodiments, the kidney cancer is renal cell carcinoma (RCC). In some embodiments, the kidney cancer is characterized by amplification or overexpression of CCNE1 and/or CCNE2.

[00155] In some embodiments, the cancer is liver cancer. In some embodiments, the liver cancer is hepatocellular carcinoma (HCC). In some embodiments, the liver cancer is characterized by amplification or overexpression of CCNE1 and/or CCNE2.

[00156] In some embodiments, the cancer is pancreatic cancer. In some embodiments, the pancreatic cancer is characterized by amplification or overexpression of CCNE1 and/or CCNE2.

[00157] In some embodiments, the cancer is stomach cancer. In some embodiments, the stomach cancer is characterized by amplification or overexpression of CCNE1 and/or CCNE2.

[00158] In some embodiments, the cancer is melanoma. In some embodiments, the melanoma is characterized by amplification or overexpression of CCNE1 and/or CCNE2. CDK2 expression is regulated by essential melanocytic transcription factor MITF. It has been found that CDK2 depletion suppresses the growth of melanoma (Du et al., Cancer Cell. 2004 Dec; 6(6): 565-576)

[00159] In some embodiments, the cancer is thyroid cancer. In some embodiments, the thyroid cancer is characterized by amplification or overexpression of CCNE1 and/or CCNE2.

[00160] In some embodiments, the disease or disorder associated with CDK2 activity is a myeloproliferative disorder.

[00161] In some embodiments, the disease or disorder associated with CDK2 activity is a neurodegenerative disease or disorder. In some embodiments, the neurodegenerative disease or disorder is Alzheimer's disease (AD). It has been reported that neuronal cell death in subjects

suffering from AD is preceded by cell cycle events. Inhibition of one or more CDKs can inhibit cell cycle events and therefore stave off neuronal cell death (Yang et al., *J Neurosci.* 2003 Apr 1;23(7):2557-2563).

[00162] In some embodiments, the disease or disorder associated with CDK2 activity is a liver disease.

[00163] In some embodiments, the disease or disorder associated with CDK2 activity is liver fibrosis. It has been reported that CCNE1 knockout mice do not develop liver fibrosis upon exposure to pro-fibrotic toxin CCl₄, suggesting that liver fibrosis can be treated via administration of a CDK2 inhibitor (Nevzorova, et al., *Hepatology.* 2012 Sep; 56(3): 1140–1149.)

[00164] In some embodiments, the disease or disorder associated with CDK2 activity is Cushing disease. Pituitary cyclin E/E2F1 signaling is a molecular mechanism underlying neuroendocrine regulation of the hypothalamic-pituitary-adrenal axis, and therefore provides a subcellular therapeutic target for CDK2 inhibitors of pituitary ACTH-dependent hypercortisolism, also known as Cushing disease (Liu, et al., *J Clin Endocrinol Metab.* 2015 Jul; 100(7): 2557–2564.).

[00165] In some embodiments, the disease or disorder associated with CDK2 activity is a kidney disease.

[00166] In some embodiments, the disease or disorder associated with CDK2 activity is polycystic kidney disease. It has been reported that CDK2/CDK5 inhibitor roscovitine yields effective arrest of cystic kidney disease in mouse models of polycystic kidney disease (Bukanov, et al., *Nature.* 2006 Dec 14;444(7121):949-52).

[00167] In some embodiments, the disease or disorder associated with CDK2 activity is an autoimmune disorder. CDK2 ablation has been shown to promote immune tolerance by supporting the function of regulatory T cells (Chunder et al., *J Immunol.* 2012 Dec 15;189(12):5659-66).

[00168] In some embodiments, the disease or disorder associated with CDK2 activity is an inflammatory disorder. Cyclin E ablation has been shown to attenuate hepatitis in mice, while p27 knockout mice display exacerbation of renal inflammation (Ehedego et al., *Oncogene.* 2018 Jun;37(25):3329-3339.; Ophascharoensuk et al., *Nat Med.* 1998 May;4(5):575-80.). In some embodiments, the inflammatory disorder is hepatitis.

[00169] In some embodiments, the compounds and compositions of the present disclosure are useful as male contraceptives. Based on the finding that male CDK2 knockout mice are sterile, CDK2 inhibitors have been studied as possible male contraceptives (Faber, et al., *Biol Reprod.* 2020 Aug; 103(2): 357–367.). In some embodiments, the present disclosure provides a method of reducing male fertility comprising administering to a patient in need thereof, a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising an effective amount of a compound of the present disclosure, or a pharmaceutically acceptable salt thereof.

Combination Therapies

[00170] Depending upon the particular condition, or disease, to be treated, additional therapeutic agents, which are normally administered to treat that condition, may be administered in combination with compounds and compositions of this disclosure. As used herein, additional therapeutic agents that are normally administered to treat a particular disease, or condition, are known as “appropriate for the disease, or condition, being treated.”

[00171] In certain embodiments, a provided combination, or composition thereof, is administered in combination with another therapeutic agent.

[00172] In some embodiments, the present disclosure provides a method of treating a disclosed disease or condition comprising administering to a patient in need thereof an effective amount of a compound disclosed herein or a pharmaceutically acceptable salt thereof and co-administering simultaneously or sequentially an effective amount of one or more additional therapeutic agents, such as those described herein. In some embodiments, the method includes co-administering one additional therapeutic agent. In some embodiments, the method includes co-administering two additional therapeutic agents. In some embodiments, the combination of the disclosed compound and the additional therapeutic agent or agents acts synergistically.

[00173] Examples of agents that the compounds of the present disclosure may also be combined with include, without limitation: endocrine therapeutic agents, chemotherapeutic agents and other CDK inhibitory compounds.

[00174] In some embodiments, the present disclosure provides a method of treating a disclosed disease or condition comprising administering to a patient in need thereof an effective amount of

a compound disclosed herein or a pharmaceutically acceptable salt thereof and co-administering simultaneously or sequentially an effective amount of an endocrine therapeutic agent.

[00175] In some embodiments, the present disclosure provides a method of treating a disclosed disease or condition comprising administering to a patient in need thereof an effective amount of a compound disclosed herein or a pharmaceutically acceptable salt thereof and co-administering simultaneously or sequentially an effective amount of one or more additional CDK inhibitory compounds. In some embodiments, the CDK inhibitory compounds are CDK4 or CDK4/CDK6 inhibitors.

[00176] In some embodiments, the present disclosure provides a method of treating a disclosed disease or condition comprising administering to a patient in need thereof an effective amount of a compound disclosed herein or a pharmaceutically acceptable salt thereof and co-administering simultaneously or sequentially an effective amount of a chemotherapeutic agent. In some embodiments, the chemotherapeutic agent is a taxane. In some embodiments, the chemotherapeutic agent is a platinum agent. In some embodiments, the chemotherapeutic agent is trastuzumab.

[00177] As used herein, the term “combination,” “combined,” and related terms refers to the simultaneous or sequential administration of therapeutic agents in accordance with this disclosure. For example, a combination of the present disclosure may be administered with another therapeutic agent simultaneously or sequentially in separate unit dosage forms or together in a single unit dosage form.

[00178] The amount of additional therapeutic agent present in the compositions of this disclosure will be no more than the amount that would normally be administered in a composition comprising that therapeutic agent as the only active agent. Preferably the amount of additional therapeutic agent in the presently disclosed compositions will range from about 50% to 100% of the amount normally present in a composition comprising that agent as the only therapeutically active agent.

[00179] One or more other therapeutic agent may be administered separately from a compound or composition of the present disclosure, as part of a multiple dosage regimen. Alternatively, one or more other therapeutic agents may be part of a single dosage form, mixed together with a compound of this disclosure in a single composition. If administered as a multiple dosage regime, one or more other therapeutic agent and a compound or composition of the present disclosure may

be administered simultaneously, sequentially or within a period of time from one another, for example within 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 18, 20, 21, 22, 23, or 24 hours from one another. In some embodiments, one or more other therapeutic agent and a compound or composition the present disclosure are administered as a multiple dosage regimen within greater than 24 hours a parts.

[00180] In one embodiment, the present disclosure provides a composition comprising a provided compound or a pharmaceutically acceptable salt thereof and one or more additional therapeutic agents. The therapeutic agent may be administered together with a provided compound or a pharmaceutically acceptable salt thereof, or may be administered prior to or following administration of a provided compound or a pharmaceutically acceptable salt thereof. Suitable therapeutic agents are described in further detail below. In certain embodiments, a provided compound or a pharmaceutically acceptable salt thereof may be administered up to 5 minutes, 10 minutes, 15 minutes, 30 minutes, 1 hour, 2 hours, 3 hours, 4 hours, 5, hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, or 18 hours before the therapeutic agent. In other embodiments, a provided compound or a pharmaceutically acceptable salt thereof may be administered up to 5 minutes, 10 minutes, 15 minutes, 30 minutes, 1 hour, 2 hours, 3 hours, 4 hours, 5, hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, or 18 hours following the therapeutic agent.

EXAMPLES

[00181] As depicted in the Examples below, in certain exemplary embodiments, compounds are prepared according to the general procedures provided herein. It will be appreciated that, although the general methods depict the synthesis of certain compounds of the present disclosure, the general methods, and other methods known to one of ordinary skill in the art, can be applied to all compounds and subclasses and species of each of these compounds, as described herein.

General Procedures

[00182] Abbreviations: Chloroform-*d* (deuterated chloroform); DMSO-*d*₆ (deuterated dimethylsulfoxide); Boc (*tert*-butoxycarbonyl); Boc₂O (di-*tert*-butyl dicarbonate); DMF (*N,N*-dimethylformamide); NMP (1-methyl-2-pyrrolidinone); DMSO (dimethylsulfoxide); PE (petroleum ether); EDCI (1-ethyl-3-(3-dimethylaminopropyl) carbodiimide); ESI (electrospray

atmospheric pressure ionization); TEA (triethylamine); TFA (trifluoroacetic acid); dioxane (1,4-dioxane); THF (tetrahydrofuran); EtOAc (ethyl acetate); g (gram); h (hour); nm (nanometer); ¹H NMR (proton nuclear magnetic resonance); Hz (hertz); LCMS (liquid chromatography-mass spectrometry); MS (mass spectrometry); mg (milligrams); MHz (megahertz); min (minutes); mL (millilitres); mmol (millimoles); ppm (parts per million); R_t (retention time); RT (room temperature); TLC (thin layer chromatography); v/v (volume/volume); m/z (mass charge ratio); HCl (hydrochloric acid); KOAc (potassium acetate); NaOAc (sodium acetate); Pd/C (palladium on activated carbon); *n*-BuLi (*n*-butyllithium); MeI (iodomethane); EtI (iodoethane); LiHMDS (lithium bis(trimethylsilyl)amide); NaHMDS (sodium bis(trimethylsilyl)amide); TMSOI (trimethylsulfoxonium iodide); TMSCHN₂ (trimethylsilyldiazomethane); LDA (lithium diisopropylamide); DIAD (diisopropyl azodicarboxylate); DEAD (diethyl azodicarboxylate); DBAD (di-*tert*-butyl azodicarboxylate); TMSCF₃ (Trimethyl(trifluoromethyl)silane); X-Phos (2-(dicyclohexylphosphino)-2',4',6'-triisopropylbiphenyl); NCS (*N*-chlorosuccinimide); NBS (*N*-bromosuccinimide); SEMCl (2-(trimethylsilyl)ethoxymethyl chloride); AIBN (2,2'-azobis(isobutyronitrile)); CO (carbon monoxide); DIPEA or DIEA (*N,N*-diisopropylethylamine); TBAF (tetrabutylammonium fluoride); TBAI (tetrabutylammonium iodide); DAST (diethylaminosulfur trifluoride); MW (microwave); Pd(PPh₃)₄ (tetrakis(triphenylphosphine)palladium); Pd₂(dba)₃ (tris(dibenzylideneacetone)dipalladium); Pd(dppf)Cl₂ ([1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium); NaH (sodium hydride); PPh₃ (triphenylphosphine); HATU (2-(7-*aza-1H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate); TBSCl (tert-butyldimethylchlorosilane); ee (enantiomeric excess); NiCl₂(dme) (dichloro(dimethoxyethane)nickel); HOBt (hydroxybenzotriazole); DCM (dichloromethane); DMA (dimethylacetamide); prep-TLC (preparative thin layer chromatography), prep-HPLC (preparative HPLC); DEA (diethylamine); CbzCl (benzyl chloroformate); ACN (acetonitrile); DCC (dicyclohexylcarbodiimide); HOSu (*N*-hydroxysuccinimide); quant. (quantitative yield); MTBE (methyl *tert*-butyl ether); DIBAL-H (diisobutylaluminium hydride); DCE (1,2-dichloroethane); DMAP (4-(dimethylamino)pyridine); IPA (isopropyl alcohol); LDA (lithium diisopropylamide); TBN (tert-butyl nitrite); PMBCl (4-methoxybenzyl chloride); CAN (ceric ammonium nitrate); CDI (*N,N'*-carbonyldiimidazole); FmocOSu (*N*-(9H-fluoren-9-ylmethoxycarbonyloxy)succinimide).

Materials and Methods

[00183] NMR: ^1H NMR spectra were recorded at 400 MHz using a Bruker AVANCE 400 MHz spectrometer. Data for ^1H are reported as chemical shift (ppm) and multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet).

[00184] LCMS (Shimadzu 3 min method):

- LC: Shimadzu LC-20AD series, Binary Pump, Diode Array Detector. Agilent Poroshell 120 EC-C18, 2.7 μm , 4.6 $\times$ 50 mm column. Mobile phase: A: 0.05% formic acid in water (v/v), B: 0.05% formic acid in MeCN (v/v). Acquire time: 3 min. LC gradient: hold 15% B for 0.28 min; then 15% to 90% in 2.1 min; then 90% to 100% in 0.01 min; then hold 100 % for 0.3 min; then 100% to 15% in 0.01 min; hold at 15% for 0.3 min. Flow Rate: 1.5 mL/min at 25 $^{\circ}\text{C}$. Detection wavelength: 214 nm, 254 nm.
- MS: 2020, Quadrupole LC/MS, Ion Source: API-ESI, TIC: 100~900 m/z, Drying gas flow: 15 L/min, Nebulizer pressure: 1.5 L/min, Drying gas temperature: 250 $^{\circ}\text{C}$, Vcap: 4500V.

[00185] LC-MS (Shimadzu 5 min method):

- LC: Shimadzu LC-20AD series, Binary Pump, Diode Array Detector. Agilent Poroshell 120 EC-C18, 2.7 μm , 4.6 $\times$ 50 mm column. Mobile phase: A: 0.05% formic acid in water (v/v), B: 0.05% formic acid in MeCN (v/v). Acquire time: 5 min. LC gradient: hold 15% B for 0.5 min; then 15% to 85% in 3.5 min; then 85% to 100% in 0.01 min; then hold 100 % for 0.49 min; then 100% to 15% in 0.01 min; hold at 15% for 0.49 min. Flow Rate: 1 mL/min at 25 $^{\circ}\text{C}$. Detection wavelength: 214 nm, 254 nm.
- MS: 2020, Quadrupole LC/MS, Ion Source: API-ESI, TIC: 100~900 m/z, Drying gas flow: 15 L/min, Nebulizer pressure: 1.5 L/min, Drying gas temperature: 250 $^{\circ}\text{C}$, Vcap: 4500V.

[00186] LC-MS (Agilent 5 min method):

- LC: Agilent Technologies 1290 series, Binary Pump, Diode Array Detector. Agilent Poroshell 120 EC-C18, 2.7 μm , 4.6 $\times$ 50 mm column. Mobile phase: A: 0.05% formic acid in water (v/v), B: 0.05% formic acid in MeCN (v/v). Acquire time: 5 min. LC gradient: hold 10% B for 0.5 min; then 10% to 90% in 3.5 min; then 90% to 100% in 0.01 min; then hold 100 % for 0.49 min; then 100% to 10% in 0.01 min; hold at 10% for 0.49 min. Flow Rate: 1 mL/min at 25 $^{\circ}\text{C}$. Detection wavelength: 214 nm, 254 nm.

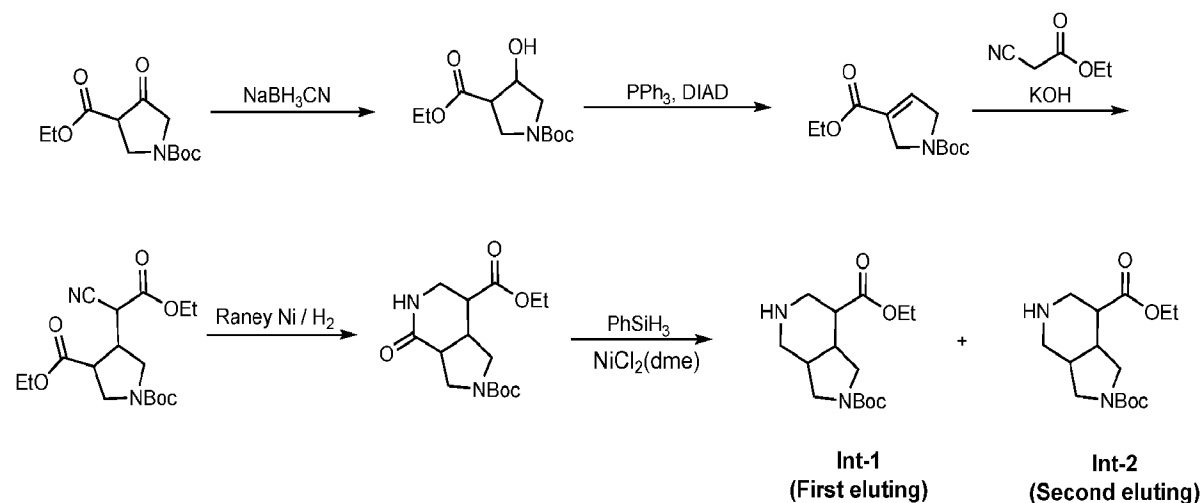
- MS: G6120A, Quadrupole LC/MS, Ion Source: API-ESI, TIC: 70~1000 m/z, Fragmentor: 70, Drying gas flow: 12 L/min, Nebulizer pressure: 36 psi, Drying gas temperature: 350 °C, Vcap: 3000V.

[00187] Preparative HPLC Generic Methods:

- HPLC Instruments: Shimadzu 20AP UV detector: SPD-20A. UV wavelength: 214 nm and 254 nm.
- Condition 1: Mobile phase A: water with 0.1% trifluoroacetic acid; Mobile phase B: methanol.
- Condition 2: Mobile phase A: water with 0.1% trifluoroacetic acid; Mobile phase B: acetonitrile.
- Column: Agilent 10 Prep-C18 250 x 21.2 mm. Column temperature: Ambient
- LC gradient: 20% to 85% in 20 min; then 85% to 100% in 0.01 min; then hold 100% for 5 min; then 100 % to 20% in 0.01 min; hold at 20% for 5 min.
- LC Flow rate: 20 mL/min binary pump.

Example 1: Synthesis of Precursor Compounds and Intermediates

Synthesis of Int-1 and Int-2



[00188] Step 1: 1-(tert-butyl) 3-ethyl 4-hydroxypyrrolidine-1,3-dicarboxylate

[00189] To a solution of 1-(tert-butyl) 3-ethyl 4-oxopyrrolidine-1,3-dicarboxylate (30.0 g, 0.117 mol) in MeOH (500 mL) was added NaBH_3CN (8.04 g, 0.128 mol). Aqueous HCl (1M, 110 mL) was added dropwise with stirring maintaining the pH at ~3-4. When the addition was complete the reaction was stirred for 5 h and extracted with EtOAc three times. The combined organic layers

were washed with aqueous NaHCO₃, brine, dried over Na₂SO₄ and concentrated *in vacuo*. The crude residue was purified by column chromatography (20% EtOAc/PE) to give the product (27.0 g, 89.4%) as a colourless oil. LCMS m/z = 260.1 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 4.57 – 4.49 (m, 1H), 4.17 (dq, J = 7.2, 1.6 Hz, 2H), 3.78 – 3.41 (m, 3H), 3.37 – 2.64 (m, 3H), 1.44 (app d, J = 1.4 Hz, 9H), 1.32 – 1.19 (m, 3H).

[00190] Step 2: 1-(tert-butyl) 3-ethyl 2,5-dihydro-1H-pyrrole-1,3-dicarboxylate

[00191] To a solution of 1-(tert-butyl) 3-ethyl 4-hydroxypyrrolidine-1,3-dicarboxylate (27.0 g, 0.104 mol) and PPh₃ (32.8 g, 0.125 mol) in dry toluene (300 mL) at 0°C was added DIAD (25.3 g, 0.125 mol) dropwise. The mixture was allowed to warm to room temperature and stirred overnight. The solvent was removed under vacuum and the residue purified by column chromatography (10% EtOAc/PE) to give the product (19.0 g, 76.4%) as a colourless oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 6.77 (dt, J = 13.4, 1.9 Hz, 1H), 4.23 – 4.07 (m, 6H), 1.41 (d, J = 2.3 Hz, 9H), 1.22 (t, J = 7.1 Hz, 3H).

[00192] Step 3: 1-(tert-butyl) 3-ethyl 4-(1-cyano-2-ethoxy-2-oxoethyl)pyrrolidine-1,3-dicarboxylate

[00193] To a solution of 1-(tert-butyl) 3-ethyl 2,5-dihydro-1H-pyrrole-1,3-dicarboxylate (19.0 g, 0.079 mol) and ethyl 2-cyanoacetate (17.8 g, 0.157 mol) in DMF (250 mL) was added KOH (8.83 g, 0.158 mol). The mixture was stirred for 4 h, then extracted with EtOAc three times. The combined organic layers were washed with water and brine, dried over Na₂SO₄ and concentrated *in vacuo*. The crude was purified by column chromatography (30% EtOAc/PE) to give the product (19.8 g, 71%) as a colourless oil. ¹H NMR (400 MHz, CD₃OD) δ 4.38 – 4.19 (m, 4H), 3.85 – 3.38 (m, 6H), 3.19 – 3.09 (m, 1H), 1.54 – 1.50 (m, 9H), 1.42 – 1.23 (m, 6H).

[00194] Step 4: 2-(tert-butyl) 7-ethyl 4-oxooctahydro-2H-pyrrolo[3,4-c]pyridine-2,7-dicarboxylate

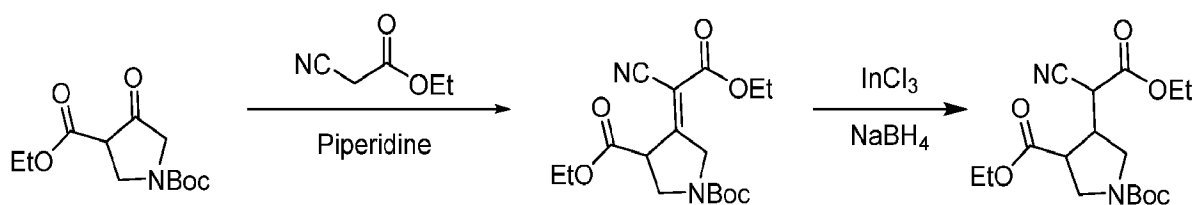
[00195] To a solution of 1-(tert-butyl) 3-ethyl 4-(1-cyano-2-ethoxy-2-oxoethyl)pyrrolidine-1,3-dicarboxylate (19.8 g, 0.056 mol) in EtOH (250 mL) was added Raney Ni (5 g). The resulting mixture was stirred under an atmosphere of H₂ overnight. The reaction mixture was filtered through a pad of celite and the filtrate was concentrated *in vacuo*. The crude was purified by column chromatography (50% EtOAc/PE) to give the product (13.9 g, 79%) as a colourless oil.

^1H NMR (400 MHz, CD_3OD) δ 4.25 – 4.14 (m, 2H), 3.84 – 3.33 (m, 6H), 3.28 – 2.67 (m, 3H), 1.46 (d, $J = 3.7$ Hz, 9H), 1.28 (dt, $J = 7.2, 3.0$ Hz, 3H).

[00196] Step 5: 2-(tert-butyl) 7-ethyl octahydro-2H-pyrrolo[3,4-c]pyridine-2,7-dicarboxylate (Int-1) and (Int-2)

[00197] To a solution of 2-(tert-butyl) 7-ethyl 4-oxooctahydro-2H-pyrrolo[3,4-c]pyridine-2,7-dicarboxylate (13.9 g, 0.044 mol) and PhSiH_3 (12.11 g, 0.112 mol) in dry toluene (300 mL) was added $\text{NiCl}_2(\text{dme})$ (1.23 g, 0.006 mol). The mixture was heated at reflux under N_2 overnight. The solvent was removed and the residue taken up in EtOAc. The organic phase was washed with aqueous NaHCO_3 and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by column chromatography (2.5% MeOH/DCM) to give **Int-1** (4.0 g, 30%) as the first eluting diastereomer and **Int-2** (2.1 g, 14%) as the second eluting diastereomer. **Int-1**: LCMS $m/z = 299.1$ $[\text{M}+\text{H}]^-$; ^1H NMR (400 MHz, CD_3OD) δ 4.16 – 4.04 (m, 2H), 3.36 – 3.18 (m, 4H), 3.10 – 3.02 (m, 1H), 2.86 – 2.75 (m, 2H), 2.69 – 2.57 (m, 1H), 2.47 – 2.39 (m, 1H), 2.38 – 2.28 (m, 2H), 1.43 – 1.37 (m, 9H), 1.24 – 1.17 (m, 3H). **Int-2**: LCMS $m/z = 299.1$ $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, CD_3OD) δ 4.21 – 4.10 (m, 2H), 3.46 – 3.34 (m, 2H), 3.30 – 3.25 (m, 1H), 3.18 – 3.00 (m, 2H), 2.95 – 2.68 (m, 4H), 2.41 – 2.22 (m, 2H), 1.50 – 1.43 (m, 9H), 1.30 – 1.23 (m, 3H).

[00198] Alternative synthesis of 1-(tert-butyl) 3-ethyl 4-(1-cyano-2-ethoxy-2-oxoethyl)pyrrolidine-1,3-dicarboxylate

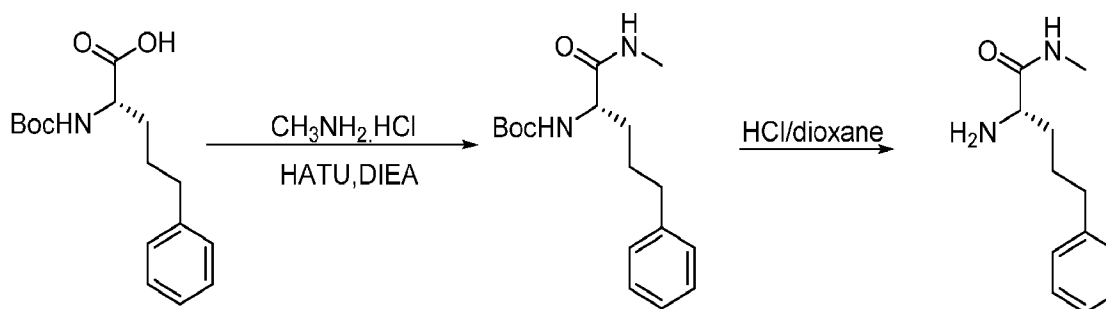


[00199] Step 1: 1-(tert-butyl) 3-ethyl 4-(1-cyano-2-ethoxy-2-oxoethylidene)pyrrolidine-1,3-dicarboxylate A mixture of 1-(tert-butyl) 3-ethyl 4-oxopyrrolidine-1,3-dicarboxylate (20.0 g, 0.078 mol), ethyl 2-cyanoacetate (8.8 g, 0.093 mol) and piperidine (20.0 g, 0.078 mol) was stirred for 2 days under N_2 . The resulting mixture was concentrated *in vacuo* and the crude purified by column chromatography (6% EtOAc/PE) to afford the product (8.11 g, 29.6%) as a yellow oil. ^1H NMR (400 MHz, CD_3OD) δ 4.66 – 4.49 (m, 1H), 4.46 – 3.60 (m, 8H), 1.53 – 1.44 (m, 9H), 1.39 – 1.22 (m, 6H).

[00200] Step 2: 1-(tert-butyl) 3-ethyl 4-(1-cyano-2-ethoxy-2-oxoethyl)pyrrolidine-1,3-dicarboxylate

[00201] To a solution of InCl_3 (204 mg, 0.92 mmol) and NaBH_4 (387 mg, 10.2 mmol) in acetonitrile (10 mL) was added a solution of 1-(tert-butyl) 3-ethyl 4-(1-cyano-2-ethoxy-2-oxoethylidene)pyrrolidine-1,3-dicarboxylate (2.4 g, 6.8 mmol) in acetonitrile (15 mL). The mixture was stirred at room temperature for 3 h. The reaction mixture was quenched with water and extracted with EtOAc three times. The combined organic layers were washed with water, brine, and dried over Na_2SO_4 . The solvent was removed and the crude purified by column chromatography (30% EtOAc/PE) to afford the product (1.5 g, 62.2%) as a colorless oil. LCMS $m/z = 299.1$ $[\text{M}-\text{tBu}+\text{H}]^+$; ^1H NMR (400 MHz, CD_3OD) δ 4.39 – 4.17 (m, 4H), 3.85 – 3.65 (m, 2H), 3.64 – 3.35 (m, 4H), 3.18 – 3.05 (m, 1H), 1.55 – 1.48 (m, 9H), 1.41 – 1.28 (m, 6H).

Synthesis of (S)-2-amino-N-methyl-5-phenylpentanamide



[00202] Step 1: tert-butyl (S)-(1-(methylamino)-1-oxo-5-phenylpentan-2-yl)carbamate

[00203] A solution of (S)-2-((tert-butoxycarbonyl)amino)-5-phenylpentanoic acid (3.0 g, 10.2 mmol), HATU (5.83 g, 15.3 mmol) and DIEA (5.3 g, 40.8 mmol) in DMF (15 mL) was stirred at room temperature for 30 min. Methylamine hydrochloride (830 mg, 12.3 mmol) was then added and the mixture stirred for another 6 h. Water was added and the precipitate collected by filtration, then washed with water and dried under vacuum to afford the product (2.1 g, 67%) as a white solid. LCMS $m/z = 307.2$ $[\text{M}+\text{H}]^+$.

[00204] Step 2: (S)-2-amino-N-methyl-5-phenylpentanamide

[00205] To a solution of tert-butyl (S)-(1-(methylamino)-1-oxo-5-phenylpentan-2-yl)carbamate (2.1 g, 6.85 mmol) in DCM (20 mL) was added HCl (4M in dioxane, 20 mL) and the mixture was

stirred at room temperature for 2 h. The solvent was removed to afford the product (1.65 g, quant.) as white solid. LCMS $m/z = 207.1$ $[M+H]^+$.

Synthesis of (S)-2-amino-3-(1H-indol-3-yl)-N-methylpropanamide

[00206] Made using a similar method as described for the synthesis of (S)-2-amino-N-methyl-5-phenylpentanamide, starting with (tert-butoxycarbonyl)-L-tryptophan in place of (S)-2-((tert-butoxycarbonyl)amino)-5-phenylpentanoic acid. LCMS $m/z = 218.0$ $[M+H]^+$.

Synthesis of (R)-2-amino-N-methyl-3-phenylpropanamide

[00207] Made using a similar method as described for the synthesis of (S)-2-amino-N-methyl-5-phenylpentanamide, starting with (tert-butoxycarbonyl)-D-phenylalanine in place of (S)-2-((tert-butoxycarbonyl)amino)-5-phenylpentanoic acid. LCMS $m/z = 179.1$ $[M+H]^+$.

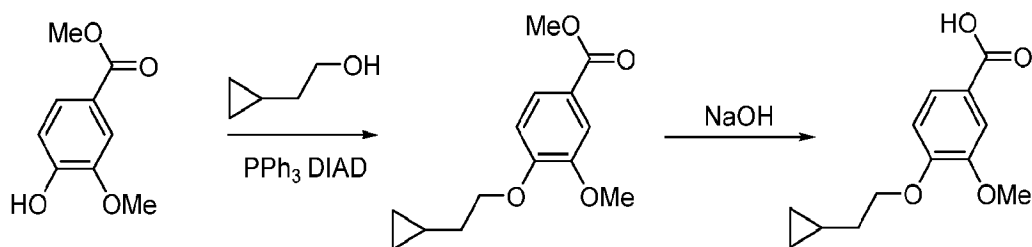
Synthesis of (R)-2-amino-3-(4-hydroxyphenyl)-N-methylpropanamide

[00208] Made using a similar method as described for the synthesis of (S)-2-amino-N-methyl-5-phenylpentanamide, starting with (tert-butoxycarbonyl)-D-tyrosine in place of (S)-2-((tert-butoxycarbonyl)amino)-5-phenylpentanoic acid. LCMS $m/z = 195.2$ $[M+H]^+$.

Synthesis of (R)-2-amino-3-(4-hydroxyphenyl)-N-methylpropanamide

[00209] Made using a similar method as described for the synthesis of (S)-2-amino-N-methyl-5-phenylpentanamide, starting with (tert-butoxycarbonyl)-L-phenylalanine in place of (S)-2-((tert-butoxycarbonyl)amino)-5-phenylpentanoic acid. LCMS $m/z = 179.2$ $[M+H]^+$.

Synthesis of 4-(2-cyclopropylethoxy)-3-methoxybenzoic acid



[00210] Step 1: methyl 4-(2-cyclopropylethoxy)-3-methoxybenzoate

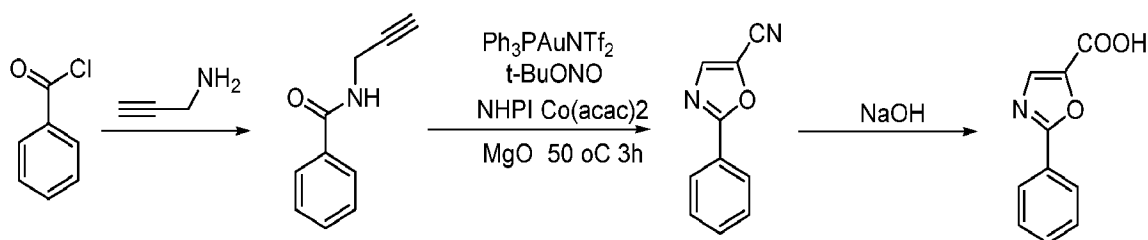
[00211] To a solution of methyl 4-hydroxy-3-methoxybenzoate (100 mg, 0.55 mmol) in dry THF (3 mL) was added 2-cyclopropylethan-1-ol (57 mg, 0.66 mmol) and PPh₃ (288 mg, 1.10 mmol). After stirring at 0°C for 10 min, DIAD (166 mg, 0.82 mmol) was added and the reaction mixture

was allowed to warm to room temperature and stirred for another 2 h. Water was added and the aqueous extracted with EtOAc three times. The combined organic layers were washed with water, brine and dried over Na₂SO₄. The solvent was removed and the residue purified by prep-TLC (50% PE/EtOAc) to afford methyl 4-(2-cyclopropylethoxy)-3-methoxybenzoate (80 mg, 59%) as a white solid. ¹H NMR (400 MHz, CD₃OD) δ 7.63 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.54 (d, *J* = 2.0 Hz, 1H), 7.01 (d, *J* = 8.4 Hz, 1H), 4.13 (t, *J* = 6.5 Hz, 2H), 3.87 (d, *J* = 1.5 Hz, 6H), 1.71 (q, *J* = 6.7 Hz, 2H), 0.96 – 0.84 (m, 1H), 0.53 – 0.45 (m, 2H), 0.18 – 0.11 (m, 2H).

[00212] Step 2: 4-(2-cyclopropylethoxy)-3-methoxybenzoic acid ()

[00213] To a solution of methyl 4-(2-cyclopropylethoxy)-3-methoxybenzoate (80 mg, 0.32 mmol) in MeOH (2 mL) was added aqueous NaOH (1M, 0.5 mL). The resulting mixture was stirred for 3 h. The residue obtained after concentration was diluted with water and the pH adjusted to ~1 by addition of 1M HCl. The aqueous layer was extracted with EtOAc three times and the combined organic layers were washed with water, brine and dried over Na₂SO₄. 4-(2-cyclopropylethoxy)-3-methoxybenzoic acid (50 mg, 67%) was obtained after removal of the solvent as a white solid. ¹H NMR (400 MHz, CD₃OD) δ 7.65 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.56 (d, *J* = 2.0 Hz, 1H), 7.01 (d, *J* = 8.4 Hz, 1H), 4.13 (t, *J* = 6.6 Hz, 2H), 3.87 (s, 3H), 1.71 (q, *J* = 6.7 Hz, 2H), 0.89 (td, *J* = 7.3, 4.0 Hz, 2H), 0.55 – 0.45 (m, 1H), 0.22 – 0.11 (m, 2H).

Synthesis of 2-phenyloxazole-5-carboxylic acid



[00214] Step 1: N-(prop-2-yn-1-yl)benzamide

[00215] To a solution of benzoyl chloride (1.0 g, 7.14 mmol) and TEA (2.7g, 26.7 mmol) in DCM (5mL) was added prop-2-yn-1-amine (0.43 g, 7.80 mmol) dropwise. The mixture was stirred at r.t. overnight. The resulting mixture was extracted with EtOAc three times. The combined organic layers were washed with water and brine, dried over Na₂SO₄ and concentrated *in vacuo*. The obtained residue was purified by column chromatography (10% EtOAc/PE) to afford N-(prop-2-yn-1-yl)benzamide (0.80g, 71.4%) as a colourless solid. LCMS *m/z* = 160.1 [M+H]⁺; ¹H NMR

(400 MHz, DMSO-*d*₆) δ 8.92 (t, J = 5.6 Hz, 1H), 7.90 – 7.80 (m, 2H), 7.58 – 7.42 (m, 3H), 4.05 (dd, J = 5.6, 2.5 Hz, 2H), 3.11 (t, J = 2.5 Hz, 1H).

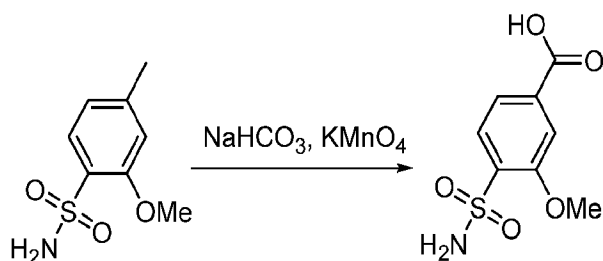
[00216] Step 2: 2-phenyloxazole-5-carbonitrile

[00217] To a solution of N-(prop-2-yn-1-yl)benzamide (350 mg, 2.201 mmol) in acetonitrile (5 mL) was added Ph₃PauNTf₂ (23.2 mg, 0.110 mmol), t-BuONO (680.1 mg, 6.603 mmol), N-Hydroxyphthalimide (107.6 mg, 0.660 mmol), bis(2,4-pentanedionato)cobalt (42.2 mg, 0.165 mmol) and magnesium oxide (266.1 mg, 6.603 mmol). The mixture was heated at 50°C for 3h. The solvent was removed under vacuum and the residue was purified by prep-TLC (6.6% MeOH/DCM) to give 2-phenyloxazole-5-carbonitrile (34 mg, 9.1%) as a colorless oil. LCMS m/z = 171.1 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.42 (s, 1H), 8.12 – 8.03 (m, 2H), 7.69 – 7.57 (m, 3H).

[00218] Step 3: 2-phenyloxazole-5-carboxylic acid

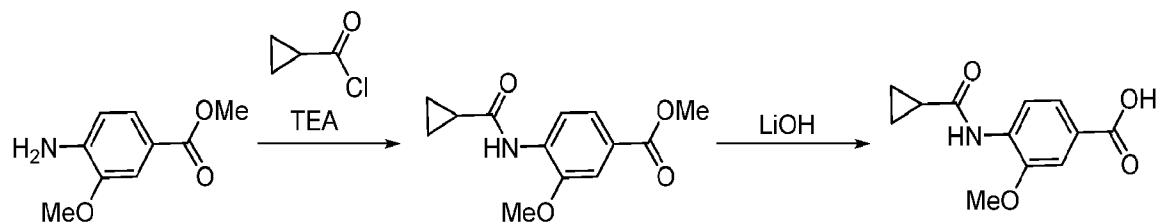
[00219] To a solution of 2-phenyloxazole-5-carbonitrile (35mg, 0.205mmol) in a mixture of DMSO (1 mL) and H₂O (0.5 mL) was added NaOH (24.6 mg, 0.615 mmol). The mixture was heated at 100°C for 3h. After pH was adjusted to ~1 with adding of 1M HCl, the aqueous was extracted with EtOAc three times. 2-phenyloxazole-5-carboxylic acid (34 mg, 87.2%) was obtained after removal of the solvent as a white solid. LCMS m/z = 190.0 [M+H]⁺.

Synthesis of 3-methoxy-4-sulfamoylbenzoic acid



[00220] To a solution of 2-methoxy-4-methylbenzenesulfonamide (1.00 g, 4.97 mmol) in H₂O (5 mL) was added NaHCO₃ (0.34 g, 3.98 mmol) and KMnO₄ (3.14g 19.88 mmol). The resulting mixture was stirred at 100°C overnight. After filtration, the filtrate was acidified by adding of 1M HCl until pH to ~2 then extracted by EtOAc three times. The combined organic layers were washed with water, brine, dried over Na₂SO₄. 3-methoxy-4-sulfamoylbenzoic acid (200 mg, 17%) was obtained after removal of the solvent as a white solid. LCMS m/z = 232.1 [M+H]⁺.

Synthesis of 4-(cyclopropanecarboxamido)-3-methoxybenzoic acid



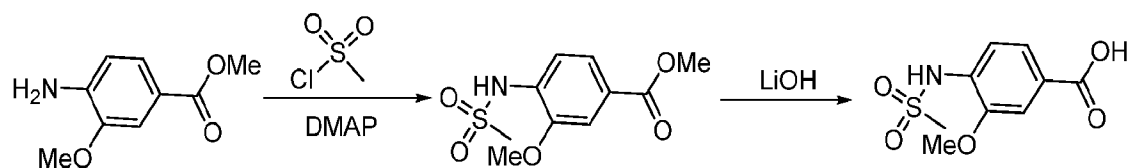
[00221] *Step 1: methyl 4-(cyclopropanecarboxamido)-3-methoxybenzoate*

[00222] To a solution of methyl 4-amino-3-methoxybenzoate (500 mg, 2.76 mmol) in DCM (5 mL) at 0°C was added TEA (836 mg, 8.26 mmol) and cyclopropanecarbonyl chloride (346 mg, 3.31 mmol). The resulting mixture was stirred at 0°C for 1 h. The residue after concentration was purified by column chromatography (30% EtOAc/PE) to afford methyl 4-(cyclopropanecarboxamido)-3-methoxybenzoate (400 mg, 58.2%) as a white solid. LCMS m/z = 250.1 $[M+H]^+$.

[00223] *Step 2: 4-(cyclopropanecarboxamido)-3-methoxybenzoic acid*

[00224] To a solution of methyl 4-(cyclopropanecarboxamido)-3-methoxybenzoate (150.0 mg, 0.60 mmol) in a mixture of THF (2 mL) and H₂O (2 mL) was added LiOH (43 mg, 1.8 mmol). The resulting mixture was stirred at room temperature for 3 h. The pH of reaction mixture was adjusted to ~2 by adding of 1M HCl then extracted with EtOAc three times. The combined organic layers were washed with water and brine, dried over Na₂SO₄. 4-(Cyclopropanecarboxamido)-3-methoxybenzoic acid (140 mg, 98.9%) was obtained after removal of the solvent as a white solid. LCMS m/z = 236.0 $[M+H]^+$.

Synthesis of 3-methoxy-4-(methylsulfonamido)benzoic acid



[00225] *Step 1: methyl 3-methoxy-4-(methylsulfonamido)benzoate*

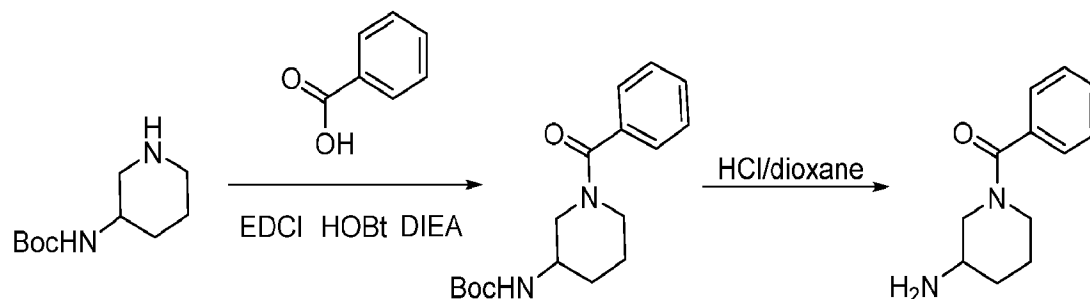
[00226] To a solution of methyl 4-amino-3-methoxybenzoate (500 mg, 2.7 mmol) in DCM (5 mL) and pyridine (0.5 mL) was added methanesulfonyl chloride (720 mg, 4.2 mmol) and DMAP (20 mg, 0.135 mmol) at 0°C. The resulting mixture was stirred for 4 h. Water was added and the

aqueous extracted with EtOAc three times. The combined organic layers were washed with water, brine and dried over Na_2SO_4 . The residue after concentration was purified by column chromatography (2% MeOH/DCM) to afford methyl 3-methoxy-4-(methylsulfonamido)benzoate (680 mg, 97%) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ 7.68 (dd, $J = 8.4, 1.7$ Hz, 1H), 7.58 (d, $J = 1.4$ Hz, 2H), 7.12 (s, 1H), 3.92 (d, $J = 13.0$ Hz, 6H), 3.03 (s, 3H).

[00227] Step 2: 3-methoxy-4-(methylsulfonamido)benzoic acid

[00228] To a solution of methyl 3-methoxy-4-(methylsulfonamido)benzoate (680 mg, 2.62 mmol) in MeOH (10 mL) and THF (5 mL) was added LiOH (275 mg, 6.55 mmol). The mixture was stirred for 2 h. The solvent was removed under vacuum and the residue obtained was diluted with water and the pH adjusted to ~ 1 by addition of 1M HCl. The aqueous layer was extracted with EtOAc three times. The combined organic layers were washed with water and brine, dried over Na_2SO_4 and the solvent removed to afford methyl 3-methoxy-4-(methylsulfonamido)benzoate (563 mg, 87.8%) as a white solid. ^1H NMR (400 MHz, CD_3OD) δ 6.83 (t, $J = 1.0$ Hz, 2H), 6.77 – 6.69 (m, 1H), 3.14 (d, $J = 0.9$ Hz, 3H), 2.20 (d, $J = 1.0$ Hz, 3H).

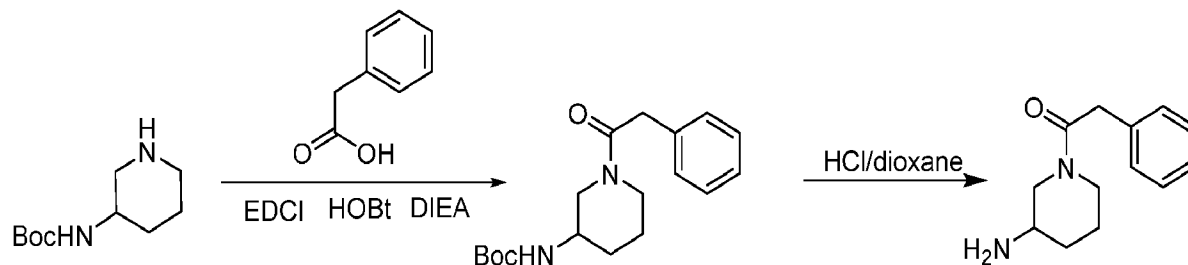
Synthesis of (3-aminopiperidin-1-yl)(phenyl)methanone hydrochloride



[00229] Step 1: tert-butyl (1-benzoylpiperidin-3-yl)carbamate To a solution of tert-butyl piperidin-3-ylcarbamate (300 mg, 1.5 mmol) in DMA (5 mL) was added benzoic acid (275.0 mg, 28.2 mmol), EDCI (430.7 mg, 2.25 mmol), HOBt (243 mg, 1.85 mmol) and DIPEA (232.3 mg, 1.85 mmol). The resulting mixture was stirred overnight. Water was added into the reaction mixture then extracted with EtOAc three times. The combined organic layers were washed with water, brine, dried over Na_2SO_4 . The residue after concentration was purified by column chromatography (10% EtOAc/PE) to afford tert-butyl (1-benzoylpiperidin-3-yl)carbamate (367 mg, 81%) as a white solid. LCMS $m/z = 305.2$ $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, CD_3OD) δ 7.54 – 7.31 (m, 5H), 3.46 (d, $J = 58.1$ Hz, 2H), 3.05 (d, $J = 47.2$ Hz, 2H), 2.11 – 1.68 (m, 3H), 1.66 – 1.20 (m, 12H).

[00230] Step 2: (3-aminopiperidin-1-yl)(phenyl)methanone hydrochloride To a solution of tert-butyl (1-benzoylpiperidin-3-yl)carbamate (367 mg, 1.2 mmol) in DCM (5 mL) was added HCl (4M in dioxane, 3 mL). The resulting mixture was stirred for 4 h. The solvent was removed to afford (3-aminopiperidin-1-yl)(phenyl)methanone hydrochloride (390 mg, quant.) LCMS m/z = 205.1 $[M+H]^+$.

Synthesis of 1-(3-aminopiperidin-1-yl)-2-phenylethan-1-one hydrochloride



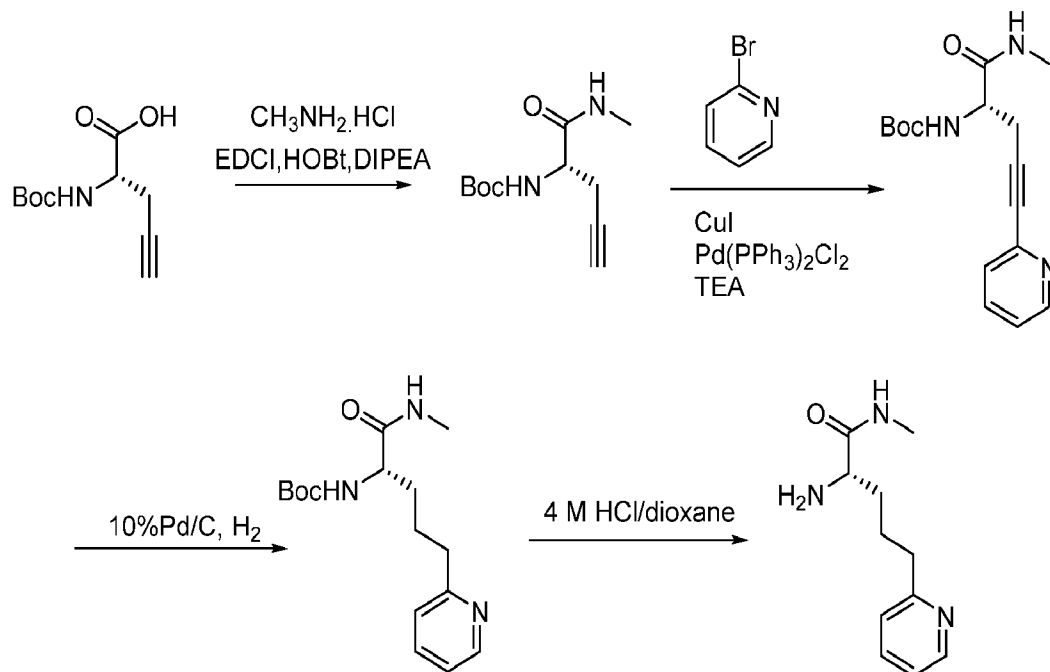
[00231] Step 1: tert-butyl (1-(2-phenylacetyl)piperidin-3-yl)carbamate

[00232] To a solution of tert-butyl piperidin-3-ylcarbamate (200 mg, 1.0 mmol) in DMA (5 mL) was added 2-phenylacetic acid (204.0 mg, 1.5 mmol), EDCI (287.1 mg, 1.5 mmol), HOBt (162.0 mg, 1.2 mmol) and DIPEA (154.9 mg, 1.2 mmol). The resulting mixture was stirred overnight. Water was added into the reaction mixture then extracted with EtOAc three times. The combined organic layers were washed with water, brine and dried over Na_2SO_4 . The solvent was removed and the residue purified by column chromatography (10% EtOAc/PE) to afford tert-butyl (1-(2-phenylacetyl)piperidin-3-yl)carbamate (234 mg, 74%) as a white solid. LCMS m/z = 319.2 $[M+H]^+$; 1H NMR (400 MHz, CD_3OD) δ 7.39 – 7.17 (m, 5H), 3.94 – 3.66 (m, 4H), 3.44 – 3.34 (m, 1H), 3.19 – 3.05 (m, 2H), 2.01 – 1.66 (m, 1H), 1.57 – 1.36 (m, 12H).

[00233] Step 2: 1-(3-aminopiperidin-1-yl)-2-phenylethan-1-one hydrochloride

[00234] To a solution of tert-butyl (1-(2-phenylacetyl)piperidin-3-yl)carbamate (367 mg, 1.2 mmol) in DCM (5 mL) was added HCl (4M in dioxane, 3 mL). The resulting mixture was stirred for 4 h. The solvent was removed to afford 1-(3-aminopiperidin-1-yl)-2-phenylethan-1-one hydrochloride (240 mg, quant.) LCMS m/z = 219.1 $[M+H]^+$.

Synthesis of (S)-2-amino-N-methyl-5-(pyridin-2-yl)pentanamide



[00235] Step 1: *tert*-butyl (S)-((1-(methylamino)-1-oxopent-4-yn-2-yl) carbamate

[00236] To a solution of methanamine hydrochloride (950 mg, 14.07 mmol) in DMF (20 mL) was added (S)-2-((tert-butoxycarbonyl)amino)pent-4-ynoic acid (2.0 g, 9.38 mmol), EDCI (2.7g, 14.07 mmol), HOBT (1.9 g, 14.07 mmol) and DIPEA (3.6 g, 28.14 mmol). The resulting mixture was stirred at room temperature for 4h. Water was added and the aqueous extracted with EtOAc three times. The combined organic layers were washed with water, brine and dried over Na₂SO₄. The solvent was removed and the residue purified by column chromatography (5% MeOH/DCM) to afford *tert*-butyl (S)-((1-(methylamino)-1-oxopent-4-yn-2-yl) carbamate (1.6 g, 76%) as a white solid. ¹H NMR (400 MHz, CD₃OD) δ 4.18 (t, *J* = 6.7 Hz, 1H), 2.74 (s, 3H), 2.67 – 2.60 (m, 1H) 2.58 – 2.49 (m, 1H), 2.36 (s, 1H), 1.45 (s, 9H).

[00237] Step 2: *tert*-butyl (S)-((1-(methylamino)-1-oxo-5-(pyridin-2-yl)pent-4-yn-2-yl) carbamate

A mixture of *tert*-butyl (S)-((1-(methylamino)-1-oxopent-4-yn-2-yl) carbamate (300 mg, 1.33 mmol), 2-bromopyridine (210 mg, 1.33 mmol), Pd(PPh₃)₄ (116 mg, 0.13 mmol), CsF (445 mg, 2.93 mmol), CuI (25 mg, 0.13 mmol) in DMF (5 mL) was heated at 100°C for 3 h under an atmosphere of N₂. Water was added and the aqueous extracted with EtOAc three times. The combined organic layers were washed with water, brine and dried over Na₂SO₄. The solvent was removed and the residue purified by prep-TLC (7% MeOH/DCM) to afford *tert*-butyl (S)-((1-

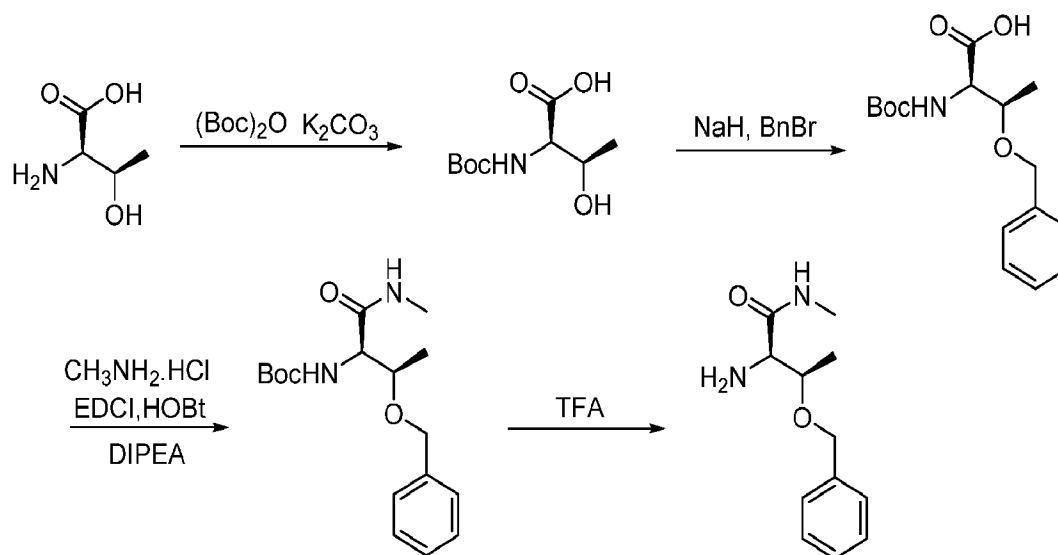
(methylamino)-1-oxo-5-(pyridin-2-yl)pent-4-yn-2-yl) carbamate (142 mg, 35 %) as a brown oil. LCMS $m/z = 304$ $[M+H]^+$; 1H NMR (400 MHz, CD_3OD) δ 8.47 (d, $J = 5.4$ Hz, 1H), 7.80 (tt, $J = 7.7, 1.2$ Hz, 1H), 7.49 (d, $J = 7.9$ Hz, 1H), 7.40 – 7.33 (m, 1H), 4.32 (t, $J = 6.6$ Hz, 1H), 2.95 – 2.81 (m, 2H), 2.76 (s, 3H), 1.44 (d, $J = 0.9$ Hz, 9H).

[00238] Step 3: tert-butyl (S)-(1-(methylamino)-1-oxo-5-(pyridin-2-yl)pentan-2-yl)carbamate To a solution of tert-butyl (S)-(1-(methylamino)-1-oxo-5-(pyridin-2-yl)pent-4-yn-2-yl) carbamate (100 mg, 0.33 mmol) in MeOH (2 mL) was added Pd/C (10%, 10 mg). The resulting mixture was stirred for 3 h under an atmosphere of H_2 . The reaction mixture was filtered through celite, the solvent removed and the residue purified by prep-TLC (7% MeOH/DCM) to afford tert-butyl (S)-(1-(methylamino)-1-oxo-5-(pyridin-2-yl)pentan-2-yl)carbamate (30 mg, 33%) as a colorless oil LCMS $m/z = 308$ $[M+H]^+$.

[00239] Step 4: (S)-2-amino-N-methyl-5-(pyridin-2-yl)pentanamide

[00240] To a solution of tert-butyl (S)-(1-(methylamino)-1-oxo-5-(pyridin-2-yl)pentan-2-yl)carbamate (30 mg, 0.098 mmol) in MeOH (1 mL) was added HCl (4M in dioxane, 1 mL). The resulting mixture was stirred at room temperature for 3 h. The solvent was removed under reduced pressure to afford (S)-2-amino-N-methyl-5-(pyridin-2-yl)pentanamide (22 mg, quant.). LCMS $m/z = 208$ $[M+H]^+$.

Synthesis of (2R,3R)-2-amino-3-(benzyloxy)-N-methylbutanamide



[00241] Step 1: (tert-butoxycarbonyl)-D-allothreonine

[00242] To a solution of D- allothreonine (1.0 g, 8.4 mmol) in a mixture of THF and H₂O (10 mL/2 mL) was added K₂CO₃ (2.3 g, 16.8 mmol) and Boc anhydride (2.0 g, 9.2 mmol). The resulting mixture was stirred overnight. Water was added and the aqueous extracted with EtOAc. The combined organic layers were washed with water, brine and dried over Na₂SO₄. The solvent was removed to afford (tert-butoxycarbonyl)-D-allothreonine (700 mg, 39%) as a yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 6.78 (d, *J* = 7.7 Hz, 1H), 3.90 – 3.79 (m, 2H), 1.38 (s, 9H), 1.08 (d, *J* = 5.5 Hz, 3H).

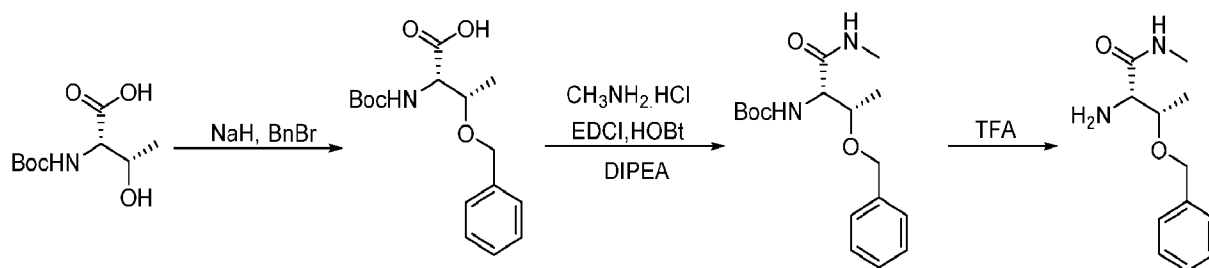
[00243] Step 2: O-benzyl-N-(tert-butoxycarbonyl)-D-allothreonine

[00244] To a solution of (tert-butoxycarbonyl)-D-allothreonine (700 mg, 3.2 mmol) in DMF (5.0 mL) was added NaH (270 mg, 6.7 mmol) portionwise at 0°C. After stirring for 1h, BnBr (544 mg, 3.2 mmol) was added and the reaction mixture was stirred for another 14 h. The solvent was removed and the residue purified by RP column to afford O-benzyl-N-(tert-butoxycarbonyl)-D-allothreonine (345 mg, 35%) as a white solid. ¹H NMR (400 MHz, CD₃OD) δ 7.38 – 7.23 (m, 5H), 4.63 – 4.51 (m, 2H), 4.46 (d, *J* = 4.9 Hz, 1H), 3.92 (p, *J* = 6.5 Hz, 1H), 1.45 (s, 9H), 1.21 (d, *J* = 6.4 Hz, 3H).

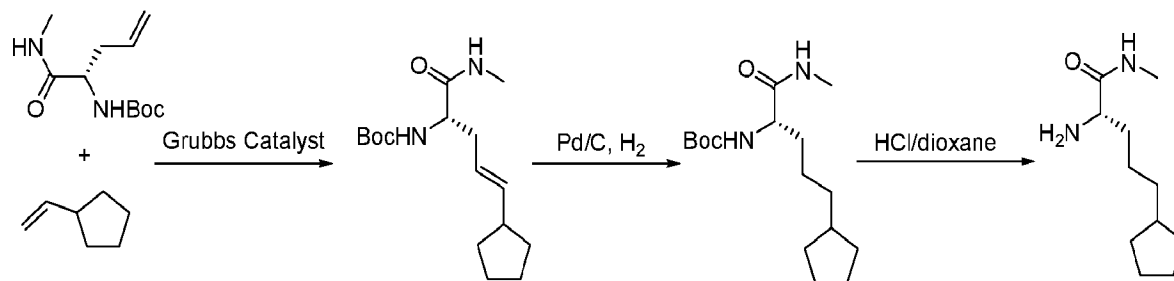
[00245] Step 3: tert-butyl ((2R,3R)-3-(benzyloxy)-1-(methylamino)-1-oxobutan-2-yl)carbamate

[00246] To a solution of O-benzyl-N-(tert-butoxycarbonyl)-D-allothreonine (100 mg, 0.32 mmol) in DMF (2 mL) was added CH₃NH₂.HCl (26 mg, 0.39 mmol), EDCI (93 mg, 0.48 mmol), HOBT (66 mg, 0.48 mmol) and DIPEA (209 mg, 1.62 mmol). The resulting mixture was stirred at room temperature for 14 h. Water was added and the aqueous extracted with EtOAc. The combined organic layers were washed with water, brine and dried over Na₂SO₄. The solvent was removed and the residue purified by column chromatography (1% MeOH/DCM) to afford tert-butyl ((2R,3R)-3-(benzyloxy)-1-(methylamino)-1-oxobutan-2-yl)carbamate (80 mg, 80%) as a white solid. ¹H NMR (400 MHz, CD₃OD) δ 7.35 – 7.21 (m, 5H), 4.52 (q, *J* = 11.5 Hz, 2H), 3.83 (t, *J* = 6.4 Hz, 1H), 2.73 (s, 3H), 2.45 – 2.30 (m, 1H), 1.44 (s, 9H), 1.19 (t, *J* = 6.7 Hz, 3H).

[00247] Step 4: (2R,3R)-2-amino-3-(benzyloxy)-N-methylbutanamide To a solution of tert-butyl ((2R,3R)-3-(benzyloxy)-1-(methylamino)-1-oxobutan-2-yl)carbamate (80 mg, 0.25 mmol) in DCM (2 mL) was added TFA (0.5 mL). The resulting mixture was stirred for 3h. The solvent was removed under reduced pressure to afford (2R,3R)-2-amino-3-(benzyloxy)-N-methylbutanamide (55 mg, quant.). This product was used directly in next step.

Synthesis of (2S,3S)-2-amino-3-(benzyloxy)-N-methylbutanamide

[00248] Made using a similar method as described for the synthesis of (2R,3R)-2-amino-3-(benzyloxy)-N-methylbutanamide. LCMS $m/z = 223.1$ $[M+H]^+$.

Synthesis of (S)-2-amino-5-cyclopentyl-N-methylpentanamide

[00249] **Step 1: tert-butyl (S)-(5-cyclopentyl-1-(methylamino)-1-oxopent-4-en-2-yl)carbamate** To a solution of tert-butyl (S)-(1-(methylamino)-1-oxopent-4-en-2-yl)carbamate (200 mg, 0.877 mmol) in DCM (3 mL) was added vinylcyclopentane (169 mg, 1.754 mmol) and Grubbs catalyst (150 mg, 0.17 mmol). The resulting mixture was stirred at room temperature for 12 h. Water was added and the aqueous extracted with EtOAc. The combined organic layers were washed with water, brine and dried over Na_2SO_4 . The solvent was removed and the residue purified by column chromatography (33% EtOAc/PE) to afford tert-butyl (S)-(5-cyclopentyl-1-(methylamino)-1-oxopent-4-en-2-yl)carbamate (58 mg, 22%) as a white solid. LCMS $m/z = 297$ $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 5.61 – 5.17 (m, 2H), 4.05 – 3.84 (m, 1H), 2.72 (d, $J = 3.6$ Hz, 3H), 2.32 (ddt, $J = 61.8, 14.6, 7.8$ Hz, 3H), 1.81 – 1.52 (m, 6H), 1.44 (s, 9H), 1.34 – 1.24 (m, 2H).

[00250] Step 2: tert-butyl (S)-(5-cyclopentyl-1-(methylamino)-1-oxopentan-2-yl)carbamate

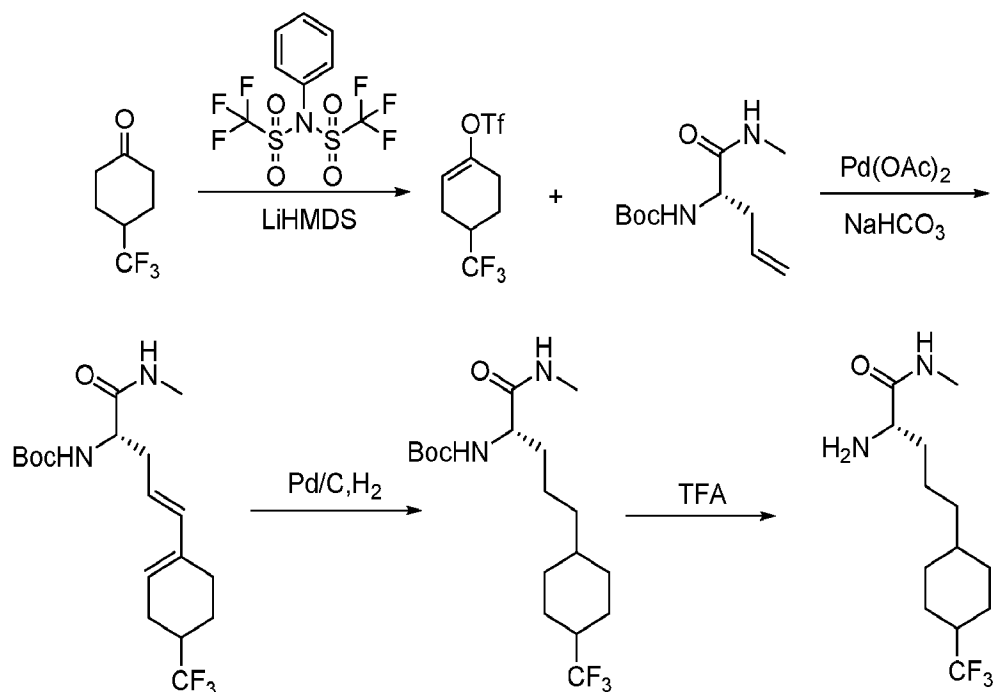
[00251] To a solution of tert-butyl (S)-(5-cyclopentyl-1-(methylamino)-1-oxopent-4-en-2-yl)carbamate (58 mg, 0.196 mmol) in MeOH (1 mL) was added 10% Pd/C (10 mg). The resulting mixture was stirred at room temperature for 3 h under an atmosphere of H_2 . The filtrate through a pad of celite was concentrated to afford tert-butyl (S)-(5-cyclopentyl-1-(methylamino)-1-

oxopentan-2-yl)carbamate (50 mg, 99%) as a white solid. ^1H NMR (400 MHz, CD_3OD) δ 3.97 (dd, $J = 9.2, 5.3$ Hz, 1H), 2.73 (s, 3H), 1.87 – 1.47 (m, 9H), 1.44 (s, 9H), 1.41 – 0.82 (m, 7H).

[00252] Step 3: (S)-2-amino-5-cyclopentyl-N-methylpentanamide

[00253] To a solution of tert-butyl (S)-(5-cyclopentyl-1-(methylamino)-1-oxopentan-2-yl)carbamate (50 mg, 0.167 mmol) in MeOH (1 mL) was added HCl (4M in dioxane, 1 ml). The mixture was stirred at room temperature for 3 h. The mixture was concentrated to afford (S)-2-amino-5-cyclopentyl-N-methylpentanamide.

Synthesis of (S)-2-amino-N-methyl-5-(4-(trifluoromethyl)cyclohexyl)pentanamide



[00254] Step 1: 4-(trifluoromethyl)cyclohex-1-en-1-yl trifluoromethanesulfonate

[00255] To a solution of 4-(trifluoromethyl)cyclohexan-1-one (500 mg, 3.01 mmol) in THF (8 mL) at -78°C was added LiHMDS (3.6 mL, 3.61 mmol) dropwise and stirred for 30 minute. Then a solution of 1,1,1-trifluoro-N-phenyl-N-((trifluoromethyl)sulfonyl)methanesulfonamide (1.18 g, 3.31 mmol) in THF (1 mL) was added thereto and the mixture was stirred at room temperature overnight. Water was added and the aqueous extracted with EtOAc. The combined organic layers were washed with water, brine and dried over Na_2SO_4 . The solvent was removed and the residue purified by column chromatography (2% MeOH/DCM) to afford 4-(trifluoromethyl)cyclohex-1-en-1-yl trifluoromethanesulfonate (400 mg, 45%). ^1H NMR (400 MHz, Chloroform- d) δ 5.81 –

5.76 (m, 1H), 2.55 – 2.39 (m, 3H), 2.38 – 2.25 (m, 2H), 2.15 (ddt, $J = 13.1, 4.9, 2.5$ Hz, 1H), 1.77 (dtd, $J = 13.0, 11.1, 6.3$ Hz, 1H).

[00256] Step 2: *tert*-butyl ((2*S*,*E*)-1-(methylamino)-1-oxo-5-(4-(trifluoromethyl)cyclohex-1-en-1-yl)pent-4-en-2-yl)carbamate

[00257] A mixture of 4-(trifluoromethyl)cyclohex-1-en-1-yl trifluoromethanesulfonate (250 mg, 0.838 mmol), *tert*-butyl (S)-(1-(methylamino)-1-oxopent-4-en-2-yl)carbamate (172 mg, 0.755 mmol), Pd(OAc)₂ (19 mg, 0.084 mmol) and NaHCO₃ (211 mg, 2.52 mmol) in DMF/H₂O(4mL/1mL) was stirred at 70°C overnight. Water was added and the aqueous extracted with EtOAc. The combined organic layers were washed with water, brine and dried over Na₂SO₄. The solvent was removed and the residue purified by column chromatography (1.5% MeOH/DCM) to afford *tert*-butyl ((2*S*,*E*)-1-(methylamino)-1-oxo-5-(4-(trifluoromethyl)cyclohex-1-en-1-yl)pent-4-en-2-yl)carbamate (120 mg, 38%). LCMS $m/z = 377$ [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 6.23 – 5.63 (m, 2H), 5.56 – 4.80 (m, 2H), 4.12 (d, $J = 7.1$ Hz, 1H), 2.82 (d, $J = 4.9$ Hz, 3H), 2.60 – 2.26 (m, 3H), 2.27 – 1.92 (m, 3H), 1.48 – 1.39 (m, 9H), 1.29 – 1.23 (m, 2H).

[00258] Step 3: *tert*-butyl (S)-(1-(methylamino)-1-oxo-5-(4-(trifluoromethyl)cyclohexyl)pentan-2-yl)carbamate

[00259] To a solution of ((2*S*,*E*)-1-(methylamino)-1-oxo-5-(4-(trifluoromethyl)cyclohex-1-en-1-yl)pent-4-en-2-yl)carbamate (120 mg, 0.319 mmol) in MeOH (2 mL) was added 10% Pd/C (12 mg). The resulting mixture was stirred under H₂ overnight. The mixture was filtered through a pad of celite and the solvent remove from the filtrate to afford *tert*-butyl (S)-(1-(methylamino)-1-oxo-5-(4-(trifluoromethyl)cyclohexyl)pentan-2-yl)carbamate (100 mg, 83%). LCMS $m/z = 381$ [M+H]⁺.

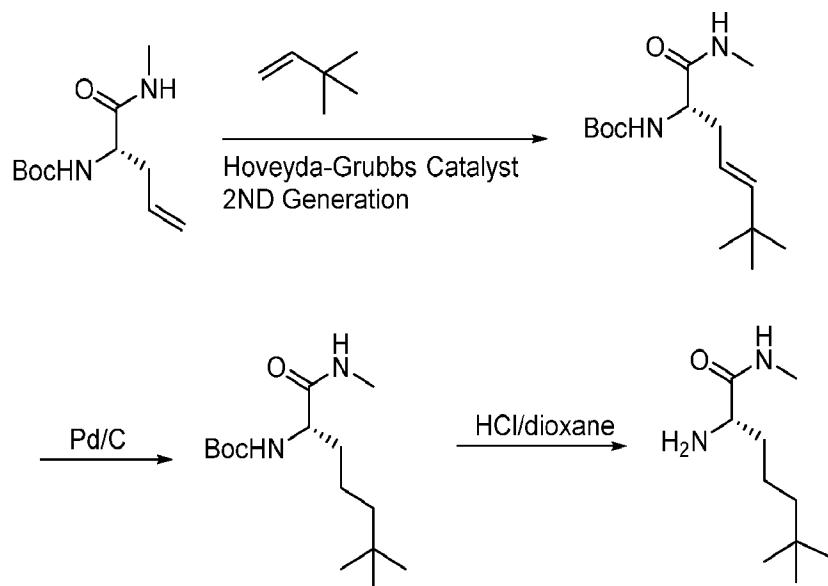
[00260] Step 4: (S)-2-amino-N-methyl-5-(4-(trifluoromethyl)cyclohexyl)pentanamide

[00261] To a solution of *tert*-butyl (S)-(1-(methylamino)-1-oxo-5-(4-(trifluoromethyl)cyclohexyl)pentan-2-yl)carbamate (100 mg, 0.263 mmol) in DCM (3 mL) was added TFA (3 mL). The mixture was stirred for 3 h. The solvent was removed to afford (S)-2-amino-N-methyl-5-(4-(trifluoromethyl)cyclohexyl)pentanamide (76 mg, quant.). LCMS $m/z = 281$ [M+H]⁺

Synthesis of (S)-2-amino-5-cycloheptyl-N-methylpentanamide

[00262] Made using a similar method as described for the synthesis of (S)-2-amino-N-methyl-5-(4-(trifluoromethyl)cyclohexyl)pentanamide, starting from cycloheptanone, in place of 4-(trifluoromethyl)cyclohexan-1-one. LCMS $m/z = 227.1$ $[M+H]^+$.

Synthesis of (S)-2-amino-N,6,6-trimethylheptanamide



[00263] Step 1: tert-butyl (S,E)-(6,6-dimethyl-1-(methylamino)-1-oxohept-4-en-2-yl)carbamate

[00264] To a solution of tert-butyl (S)-(1-(methylamino)-1-oxopent-4-en-2-yl)carbamate (500 mg, 2.19 mmol) and 3,3-dimethylbut-1-ene (992.0 mg, 10.9 mmol) in toluene (10 mL) was added Hoveyda-Grubbs Catalyst 2nd Generation (274.4 mg, 0.428 mmol). The mixture was stirred at 100°C for two days. The resulting mixture was concentrated *in vacuo*. The solvent was removed and the residue purified by column chromatography (25% EtOAc/PE) to afford tert-butyl (S,E)-(6,6-dimethyl-1-(methylamino)-1-oxohept-4-en-2-yl)carbamate (85.0 mg, 14%) as colourless oil. ^1H NMR (400 MHz, CDCl_3) δ 6.15 (s, 1H), 5.56 (m, 1H), 5.41 – 5.04 (m, 1H), 2.80 (d, $J = 4.9$ Hz, 3H), 2.54 – 2.22 (m, 2H), 1.43 (s, 9H), 0.98 (s, 9H).

[00265] Step 2: tert-butyl (S)-(6,6-dimethyl-1-(methylamino)-1-oxoheptan-2-yl)carbamate

[00266] To a solution of tert-butyl (S,E)-(6,6-dimethyl-1-(methylamino)-1-oxohept-4-en-2-yl)carbamate (85 mg, 0.299 mmol) in MeOH (3 mL) was added Pd/C (10 mg). The mixture was stirred under an atmosphere of H_2 for 8 h. The mixture was filtered through a pad of celite and the

solvent removed from the filtrate to afford tert-butyl (S)-(6,6-dimethyl-1-(methylamino)-1-oxoheptan-2-yl)carbamate (76.0 mg, 80%) as colourless oil. LCMS $m/z = 287$ $[M+H]^+$.

[00267] Step 3: (S)-2-amino-N,6,6-trimethylheptanamide

[00268] To a solution of tert-butyl (S)-(6,6-dimethyl-1-(methylamino)-1-oxoheptan-2-yl)carbamate (76.0 mg, 0.27 mmol) in DCM (5 mL) was added HCl (4 M in dioxane, 3 mL). The resulting mixture was stirred for 3 h. The solvent was removed to afford (S)-2-amino-N,6,6-trimethylheptanamide (80 mg, quant.). LCMS $m/z = 186$ $[M+H]^+$.

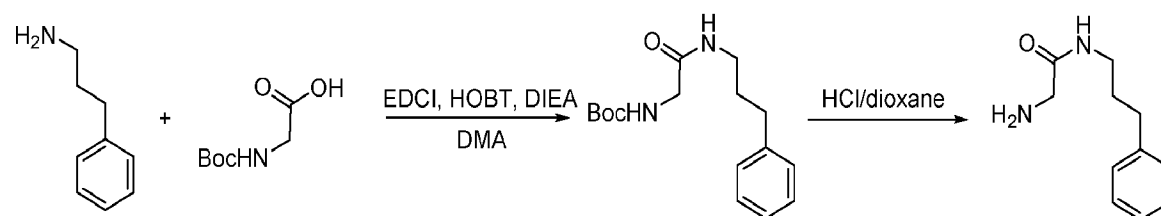
Synthesis of (S)-2-amino-N,6-dimethylheptanamide

[00269] Made using a similar method as described for the synthesis of (S)-2-amino-N,6,6-trimethylheptanamide, using 3-methylbut-1-ene and Grubbs catalyst in place of 3,3-dimethylbut-1-ene and Hoveyda-Grubbs catalyst, respectively. The solvent was removed *in vacuo* and the crude product was used directly in the synthesis of additional compounds.

Synthesis of (S)-2-amino-5-cyclohexyl-N-methylpentanamide

[00270] Made using a similar method as described for the synthesis of (S)-2-amino-N,6,6-trimethylheptanamide, using vinylcyclohexane and Grubbs catalyst in place of 3,3-dimethylbut-1-ene and Hoveyda-Grubbs catalyst, respectively. LCMS $m/z = 213.1$ $[M+H]^+$.

Synthesis of 2-amino-N-(3-phenylpropyl)acetamide



[00271] Step 1: tert-butyl (2-oxo-2-((3-phenylpropyl)amino)ethyl)carbamate

[00272] To a solution of (tert-butoxycarbonyl)glycine (500 mg, 2.85 mmol), EDCI (821 mg, 4.28 mmol) and HOBT (463 mg, 3.42 mmol) in DMA (10 mL) was added 3-phenylpropan-1-amine (424 mg, 3.14 mmol) and DIEA (1.11 g, 8.56 mmol). The mixture was stirred at room temperature overnight. Water was added and the aqueous extracted with EtOAc three times. The combined organic layers were washed with water and brine, dried over Na_2SO_4 and the solvent removed in

vacuo. The crude was purified by column chromatography (2.5% MeOH/DCM) to give tert-butyl (2-oxo-2-((3-phenylpropyl)amino)ethyl)carbamate (538 mg, 64%). LCMS $m/z = 293.3$ $[M+H]^+$.

[00273] Step 2: 2-amino-N-(3-phenylpropyl)acetamide

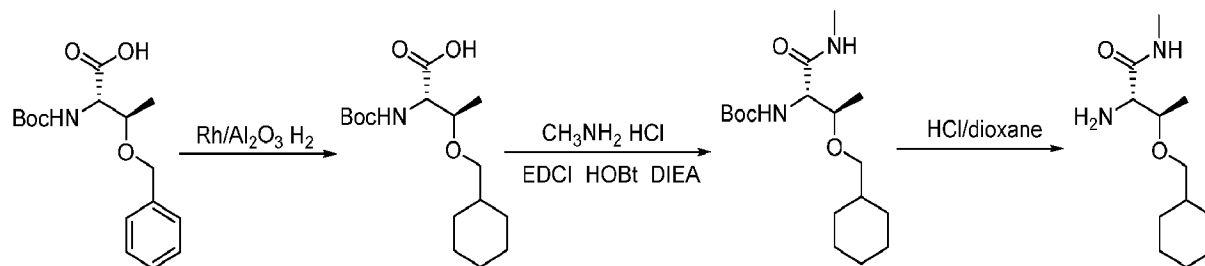
[00274] A solution of tert-butyl (2-oxo-2-((3-phenylpropyl)amino)ethyl)carbamate (500 mg, 1.71 mmol) in HCl (4M in dioxane, 5mL) was stirred for 1h. The volatiles were removed in *vacuo* to give 2-amino-N-(3-phenylpropyl)acetamide (486 mg, quant.).

[00275] Synthesis of (S)-2-amino-N-methyl-N-(3-phenylpropyl)propanamide

[00276] Made using a similar method as described for the synthesis of 2-amino-N-(3-phenylpropyl)acetamide, starting from N-methyl-3-phenylpropan-1-amine and (tert-butoxycarbonyl)-L-alanine. LCMS $m/z = 221.3$ $[M+H]^+$.

Synthesis of 2-amino-N-methyl-N-(3-phenylpropyl)acetamide Made using a similar method as described for the synthesis of 2-amino-N-(3-phenylpropyl)acetamide, starting from N-methyl-3-phenylpropan-1-amine and (tert-butoxycarbonyl)glycine. LCMS $m/z = 207.2$ $[M+H]^+$.

Synthesis of (2S,3R)-2-amino-3-(cyclohexylmethoxy)-N-methylbutanamide



[00277] Step 1: N-(tert-butoxycarbonyl)-O-(cyclohexylmethyl)-L-threonine

[00278] To a solution of O-benzyl-N-(tert-butoxycarbonyl)-L-threonine (400 mg, 1.29 mmol) in IPA (15 mL) was added Rh- Al_2O_3 (5%, 50 mg). The resulting mixture was stirred overnight under H_2 . The reaction mixture was filtered through a pad of celite, the solvent removed and the residue purified by column chromatography (10% MeOH/DCM) to afford N-(tert-butoxycarbonyl)-O-(cyclohexylmethyl)-L-threonine (390 mg, 95.6%) as a colorless oil. 1H NMR (400 MHz, CD_3OD) δ 4.09 (d, $J = 2.8$ Hz, 1H), 4.04 – 3.94 (m, 1H), 3.39 – 3.33 (m, 1H), 3.17 – 3.09 (m, 1H), 1.79 – 1.62 (m, 4H), 1.53 – 1.40 (m, 9H), 1.34 – 1.09 (m, 8H), 1.00 – 0.81 (m, 2H).

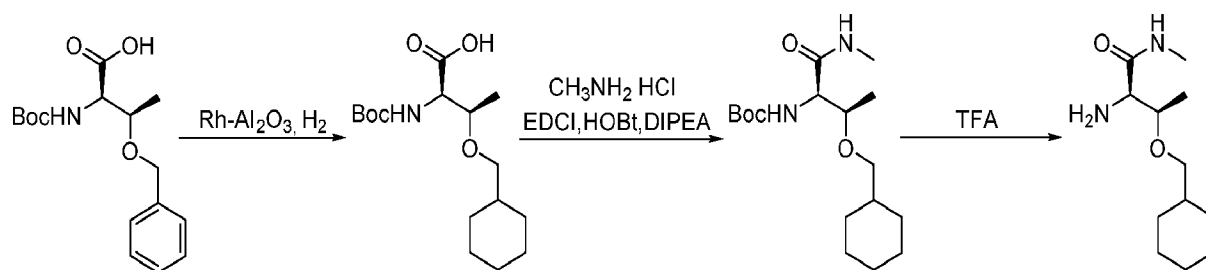
[00279] Step 2: *tert*-butyl ((2*S*,3*R*)-3-(cyclohexylmethoxy)-1-(methylamino)-1-oxobutan-2-yl) carbamate

[00280] To a solution of *N*-(*tert*-butoxycarbonyl)-*O*-(cyclohexylmethyl)-*L*-threonine (390 mg, 1.24 mmol) in DMF (8 mL) was added methylamine hydrochloride (167 mg, 2.47 mmol), EDCI (357 mg, 1.86 mmol), HOBt (202 mg, 1.49 mmol) and DIPEA (320 mg, 2.47 mmol). The resulting mixture was stirred at room temperature overnight. Water was added and the aqueous extracted with EtOAc three times. The combined organic layers were washed with water, brine and dried over Na₂SO₄. The solvent was removed and the residue purified by column chromatography (1.9% MeOH/DCM) to afford *tert*-butyl ((2*S*,3*R*)-3-(cyclohexylmethoxy)-1-(methylamino)-1-oxobutan-2-yl) carbamate (360 mg, 88%) as a white solid. LCMS *m/z* = 329.3 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 6.53 (br, 1H), 5.47 (d, *J* = 6.8 Hz, 1H), 4.20 – 4.13 (m, 1H), 3.99 – 3.90 (m, 1H), 3.41 – 3.21 (m, 2H), 2.83 (d, *J* = 4.9 Hz, 3H), 1.75 – 1.61 (m, 6H), 1.45 (s, 9H), 1.29 – 1.04 (m, 6H), 0.96 – 0.83 (m, 2H)

[00281] Step 3: (2*S*,3*R*)-2-amino-3-(cyclohexylmethoxy)-*N*-methylbutanamide

[00282] To a solution of *tert*-butyl ((2*S*,3*R*)-3-(cyclohexylmethoxy)-1-(methylamino)-1-oxobutan-2-yl) carbamate (350 mg, 1.06 mmol) in DCM (2 mL) was added TFA (1 mL). The resulting mixture was stirred for 2 h. The solvent was removed to afford (2*S*,3*R*)-2-amino-3-(cyclohexylmethoxy)-*N*-methylbutanamide (370 mg, quant.). LCMS *m/z* = 229.2 [M+H]⁺.

Synthesis of (2*R*,3*R*)-2-amino-3-(cyclohexylmethoxy)-*N*-methylbutanamide



[00283] Step 1: *N*-(*tert*-butoxycarbonyl)-*O*-(cyclohexylmethyl)-*D*-allothreonine

[00284] To a solution of *O*-benzyl-*N*-(*tert*-butoxycarbonyl)-*D*-allothreonine (70 mg, 0.22 mmol) in IPA (2 mL) was added Rh-Al₂O₃ (5%, 20 mg). The resulting mixture was stirred overnight under an atmosphere of H₂. The reaction mixture was filtered through celite and the solvent removed to

afford N-(tert-butoxycarbonyl)-O-(cyclohexylmethyl)-D-allothreonine (50 mg, 71 %) as a colorless oil. LCMS $m/z = 316.1$ $[M+H]^+$.

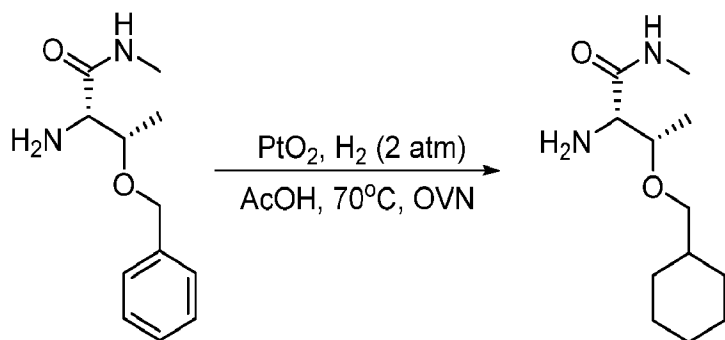
[00285] Step 2: tert-butyl ((2R,3R)-3-(cyclohexylmethoxy)-1-(methylamino)-1-oxobutan-2-yl)carbamate

[00286] To a solution of N-(tert-butoxycarbonyl)-O-(cyclohexylmethyl)-D-allothreonine (50 mg, 0.16 mmol) in DMF (1 mL) was added methylamine hydrochloride (13 mg, 0.19 mmol), EDCI (46 mg, 0.24 mmol), HOBt (32 mg, 0.24 mmol) and DIPEA (62 mg, 0.48 mmol). The resulting mixture was stirred overnight. Water was added and the aqueous extracted with EtOAc. The combined organic layers were washed with water, brine and dried over Na_2SO_4 . The solvent was removed and the residue purified by column chromatography (2% MeOH/DCM) to afford tert-butyl ((2R,3R)-3-(cyclohexylmethoxy)-1-(methylamino)-1-oxobutan-2-yl)carbamate (38 mg, 73%) as a white solid. LCMS $m/z = 329.3$ $[M+H]^+$.

[00287] Step 3: (2R,3R)-2-amino-3-(cyclohexylmethoxy)-N-methylbutanamide

[00288] To a solution of tert-butyl ((2R,3R)-3-(cyclohexylmethoxy)-1-(methylamino)-1-oxobutan-2-yl)carbamate (38 mg, 0.12 mmol) in a mixture of DCM (1 mL) and MeOH (1 mL) was added TFA (1 mL). The resulting mixture was stirred for 2 h. The solvent was removed under reduced pressure to afford (2R,3R)-2-amino-3-(cyclohexylmethoxy)-N-methylbutanamide (27 mg, quant.) as a yellow oil. LCMS $m/z = 229.2$ $[M+H]^+$.

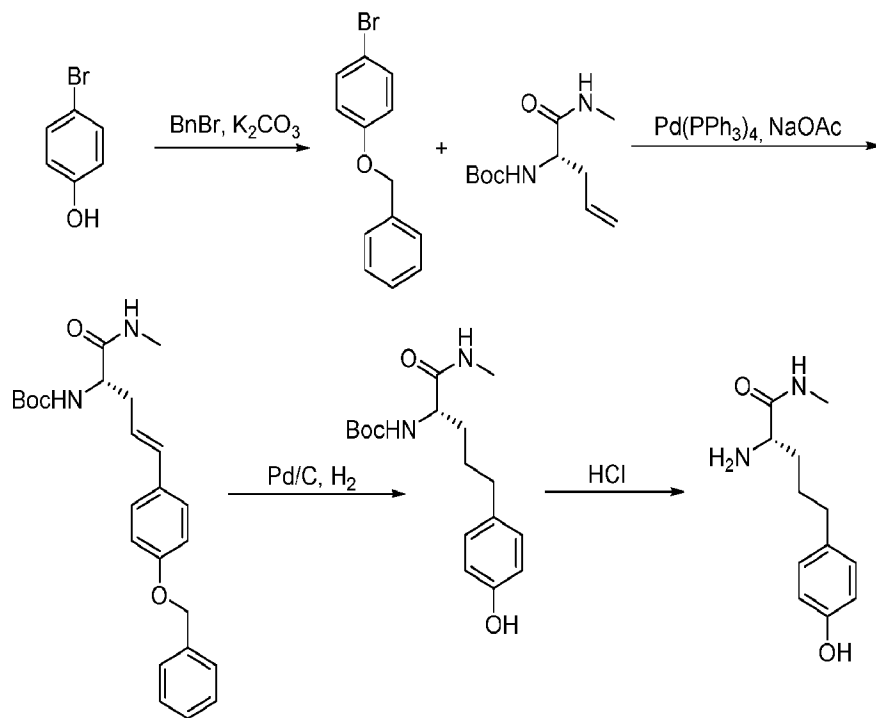
Synthesis of (2S,3S)-2-amino-3-(cyclohexylmethoxy)-N-methylbutanamide



[00289] To a solution of (2S,3S)-2-amino-3-(benzyloxy)-N-methylbutanamide (100 mg, 0.45 mmol) in AcOH (2 mL) was added PtO_2 (20 mg) and the mixture was stirred under an atmosphere of H_2 (2 atm) overnight. The mixture was filtered through a pad of celite and the filtrate

concentrated to afford (2S,3S)-2-amino-3-(cyclohexylmethoxy)-N-methylbutanamide (90 mg, 87%). LCMS $m/z = 229.2$ $[M+H]^+$.

Synthesis of (S)-2-amino-5-(4-hydroxyphenyl)-N-methylpentanamide



[00290] Step 1: 1-(benzyloxy)-4-bromobenzene

[00291] To a solution of 4-bromophenol (1 g, 5.78 mmol) in DMF (20 mL) was added BnBr (1.037 g, 6.07 mmol) and K_2CO_3 (2.4 g, 17.3 mmol). The resulting mixture was stirred at room temperature for 4h. Water was added and the aqueous extracted with EtOAc three times. The combined organic layers were washed with water, brine and dried over Na_2SO_4 . The solvent was removed and the residue purified by column chromatography (5% MeOH/DCM) to afford 1-(benzyloxy)-4-bromobenzene (1.215g, 80%) as a white solid. 1H NMR (400 MHz, CD_3OD) δ 7.44 – 7.27 (m, 7H), 6.94 – 6.88 (m, 2H), 5.04 (s, 2H).

[00292] Step 2: tert-butyl (S,E)-5-(4-(benzyloxy)phenyl)-1-(methylamino)-1-oxopent-4-en-2-ylcarbamate

[00293] To a solution of 1-(benzyloxy)-4-bromobenzene (100 mg, 0.38 mmol) in NMP (2 mL) was added tert-butyl (S)-1-(methylamino)-1-oxopent-4-en-2-ylcarbamate (86.6 mg, 0.38 mmol), $Pd(PPh_3)_4$ (22 mg, 0.019 mmol) and NaOAc (62.3 mg, 0.76 mmol). The mixture was heated at 110°C overnight. Water was added and the aqueous extracted with EtOAc three times. The

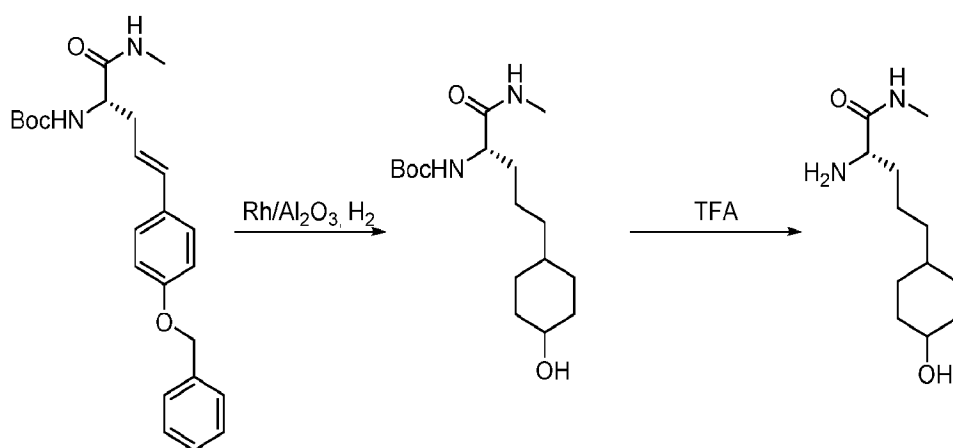
combined organic layers were washed with water, brine and dried over Na_2SO_4 . The solvent was removed and the residue purified by column chromatography (50% EtOAc/PE) to afford tert-butyl (S,E)-(5-(4-(benzyloxy)phenyl)-1-(methylamino)-1-oxopent-4-en-2-yl)carbamate (37.8 mg, 24.3%) as a white solid. LCMS $m/z = 411.2$ $[\text{M}+\text{H}]^+$.

[00294] Step 3: tert-butyl (S)-(5-(4-hydroxyphenyl)-1-(methylamino)-1-oxopentan-2-yl)carbamate To a solution of tert-butyl (S,E)-(5-(4-(benzyloxy)phenyl)-1-(methylamino)-1-oxopent-4-en-2-yl)carbamate (37.8 mg, 0.092 mmol) in MeOH (1 mL) was added Pd/C (10%, 50 mg). The resulting mixture was stirred for 3 h under an atmosphere of H_2 . The reaction mixture was filtered through celite and the solvent was removed to afford tert-butyl (S)-(5-(4-hydroxyphenyl)-1-(methylamino)-1-oxopentan-2-yl)carbamate (33 mg, quant) as a colorless oil. LCMS $m/z = 323.2$ $[\text{M}+\text{H}]^+$.

[00295] Step 4: (S)-2-amino-5-(4-hydroxyphenyl)-N-methylpentanamide

[00296] To a solution of tert-butyl (S)-(5-(4-hydroxyphenyl)-1-(methylamino)-1-oxopentan-2-yl)carbamate (33 mg, 0.102 mmol) in DCM (1 mL) was added HCl (4M in dioxane, 0.5 mL). The mixture was stirred at room temperature for 2 h. The solvent was removed to afford (S)-2-amino-5-(4-hydroxyphenyl)-N-methylpentanamide (25.5 g, quant.). LCMS $m/z = 223.1$ $[\text{M}+\text{H}]^+$.

Synthesis of (S)-2-amino-5-(4-hydroxycyclohexyl)-N-methylpentanamide



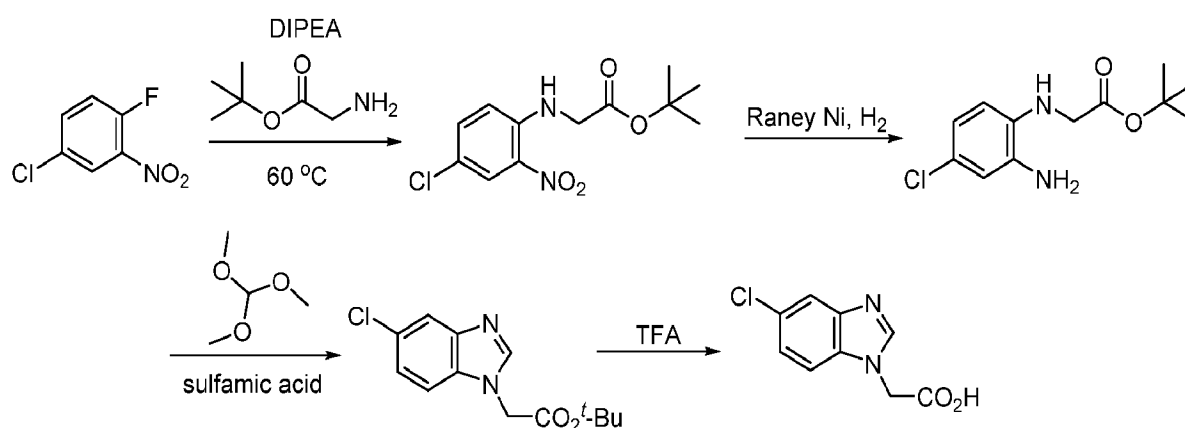
[00297] Step 1: tert-butyl (S)-(5-(4-hydroxycyclohexyl)-1-(methylamino)-1-oxopentan-2-yl)carbamate To a solution of tert-butyl (S)-(5-(4-hydroxycyclohexyl)-1-(methylamino)-1-oxopentan-2-yl)carbamate (200 mg, 0.048 mmol) in IPA (1 mL) was added Rh/ Al_2O_3 (5%, 49 mg). The mixture was stirred at room temperature under H_2 for 2h. The reaction mixture was

filtered through celite and the filtrate concentrated to afford tert-butyl (S)-(5-(4-hydroxycyclohexyl)-1-(methylamino)-1-oxopentan-2-yl)carbamate (16.7mg, quant.) as a colorless oil LCMS $m/z = 329.2$ $[M+H]^+$.

[00298] Step 2: (S)-2-amino-5-(4-hydroxycyclohexyl)-N-methylpentanamide

[00299] To a solution of tert-butyl (S)-(5-(4-hydroxycyclohexyl)-1-(methylamino)-1-oxopentan-2-yl)carbamate (16 mg, 0.048 mmol) in DCM (1 mL) was added TFA (1 mL). The mixture was stirred at room temperature for 1 h. The solvent was removed to afford (S)-2-amino-5-(4-hydroxycyclohexyl)-N-methylpentanamide (16 mg, quant). LCMS $m/z = 226.9$ $[M-H]^-$.

Synthesis of 2-(5-chloro-1H-benzo[d]imidazol-1-yl)acetic acid



[00300] Step 1: tert-butyl (4-chloro-2-nitrophenyl)glycinate

[00301] To a solution of 4-chloro-1-fluoro-2-nitrobenzene (200 mg, 1.14 mmol) in DMSO (3 mL) was added tert-butyl glycinate (164 mg, 1.25 mmol) and DIPEA (294 mg, 2.28 mmol). The resulting mixture was stirred and heated to 60°C overnight. Water was added into the reaction mixture and the aqueous extracted with EtOAc. The combined organic layers were washed with water, brine and dried over Na_2SO_4 . The residue, after concentration was purified by column chromatography (10% EtOAc/PE) to afford tert-butyl (4-chloro-2-nitrophenyl)glycinate (1.1 g, 73%) as a yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.42 (t, $J = 5.6$ Hz, 1H), 8.10 (d, $J = 9.1$ Hz, 1H), 6.99 (d, $J = 2.1$ Hz, 1H), 6.76 (dd, $J = 9.1, 2.1$ Hz, 1H), 4.19 (d, $J = 5.6$ Hz, 2H), 1.44 (s, 9H).

[00302] Step 2: tert-butyl (2-amino-4-chlorophenyl)glycinate

[00303] To a solution of tert-butyl (4-chloro-2-nitrophenyl)glycinate (100 mg, 0.33 mmol) in MeOH (2 mL) was added Raney Ni (0.2 mL). The resulting mixture was stirred for 3 h under an atmosphere of H₂. The residue was filtered through celite, the solvent removed and the residue purified by prep-TLC (50% PE/EtOAc) to afford tert-butyl (2-amino-4-chlorophenyl)glycinate (40 mg, 42 %) as a light yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 6.52 (d, *J* = 8.2 Hz, 1H), 6.43 (dd, *J* = 8.2, 2.3 Hz, 1H), 6.20 (d, *J* = 2.3 Hz, 1H), 5.21 (t, *J* = 6.3 Hz, 1H), 4.66 (s, 2H), 3.79 (d, *J* = 6.2 Hz, 2H), 1.42 (s, 9H).

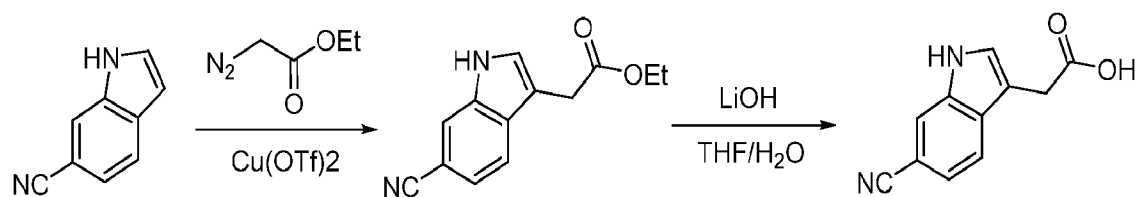
[00304] Step 3: tert-butyl 2-(5-chloro-1H-benzo[d]imidazol-1-yl)acetate

[00305] To a solution of tert-butyl (2-amino-4-chlorophenyl)glycinate (20 mg, 0.078 mmol) in MeOH (1 mL) was added trimethoxymethane (10 mg, 0.093 mmol) and sulfamic acid (1 mg, 0.008 mmol). The resulting mixture was stirred overnight. The solvent was removed under reduced pressure and the residue was purified by prep-TLC (50% PE/EtOAc) to afford tert-butyl 2-(5-chloro-1H-benzo[d]imidazol-1-yl)acetate (7 mg, 33%) as a light yellow solid. ¹H NMR (400 MHz, CD₃OD) δ 8.22 (d, *J* = 1.4 Hz, 1H), 7.67 (d, *J* = 8.7 Hz, 1H), 7.56 (d, *J* = 2.0 Hz, 1H), 7.29 (dd, *J* = 8.6, 2.0 Hz, 1H), 5.07 (s, 2H), 1.47 (s, 9H).

[00306] Step 4: 2-(5-chloro-1H-benzo[d]imidazol-1-yl)acetic acid

[00307] To a solution of tert-butyl 2-(5-chloro-1H-benzo[d]imidazol-1-yl)acetate (50 mg, 0.19 mmol) in DCM (2 mL) was added TFA (1.5 mL). The resulting mixture was stirred overnight. The solvent was removed under reduced pressure to afford 2-(5-chloro-1H-benzo[d]imidazol-1-yl)acetic acid as a yellow oil. LCMS *m/z* = 210.9 [M+H]⁺.

Synthesis of 2-(6-cyano-1H-indol-3-yl)acetic acid



[00308] Step 1: ethyl 2-(6-cyano-1H-indol-3-yl)acetate

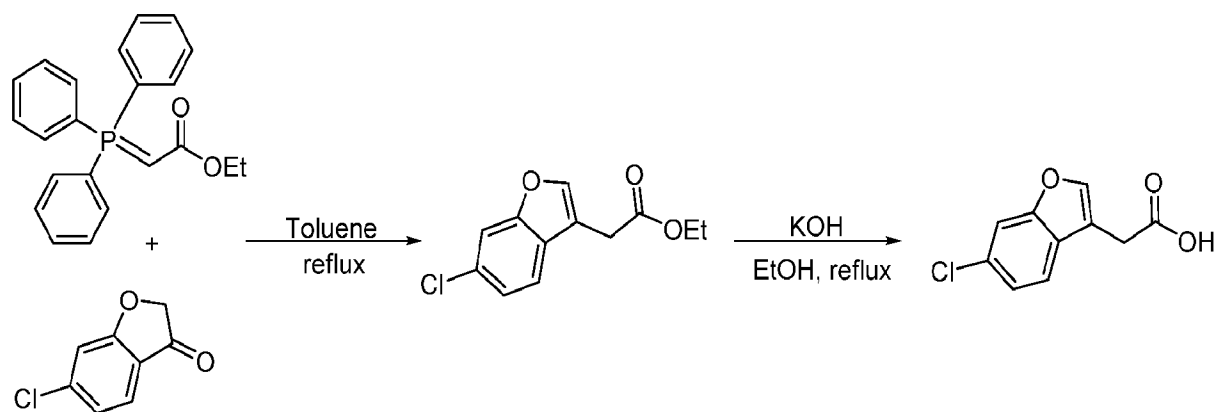
[00309] To a solution of 1H-indole-6-carbonitrile (200 mg, 1.41 mmol) in DCM (5 mL) was added ethyl 2-diazoacetate (293 mg, 2.57 mmol) and Cu(OTf)₂ (62 mg, 0.17 mmol). The resulting mixture was stirred at room temperature overnight. The residue, after concentration, was purified

by column chromatography (10% EtOAc/PE) to afford ethyl 2-(6-cyano-1H-indol-3-yl)acetate (40 mg, 12.4%) as a colorless oil.

[00310] Step 2: 2-(6-cyano-1H-indol-3-yl)acetic acid

[00311] To a solution of ethyl 2-(6-cyano-1H-indol-3-yl)acetate (40 mg, 0.18mmol) in THF/H₂O (1.5 mL/1.5 mL) was added LiOH·H₂O (22.1 mg, 0.53 mmol). The resulting mixture was stirred at room temperature for 3 h. The aqueous was acidified to pH =2-3 by adding 1 M HCl and extracted with EtOAc three times. The combined organic phases were concentrated under reduced pressure to afford 2-(6-cyano-1H-indol-3-yl)acetic acid (28 mg, 79.8%) as a white solid. LCMS *m/z*=199.0 [M-H]⁻.

Synthesis of 2-(6-chlorobenzofuran-3-yl)acetic acid



[00312] Step 1: ethyl 2-(6-chlorobenzofuran-3-yl)acetate

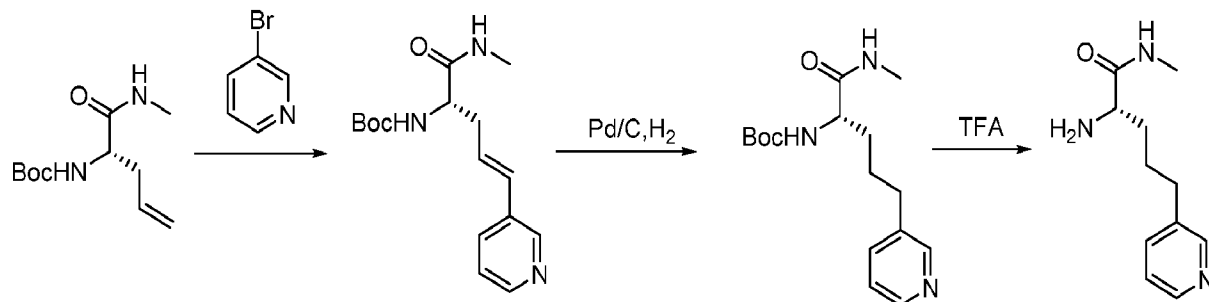
[00313] A mixture of 6-chlorobenzofuran-3(2H)-one (169 mg, 1.0mmol) and ethyl (triphenylphosphoranylidene)acetate (524 mg, 1.5 mmol) in toluene (10mL) was heated at reflux for 24h. The reaction mixture was concentrated *in vacuo* and the residue purified by column chromatography (10% EtOAc/PE) to give ethyl 2-(6-chlorobenzofuran-3-yl)acetate (171 mg, 72%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.95 (d, *J* = 1.1 Hz, 1H), 7.74 (d, *J* = 1.8 Hz, 1H), 7.61 (d, *J* = 8.4 Hz, 1H), 7.32 (dd, *J* = 8.4, 1.9 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.79 (d, *J* = 1.1 Hz, 2H), 1.19 (t, *J* = 7.1 Hz, 3H).

[00314] Step 2: 2-(6-chlorobenzofuran-3-yl)acetic acid

[00315] A mixture of ethyl 2-(6-chlorobenzofuran-3-yl)acetate (155 mg, 0.65 mmol) and KOH (55 mg, 0.98 mmol) in EtOH (5 mL) was heated at 80°C for 1 h. The reaction mixture was acidified by adding of 1M HCl and extracted with EtOAc three times. The combined organic layers were

washed with water and brine, dried over Na_2SO_4 and concentrated *in vacuo* to give 2-(6-chlorobenzofuran-3-yl)acetic acid (132 mg, 96% yield).

Synthesis of (S)-2-amino-N-methyl-5-(pyridin-2-yl)pentanamide



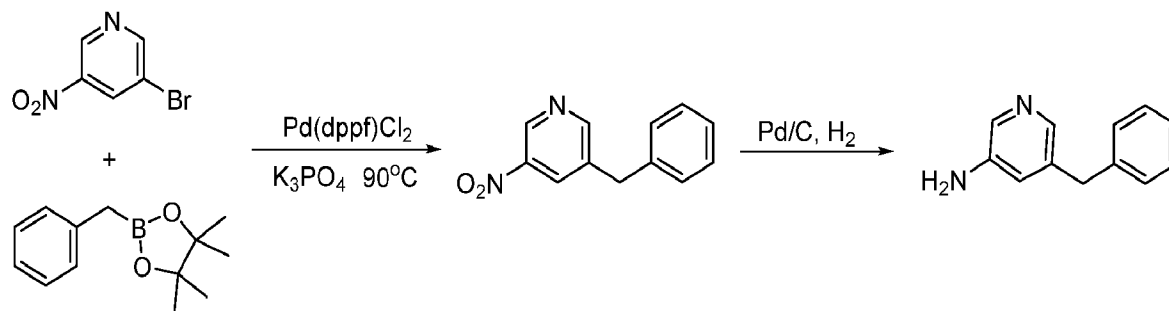
[00316] **Step 1: tert-butyl (S,E)-(1-(methyamino)-1-oxo-5-(pyridin-3-yl)pent-4-en-2-yl)carbamate** A mixture of tert-butyl (S)-(1-(methyamino)-1-oxopent-4-en-2-yl)carbamate (50 mg, 0.22 mmol), 3-bromopyridine (31 mg, 0.20 mmol), $\text{Pd}(\text{OAc})_2$ (5 mg), NaHCO_3 (55 mg, 0.66 mmol) in $\text{DMF}/\text{H}_2\text{O}$ (1 mL/0.2 mL) was heated at 70°C for 4 h under an atmosphere of N_2 . Water was added and the aqueous extracted with EtOAc. The combined organic layers were washed with water, brine and dried over Na_2SO_4 . The solvent was removed and the residue purified by prep-TLC (8% MeOH/DCM) to afford tert-butyl (S,E)-(1-(methyamino)-1-oxo-5-(pyridin-3-yl)pent-4-en-2-yl)carbamate (24 mg, 35 %) as a yellow oil. LCMS $m/z = 306.1[\text{M}+\text{H}]^+$.

[00317] Step 2: tert-butyl (S)-(1-(methyamino)-1-oxo-5-(pyridin-3-yl)pentan-2-yl)carbamate

[00318] To a solution of tert-butyl (S,E)-(1-(methyamino)-1-oxo-5-(pyridin-3-yl)pent-4-en-2-yl)carbamate (80 mg, 0.26 mmol) in MeOH (10 mL) was added Pd/C (10%, 8 mg). The resulting mixture was stirred for 14 h under an atmosphere of H_2 . The reaction mixture was filtered through celite and the filtrate was concentrated to afford tert-butyl (S)-(1-(methyamino)-1-oxo-5-(pyridin-3-yl)pentan-2-yl)carbamate (80.5 mg, quant.) as a yellow oil. LCMS $m/z = 308.2[\text{M}+\text{H}]^+$.

[00319] Step 3: (S)-2-amino-N-methyl-5-(pyridin-2-yl)pentanamide

[00320] To a solution of tert-butyl (S)-(1-(methyamino)-1-oxo-5-(pyridin-3-yl)pentan-2-yl)carbamate (74 mg, 0.23 mmol) in DCM (3.0 mL) was added TFA (0.5 mL). The resulting mixture was stirred for 3 h. The solvent was removed under reduced pressure to afford (S)-2-amino-N-methyl-5-(pyridin-2-yl)pentanamide (51 mg, quant.).

Synthesis of 5-benzylpyridin-3-amine**[00321] Step 1: 3-benzyl-5-nitropyridine**

[00322] To a solution of 3-bromo-5-nitropyridine (200 mg, 0.985 mmol) in a mixture of dioxane (15 mL) and water (3 mL) was added 2-benzyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (322.3 mg, 1.48 mmol), Pd(dppf)₂Cl₂ (144.2 mg, 0.197 mmol) and K₃PO₄ (627.4 mg, 2.96 mmol). The resulting mixture was heated at 90°C for 5 h. Water was added into the reaction mixture and the aqueous extracted with EtOAc three times. The combined organic layers were washed with water, brine and dried over Na₂SO₄. The residue, after concentration was purified by column chromatography (25% EtOAc/PE) to afford 3-benzyl-5-nitropyridine (92 mg, 44%). LCMS *m/z* = 215.0 [M+H]⁺; ¹H NMR (400 MHz, CD₃OD) δ 9.20 (d, *J* = 2.4 Hz, 1H), 8.79 (d, *J* = 1.9 Hz, 1H), 8.39 (t, *J* = 2.2 Hz, 1H), 7.38 – 7.21 (m, 5H), 4.16 (s, 2H).

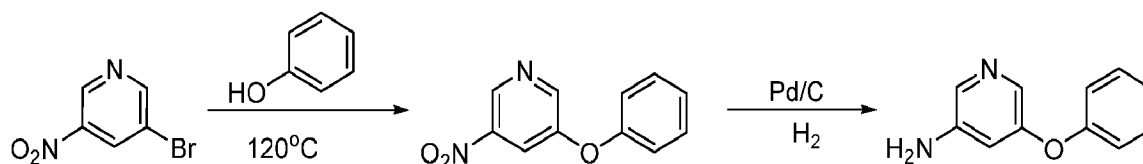
[00323] Step 2: 5-benzylpyridin-3-amine

[00324] To a solution of 3-benzyl-5-nitropyridine (92 mg, 0.43 mmol) in MeOH (3 mL) was added Pd/C (10.0 mg). The reaction mixture was stirred under H₂ for 5 h. After filtration through a pad of celite, the filtrate was concentrated to afford 5-benzylpyridin-3-amine (60 mg, 75%) as a white solid. LCMS *m/z* = 185.1 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.75 (d, *J* = 2.6 Hz, 1H), 7.66 (d, *J* = 1.9 Hz, 1H), 7.35 – 7.25 (m, 2H), 7.20 (d, *J* = 7.5 Hz, 3H), 6.68 (s, 1H), 5.21 (s, 2H), 3.79 (s, 2H).

Synthesis of 2-benzylpyridin-4-amine

[00325] Made using a similar method as described for the synthesis of 5-benzylpyridin-3-amine, using 2-bromo-4-nitropyridine in place of 3-bromo-5-nitropyridine

Synthesis of 5-phenoxy pyridin-3-amine

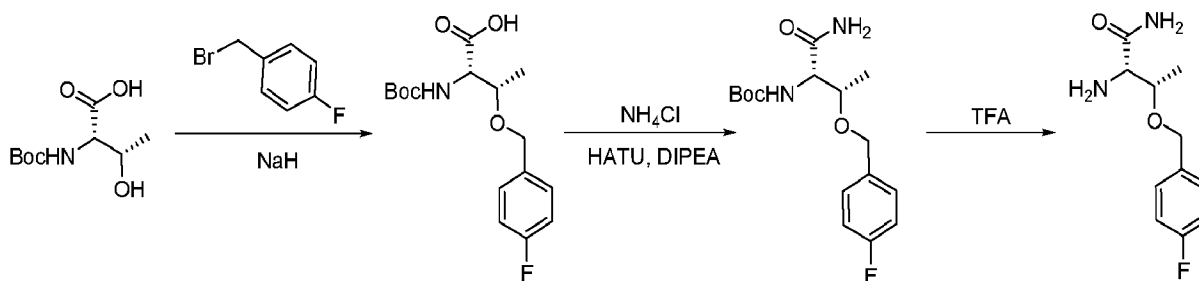


[00326] Step 1: 3-nitro-5-phenoxy pyridine

[00327] A mixture of 3-bromo-5-nitropyridine (500 mg, 2.46 mmol), phenol (255 mg, 2.71 mmol) and K_3CO_3 (408 mg, 2.96 mmol) in DMSO (6 mL) was stirred at 120°C for 3h. Water was added into the reaction mixture and the aqueous extracted with EtOAc three times. The combined organic layers were washed with water, brine, dried over Na_2SO_4 . The residue, after concentration was purified by column chromatography (10% EtOAc/PE) to afford 3-nitro-5-phenoxy pyridine (93 mg, 17%) as a white solid. LCMS $m/z = 217.0 [M+H]^+$.

[00328] Step 2: 5-phenoxy pyridin-3-amine To a solution of 3-nitro-5-phenoxy pyridine (93 mg, 0.43 mmol) in MeOH (1 mL) was added 10% Pd/C (10 mg). The resulting mixture was stirred under H_2 for 3h. After filtration through a pad of celite, the filtrate was concentrated to afford 5-phenoxy pyridin-3-amine (50 mg, 62%) as a white solid. LCMS $m/z = 187.1 [M+H]^+$.

Synthesis of (2S,3S)-2-amino-3-((4-fluorobenzyl)oxy)butanamide



[00329] Step 1: N-(tert-butoxycarbonyl)-O-(4-fluorobenzyl)-L-allothreonine

[00330] To a solution of (tert-butoxycarbonyl)-L-allothreonine (500 mg, 2.28 mmol) in DMF (5.0 mL) was added NaH (187 mg, 4.67 mmol) portionwise at 0°C. After stirring for 1h, 1-(bromomethyl)-4-fluorobenzene (431 mg, 2.28 mmol) was added and the reaction mixture was stirred for another 14 h. The residue, after concentration was purified by reverse-phase column to afford N-(tert-butoxycarbonyl)-O-(4-fluorobenzyl)-L-allothreonine (140 mg, 19%) as off-white solid. LCMS $m/z = 328.2 [M+H]^+$.

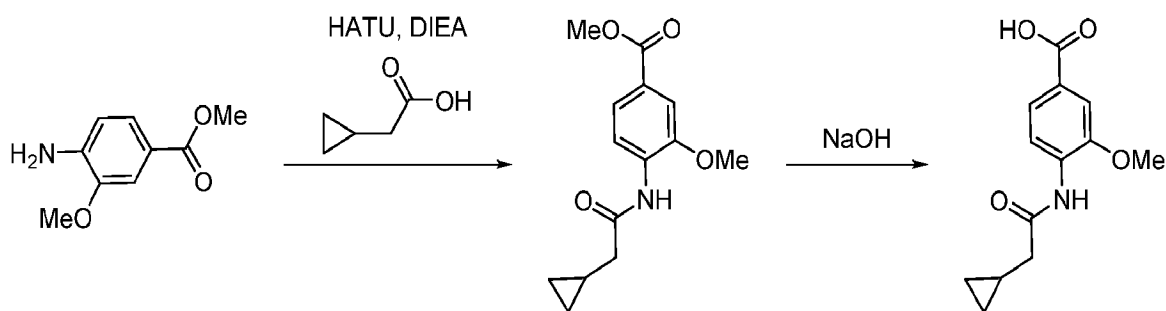
[00331] Step 2: *tert*-butyl ((2*S*,3*S*)-1-amino-3-((4-fluorobenzyl)oxy)-1-oxobutan-2-yl)carbamate

[00332] HATU (179 mg, 0.47 mmol) was added to the solution of N-(*tert*-butoxycarbonyl)-O-(4-fluorobenzyl)-L-allothreonine (100 mg, 0.92 mmol) in DMF (2.0 mL) at 0°C. After stirring for 30 min, NH₄Cl (50mg, 0.93 mmol) was added and the solution was stirred for another 2 h. The residue, after concentration was purified by reverse-phase column to afford *tert*-butyl ((2*S*,3*S*)-1-amino-3-((4-fluorobenzyl)oxy)-1-oxobutan-2-yl)carbamate (50 mg, 50%) as a colorless oil. LCMS *m/z* = 327.1 [M+1]⁺; ¹H NMR (400 MHz, CD₃OD) δ 7.40 – 7.33 (m, 2H), 7.07 – 7.00 (m, 2H), 4.53 (s, 2H), 4.33 (d, *J* = 6.0 Hz, 1H), 3.85 (t, *J* = 6.4 Hz, 1H), 1.45 (s, 9H), 1.19 (d, *J* = 6.3 Hz, 3H).

[00333] **Step 3: (2*S*,3*S*)-2-amino-3-((4-fluorobenzyl)oxy)butanamide** TFA (2.0 mL) was added to the solution of *tert*-butyl ((2*S*,3*S*)-1-amino-3-((4-fluorobenzyl)oxy)-1-oxobutan-2-yl)carbamate (50 mg, 0.15 mmol) in DCM (2.0 mL) and the reaction mixture was stirred for 3h. The solvent was removed under reduced pressure to afford (2*S*,3*S*)-2-amino-3-((4-fluorobenzyl)oxy)butanamide (209 mg, quant.) as a yellow oil. LCMS *m/z* = 226.9 [M+H]⁺.

Synthesis of (2*S*,3*R*)-2-amino-3-((4-fluorobenzyl)oxy)butanamide

[00334] Made using a similar method as described for the synthesis of (2*S*,3*S*)-2-amino-3-((4-fluorobenzyl)oxy)butanamide, starting from (*tert*-butoxycarbonyl)-L-threonine. LCMS *m/z* = 227.0 [M+H]⁺.

Synthesis of 4-(2-cyclopropylacetamido)-3-methoxybenzoic acid

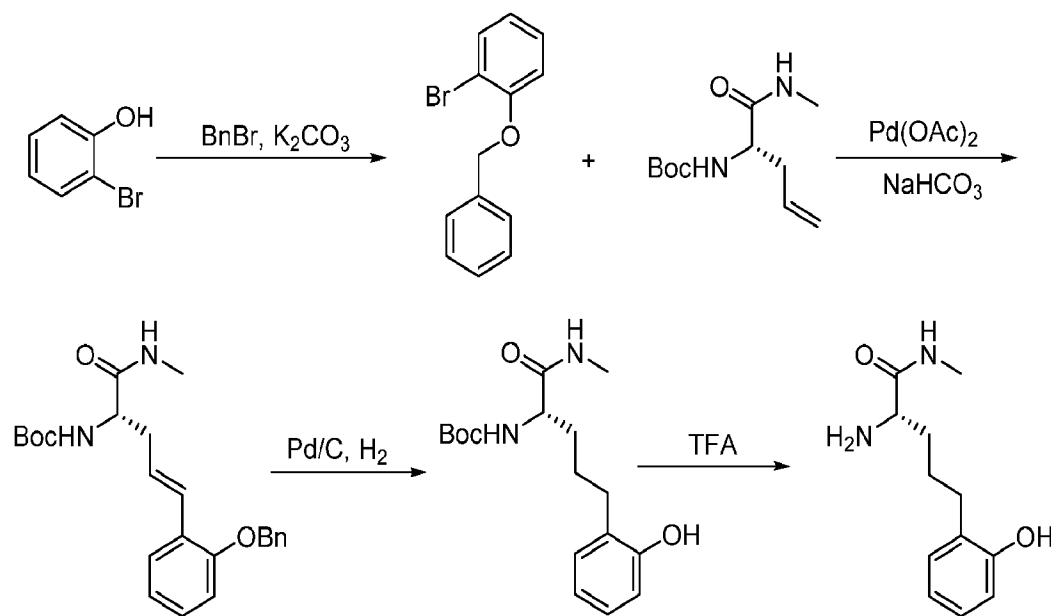
[00335] **Step 1: Methyl 4-(2-cyclopropylacetamido)-3-methoxybenzoate** 2-cyclopropylacetic acid (332 mg, 3.31 mmol) was added to the solution of methyl 4-amino-3-methoxybenzoate (500 mg, 2.76 mmol), DIEA (1.07 g, 8.28 mmol) and HATU (380.23 mg, 4.14 mmol) in DMA (15.0 mL). The solution was stirred at room temperature for 14 h. The reaction was treated with water and

extracted with EtOAc three times. The combined organic layers were washed with water and brine, dried over Na₂SO₄ and concentrated. The residue was purified by column chromatography (2% MeOH/DCM) to give methyl 4-(2-cyclopropylacetamido)-3-methoxybenzoate (333 mg, 46%) as a white solid. LCMS m/z = 264.1 [M+H]⁺.

[00336] Step 2: 4-(2-cyclopropylacetamido)-3-methoxybenzoic acid

[00337] To a solution of methyl 4-(2-cyclopropylacetamido)-3-methoxybenzoate (50 mg, 0.19 mmol) in MeOH/H₂O (1 mL/0.2 mL) was added NaOH (22.8 mg, 0.57 mmol). The resulting mixture was stirred for 4h. The reaction was treated with water and pH of the aqueous was adjusted to ~1 by adding of 1M HCl then extracted with EtOAc. The combined organic layers were washed with water, brine and dried over Na₂SO₄. Concentration afforded 4-(2-cyclopropylacetamido)-3-methoxybenzoic acid (40 mg, 85%) as a yellow solid. LCMS m/z = 250.1 [M+H]⁺.

Synthesis of (S)-2-amino-5-(2-hydroxyphenyl)-N-methylpentanamide



[00338] Step 1: 1-(benzyloxy)-2-bromobenzene ()

[00339] BnBr (2.17 g, 12.7 mmol) was added to the solution of 3-bromophenol (2 g, 11.6 mmol) and K₂CO₃ (3.2 g, 23.2 mmol) in DMF (10.0 mL). The solution was stirred at room temperature for 3 h. The reaction was treated with water and extracted with EtOAc three times. The combined organic layers were washed with water and brine, dried over Na₂SO₄ and concentrated. The residue was purified by column chromatography (20% EtOAc/PE) to afford 1-(benzyloxy)-2-

bromobenzene (2.8 g, 92%) as a yellow oil. ^1H NMR (400 MHz, CD_3OD) δ 7.58 – 7.20 (m, 7H), 7.00 – 6.82 (m, 2H), 5.04 (s, 2H).

[00340] Step 2: *tert*-butyl (S,Z)-(5-(2-(benzyloxy)phenyl)-1-(methylamino)-1-oxopent-4-en-2-yl)carbamate To a solution of 1-(benzyloxy)-2-bromobenzene (1 g, 3.80 mmol) in NMP (10.0 mL) was added *tert*-butyl (S)-(1-(methylamino)-1-oxopent-4-en-2-yl)carbamate (1.04 g, 4.56 mmol), $\text{Pd}(\text{PPh}_3)_4$ (218 mg, 1.90 mmol) and NaOAc (1.55 g, 11.4 mmol). The resulting mixture was heated at 100°C for 14 h. The reaction was treated with water and extracted with EtOAc. The combined organic layers were washed with water and brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (20% EtOAc/PE) to afford *tert*-butyl (S,Z)-(5-(2-(benzyloxy)phenyl)-1-(methylamino)-1-oxopent-4-en-2-yl)carbamate (300 mg, 40%) as a yellow oil. LCMS m/z = 411.1 $[\text{M}+\text{H}]^+$.

[00341] Step 3: *tert*-butyl (S)-(5-(2-hydroxyphenyl)-1-(methylamino)-1-oxopentan-2-yl)carbamate

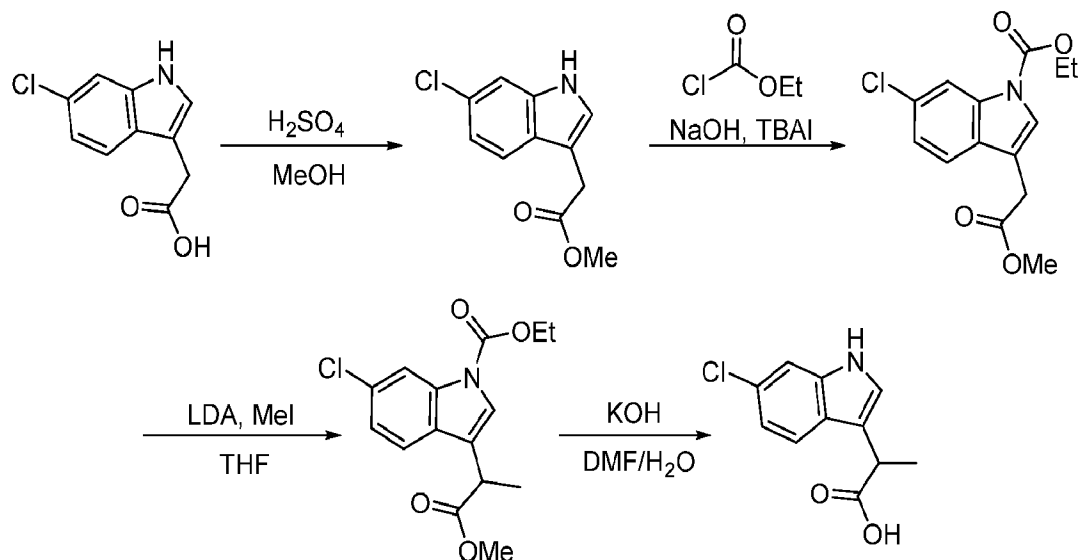
[00342] Pd/C (5 mg) was added to the solution of *tert*-butyl (S,Z)-(5-(2-(benzyloxy)phenyl)-1-(methylamino)-1-oxopent-4-en-2-yl)carbamate (50 mg, 0.12 mmol) in MeOH (1.5 mL) and the reaction was stirred at room temperature for 14 h under an atmosphere of H_2 . The mixture was filtered through a pad of celite and the filtrate was concentrated to afford *tert*-butyl (S)-(5-(2-hydroxyphenyl)-1-(methylamino)-1-oxopentan-2-yl)carbamate (35 mg, quant.) which was used in next step without further purification. LCMS m/z = 323.3 $[\text{M}+\text{H}]^+$.

[00343] Step 4: (S)-2-amino-5-(2-hydroxyphenyl)-N-methylpentanamide

[00344] TFA (1.5 mL) was added to a solution of *tert*-butyl (S)-(5-(2-hydroxyphenyl)-1-(methylamino)-1-oxopentan-2-yl)carbamate (40 mg, 0.12 mmol) in DCM (2.0 mL) and the reaction was stirred for 4 h. The solvent was removed to afford (S)-2-amino-5-(2-hydroxyphenyl)-N-methylpentanamide (30 mg, quant.) which was used without further purification.

[00345] Synthesis of (S)-2-amino-5-(3-hydroxyphenyl)-N-methylpentanamide

[00346] Made using a similar method as described for the synthesis of (S)-2-amino-5-(2-hydroxyphenyl)-N-methylpentanamide. LCMS m/z = 223.1 $[\text{M}+\text{H}]^+$.

Synthesis of 2-(6-chloro-1H-indol-3-yl)propanoic acid**[00347] Step 1: methyl 2-(6-chloro-1H-indol-3-yl)acetate**

[00348] To a solution of 2-(6-chloro-1H-indol-3-yl)acetic acid (500 mg, 2.392 mmol) in MeOH (5 mL) was added conc. H_2SO_4 (1 mL). The resulting mixture was heated at 80°C for 2 h then the solvent removed under vacuum. The residue obtained was diluted with water and the pH adjusted to ~ 8 by addition of 10% NaOH. The aqueous layer was extracted with EtOAc three times and the combined organic layers were washed with water and brine, dried over Na_2SO_4 and concentrated to afford methyl 2-(6-chloro-1H-indol-3-yl)acetate (490 mg, 92%) as a white solid. LCMS $m/z = 223.9$ $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, CD_3OD) δ 7.46 (d, $J = 8.4$ Hz, 1H), 7.34 (d, $J = 1.9$ Hz, 1H), 7.18 (d, $J = 0.9$ Hz, 1H), 6.99 (dd, $J = 8.4, 1.9$ Hz, 1H), 3.75 (d, $J = 0.8$ Hz, 2H), 3.67 (s, 3H).

[00349] Step 2: ethyl 6-chloro-3-(2-methoxy-2-oxoethyl)-1H-indole-1-carboxylate

[00350] To a solution of methyl 2-(6-chloro-1H-indol-3-yl)acetate (350 mg, 1.569 mmol) in DCM (3 mL) was added ethyl chloroformate (340 mg, 3.139 mmol) and TBAI (57 mg, 0.157 mmol). The resulting mixture was stirred at 0°C for 2 h. The mixture was diluted with water and extracted with EtOAc three times. The combined organic layers were washed with water and brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (20% EtOAc/PE) to afford ethyl 6-chloro-3-(2-methoxy-2-oxoethyl)-1H-indole-1-carboxylate (440 mg, 95%) as a white solid. ^1H NMR (400 MHz, CD_3OD) δ 8.13 (d, $J = 1.9$ Hz, 1H), 7.61 (t, $J = 1.1$

Hz, 1H), 7.49 (d, $J = 8.4$ Hz, 1H), 7.23 (dd, $J = 8.4, 1.9$ Hz, 1H), 4.48 (q, $J = 7.1$ Hz, 2H), 3.74 (d, $J = 1.0$ Hz, 2H), 3.70 (s, 3H), 1.45 (t, $J = 7.1$ Hz, 3H).

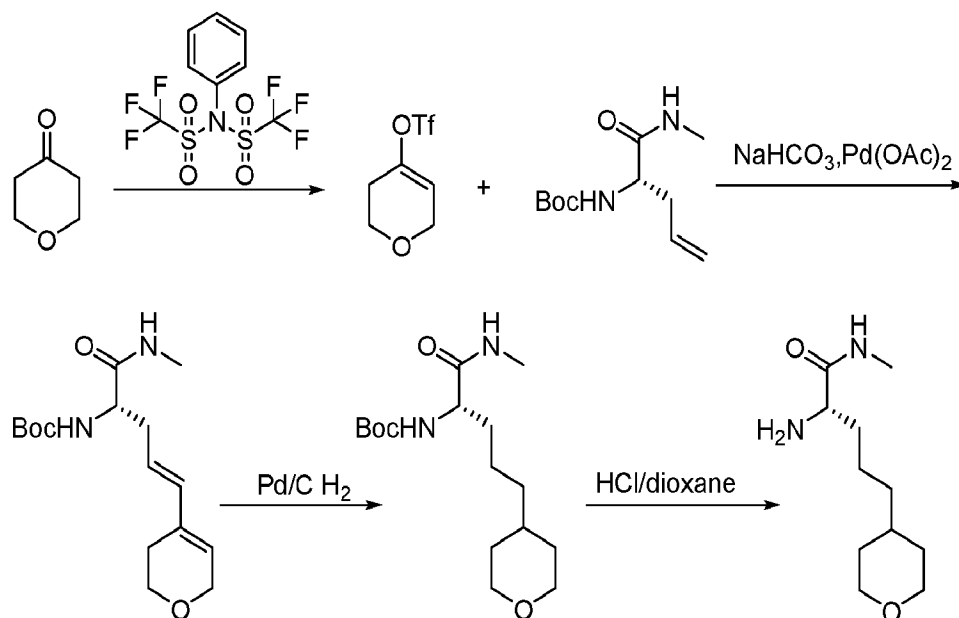
[00351] Step 3: ethyl 6-chloro-3-(1-methoxy-1-oxopropan-2-yl)-1H-indole-1-carboxylate

[00352] To a solution of ethyl 6-chloro-3-(2-methoxy-2-oxoethyl)-1H-indole-1-carboxylate (440 mg, 1.49 mmol) in dry THF (3 mL) was added LDA (2M in THF, 1.2 mL, 2.4 mmol) and MeI (318 mg, 2.24 mmol) under N₂ atmosphere at -70°C. The mixture was allowed to warm to room temperature and stirred for another 5h. Water was added and the aqueous extracted with EtOAc three times. The combined organic layers were washed with water, brine and dried over Na₂SO₄. The residue obtained after concentration was purified by column chromatography (10% EtOAc/PE) to afford ethyl 6-chloro-3-(1-methoxy-1-oxopropan-2-yl)-1H-indole-1-carboxylate (70 mg, 15%) as a white solid. ¹H NMR (400 MHz, CD₃OD) δ 8.08 (s, 1H), 7.57 (dd, $J = 2.5, 1.3$ Hz, 1H), 7.45 (dt, $J = 8.5, 1.9$ Hz, 1H), 7.20 (dq, $J = 8.5, 1.6$ Hz, 1H), 4.46 (qd, $J = 7.1, 1.0$ Hz, 2H), 3.70 (d, $J = 7.3$ Hz, 6H), 1.44 (t, $J = 7.1$ Hz, 4H).

[00353] Step 4: 2-(6-chloro-1H-indol-3-yl)propanoic acid

[00354] To a solution of ethyl 6-chloro-3-(1-methoxy-1-oxopropan-2-yl)-1H-indole-1-carboxylate (70 mg, 0.226 mmol) in DMF (1 mL) was added 10% NaOH(1 ml). The resulting mixture was stirred for 3 h then the solvent removed under vacuum. The residue obtained was diluted with water and the pH adjusted to ~2 by addition of 1M HCl. The aqueous layer was extracted with EtOAc three times and the combined organic layers were washed with water and brine, dried over Na₂SO₄ and concentrated to afford 2-(6-chloro-1H-indol-3-yl)propanoic acid (45 mg, 90%) as a white solid. LCMS $m/z = 221.9$ [M-H]⁻.

Synthesis of (S)-2-amino-N-methyl-5-(tetrahydro-2H-pyran-4-yl)pentanamide



[00355] Step 1: 3,6-dihydro-2H-pyran-4-yl trifluoromethanesulfonate

[00356] To a solution of tetrahydro-4H-pyran-4-one (500 mg, 4.995 mmol) in dry THF (3 mL) was added LiHMDS (1M in THF, 6 mL, 5.994 mmol) and phenyl triflimide (1.96g, 5.494 mmol) at -78°C. The resulting mixture was stirred at room temperature overnight. Water was added and the aqueous extracted with EtOAc three times. The combined organic layers were washed with water, brine and dried over Na₂SO₄. The residue, after concentration was purified by column chromatography (6% EtOAc/PE) to afford 3,6-dihydro-2H-pyran-4-yl trifluoromethanesulfonate (350 mg, 30%) as a yellow oil. ¹H NMR (400 MHz, CD₃OD) δ 5.92 (tt, *J* = 2.9, 1.4 Hz, 1H), 4.24 (q, *J* = 2.9 Hz, 2H), 3.87 (t, *J* = 5.5 Hz, 2H), 2.46 (ttd, *J* = 5.5, 2.8, 1.4 Hz, 2H).

[00357] Step 2: *tert*-butyl (S,E)-(5-(3,6-dihydro-2H-pyran-4-yl)-1-(methylamino)-1-oxopent-4-en-2-yl)carbamate To a solution of 3,6-dihydro-2H-pyran-4-yl trifluoromethanesulfonate (300 mg, 1.293 mmol) in a mixture of DMF (4 mL) and H₂O (1 mL) was added *tert*-butyl (S)-(1-(methylamino)-1-oxopent-4-en-2-yl)carbamate (265 mg, 1.164 mmol), NaHCO₃ (326 mg, 3.879 mmol) and Pd(OAc)₂ (29 mg, 0.129 mmol). The resulting mixture was heated at 100°C overnight under N₂ atmosphere. Water was added and the aqueous extracted with EtOAc three times. The combined organic layers were washed with water, brine and dried over Na₂SO₄. The residue after concentration was purified by column chromatography (20% EtOAc/PE) to afford *tert*-butyl (S,E)-

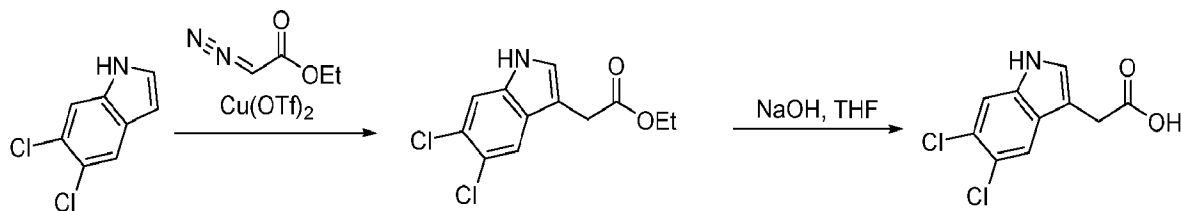
(5-(3,6-dihydro-2H-pyran-4-yl)-1-(methylamino)-1-oxopent-4-en-2-yl)carbamate (180 mg, 45%) as a yellow oil. LCMS $m/z = 311.2$ $[M+H]^+$.

[00358] Step 3: *tert*-butyl (S)-(1-(methylamino)-1-oxo-5-(tetrahydro-2H-pyran-4-yl)pentan-2-yl)carbamate To a solution of *tert*-butyl (S,E)-(5-(3,6-dihydro-2H-pyran-4-yl)-1-(methylamino)-1-oxopent-4-en-2-yl)carbamate (45 mg, 0.145 mmol) in MeOH (1 mL) was added 10% Pd/C (10 mg). The resulting mixture was stirred at room temperature for 3 h under H_2 atmosphere. The mixture was filtered through celite and the filtrate was concentrated to afford *tert*-butyl (S)-(1-(methylamino)-1-oxo-5-(tetrahydro-2H-pyran-4-yl)pentan-2-yl)carbamate (40 mg, 88%) as a white oil. LCMS $m/z = 315.2$ $[M+H]^+$.

[00359] Step 4: (S)-2-amino-N-methyl-5-(tetrahydro-2H-pyran-4-yl)pentanamide

[00360] To a solution of *tert*-butyl (S)-(1-(methylamino)-1-oxo-5-(tetrahydro-2H-pyran-4-yl)pentan-2-yl)carbamate (40 mg, 0.127 mmol) in MeOH (1 mL) was added HCl (4M in dioxane, 1 mL). The mixture was stirred at room temperature for 3h. The solvent was removed under reduced pressure to afford (S)-2-amino-N-methyl-5-(tetrahydro-2H-pyran-4-yl)pentanamide which was used directly in next step. LCMS $m/z = 215.1$ $[M+H]^+$.

Synthesis of 2-(5,6-dichloro-1H-indol-3-yl)acetic acid



[00361] Step 1: ethyl 2-(5,6-dichloro-1H-indol-3-yl)acetate

[00362] To a solution of 5,6-dichloro-1H-indole (2.0 g, 10.82 mmol) in DCM (10 mL) was added ethyl 2-diazoacetate (1.8 g, 16.2 mmol) and $Cu(OTf)_2$ (180 mg, 1.1 mmol). The resulting mixture was stirred at room temperature overnight. Water was added and the aqueous extracted with DCM three times. The combined organic layers were washed with water, brine, dried over Na_2SO_4 . The residue after concentration was purified by column chromatography (20% EtOAc/PE) to afford ethyl 2-(5,6-dichloro-1H-indol-3-yl)acetate (700 mg, 24%) as a yellow oil. LCMS $m/z = 269.8$ $[M-H]^+$.

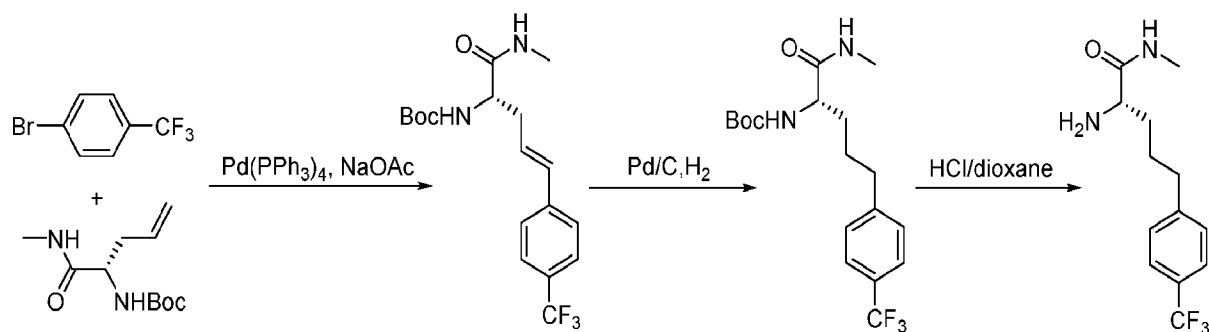
[00363] Step 2: 2-(5,6-dichloro-1H-indol-3-yl)acetic acid

[00364] To a solution of ethyl 2-(5,6-dichloro-1H-indol-3-yl)acetate (100 mg, 0.37 mmol) in THF (1 mL) was added 10% NaOH (1 mL). The resulting mixture was stirred for 3 h then the solvent removed under vacuum. The residue obtained was diluted with water and the pH adjusted to ~2 by addition of 1M HCl. The aqueous layer was extracted with EtOAc three times and the combined organic layers were washed with water and brine, dried over Na₂SO₄ and concentrated to afford 2-(5,6-dichloro-1H-indol-3-yl)acetic acid (70 mg, 78%) as a white solid. LCMS m/z = 241.8 [M-H]⁻. ¹H NMR (400 MHz, CD₃OD) δ 7.68 (d, J = 9.1 Hz, 1H), 7.49 (d, J = 2.1 Hz, 1H), 7.23 (d, J = 7.3 Hz, 1H), 3.70 (d, J = 0.9 Hz, 2H).

Synthesis of 2-(7-methoxy-1H-indol-3-yl)acetic acid

[00365] Made using a similar method as described for the synthesis of 2-(5,6-dichloro-1H-indol-3-yl)acetic acid, starting from 7-methoxy-1H-indole. LCMS m/z = 206.0 [M+H]⁺.

Synthesis of (S)-2-amino-N-methyl-5-(4-(trifluoromethyl)phenyl)pentanamide



[00366] Step 1: tert-butyl (S,E)-(1-(methylamino)-1-oxo-5-(4-(trifluoromethyl)phenyl)pent-4-en-2-yl)carbamate

[00367] To a solution of tert-butyl (S)-1-(methylamino)-1-oxopent-4-en-2-ylcarbamate (100 mg, 0.446 mmol) in NMP (3 mL) was added 1-bromo-4-(trifluoromethyl)benzene (100 mg, 0.446 mmol), Pd(PPh₃)₄ (25 mg, 0.023 mmol) and NaOAc (73 mg, 0.892 mmol). The resulting mixture was heated at 100°C for 4 h. Water was added and the aqueous extracted with EtOAc three times. The combined organic layers were washed with water, brine and dried over Na₂SO₄. The residue after concentration was purified by column chromatography (20% EtOAc/PE) to afford tert-butyl (S,E)-(1-(methylamino)-1-oxo-5-(4-(trifluoromethyl)phenyl)pent-4-en-2-yl)carbamate (140 mg, 84%) as a white oil. LCMS m/z = 373.0 [M+H]⁺.

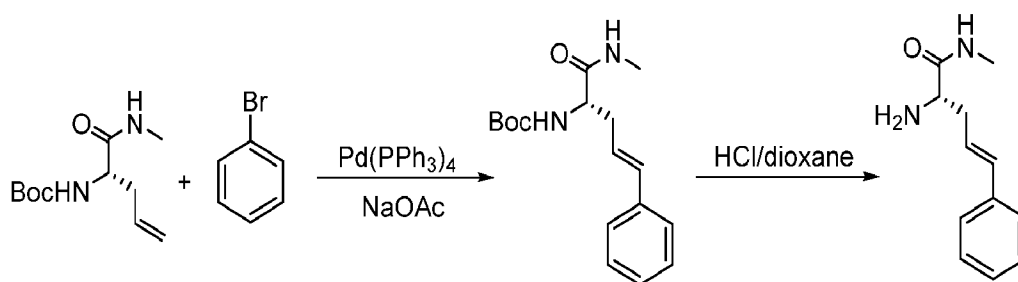
[00368] Step 2: tert-butyl (S)-(1-(methylamino)-1-oxo-5-(4-(trifluoromethyl)phenyl)pentan-2-yl)carbamate

[00369] To a solution of tert-butyl (S,E)-(1-(methylamino)-1-oxo-5-(4-(trifluoromethyl)phenyl)pent-4-en-2-yl)carbamate (100 mg, 0.27 mmol) in MeOH (1 mL) was added 10% Pd/C (14 mg). The resulting mixture was stirred at room temperature for 6 h under H₂ atmosphere. The mixture was filtered through a pad of celite and the filtrate was concentrated to afford tert-butyl (S)-(1-(methylamino)-1-oxo-5-(4-(trifluoromethyl)phenyl)pentan-2-yl)carbamate (70 mg, 71%) as a colorless oil. LCMS m/z = 375.1 [M+H]⁺.

[00370] Step 3: (S)-2-amino-N-methyl-5-(4-(trifluoromethyl)phenyl)pentanamide

[00371] To a solution of tert-butyl (S)-(1-(methylamino)-1-oxo-5-(4-(trifluoromethyl)phenyl)pentan-2-yl)carbamate (50 mg, 0.167 mmol) in MeOH (1 mL) was added HCl (4M in dioxane, 1 mL). The mixture was stirred at room temperature for 3h. The solvent was removed under reduced pressure and the product was used directly. LCMS m/z = 275.0 [M+H]⁺.

Synthesis of (S,E)-2-amino-N-methyl-5-phenylpent-4-enamide



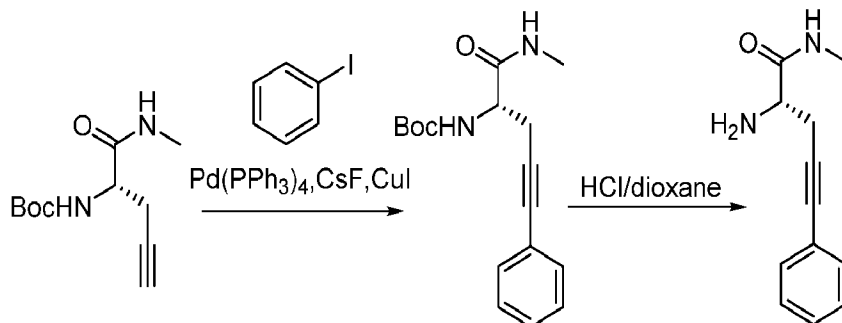
[00372] Step 1: tert-butyl (S,E)-(1-(methylamino)-1-oxo-5-phenylpent-4-en-2-yl)carbamate

[00373] To a solution of tert-butyl (S)-(1-(methylamino)-1-oxopent-4-en-2-yl)carbamate (450 mg, 1.973 mmol) in NMP (3 mL) was added bromobenzene (300 mg, 1.923 mmol), Pd(PPh₃)₄ (114 mg, 0.099 mmol) and NaOAc (324 mg, 3.946 mmol). The resulting mixture was heated at 100°C for 4 h. Water was added and the aqueous extracted with EtOAc three times. The combined organic layers were washed with water, brine and dried over Na₂SO₄. The residue after concentration was purified by column chromatography (20% EtOAc/PE) to afford tert-butyl (S,E)-(1-(methylamino)-1-oxo-5-phenylpent-4-en-2-yl)carbamate (140 mg, 84%) as a white solid. LCMS m/z = 305.0 [M+H]⁺.

[00374] Step 2: (S,E)-2-amino-N-methyl-5-phenylpent-4-enamide

[00375] To a solution of tert-butyl (S,E)-(1-(methylamino)-1-oxo-5-phenylpent-4-en-2-yl)carbamate (50 mg, 0.167 mmol) in MeOH (1 mL) was added HCl (4M in dioxane, 1 mL). The mixture was stirred at room temperature for 3 h. The solvent was removed under reduced pressure to afford (S,E)-2-amino-N-methyl-5-phenylpent-4-enamide which was used directly. LCMS m/z = 205.0 $[M+H]^+$.

Synthesis of (S)-2-amino-N-methyl-5-phenylpent-4-ynamide



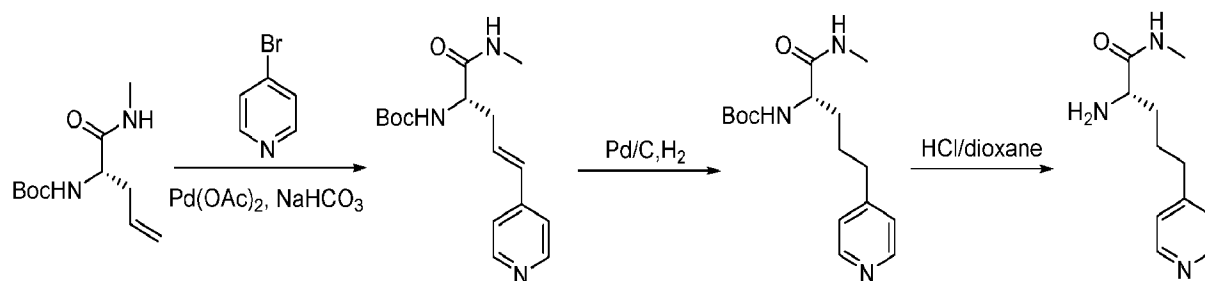
[00376] Step 1: tert-butyl (S)-((1-(methylamino)-1-oxo-5-phenylpent-4-yn-2-yl)carbamate

[00377] To a solution of tert-butyl (S)-((1-(methylamino)-1-oxopent-4-en-2-yl)carbamate (100 mg, 0.442 mmol) in NMP (3 mL) was added iodobenzene (300 mg, 1.923 mmol), $\text{PdCl}_2(\text{PPh}_3)_2$ (30 mg, 0.044 mmol) and CuI (8 mg, 0.044 mmol). The resulting mixture was heated at 100°C for 4 h under N_2 atmosphere. Water was added and the aqueous extracted with EtOAc three times. The combined organic layers were washed with water, brine and dried over Na_2SO_4 . The residue after concentration was purified by column chromatography (20% EtOAc/PE) to afford tert-butyl (S)-((1-(methylamino)-1-oxo-5-phenylpent-4-yn-2-yl)carbamate (82 mg, 62%) as a white solid. LCMS m/z = 303.2 $[M+H]^+$.

[00378] Step 2: (S)-2-amino-N-methyl-5-phenylpent-4-ynamide

[00379] To a solution of tert-butyl (S)-((1-(methylamino)-1-oxo-5-phenylpent-4-yn-2-yl)carbamate (50 mg, 0.167 mmol) in MeOH (1 mL) was added HCl (4M in dioxane, 1 mL). The mixture was stirred at room temperature for 3 h. The solvent was removed under reduced pressure to afford (S)-2-amino-N-methyl-5-phenylpent-4-ynamide which was used directly in next step. LCMS m/z = 203.2 $[M+H]^+$.

Synthesis of (S)-2-amino-N-methyl-5-(pyridin-4-yl)pentanamide



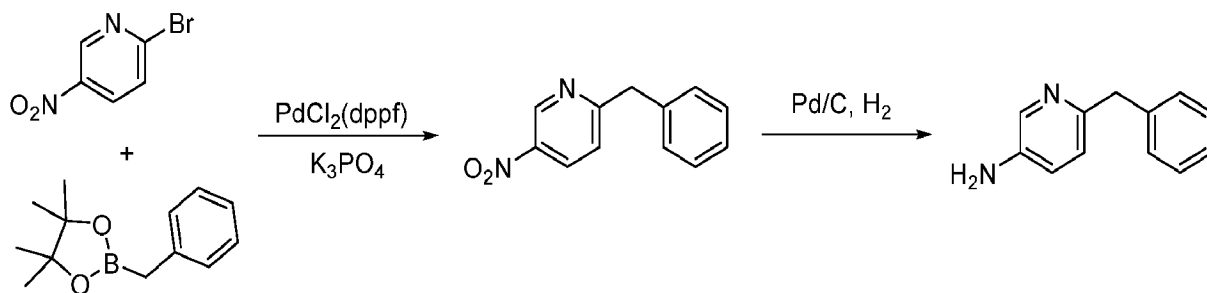
[00380] Step 1: *tert*-butyl (S,E)-(1-(methylanino)-1-oxo-5-(pyridin-4-yl)pent-4-en-2-yl)carbamate To a solution of *tert*-butyl (S)-(1-(methylanino)-1-oxopent-4-en-2-yl)carbamate (200 mg, 0.877 mmol) in a mixture of DMF (4 mL) and H₂O (2 mL) was added 4-bromopyridine (187 mg, 0.964 mmol), Pd(OAc)₂ (20 mg) and NaHCO₃ (294 mg, 3.5 mmol). The resulting mixture was heated at 70°C overnight. Water was added and the aqueous extracted with EtOAc three times. The combined organic layers were washed with water, brine and dried over Na₂SO₄. Residue after concentration was purified by prep-HPLC to afford *tert*-butyl (S,E)-(1-(methylanino)-1-oxo-5-(pyridin-4-yl)pent-4-en-2-yl)carbamate (70 mg, 26%) as a white solid. LCMS *m/z* = 306.0 [M+H]⁺.

[00381] Step 2: *tert*-butyl (S)-(1-(methylanino)-1-oxo-5-(pyridin-4-yl)pentan-2-yl)carbamate To a solution of *tert*-butyl (S,E)-(1-(methylanino)-1-oxo-5-(pyridin-4-yl)pent-4-en-2-yl)carbamate (70 mg, 0.23 mmol) in THF (2 mL) was added Pd/C (10%, 50 mg). The mixture was stirred at room temperature for 2h under an atmosphere of H₂. The reaction mixture was filtered through celite and the filtrate was concentrated to afford *tert*-butyl (S)-(1-(methylanino)-1-oxo-5-(pyridin-4-yl)pentan-2-yl)carbamate (70 mg, quant.) as a colorless oil. LCMS *m/z* = 308.0 [M+H]⁺.

[00382] Step 3: (S)-2-amino-N-methyl-5-(pyridin-4-yl)pentanamide

[00383] To a solution of *tert*-butyl (S)-(1-(methylanino)-1-oxo-5-(pyridin-4-yl)pentan-2-yl)carbamate (70 mg, 0.228 mmol) in MeOH (1 mL) was added HCl (4M in dioxane, 2mL). The resulting mixture was stirred at room temperature for 1 h. The solvent was removed to afford (S)-2-amino-N-methyl-5-(pyridin-4-yl)pentanamide (50 mg, quant.) LCMS *m/z* = 208.0 [M+H]⁺.

Synthesis of 6-benzylpyridin-3-amine

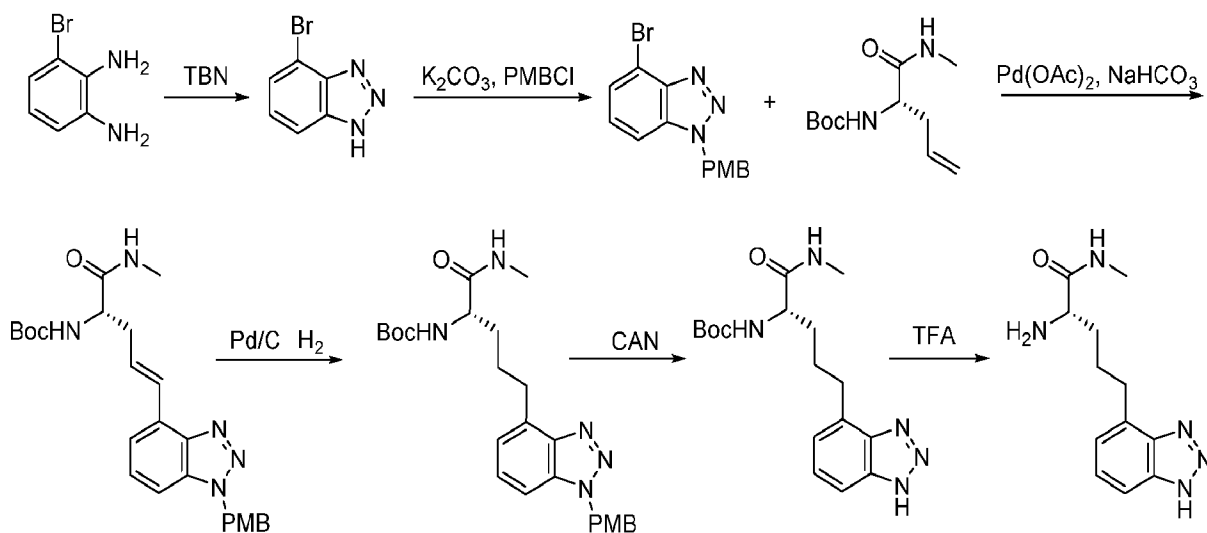


[00384] Step 1: 2-benzyl-5-nitropyridine A mixture of 2-bromo-5-nitropyridine (500 mg, 2.46 mmol), 2-benzyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (218 mg, 3.69 mmol) Pd(dppf)Cl₂ (cat.) and K₃PO₄ (1.57g, 7.39 mmol) in a mixture of dioxane (5 mL) and H₂O (1 mL) was heated at 90°C for 2h. Water was added and the aqueous extracted with EtOAc three times. The combined organic layers were washed with water and brine, dried over Na₂SO₄ and concentrated. The residue was purified by column chromatography (10% EtOAc/PE) to afford 2-benzyl-5-nitropyridine (249 mg, 47%) as a white solid. LCMS m/z = 215.2 [M+H]⁺.

[00385] Step 2: 6-benzylpyridin-3-amine

[00386] To a solution of 2-benzyl-5-nitropyridine (249 mg, 1.16 mmol) in MeOH (3 mL) was added 10% Pd/C (10 mg). The resulting mixture was stirred for 3h under an atmosphere of H₂. The mixture was filtered through celite and the filtrate was concentrated to afford 6-benzylpyridin-3-amine (100 mg, 47% yield) as a white solid. LCMS m/z = 185.1 [M+H]⁺.

Synthesis of (S)-2-amino-5-(1H-benzo[d][1,2,3]triazol-4-yl)-N-methylpentanamide



[00387] Step 1: 4-bromo-1H-benzo[d][1,2,3]triazole

[00388] TBN (2.2 g, 21.4 mmol) was added to a solution of 3-bromobenzene-1,2-diamine (2 g, 10.7 mmol) in DCM (15 mL). The solution was stirred at room temperature for 2 h. The solvent was removed and the residue was purified by column chromatography (2% MeOH/DCM) to give 4-bromo-1H-benzo[d][1,2,3]triazole (1.7 g, 81%) as a yellow oil. LCMS m/z = 197.9 $[M+H]^+$.

[00389] Step 2: 4-bromo-1-(4-methoxybenzyl)-1H-benzo[d][1,2,3]triazole

[00390] To a solution of 4-bromo-1H-benzo[d][1,2,3]triazole (1.6 mg, 8.04 mmol) in DCM (10.0 mL) was added PMBCl (1.38 g, 8.84 mmol) and TEA (2.9 g, 27.21 mmol). The resulting mixture was stirred for 4 h. The solvent was removed and the residue was purified by column chromatography (2% MeOH/DCM) to give 4-bromo-1-(4-methoxybenzyl)-1H-benzo[d][1,2,3]triazole (1.1 g, 41%) as a yellow solid. LCMS m/z = 317.8 $[M+H]^+$.

[00391] **Step 3: tert-butyl (S,E)-(5-(1-(4-methoxybenzyl)-1H-benzo[d][1,2,3]triazol-4-yl)-1-(methylamino)-1-oxopent-4-en-2-yl)carbamate** To a solution of 4-bromo-1-(4-methoxybenzyl)-1H-benzo[d][1,2,3]triazole (950 mg, 2.99 mmol) in a mixture of DMF (10 mL) and H₂O (2 mL) was added tert-butyl (S)-(1-(methylamino)-1-oxopent-4-en-2-yl)carbamate (820 mg, 3.60 mmol), Pd(OAc)₂ (67 mg, 0.03 mmol) and NaHCO₃ (754 mg, 8.97 mmol). The resulting mixture was heated at 70°C for 14 h. Water was added and the aqueous extracted with EtOAc three times. The combined organic layers were washed with water and brine, dried over Na₂SO₄ and concentrated. The residue was purified by column chromatography (2% MeOH/DCM) to afford tert-butyl (S,E)-(5-(1-(4-methoxybenzyl)-1H-benzo[d][1,2,3]triazol-4-yl)-1-(methylamino)-1-oxopent-4-en-2-yl)carbamate (600 mg, 43%) as a white solid. LCMS m/z = 466.1 $[M+H]^+$.

[00392] Step 4: tert-butyl (S)-(5-(1-(4-methoxybenzyl)-1H-benzo[d][1,2,3]triazol-4-yl)-1-(methylamino)-1-oxopentan-2-yl)carbamate

[00393] Pd/C (10%, 84 mg) was added to a solution of tert-butyl (S,E)-(5-(1-(4-methoxybenzyl)-1H-benzo[d][1,2,3]triazol-4-yl)-1-(methylamino)-1-oxopent-4-en-2-yl)carbamate (280 mg, 0.77 mmol) in MeOH (5 mL) and the reaction mixture was stirred under H₂ atmosphere for 14 h. The mixture was filtered through a pad of celite and the filtrate was concentrated to afford tert-butyl (S)-(5-(1-(4-methoxybenzyl)-1H-benzo[d][1,2,3]triazol-4-yl)-1-(methylamino)-1-oxopentan-2-

yl)carbamate (250 mg, quant.) which was used in next step without further purification. LCMS m/z = 468.1 $[M+H]^+$.

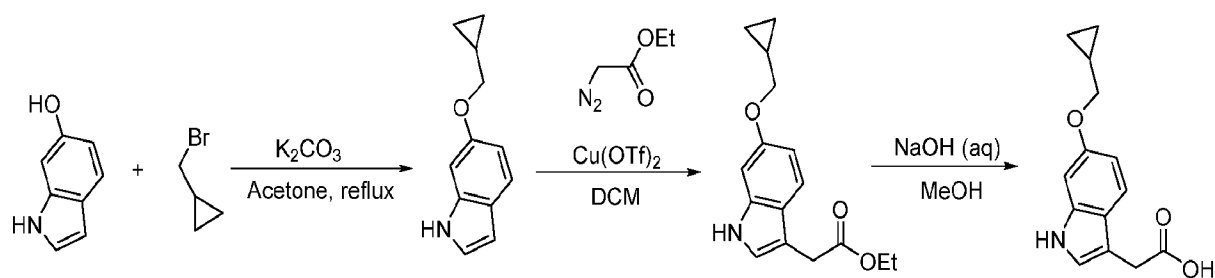
[00394] Step 5: tert-butyl (S)-(5-(1H-benzo[d][1,2,3]triazol-4-yl)-1-(methylamino)-1-oxopentan-2-yl)carbamate

[00395] To a solution of tert-butyl (S)-(5-(1-(4-methoxybenzyl)-1H-benzo[d][1,2,3]triazol-4-yl)-1-(methylamino)-1-oxopentan-2-yl)carbamate (180 mg, 0.48 mmol) in a mixture of DMF (5 mL) and H₂O (1 mL) was added CAN (808 mg, 1.48 mmol). The resulting mixture was stirred at room temperature for 4 h. Water was added and the aqueous extracted with EtOAc three times. The combined organic layers were washed with water and brine, dried over Na₂SO₄ and concentrated. The residue was purified by prep-TLC to give tert-butyl (S)-(5-(1H-benzo[d][1,2,3]triazol-4-yl)-1-(methylamino)-1-oxopentan-2-yl)carbamate (40 mg, 34%) as a yellow solid. LCMS m/z = 348.0 $[M+H]^+$.

[00396] Step 6: (S)-2-amino-5-(1H-benzo[d][1,2,3]triazol-4-yl)-N-methylpentanamide

[00397] TFA (0.5 mL) was added to a solution of tert-butyl (S)-(5-(1H-benzo[d][1,2,3]triazol-4-yl)-1-(methylamino)-1-oxopentan-2-yl)carbamate (40 mg, 0.11 mmol) in DCM (1.5 mL) and the reaction was stirred for 4 h. The solvent was removed to afford (S)-2-amino-5-(1H-benzo[d][1,2,3]triazol-4-yl)-N-methylpentanamide (32 mg, quant.) which was used without further purification.

Synthesis of 2-(6-(cyclopropylmethoxy)-1H-indol-3-yl)acetic acid



[00398] Step 1: 6-(cyclopropylmethoxy)-1H-indole

[00399] To a solution of 1H-indol-6-ol (500 mg, 3.76 mmol) in acetone (10 mL) was added (bromomethyl)cyclopropane (0.8 mL) and K₂CO₃ (1.55 g, 11.3 mmol). The mixture was heated at reflux for 24 h and an additional amount of (bromomethyl)cyclopropane (0.5 mL) was added. The mixture was heated at reflux for additional 2 days. The reaction mixture was concentrated *in*

vacuo. The crude was purified by column chromatography (15% EtOAc/PE) to give 6-(cyclopropylmethoxy)-1H-indole (570 mg, 81%). LCMS m/z = 188.0 $[M+H]^+$.

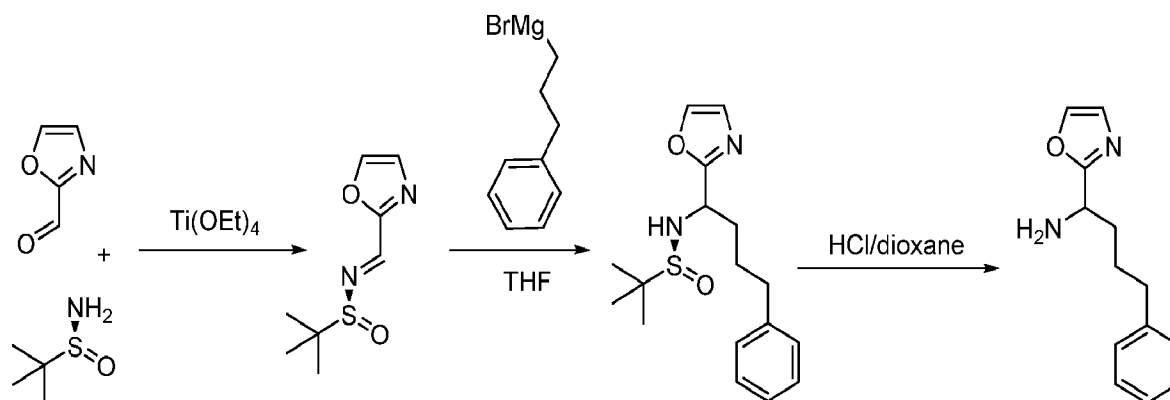
[00400] Step 2: ethyl 2-(6-(cyclopropylmethoxy)-1H-indol-3-yl)acetate

[00401] To a solution of 6-(cyclopropylmethoxy)-1H-indole (100 mg, 0.53 mmol) and $\text{Cu}(\text{OTf})_2$ (19 mg, 0.05 mmol) in DCM (3 mL) was added ethyl diazoacetate (430 mg, 3.77 mmol) dropwise. The mixture was stirred at room temperature for 24 h. The reaction mixture was concentrated *in vacuo* and the residue was purified by column chromatography (12% EtOAc/PE) to give ethyl 2-(6-(cyclopropylmethoxy)-1H-indol-3-yl)acetate (122 mg, 14.6%). LCMS m/z = 274.1 $[M+H]^+$.

[00402] Step 3: 2-(6-(cyclopropylmethoxy)-1H-indol-3-yl)acetic acid

[00403] To a solution of ethyl 2-(6-(cyclopropylmethoxy)-1H-indol-3-yl)acetate (122 mg, 0.45 mmol) in MeOH (1 mL) was added 10% NaOH (4 mL). The mixture was stirred at room temperature for 3 h. The pH was adjusted to ~2 by addition of 1M HCl and the aqueous extracted with EtOAc three times. The combined organic layers were concentrated *in vacuo* to afford 2-(6-(cyclopropylmethoxy)-1H-indol-3-yl)acetic acid which was used directly in the synthesis of further compounds.

Synthesis of 1-(oxazol-2-yl)-4-phenylbutan-1-amine



[00404] Step 1: (S)-2-methyl-N-(oxazol-2-ylmethylene)propane-2-sulfonamide

[00405] A mixture of oxazole-2-carbaldehyde (300 mg, 3.09 mmol), (S)-2-methylpropane-2-sulfonamide (450 mg, 3.71 mmol) and $\text{Ti}(\text{OEt})_4$ (1.41 g, 6.18 mmol) in THF (10.0 mL) was stirred at room temperature overnight. Water was added and the aqueous extracted with EtOAc three times. The organic layers were washed with water, brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude was purified by silica column chromatography (30% EtOAc/PE) to give (S)-2-

methyl-N-(oxazol-2-ylmethylene)propane-2-sulfonamide (300 mg, 49%). LCMS m/z = 201.2 $[M+H]^+$; 1H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, J = 1.0 Hz, 1H), 7.84 (s, 1H), 7.41 (s, 1H), 1.29 (d, J = 1.1 Hz, 9H).

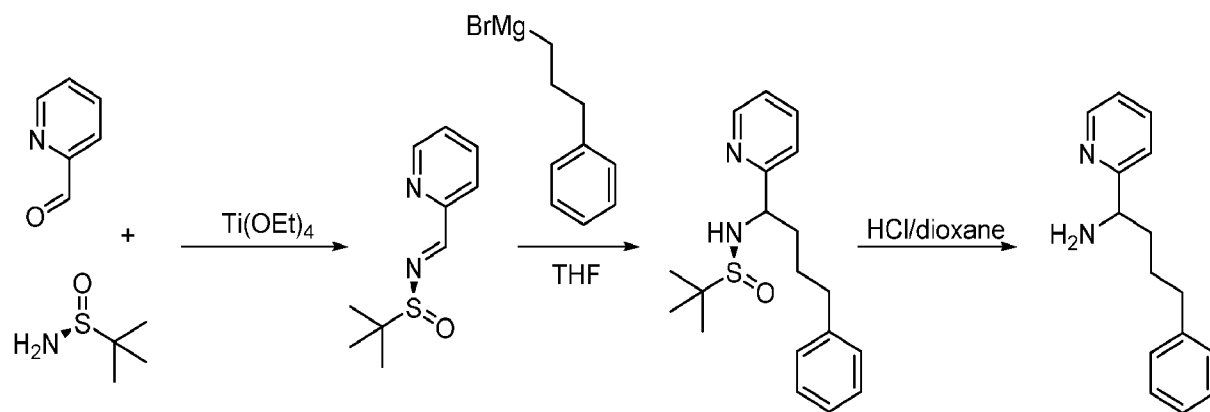
[00406] Step 2: (S)-2-methyl-N-(1-(oxazol-2-yl)-4-phenylbutyl)propane-2-sulfonamide

[00407] To a solution of (S)-2-methyl-N-(oxazol-2-ylmethylene)propane-2-sulfonamide (300 mg, 1.5 mmol) in dry THF was added (3-phenylpropyl)magnesium bromide (1.67 g, 7.49 mmol) at -78°C. The mixture was stirred at room temperature under an atmosphere of N_2 . NH_4Cl solution was added and the aqueous extracted with EtOAc three times. The combined organic layers were washed with water, brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude was purified by prep-HPLC to give (S)-2-methyl-N-(1-(oxazol-2-yl)-4-phenylbutyl)propane-2-sulfonamide (82 mg, 17%). LCMS m/z = 321.2 $[M+H]^+$.

[00408] Step 3: 1-(oxazol-2-yl)-4-phenylbutan-1-amine

[00409] A solution of (S)-2-methyl-N-(1-(oxazol-2-yl)-4-phenylbutyl)propane-2-sulfonamide (82 mg, 0.256 mmol) in HCl (4M in dioxane, 3 mL) was stirred at room temperature for 3 h. The reaction mixture was concentrated *in vacuo* to give 1-(oxazol-2-yl)-4-phenylbutan-1-amine (60 mg, quant.). LCMS m/z = 217.2 $[M+H]^+$.

Synthesis of 4-phenyl-1-(pyridin-2-yl)butan-1-amine



[00410] Step 1: (S)-2-methyl-N-(pyridin-2-ylmethylene)propane-2-sulfonamide

[00411] A mixture of picolinaldehyde (3.0 g, 28.0 mmol), (S)-2-methylpropane-2-sulfonamide (4.06 g, 33.6 mmol) and $Ti(OEt)_4$ (12.8 g, 56 mmol) in THF (50 mL) was stirred at room temperature overnight. Water was then added and the mixture extracted with EtOAc three times.

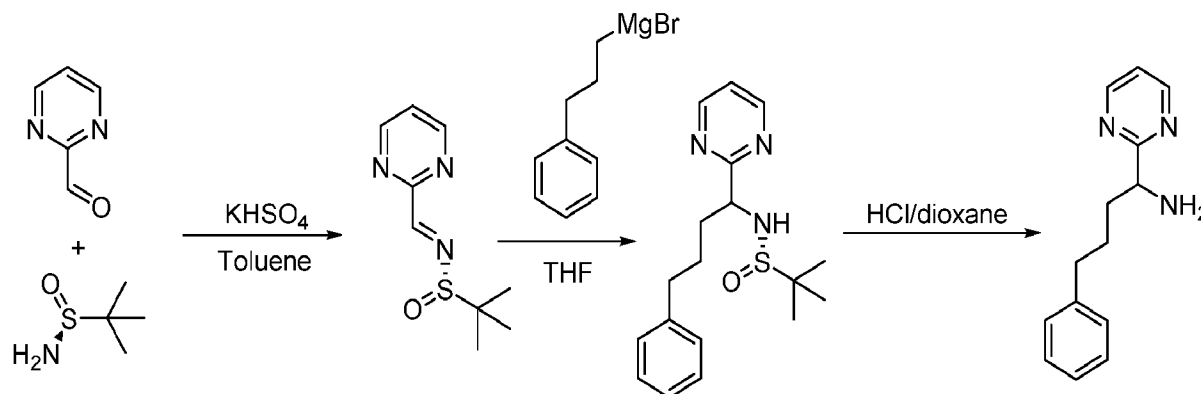
The combined organic layers were washed with water, brine and dried over Na₂SO₄. The solvent was removed and the residue purified by silica column chromatography (10% EtOAc/PE) to afford (S,E)-2-methyl-N-(pyridin-2-ylmethylene)propane-2-sulfonamide (1.1 g, 21%): ¹H NMR (400 MHz, CD₃OD) δ 8.72 (ddd, *J* = 4.9, 1.7, 0.9 Hz, 1H), 8.62 (s, 1H), 8.13 (dt, *J* = 8.0, 1.1 Hz, 1H), 8.00 (td, *J* = 7.7, 1.7 Hz, 1H), 7.58 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 1.29 (s, 9H).

[00412] Step 2: (S)-2-methyl-N-(4-phenyl-1-(pyridin-2-yl)butyl)propane-2-sulfonamide

[00413] To a solution of (S)-2-methyl-N-(pyridin-2-ylmethylene)propane-2-sulfonamide (300 mg, 1.4 mmol) in dry THF was added (3-phenylpropyl)magnesium bromide (466 mg, 2.1 mmol) dropwise at -78 °C under N₂. The reaction mixture was stirred at this temperature for 2 hours. The reaction was quenched with sat. aq. NH₄Cl solution and extracted with EtOAc three times. The combined organic layers were washed with water, brine and dried over Na₂SO₄. The residue was concentrated and purified by silica column chromatography (5% MeOH/DCM) to give (S)-2-methyl-N-(4-phenyl-1-(pyridin-2-yl)butyl)propane-2-sulfonamide (86 mg, 18%) as a mixture of diastereomers (2/5). ¹H NMR (400 MHz, CD₃OD) δ 8.48 (ddd, *J* = 4.9, 1.7, 1.0 Hz, 1H), 7.80 (qd, *J* = 7.6, 1.8 Hz, 1H), 7.44 (ddt, *J* = 10.8, 8.0, 1.1 Hz, 1H), 7.33 – 7.27 (m, 1H), 7.26 – 7.18 (m, 2H), 7.13 (td, *J* = 6.1, 5.6, 2.9 Hz, 3H), 4.47 – 4.37 (m, 1H), 2.62 (t, *J* = 7.5 Hz, 2H), 2.02 – 1.54 (m, 4H), 1.19 (s, 9H, major isomer), 1.15 (s, 9H, minor isomer).

[00414] Step 3: 4-phenyl-1-(pyridin-2-yl)butan-1-amine

[00415] A solution of (S)-2-methyl-N-(4-phenyl-1-(pyridin-2-yl)butyl)propane-2-sulfonamide (30 mg, 0.09 mmol) in HCl (4 M in dioxane, 2 mL) was stirred at room temperature for 3h. The reaction mixture was concentrated to afford 4-phenyl-1-(pyridin-2-yl)butan-1-amine which was used directly.

Synthesis of 4-phenyl-1-(pyrimidin-2-yl)butan-1-amine**[00416] Step 1: (S)-2-methyl-N-(pyrimidin-2-ylmethylene)propane-2-sulfonamide**

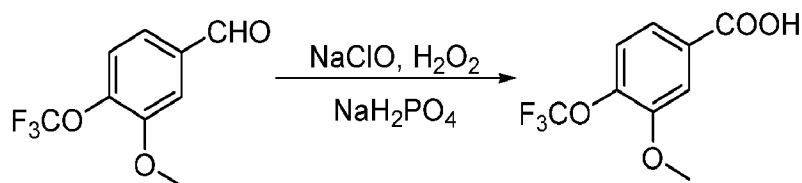
[00417] (S)-2-methylpropane-2-sulfonamide (353 mg, 2.91 mmol) was added to a solution of pyrimidine-2-carbaldehyde (300 mg, 2.78 mmol) and KHSO₄ (397 mg, 2.91 mmol) in toluene (20 mL) and the mixture was heated at 50 °C for 14 h. The reaction mixture was concentrated in *vacuo* and the residue purified by silica column chromatography (30% EtOAc/PE) to give (S)-2-methyl-N-(pyrimidin-2-ylmethylene)propane-2-sulfonamide (330 mg, 56%). LCMS *m/z* = 212.0 [M+H]⁺; ¹H NMR (400 MHz, CD₃OD) δ 9.00 (d, *J* = 4.8 Hz, 2H), 8.61 (s, 1H), 7.61 (t, *J* = 4.8 Hz, 1H), 1.31 (s, 9H).

[00418] Step 2: (S)-2-methyl-N-(4-phenyl-1-(pyrimidin-2-yl)butyl)propane-2-sulfonamide

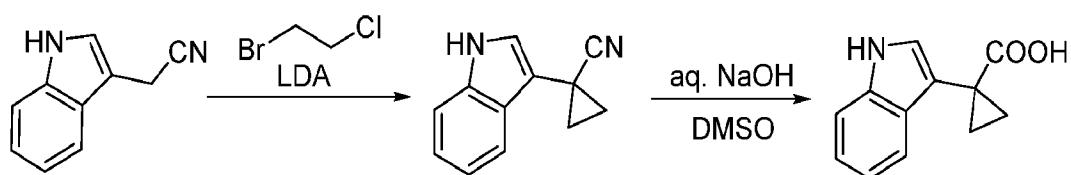
[00419] To a solution of (S)-2-methyl-N-(pyrimidin-2-ylmethylene)propane-2-sulfonamide (130 mg, 0.62 mmol) in THF (3.0 mL) was added (3-phenylpropyl)magnesium bromide (1M in THF, 2.0 mL) at -78 °C under N₂. The mixture stirred at -78 °C for 10 min then allowed to warm to room temperature and stirring continued for 2 h. The reaction mixture was concentrated in *vacuo* and the residue purified by silica column chromatography (50% EtOAc/PE) to give (S)-2-methyl-N-(4-phenyl-1-(pyrimidin-2-yl)butyl)propane-2-sulfonamide (54 mg, 26%).

[00420] Step 3: 4-phenyl-1-(pyrimidin-2-yl)butan-1-amine

[00421] A solution of (S)-2-methyl-N-(4-phenyl-1-(pyrimidin-2-yl)butyl)propane-2-sulfonamide (54 mg, 0.16 mmol) in HCl (4 M in dioxane, 2 mL) was stirred at room temperature for 1 h. The reaction mixture was concentrated in *vacuo* to give 4-phenyl-1-(pyrimidin-2-yl)butan-1-amine 4-phenyl-1-(pyrimidin-2-yl)butan-1-amine (37 mg, quant.) which was used directly.

Synthesis of 3-methoxy-4-(trifluoromethoxy)benzoic acid

[00422] H_2O_2 (72 mg, 1.19 mmol) was added to a solution of 3-methoxy-4-(trifluoromethoxy)benzaldehyde (80 mg, 0.36 mmol), NaH_2PO_4 (282 mg, 1.19 mmol) and NaClO (164 mg, 1.19 mmol) in DMSO/ H_2O (2.0 mL/ 0.5 mL). The solution was stirred at room temperature for 5 h. Water was added and pH adjusted to ~ 1 by addition of 1M HCl. The aqueous was extracted with EtOAc three times. The combined organic layers were washed with water, brine and dried over Na_2SO_4 . The residue was concentrated and used without further purification. LCMS $m/z = 234.9$ $[\text{M}-\text{H}]^-$.

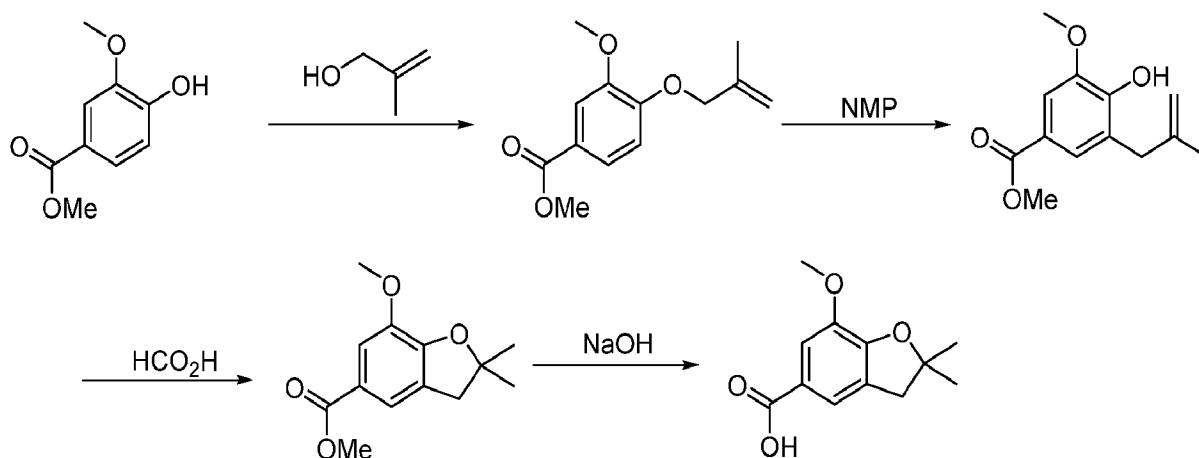
Synthesis of 1-(1H-indol-3-yl)cyclopropane-1-carboxylic acid**[00423] Step 1: 1-(1H-indol-3-yl)cyclopropane-1-carbonitrile**

[00424] A solution of 2-(1H-indol-3-yl)acetonitrile (500 mg, 3.20 mmol) in THF was treated with LDA (2M in THF, 6.4 mL, 12.8 mmol) at $-30\text{ }^\circ\text{C}$. The solution was allowed to warm to $-5\text{ }^\circ\text{C}$ and stirred for 30 min, then cooled to $-30\text{ }^\circ\text{C}$ and 1-bromo-2-chloroethane (550 mg, 3.84 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 2h. Water was added and the pH adjusted to ~ 1 by addition of 1M HCl. The aqueous was extracted with EtOAc three times and the combined organic layers washed with, water, brine and dried over Na_2SO_4 . The residue after concentration was purified by silica gel column (20% EtOAc/PE) to afford 1-(1H-indol-3-yl)cyclopropane-1-carbonitrile (235 mg, 40%) as a yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 11.17 (s, 1H), 7.72 – 7.66 (m, 1H), 7.43 – 7.35 (m, 2H), 7.19 – 7.05 (m, 2H), 1.69 – 1.56 (m, 2H), 1.41 – 1.28 (m, 2H).

[00425] Step 2: 1-(1H-indol-3-yl)cyclopropane-1-carboxylic acid

[00426] To a solution of 1-(1H-indol-3-yl)cyclopropane-1-carbonitrile (40 mg, 0.22 mmol) in DMSO (2 mL) was added NaOH (35.2 mg, 0.88 mmol). The mixture was heated at 70 °C overnight. Water was added and pH adjusted to ~1 by addition of 1M HCl. The aqueous was extracted with EtOAc three times and the combined organic layers were washed with water, brine and dried over Na₂SO₄. The solvent was removed to afford 1-(1H-indol-3-yl)cyclopropane-1-carboxylic acid (43 mg, 97%) as a colorless oil, which was used directly.

Synthesis of 7-methoxy-2,2-dimethyl-2,3-dihydrobenzofuran-5-carboxylic acid



[00427] Step 1: methyl 3-methoxy-4-((2-methylallyl)oxy)benzoate

[00428] 2-methylprop-2-en-1-ol (396 mg, 5.49 mmol) was added to a solution of methyl 4-hydroxy-3-methoxybenzoate (1 g, 5.49 mmol), DIAD (258 mg, 5.49 mmol) and PPh₃ (1.44 g, 5.49 mmol) in THF (8.0 mL). The reaction mixture was stirred at room temperature for 14 h. The solvent was removed and the residue purified by silica gel column (3% EtOAc/PE) to afford methyl 3-methoxy-4-((2-methylallyl)oxy)benzoate (1 g, 77%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.54 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.45 (d, *J* = 2.0 Hz, 1H), 7.04 (d, *J* = 8.4 Hz, 1H), 5.05 (s, 1H), 4.96 (s, 1H), 4.53 (s, 2H), 3.82 (s, 3H), 3.81 (s, 3H), 1.76 (s, 3H).

[00429] Step 2: methyl 4-hydroxy-3-methoxy-5-(2-methylallyl)benzoate

[00430] Methyl 3-methoxy-4-((2-methylallyl)oxy)benzoate (100 mg, 0.42 mmol) was dissolved in NMP (1.5 mL) and the solution heated at 205°C for 7 h. The reaction was allowed to cool, water added and the aqueous extracted with EtOAc three times. The combined organic layers were washed with water, brine and dried over Na₂SO₄. The residue was concentrated and purified by prep-TLC (5% MeOH/DCM) to afford methyl 4-hydroxy-3-methoxy-5-(2-methylallyl)benzoate

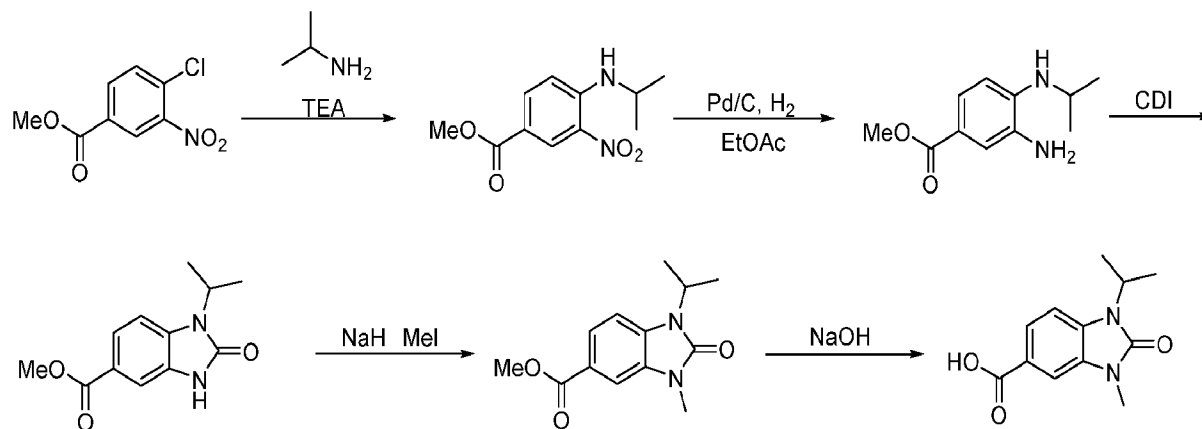
(80 mg, 80%) as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.61 (s, 1H), 7.42 – 7.29 (m, 2H), 4.75 (s, 1H), 4.61 (s, 1H), 3.84 (s, 3H), 3.78 (s, 3H), 3.28 (s, 2H), 1.64 (s, 3H).

[00431] Step 3: methyl 7-methoxy-2,2-dimethyl-2,3-dihydrobenzofuran-5-carboxylate

[00432] To a solution of methyl 4-hydroxy-3-methoxy-5-(2-methylallyl)benzoate (60 mg, 0.25 mmol) in DCM (1.5 mL) was added formic acid (0.5 mL). The resulting mixture was heated at 45°C for 14 h in a sealed tube. The solvent was removed and the residue purified by prep-TLC (7% MeOH/DCM) to afford methyl 7-methoxy-2,2-dimethyl-2,3-dihydrobenzofuran-5-carboxylate (55 mg, 92 %) as a white oil. LCMS m/z = 237.0 $[\text{M}+\text{H}]^+$.

[00433] Step 4: 7-methoxy-2,2-dimethyl-2,3-dihydrobenzofuran-5-carboxylic acid NaOH (18.6 mg, 0.47 mmol) was added to a solution of methyl 7-methoxy-2,2-dimethyl-2,3-dihydrobenzofuran-5-carboxylate (55 mg, 0.23 mmol) in a mixture of MeOH (2 mL) and H_2O (0.4 mL). The reaction mixture was stirred at room temperature for 14 h. Water was added and the pH adjusted to ~1 by addition of 1M HCl. The aqueous was extracted with EtOAc three times and the combined organic layers were washed with water, brine and dried over Na_2SO_4 . The solvent was removed to afford 7-methoxy-2,2-dimethyl-2,3-dihydrobenzofuran-5-carboxylic acid (205 mg, quant.) which was used without further purification. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.43 (d, J = 1.6 Hz, 1H), 7.35 (d, J = 1.6 Hz, 1H), 3.78 (s, 3H), 3.04 (s, 2H), 1.42 (s, 6H).

Synthesis of isopropyl-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazole-5-carboxylic acid



[00434] Step 1: methyl 4-(isopropylamino)-3-nitrobenzoate

[00435] To a solution of propan-2-amine (274 mg, 4.64 mmol) in THF (5 mL) was added methyl 4-chloro-3-nitrobenzoate (500 mg, 2.32 mmol) and Et_3N (704 mg, 6.96 mmol). The mixture was

stirred at room temperature overnight. Water was added and the aqueous extracted with EtOAc three times. The combined organic layers were washed with water, brine and dried over Na₂SO₄. The crude obtained, after concentration, was purified by silica gel column (20% EtOAc/PE) to afford methyl 4-(isopropylamino)-3-nitrobenzoate (552 mg, quant.). LCMS m/z = 239.2 [M+H]⁺.

[00436] Step 2: methyl 3-amino-4-(isopropylamino)benzoate

[00437] To a solution of methyl 4-(isopropylamino)-3-nitrobenzoate (552 mg, 2.32 mmol) in MeOH (5 mL) was added Pd/C (10%, 52 mg). The mixture was stirred at room temperature overnight under an atmosphere of H₂. The reaction mixture was filtered through celite and the filtrate was concentrated under reduced pressure to afford methyl 3-amino-4-(isopropylamino)benzoate (442 mg, 92%). LCMS m/z = 209.2 [M+H]⁺.

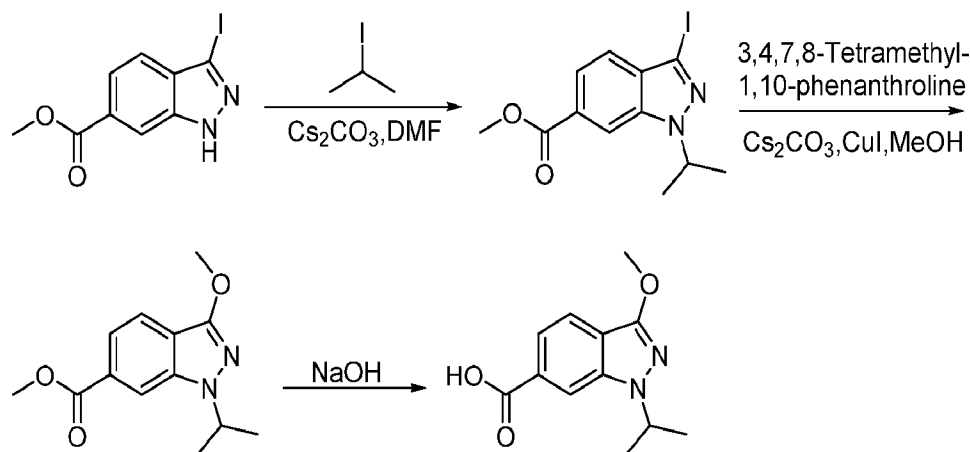
[00438] Step 3: methyl 1-isopropyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazole-5-carboxylate To a solution of methyl 3-amino-4-(isopropylamino)benzoate (370 mg, 1.78 mmol) in dioxane (4 mL) was added CDI (346 mg, 2.13 mmol) and the reaction mixture stirred at room temperature overnight. Water was added and the aqueous extracted with EtOAc three times. The combined organic layers were washed with water, brine, dried over Na₂SO₄ and concentrated *in vacuo*. The crude was purified by silica gel column (5% MeOH/DCM) to afford methyl 1-isopropyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazole-5-carboxylate (224 mg, 54%).

[00439] Step 4: methyl 1-isopropyl-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazole-5-carboxylate To a solution of methyl 1-isopropyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazole-5-carboxylate (100 mg, 0.43 mmol) in DMF (2 mL) at RT was added NaH (51 mg, 1.28 mmol). The mixture was stirred for 30 min then MeI (91 mg, 0.64 mmol) was added. The reaction mixture was then stirred for a further 4 h. Water was added and the aqueous extracted with EtOAc three times. The combined organic layers were washed with water, brine, dried over Na₂SO₄ and concentrated *in vacuo*. The crude was purified by silica gel column (3% MeOH/DCM) to afford methyl 1-isopropyl-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazole-5-carboxylate (93 mg, 88%). LCMS m/z = 249.2 [M+H]⁺.

[00440] Step 5: isopropyl-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazole-5-carboxylic acid To a solution of methyl 1-isopropyl-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazole-5-carboxylate (93 mg, 0.37 mmol) in MeOH (1 mL) was added NaOH (10%, 1 mL) and the reaction stirred for 2 h. Water was added and the pH adjusted to ~1 by addition of 1 M HCl. The aqueous

was extracted with EtOAc three times and the combined organic layers were washed with water, brine, dried over Na_2SO_4 and concentrated *in vacuo* to afford isopropyl-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazole-5-carboxylic acid (86 mg, quant.).

Synthesis of 1-isopropyl-3-methoxy-1H-indazole-6-carboxylic acid



[00441] Step 1: methyl 3-iodo-1-isopropyl-1H-indazole-6-carboxylate

[00442] To a solution of methyl 3-iodo-1H-indazole-6-carboxylate (300 mg, 1 mmol) in DMF (5 mL) was added 2-iodopropane (336 mg, 2 mmol) and Cs_2CO_3 (972 mg, 3 mmol). The resulting mixture was stirred at room temperature overnight. Water was added and the aqueous extracted with EtOAc three times. The combined organic layers were washed with water, brine and dried over Na_2SO_4 . The residue was concentrated and purified by silica gel column (20% EtOAc/PE) to afford methyl 3-iodo-1-isopropyl-1H-indazole-6-carboxylate (280 mg, 81%) as a yellow oil. LCMS $m/z = 345.0$ $[\text{M}+\text{H}]^+$.

[00443] Step 2: methyl 1-isopropyl-3-methoxy-1H-indazole-6-carboxylate

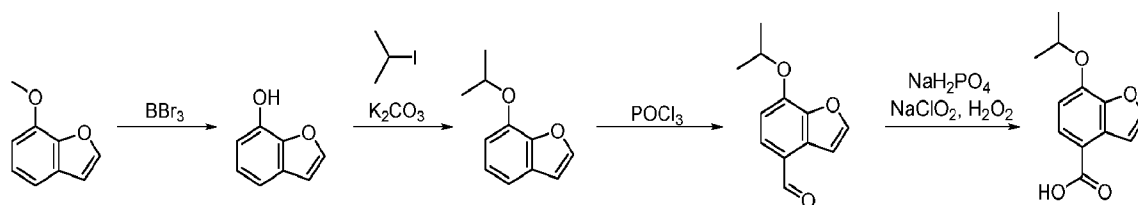
[00444] To a solution of methyl 3-iodo-1-isopropyl-1H-indazole-6-carboxylate (150 mg, 0.43 mmol) in MeOH (1 mL) was added Cs_2CO_3 (281 mg, 0.87 mmol), 3,4,7,8-tetramethyl-1,10-phenanthroline (20 mg, 0.085 mmol) and CuI (8 mg, 0.043 mmol). The resulting mixture was heated at 140°C for 2 h in a microwave reactor. Water was added and the aqueous extracted with EtOAc three times. The combined organic layers were washed with water, brine and dried over Na_2SO_4 . The residue was concentrated and purified by silica gel column (12% EtOAc/PE) to afford methyl 1-isopropyl-3-methoxy-1H-indazole-6-carboxylate (45 mg, 42%) as a yellow oil. LCMS $m/z = 249.2$ $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.31 (dd, $J = 1.6, 0.8$ Hz, 1H), 7.97 (dd, $J =$

9.0, 1.6 Hz, 1H), 7.43 (d, $J = 9.0$ Hz, 1H), 4.83 – 4.77 (m, 1H), 4.09 (s, 3H), 3.91 (s, 3H), 1.49 (d, $J = 6.4$ Hz, 6H).

[00445] Step 3: 1-isopropyl-3-methoxy-1H-indazole-6-carboxylic acid

[00446] To a solution of methyl 1-isopropyl-3-methoxy-1H-indazole-6-carboxylate (45 mg, 0.18 mmol) in MeOH (1 mL) was added 10% aq NaOH (1 mL) and the reaction stirred at room temperature for 3h. The solvent was removed and water added. The pH was adjusted to ~1 by addition of 1 M HCl and the aqueous extracted with EtOAc three times. The combined organic layers were washed with water, brine, dried over Na₂SO₄ and concentrated to afford 1-isopropyl-3-methoxy-1H-indazole-6-carboxylic acid (30 mg, 71%) as a colourless oil. LCMS $m/z = 235.1$ $[M+H]^+$.

Synthesis of 7-isopropoxybenzofuran-4-carboxylic acid



[00447] Step 1: benzofuran-7-ol

[00448] To a solution of BBr₃ (1M in DCM, 2 mL, 2 mmol) at -78°C was added a solution of 7-methoxybenzofuran (150 mg, 1 mmol) in DCM (2 mL) dropwise. The resulting mixture was allowed to warm to room temperature and stirred for 4 hours under N₂. Water was added and the aqueous extracted with diethylether three times. The combined organic layers were washed with water, brine, dried over Na₂SO₄ and concentrated. The residue was purified by prep-TLC (30% EtOAc/PE) to afford benzofuran-7-ol (55 mg, 31%) as a black oil. ¹H NMR (400 MHz, CDCl₃) δ 7.61 (d, $J = 2.2$ Hz, 1H), 7.20 – 7.08 (m, 2H), 6.84 (dd, $J = 7.8, 1.2$ Hz, 1H), 6.78 (d, $J = 2.2$ Hz, 1H).

[00449] Step 2: 7-isopropoxybenzofuran

[00450] To a solution of benzofuran-7-ol (50 mg, 0.37 mmol) in DMF (1 mL) was added 2-iodopropane (76 mg, 0.45 mmol) and K₂CO₃ (155 mg, 1.1 mmol). The resulting mixture was stirred at room temperature for 4 hours. The solvent was removed *in vacuo* and the residue purified by prep-TLC (30% EtOAc/PE) to afford 7-isopropoxybenzofuran (44 mg, 68%) as a yellow oil.

^1H NMR (400 MHz, CDCl_3) δ 7.61 (d, $J = 2.2$ Hz, 1H), 7.20 – 7.09 (m, 2H), 6.82 (dd, $J = 7.8, 1.2$ Hz, 1H), 6.75 (d, $J = 2.2$ Hz, 1H), 4.80 (p, $J = 6.0$ Hz, 1H), 1.43 (d, $J = 6.0$ Hz, 6H).

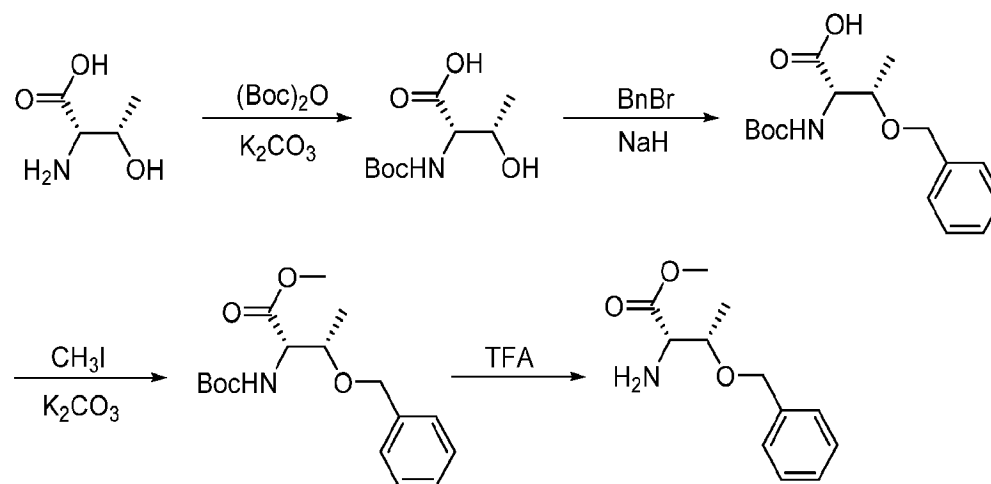
[00451] Step 3: 7-isopropoxybenzofuran-4-carbaldehyde

[00452] To a solution of 7-isopropoxybenzofuran (44 mg, 0.25 mmol) in DMF (1 mL) was added POCl_3 (230 mg, 1.5 mmol) and the reaction heated at 100 °C for 4 hours under N_2 . The reaction was cooled to room temperature and the mixture was poured into saturated Na_2CO_3 solution and extracted with ether three times. The combined organic layers were washed with water, brine and dried over Na_2SO_4 . The residue was purified by prep-TLC (30% EtOAc/PE) to afford 7-isopropoxybenzofuran-4-carbaldehyde (40 mg, 78%) as a yellow oil. LCMS $m/z = 205.1$ $[\text{M}+\text{H}]^+$.

[00453] Step 4: 7-isopropoxybenzofuran-4-carboxylic acid

[00454] To a solution of 7-isopropoxybenzofuran-4-carbaldehyde (40 mg, 0.2 mmol) in a mixture of DMSO (1 mL) and H_2O (1 mL) was added NaClO_2 (115 mg, 1.0 mmol), NaH_2PO_4 (160 mg, 1.0 mmol) and 30% H_2O_2 (113 mg, 1.0 mmol). The resulting mixture was stirred at room temperature for 4 hours under N_2 . Water was added and the pH adjusted to ~ 1 by addition of 1M HCl. The aqueous was extracted with EtOAc three times. The combined organic layers were washed with water, brine and dried over Na_2SO_4 . The residue was purified by prep-TLC (20% EtOAc/PE) to afford 7-isopropoxybenzofuran-4-carboxylic acid (20 mg, 45%) as a white solid. LCMS $m/z = 221.0$ $[\text{M}+\text{H}]^+$.

Synthesis of methyl O-benzyl-L-allothreoninate



[00455] Step 1: (tert-butoxycarbonyl)-L-allothreonine

[00456] To a solution of L-allothreonine (1.0 g, 8.4 mmol) and K_2CO_3 (2.3 g, 16.8 mmol) in a mixture of THF (10 mL) and H_2O (2 mL) at 0 °C was added $(Boc)_2O$ (2.0 g, 9.2 mmol). The resulting mixture was stirred for 5 hours, then water was added and the aqueous extracted with Et_2O three times and the organic layers discarded. The pH of the aqueous layer was adjusted to ~1 by addition of 1M HCl and extracted with 20% MeOH/DCM three times. The combined organic layers were washed with water and brine, dried over Na_2SO_4 and concentrated to afford (tert-butoxycarbonyl)-L-allothreonine (1.0 g, 55%). LCMS m/z = 164.1 $[M-t\text{Butyl}+H]^+$.

[00457] **Step 2: O-benzyl-N-(tert-butoxycarbonyl)-L-allothreonine** To a solution of (tert-butoxycarbonyl)-L-allothreonine (2.0 g, 9.12 mmol) in DMF (20 mL) at 0 °C was added NaH (728 mg, 18.2 mmol) and the resulting mixture stirred for 30 minutes. Benzyl bromide (1.1 mL, 9.12 mmol) was then added and the reaction mixture stirred for another 3 hours at room temperature. Water was added and the aqueous extracted with EtOAc three times. The combined organic layers were washed with water, brine and dried over Na_2SO_4 . The residue was concentrated and purified by reverse-phase column to afford O-benzyl-N-(tert-butoxycarbonyl)-L-allothreonine (1.7 g, 61%). LCMS m/z = 254.2 $[M-t\text{Butyl}+H]^+$; 1H NMR (400 MHz, $DMSO-d_6$) δ 12.64 (s, 1H), 7.39 – 7.21 (m, 5H), 7.01 (d, J = 8.8 Hz, 1H), 4.47 (s, 2H), 4.28 (dd, J = 9.0, 5.6 Hz, 1H), 3.88 – 3.77 (m, 1H), 1.39 (s, 9H), 1.11 (d, J = 6.4 Hz, 3H).

[00458] **Step 3: methyl O-benzyl-N-(tert-butoxycarbonyl)-L-allothreoninate**

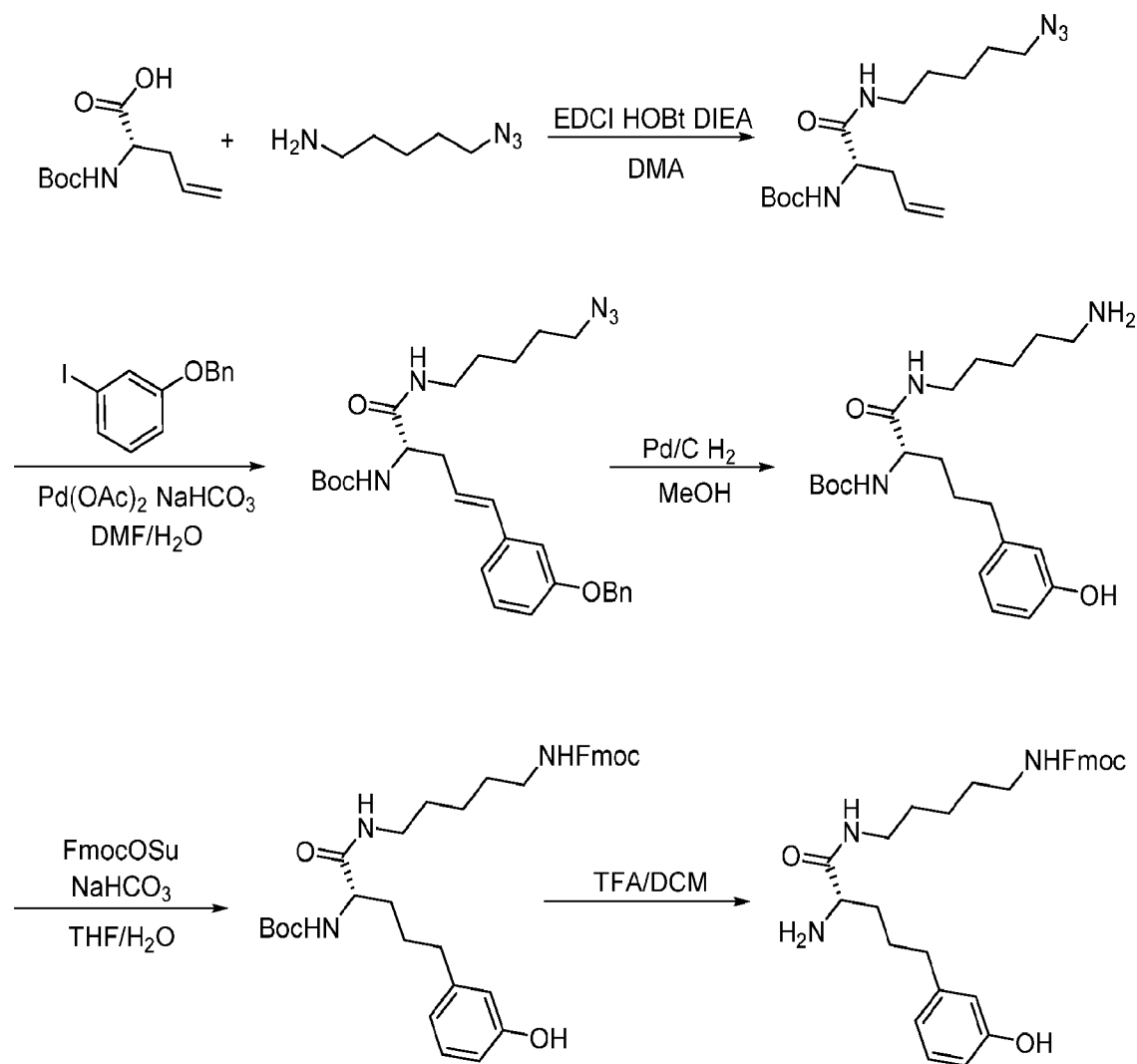
[00459] To a solution of O-benzyl-N-(tert-butoxycarbonyl)-L-allothreonine (480 mg, 1.55 mmol) and K_2CO_3 (429 mg, 3.10 mmol) in DMF (15 mL) was added CH_3I (330.7 mg, 2.33 mmol) and the reaction stirred for 4 hours. Water was added and the aqueous extracted with EtOAc three times. The combined organic layers were washed with water, brine and dried over Na_2SO_4 . The residue was concentrated and purified by silica gel column (20% EtOAc/PE) to afford methyl O-benzyl-N-(tert-butoxycarbonyl)-L-allothreoninate (498 mg, 99%) as a colourless oil. LCMS m/z = 268.2 $[M-t\text{Butyl}+H]^+$; 1H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.26 (m, 5H), 5.25 (d, J = 8.8 Hz, 1H), 4.60 – 4.49 (m, 3H), 3.97 – 3.80 (m, 1H), 3.75 (s, 3H), 1.43 (s, 9H), 1.23 (d, J = 6.4 Hz, 3H).

[00460] **Step 4: methyl O-benzyl-L-allothreoninate**

[00461] To a solution of methyl O-benzyl-N-(tert-butoxycarbonyl)-L-allothreoninate (480 mg, 1.49 mmol) in DCM (5 mL) was added TFA (2.5 mL). The mixture was stirred for 4 hours. The solvent

was removed to afford methyl O-benzyl-L-allothreoninate (400 mg, quant). LCMS m/z = 224.2 $[M+H]^+$.

Synthesis of (9H-fluoren-9-yl)methyl (S)-(5-(2-amino-5-(3-hydroxyphenyl)pentanamido)pentyl)carbamate



[00462] Step 1: tert-butyl (S)-(1-((5-azidopentyl)amino)-1-oxopent-4-en-2-yl)carbamate

[00463] A solution of (S)-2-((tert-butoxycarbonyl)amino)pent-4-enoic acid (517 mg, 2.4 mmol), 5-azidopentan-1-amine (280 mg, 2.18 mmol), EDCI (630 mg, 3.3 mmol), HOBT (443 mg, 3.3 mmol) and DIEA (1.12 g, 8.8 mmol) in DMA (5 mL) was stirred at room temperature overnight. Water was added and the aqueous extracted with EtOAc. The combined organic layers were washed with water and brine and dried over Na_2SO_4 . The residue after concentration was purified by silica gel column (50% EtOAc/PE) to afford tert-butyl (S)-(1-((5-azidopentyl)amino)-1-oxopent-4-en-2-yl)carbamate (330 mg, 46%) as a yellow oil. LCMS m/z = 326.2 $[M+H]^+$. **Step 2: tert-butyl (S,E)-**

(1-((5-azidopentyl)amino)-5-(3-(benzyloxy)phenyl)-1-oxopent-4-en-2-yl)carbamate To a solution of tert-butyl (S)-(1-((5-azidopentyl)amino)-1-oxopent-4-en-2-yl)carbamate (1.07 g, 3.3 mmol) and 1-(benzyloxy)-3-iodobenzene (1.02 g, 3.3 mmol) in a mixture of DMF (8 mL) and H₂O (2 mL) was added Pd(OAc)₂ (73 mg, 0.33 mmol) and NaHCO₃ (1.1 g, 13.2 mmol). The reaction mixture was heated at 75 °C for 4 h. Water was added and the aqueous extracted with EtOAc. The combined organic layers were washed with water and brine and dried over Na₂SO₄. The residue after concentration was purified by silica gel column (50% EtOAc/PE) to afford tert-butyl (S,E)-(1-((5-azidopentyl)amino)-5-(3-(benzyloxy)phenyl)-1-oxopent-4-en-2-yl)carbamate (1.38 g, 82%) as a white solid. ¹H NMR (400 MHz, CD₃OD) δ 7.467.40 (m, 2H), 7.39 – 7.27 (m, 3H), 7.19 (t, *J* = 8.0 Hz, 1H), 7.00 (t, *J* = 2.0 Hz, 1H), 6.95 (d, *J* = 7.6 Hz, 1H), 6.85 (dd, *J* = 8.0, 2.4 Hz, 1H), 6.47 – 6.38 (m, 1H), 6.24 – 6.12 (m, 1H), 5.07 (s, 2H), 4.16 – 4.07 (m, 1H), 3.29 – 3.20 (m, 1H), 3.17 – 3.06 (m, 3H), 2.68 – 2.43 (m, 2H), 1.51 – 1.39 (m, 12H), 1.37 – 1.27 (m, 3H).

[00464] Step 3: tert-butyl (S)-(1-((5-aminopentyl)amino)-5-(3-hydroxyphenyl)-1-oxopentan-2-yl)carbamate

[00465] To a solution of tert-butyl (S,E)-(1-((5-azidopentyl)amino)-5-(3-(benzyloxy)phenyl)-1-oxopent-4-en-2-yl)carbamate (1.4 g, 2.76 mmol) in MeOH (8 mL) was added Pd/C (10%, 200 mg). The reaction mixture was stirred at room temperature overnight. The solution was filtered through celite and the filtrate was concentrated to afford tert-butyl (S)-(1-((5-aminopentyl)amino)-5-(3-hydroxyphenyl)-1-oxopentan-2-yl)carbamate (970 mg, 89%) which was used in next step directly. ¹H NMR (400 MHz, CD₃OD) δ 7.05 (t, *J* = 8.0 Hz, 1H), 6.66 – 6.56 (m, 3H), 4.03 – 3.90 (m, 1H), 3.26 – 3.09 (m, 2H), 2.67 – 2.50 (m, 4H), 1.73 – 1.48 (m, 7H), 1.44 (s, 9H), 1.40 – 1.28 (m, 3H).

[00466] Step 4: tert-butyl (S)-(1-((5-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)pentyl)amino)-5-(3-hydroxyphenyl)-1-oxopentan-2-yl)carbamate

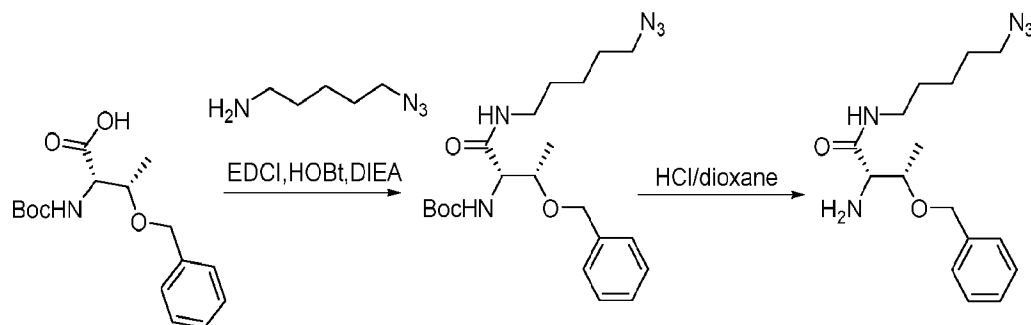
[00467] To a solution of tert-butyl (S)-(1-((5-aminopentyl)amino)-5-(3-hydroxyphenyl)-1-oxopentan-2-yl)carbamate (200 mg, 0.5 mmol) and FmocOSu (189 mg, 0.55 mmol) in a mixture of THF (4 mL) and H₂O (1 mL) was added NaHCO₃ (85 mg, 1 mmol). The reaction mixture was stirred at room temperature for 4 h. Water was added and the aqueous extracted with EtOAc. The combined organic layers were washed with water, brine and dried over Na₂SO₄. The residue after concentration was purified by silica gel column (50% EtOAc/PE) to afford tert-butyl (S)-(1-((5-

(((9H-fluoren-9-yl)methoxy)carbonyl)amino)pentyl)amino)-5-(3-hydroxyphenyl)-1-oxopentan-2-yl)carbamate (137 mg, 44%) as a white solid. LCMS $m/z = 616.2$ $[M+H]^+$

[00468] Step 5: (9H-fluoren-9-yl)methyl (S)-(5-(2-amino-5-(3-hydroxyphenyl)pentanamido)pentyl)carbamate

[00469] To a solution of tert-butyl (S)-(1-(((5-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)pentyl)amino)-5-(3-hydroxyphenyl)-1-oxopentan-2-yl)carbamate (50 mg, 0.08 mmol) in DCM (2 mL) was added TFA (2 mL) and the reaction mixture was stirred at room temperature for 2 h. The solvent was removed under reduced pressure to afford the product (57 mg, quant.) as a white solid. LCMS $m/z = 516.2$ $[M+H]^+$.

Synthesis of (2S,3S)-2-amino-N-(5-azidopentyl)-3-(benzyloxy)butanamide



[00470] Step 1: tert-butyl ((2S,3S)-1-((5-azidopentyl)amino)-3-(benzyloxy)-1-oxobutan-2-yl)carbamate To a solution of O-benzyl-N-(tert-butoxycarbonyl)-L-allothreonine (220 mg, 0.71 mmol) in DMA (1 mL) was added 5-azidopentan-1-amine (100 mg, 0.78 mmol), EDCI (205 mg, 1.07 mmol), HOBt (144 mg, 1.07 mmol) and DIEA (460 mg, 3.56 mmol). The resulting mixture was stirred at room temperature for 4 hours under N_2 . Water was added and the aqueous extracted with EtOAc three times. The combined organic layers were washed with water and brine and dried over Na_2SO_4 . The residue obtained after concentration was purified by silica gel column (30% EtOAc/PE) to afford tert-butyl ((2S,3S)-1-((5-azidopentyl)amino)-3-(benzyloxy)-1-oxobutan-2-yl)carbamate (220 mg, 73%) as a yellow oil. LCMS $m/z = 420.3$ $[M+H]^+$.

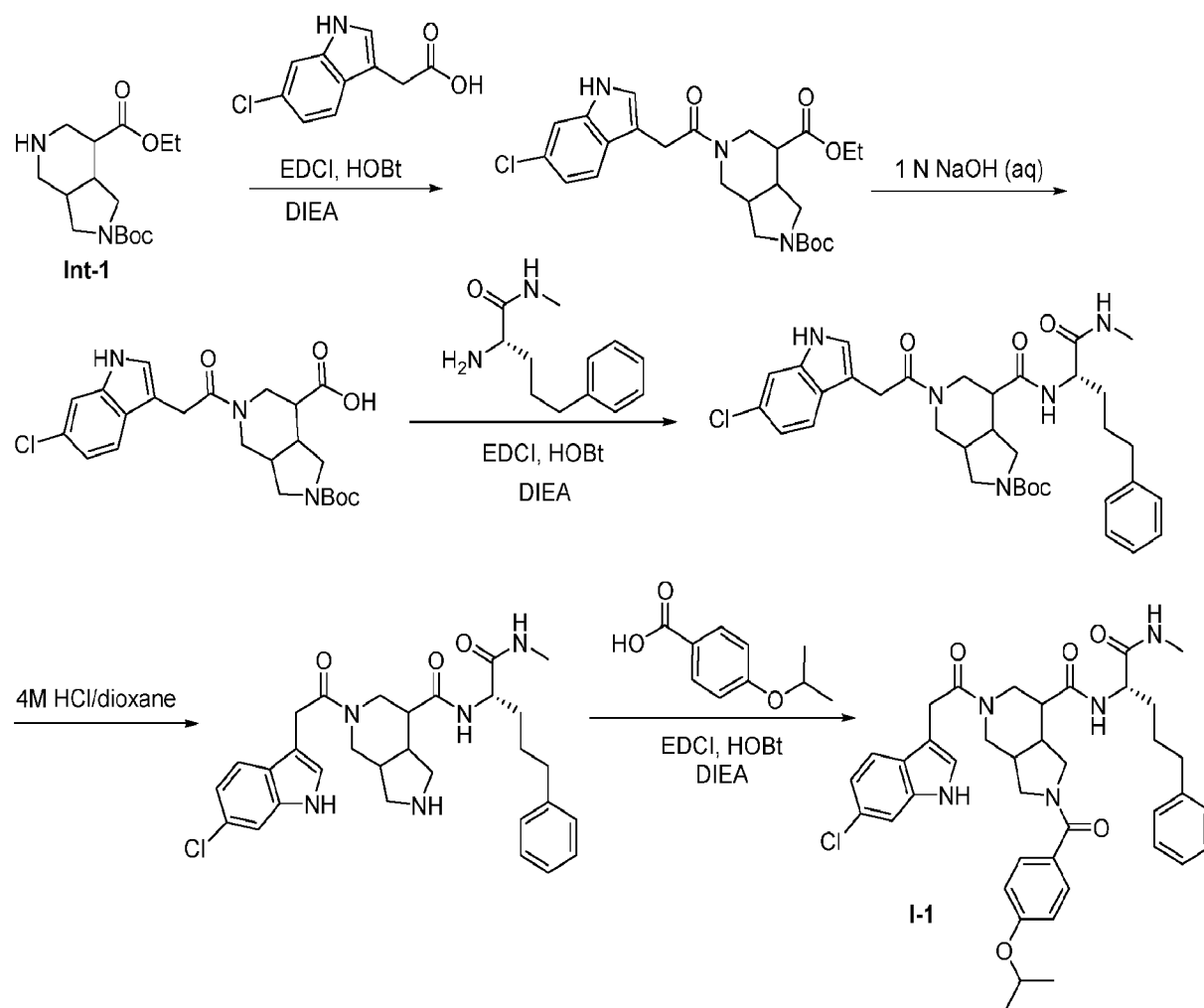
[00471] Step 2: (2S,3S)-2-amino-N-(5-azidopentyl)-3-(benzyloxy)butanamide

[00472] To a solution of tert-butyl ((2S,3S)-1-((5-azidopentyl)amino)-3-(benzyloxy)-1-oxobutan-2-yl)carbamate (244 mg, 0.58 mmol) in MeOH (1 mL) was added HCl (4M in dioxane, 2 mL). The resulting mixture was stirred at room temperature for 1 h. The solvent was removed to afford

(2S,3S)-2-amino-N-(5-azidopentyl)-3-(benzyloxy)butanamide (220 mg, quant.) LCMS m/z = 320.3 $[M+H]^+$.

Example 2: Synthesis of Exemplary Compounds

Synthesis of 5-(2-(6-chloro-1H-indol-3-yl)acetyl)-2-(4-isopropoxy-3-methoxybenzoyl)-N-((S)-1-(methylamino)-1-oxo-5-phenylpentan-2-yl)octahydro-1H-pyrrolo[3,4-c]pyridine-7-carboxamide I-1



[00473] Step 1: 2-(tert-butyl) 7-ethyl 5-(2-(6-chloro-1H-indol-3-yl)acetyl)octahydro-2H-pyrrolo[3,4-c]pyridine-2,7-dicarboxylate

[00474] To a solution of 2-(tert-butyl) 7-ethyl octahydro-2H-pyrrolo[3,4-c]pyridine-2,7-dicarboxylate (**Int-1**, 6.4 g, 21.5 mmol) in DMF (60 mL) was added 2-(6-chloro-1H-indol-3-yl)acetic acid (5.9 g, 28.2 mmol), EDCI (6.8 g, 35.3 mmol), HOBT (4.8 g, 35.3 mmol) and DIPEA

(9.1 g, 70.5 mmol). The resulting mixture was stirred at room temperature for 14 h. Water was then added and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with water and brine, dried over Na₂SO₄ and the solvent removed *in vacuo*. The residue was purified by column chromatography (2% MeOH/DCM) to afford the product (5.3 g, 46%) as a white solid. LCMS *m/z* = 490.0 [M+H]⁺; ¹H NMR (400 MHz, CD₃OD) δ 7.64 – 7.50 (m, 1H), 7.37 – 7.31 (m, 1H), 7.24 – 7.14 (m, 1H), 7.04 – 6.96 (m, 1H), 4.68 – 3.66 (m, 5H), 3.52 – 3.37 (m, 1H), 3.29 – 2.06 (m, 7H), 1.98 – 1.77 (m, 1H), 1.46 – 1.35 (m, 9H), 1.24 (t, *J* = 7.2 Hz, 3H). **Step 2:** *2-(tert-butoxycarbonyl)-5-(2-(6-chloro-1H-indol-3-yl)acetyl)octahydro-1H-pyrrolo[3,4-c]pyridine-7-carboxylic acid*

[00475] To a solution of 2-(tert-butyl) 7-ethyl 5-(2-(6-chloro-1H-indol-3-yl)acetyl)octahydro-2H-pyrrolo[3,4-c]pyridine-2,7-dicarboxylate (2.0 g, 4.1 mmol) in MeOH (20 mL) was added aqueous NaOH (1M, 4.1 mL). The resulting mixture was stirred for 3 h then the solvent removed under vacuum. The residue obtained was diluted with water and the pH adjusted to ~1 by addition of 1M HCl. The aqueous layer was extracted with EtOAc three times and the combined organic layers washed with water and brine, dried over Na₂SO₄ and concentrated to afford the product (1.7 g, 90%) as a white solid. LCMS *m/z* = 462.2 [M+H]⁺; ¹H NMR (400 MHz, CD₃OD) δ 7.63 – 7.47 (m, 1H), 7.37 – 7.31 (m, 1H), 7.25 – 7.15 (m, 1H), 7.05 – 6.96 (m, 1H), 4.71 – 4.11 (m, 2H), 4.07 – 3.70 (m, 2H), 3.54 – 3.36 (m, 1H), 3.29 – 2.04 (m, 7H), 2.00 – 1.77 (m, 1H), 1.47 – 1.35 (m, 9H).

[00476] **Step 3:** *tert-butyl 5-(2-(6-chloro-1H-indol-3-yl)acetyl)-7-(((S)-1-(methylamino)-1-oxo-5-phenylpentan-2-yl)carbamoyl)octahydro-2H-pyrrolo[3,4-c]pyridine-2-carboxylate*

[00477] In a similar manner to the procedure reported for **Step 1**, the coupling of 2-(tert-butoxycarbonyl)-5-(2-(6-chloro-1H-indol-3-yl)acetyl)octahydro-1H-pyrrolo[3,4-c]pyridine-7-carboxylic acid and (S)-2-amino-N-methyl-5-phenylpentanamide gave the product (1.8 g, quant.) after column chromatography (2% MeOH/DCM) as a white solid. LCMS *m/z* = 650.3 [M+H]⁺; ¹H NMR (400 MHz, CD₃OD) δ 7.68 – 6.87 (m, 9H), 4.53 – 3.66 (m, 5H), 3.56 – 3.38 (m, 1H), 3.28 – 2.77 (m, 4H), 2.76 – 1.98 (m, 9H), 1.87 – 1.51 (m, 4H), 1.50 – 1.33 (m, 9H).

[00478] **Step 4:** *5-(2-(6-chloro-1H-indol-3-yl)acetyl)-N-(((S)-1-(methylamino)-1-oxo-5-phenylpentan-2-yl)octahydro-1H-pyrrolo[3,4-c]pyridine-7-carboxamide hydrochloride* To a solution of tert-butyl 5-(2-(6-chloro-1H-indol-3-yl)acetyl)-7-(((S)-1-(methylamino)-1-oxo-5-

phenylpentan-2-yl)carbamoyl)octahydro-2H-pyrrolo[3,4-c]pyridine-2-carboxylate (1.8 g, 2.77 mmol) in a mixture of DCM and MeOH (20 mL/10 mL) was added HCl in dioxane (4M, 6 mL). The resulting mixture was stirred for 3h, then the solvent removed under reduced pressure to afford the product (1.7 g, quant.). LCMS m/z = 550.2 $[M+H]^+$; 1H NMR (400 MHz, CD_3OD) δ 7.68 – 6.89 (m, 9H), 4.49 – 3.73 (m, 5H), 3.61 – 3.34 (m, 1H), 3.30 – 2.81 (m, 4H), 2.78 – 2.28 (m, 8H), 1.89 – 1.55 (m, 4H).

[00479] Step 5: 5-(2-(6-chloro-1H-indol-3-yl)acetyl)-2-(4-isopropoxy-3-methoxybenzoyl)-N-((S)-1-(methylamino)-1-oxo-5-phenylpentan-2-yl)octahydro-1H-pyrrolo[3,4-c]pyridine-7-carboxamide (I-1)

[00480] A mixture of the product of Step 4 (73 mg, 0.12 mmol), 4-isopropoxy-3-methoxybenzoic acid (27 mg, 0.15 mmol), EDCI (36 mg 0.19 mmol), HOBt (20 mg, 0.15 mmol) and DIEA (65 mg, 0.5 mmol) in DMF (2.0 mL) was stirred overnight. The reaction mixture was diluted with water and extracted with EtOAc three times. The combined organic layers were washed with water and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (3.3% MeOH/DCM) to give **I-1** (33.4 mg, 39%) as a white solid. LCMS m/z = 712.4 $[M+H]^+$; 1H NMR (400 MHz, CD_3OD) δ 7.66 – 6.77 (m, 13H), 4.79 – 3.35 (m, 9H), 3.29 – 2.98 (m, 2H), 2.98 – 2.76 (m, 1H), 2.76 – 2.48 (m, 6H), 2.43 (ddd, J = 12.4, 7.2, 3.8 Hz, 1H), 2.37 – 1.99 (m, 1H), 1.97 – 1.43 (m, 4H), 1.42 – 1.22 (m, 7H).

[00481] The compounds listed in **Table 2** were synthesized using analogous methods to those shown for **I-1**, using the appropriate commercially available reagents and/or intermediates. Final examples were obtained as a mixture of diastereomers unless indicated otherwise.

Table 2. Compounds made by a method analogous to I-1

#	1H NMR Chromatography conditions, if applicable	LCMS
I-2	1H NMR (400 MHz, CD_3OD) δ 7.71 – 6.80 (m, 12H), 4.61 – 3.34 (m, 7H), 3.28 – 2.78 (m, 2H), 2.78 – 2.58 (m, 5H), 2.57 – 2.34 (m, 6H), 2.30 – 1.98 (m, 1H), 1.84 – 0.86 (m, 5H).	m/z = 707.3 $[M+H]^+$
I-3	1H NMR (400 MHz, CD_3OD) δ 7.82 – 6.86 (m, 12H), 6.57 – 6.39 (m, 1H), 4.60 – 4.15 (m, 2H), 4.15 – 3.69 (m, 3H), 3.69 – 3.39 (m, 3H), 3.27 – 2.97 (m, 2H), 2.93 – 2.34 (m, 11H), 2.35 – 2.18 (m, 1H), 2.09 – 1.34 (m, 4H), 1.24 – 1.88 (m, 1H).	m/z = 708.3 $[M+H]^+$

#	¹ H NMR Chromatography conditions, if applicable	LCMS
I-4	¹ H NMR (400 MHz, CD ₃ OD) δ 7.55 – 7.76 (m, 13H), 4.51 – 4.30 (m, 1H), 4.28 – 3.84 (m, 4H), 3.71 – 3.64 (m, 1H), 3.55 – 3.37 (m, 2H), 3.27 – 2.80 (m, 3H), 2.76 – 2.60 (m, 6H), 2.45 – 2.07 (m, 2H), 1.65 – 1.28 (m, 5H).	m/z = 670.3 [M+H] ⁺
I-5	¹ H NMR (400 MHz, CD ₃ OD) δ 7.66 – 6.76 (m, 13H), 4.44 – 3.72 (m, 8H), 3.68 – 3.40 (m, 3H), 3.13 – 2.95 (m, 1H), 2.78 – 2.56 (m, 6H), 2.46 – 2.37 (m, 1H), 2.21 – 2.00 (m, 1H), 1.82 – 1.49 (m, 4H), 1.41 – 1.32 (m, 2H).	m/z = 684.3 [M+H] ⁺
I-6	¹ H NMR (400 MHz, CD ₃ OD) δ 7.65 – 6.91 (m, 13H), 4.57 – 4.36 (m, 1H), 4.35 – 3.74 (m, 5H), 3.70 – 3.36 (m, 4H), 3.30 – 2.78 (m, 3H), 2.77 – 1.99 (m, 9H), 1.80 – 1.37 (m, 4H), 0.88 – 0.58 (m, 4H).	m/z = 710.3 [M+H] ⁺
I-7	¹ H NMR (400 MHz, CD ₃ OD) δ 7.67 – 6.80 (m, 13H), 4.61 – 3.72 (m, 6H), 3.72 – 3.34 (m, 4H), 3.30 – 2.75 (m, 3H), 2.75 – 1.92 (m, 9H), 1.85 – 1.33 (m, 4H), 1.24 – 0.88 (m, 7H).	m/z = 726.4 [M+H] ⁺
I-8	¹ H NMR (400 MHz, CD ₃ OD) δ 8.22 – 8.06 (m, 1H), 8.01 – 7.77 (m, 1H), 7.65 – 6.78 (m, 11H), 4.62 – 4.06 (m, 3H), 4.05 – 3.33 (m, 7H), 3.30 – 3.01 (m, 2H), 3.00 – 1.83 (m, 10H), 1.81 – 1.34 (m, 4H).	m/z = 694.3 [M+H] ⁺
I-9	¹ H NMR (400 MHz, CD ₃ OD) δ 7.67 – 7.45 (m, 1H), 7.45 – 6.62 (m, 11H), 4.63 – 3.35 (m, 14H), 3.29 – 2.33 (m, 11H), , 1.87 – 1.50 (m, 5H), 1.05 – 0.73 (m, 1H), 0.58 – 0.35 (m, 2H), 0.19 – 0.05 (m, 2H).	m/z = 768.3 [M+H] ⁺
I-10	¹ H NMR (400 MHz, CD ₃ OD) δ 8.97 – 6.76 (m, 15H), 4.52 – 4.10 (m, 3H), 3.94 – 3.72 (m, 3H), 3.64 – 3.35 (m, 3H), 3.30 – 2.83 (m, 2H), 2.86 – 2.28 (m, 8H), 2.08 – 2.00 (m, 1H), 1.77 – 1.41 (m, 3H), 1.12 – 0.90 (m, 1H).	m/z = 705.2 [M+H] ⁺
I-11	¹ H NMR (400 MHz, CD ₃ OD) δ 7.86 – 6.88 (m, 18H), 4.63 – 4.02 (m, 2H), 3.88 (m, 2H), 3.74 – 3.34 (m, 3H), 3.27 – 2.94 (m, 2H), 2.93 – 1.91 (m, 9H), 1.87 – 1.22 (m, 5H).	m/z = 730.3 [M+H] ⁺
I-12	¹ H NMR (400 MHz, CD ₃ OD) δ 7.92 – 6.68 (m, 13H), 4.63 – 3.84 (m, 7H), 3.83 – 3.33 (m, 3H), 3.25 – 2.75 (m, 2H), 2.75 – 2.23 (m, 8H), 1.79 – 1.57 (m, 3H), 1.54 – 1.35 (m, 1H).	m/z = 694.2 [M+H] ⁺
I-13	¹ H NMR (400 MHz, CD ₃ OD) δ 7.96 – 7.80 (m, 2H), 7.56 – 7.48 (m, 4H), 7.38 – 6.92 (m, 8H), 4.53 – 4.45 (m, 1H), 4.28 – 4.03 (m, 2H), 3.94 – 3.49 (m, 6H), 3.20 – 2.81 (m, 2H), 2.78 – 2.33 (m, 7H), 2.20 – 2.03 (m, 1H), 1.71 – 1.50 (m, 4H), 1.36 – 1.25 (m, 3H).	m/z = 721.2 [M+H] ⁺
I-14	¹ H NMR (400 MHz, CD ₃ OD) δ 8.74 – 8.52 (m, 2H), 7.87 – 6.84 (m, 15H), 4.70 – 3.87 (m, 5H), 3.85 – 3.33 (m, 4H), 3.29 – 2.81 (m, 3H), 2.80 – 2.49 (m, 7H), 2.42 – 2.13 (m, 1H), 1.86 – 1.51 (m, 3H).	m/z = 731.3 [M+H] ⁺
I-15	¹ H NMR (400 MHz, CD ₃ OD) δ 8.92 – 6.92 (m, 12H), 4.56 – 4.46 (m, 1H), 4.39 – 4.30 (m, 1H), 4.21 – 4.06 (m, 1H), 3.94 – 3.78 (m, 3H), 3.63 – 3.40 (m, 3H), 3.30 – 2.91 (m, 2H), 2.74 – 2.68 (m, 8H), 2.35 – 2.00 (m, 1H), 1.83 – 1.44 (m, 4H).	m/z = 680.3 [M+H] ⁺

#	¹ H NMR Chromatography conditions, if applicable	LCMS
I-16	¹ H NMR (400 MHz, CD ₃ OD) δ 8.72 – 8.33 (m, 1H), 8.22 – 7.84 (m, 1H), 7.60 – 6.83 (m, 9H), 4.56 – 3.76 (m, 9H), 3.73 – 3.43 (m, 3H), 3.23 – 2.76 (m, 2H), 2.75 – 2.55 (m, 6H), 2.54 – 2.16 (m, 2H), 1.79 – 1.45 (m, 4H).	m/z = 686.3 [M+H] ⁺
I-17	¹ H NMR (400 MHz, CD ₃ OD) δ 9.12 – 8.87 (m, 2H), 8.32 – 6.70 (m, 12H), 4.68 – 3.87 (m, 6H), 3.85 – 3.40 (m, 4H), 3.30 – 3.02 (m, 2H), 3.01 – 2.63 (m, 6H), 2.61 – 2.44 (m, 2H), 2.41 – 2.01 (m, 2H), 1.80 – 1.39 (m, 3H), 1.25 – 0.85 (m, 1H).	m/z = 706.3 [M+H] ⁺
I-18	¹ H NMR (400 MHz, CD ₃ OD) δ 9.40 – 9.16 (m, 1H), 8.58 – 8.43 (m, 1H), 8.16 – 6.58 (m, 13H), 4.53 – 3.87 (m, 5H), 3.64 – 3.41 (m, 3H), 3.06 – 2.44 (m, 10H), 2.29 – 1.42 (m, 5H).	m/z = 705.3 [M+H] ⁺
I-19	¹ H NMR (400 MHz, CD ₃ OD) δ 8.01 – 6.68 (m, 15H), 4.63 – 4.36 (m, 1H), 4.36 – 3.81 (m, 5H), 3.80 – 3.35 (m, 3H), 3.19 – 1.89 (m, 10H), 1.80 – 1.40 (m, 4H).	m/z = 720.3 [M+H] ⁺
I-20	¹ H NMR (400 MHz, CD ₃ OD) δ 7.96 – 6.91 (m, 12H), 4.78 – 4.17 (m, 4H), 4.06 – 3.34 (m, 6H), 3.24 – 2.16 (m, 10H), 1.74 – 1.29 (m, 5H).	m/z = 685.3 [M+H] ⁺
I-21	¹ H NMR (400 MHz, CD ₃ OD) δ 8.29 – 6.69 (m, 11H), 4.56 – 3.41 (m, 11H), 3.27 – 2.76 (m, 2H), 2.75 – 2.46 (m, 7H), 2.38 – 1.96 (m, 1H), 1.80 – 1.42 (m, 4H), 1.37 – 1.30 (m, 1H).	m/z = 686.3 [M+H] ⁺
I-22	¹ H NMR (400 MHz, CD ₃ OD) δ 7.63 – 6.88 (m, 12H), 4.54 – 3.84 (m, 5H), 3.71 – 3.36 (m, 5H), 3.26 – 1.96 (m, 12H), 1.83 – 1.40 (m, 4H). First eluting diastereomer purified by Prep-TLC (6% MeOH/DCM). R _f = 0.40	m/z = 709.3 [M+H] ⁺
I-23	¹ H NMR (400 MHz, CD ₃ OD) δ 7.67 – 6.79 (m, 12H), 4.66 – 3.39 (m, 10H), 3.32 – 2.35 (m, 11H), 2.33 – 1.52 (m, 4H). Second eluting diastereomer purified by Prep-TLC (6% MeOH/DCM). R _f = 0.32	m/z = 709.3 [M+H] ⁺
I-24	¹ H NMR (400MHz, CD ₃ OD) δ 7.61 – 6.92 (m, 12H), 4.59 – 4.27 (m, 3H), 4.89 – 3.80 (m, 3H), 3.69 – 3.40 (m, 3H), 3.23 – 3.01 (m, 2H), 2.98 – 2.75 (m, 1H), 2.72 – 2.41 (m, 7H), 2.29 – 2.13 (m, 1H), 1.78 – 1.55 (m, 3H), 1.43 – 1.24 (m, 8H).	m/z = 746.3 [M+H] ⁺
I-25	¹ H NMR (400 MHz, CD ₃ OD) δ 7.67 – 6.91 (m, 13H), 4.62 – 3.35 (m, 8H), 3.29 – 2.80 (m, 3H), 2.78 – 2.54 (m, 6H), 2.49 – 2.40 (m, 1H), 2.35 – 1.92 (m, 1H), 1.82 – 1.56 (m, 3H), 1.38 – 1.28 (m, 1H).	m/z = 738.3 [M+H] ⁺
I-26	¹ H NMR (400 MHz, CD ₃ OD) δ 7.82 – 7.77 (m, 2H), 7.56 – 6.74 (m, 13H), 4.20 – 4.00 (m, 3H), 3.98 – 3.45 (m, 9H), 3.20 – 3.07 (m, 2H), 2.97 – 2.91 (m, 1H), 2.74 – 2.29 (m, 8H), 1.84 – 1.27 (m, 5H).	m/z = 734.3 [M+H] ⁺
I-27	¹ H NMR (400 MHz, CD ₃ OD) δ 9.31 – 6.60 (m, 15H), 4.78 – 3.34 (m, 9H), 3.28 – 2.81 (m, 2H), 2.81 – 2.24 (m, 8H), 2.22 – 1.76 (m, 1H), 1.74 – 1.32 (m, 4H).	m/z = 720.4 [M+H] ⁺

#	¹ H NMR Chromatography conditions, if applicable	LCMS
I-28	¹ H NMR (400 MHz, CD ₃ OD) δ 8.17 (m, 1H), 7.70 – 6.76 (m, 12H), 4.58 – 4.36 (m, 1H), 4.35 – 4.06 (m, 2H), 4.04 – 3.57 (m, 5H), 3.56 – 3.35 (m, 1H), 3.23 – 2.85 (m, 2H), 2.77 – 2.45 (m, 7H), 2.47 – 1.93 (m, 1H), 1.87 – 1.33 (m, 5H).	m/z = 694.4 [M+H] ⁺
I-29	¹ H NMR (400 MHz, CD ₃ OD) δ 8.12 – 6.24 (m, 11H), 4.66 – 4.11 (m, 2H), 4.10 – 3.75 (m, 4H), 3.72 – 3.34 (m, 2H), 3.24 – 2.80 (m, 2H), 2.79 – 2.03 (m, 9H), 1.87 – 1.37 (m, 6H).	m/z = 644.4 [M+H] ⁺
I-30	¹ H NMR (400 MHz, CD ₃ OD) δ 7.58 – 6.21 (m, 10H), 4.55 – 3.34 (m, 9H), 3.27 – 2.86 (m, 2H), 2.75 – 2.49 (m, 7H), 2.27 – 1.34 (m, 6H), 1.05 – 0.63 (m, 4H).	m/z = 684.4 [M+H] ⁺
I-31	¹ H NMR (400 MHz, CD ₃ OD) δ 7.99 – 6.80 (m, 12H), 4.58 – 4.06 (m, 2H), 4.04 – 3.34 (m, 9H), 3.29 – 2.96 (m, 2H), 2.94 – 2.35 (m, 9H), 2.31 – 1.34 (m, 4H).	m/z = 763.3 [M+H] ⁺
I-32	¹ H NMR (400 MHz, CD ₃ OD) δ 7.71 – 6.62 (m, 12H), 4.50 – 3.44 (m, 11H), 3.24 – 2.79 (m, 3H), 2.77 – 1.87 (m, 9H), 1.81 – 1.34 (m, 7H).	m/z = 700.4 [M+H] ⁺
I-33	¹ H NMR (400 MHz, CD ₃ OD) δ 7.67 – 6.66 (m, 12H), 4.56 – 3.74 (m, 11H), 3.70 – 3.41 (m, 3H), 3.27 – 2.79 (m, 3H), 2.74 – 2.00 (m, 9H), 1.81 – 1.49 (m, 3H).	m/z = 714.3 [M+H] ⁺
I-34	¹ H NMR (400 MHz, CD ₃ OD) δ 7.44 – 6.41 (m, 12H), 4.38 – 3.20 (m, 11H), 3.09 – 2.57 (m, 3H), 2.56 – 2.29 (m, 7H), 1.62 – 1.33 (m, 3H), 1.19 – 0.97 (m, 2H).	m/z = 700.4 [M+H] ⁺
I-35	¹ H NMR (400 MHz, CD ₃ OD) δ 7.61 – 6.89 (m, 18H), 4.54 – 3.37 (m, 8H), 3.26 – 2.82 (m, 3H), 2.80 – 2.32 (m, 8H), 2.28 – 1.97 (m, 1H), 1.84 – 1.55 (m, 3H).	m/z = 746.4 [M+H] ⁺
I-36	¹ H NMR (400 MHz, CD ₃ OD) δ 9.07 – 6.72 (m, 15H), 4.60 – 3.80 (m, 5H), 3.79 – 3.47 (m, 3H), 3.26 – 3.03 (m, 2H), 2.96 – 2.42 (m, 8H), 2.36 – 1.97 (m, 2H), 1.84 – 1.47 (m, 3H), 1.15 – 0.90 (m, 1H).	m/z = 705.3 [M+H] ⁺
I-37	¹ H NMR (400 MHz, CD ₃ OD) δ 9.33 – 8.72 (m, 1H), 8.26 – 7.50 (m, 6H), 7.41 – 6.77 (m, 8H), 4.62 – 3.42 (m, 8H), 3.21 – 2.97 (m, 1H), 2.91 – 2.39 (m, 8H), 2.28 – 2.10 (m, 1H), 1.87 – 1.43 (m, 4H), 1.22 – 0.84 (m, 1H).	m/z = 705.3 [M+H] ⁺
I-38	¹ H NMR (400 MHz, CD ₃ OD) δ 7.65 – 6.70 (m, 13H), 4.66 – 3.37 (m, 10H), 3.25 – 2.83 (m, 2H), 2.78 – 2.32 (m, 11H), 2.30 – 2.14 (m, 1H), 1.92 – 1.42 (m, 4H).	m/z = 707.3 [M+H] ⁺
I-39	¹ H NMR (400 MHz, CD ₃ OD) δ 7.73 – 6.12 (m, 10H), 4.56 – 3.39 (m, 12H), 3.24 – 1.93 (m, 14H), 1.77 – 1.46 (m, 4H).	m/z = 672.4 [M+H] ⁺
I-40	¹ H NMR (400 MHz, CD ₃ OD) δ 9.12 – 8.26 (m, 3H), 7.99 – 6.61 (m, 10H), 4.61 – 3.47 (m, 9H), 3.27 – 2.84 (m, 2H), 2.75 – 1.98 (m, 8H), 1.79 – 1.41 (m, 4H).	m/z = 695.3 [M+H] ⁺
I-41	¹ H NMR (400 MHz, CD ₃ OD) δ 8.62 – 7.82 (m, 2H), 7.60 – 6.84 (m, 9H), 4.57 – 3.47 (m, 11H), 3.17 – 2.77 (m, 2H), 2.76 – 2.47 (m, 7H), 2.39 – 2.08 (m, 1H), 1.77 – 1.35 (m, 7H).	m/z = 700.3 [M+H] ⁺

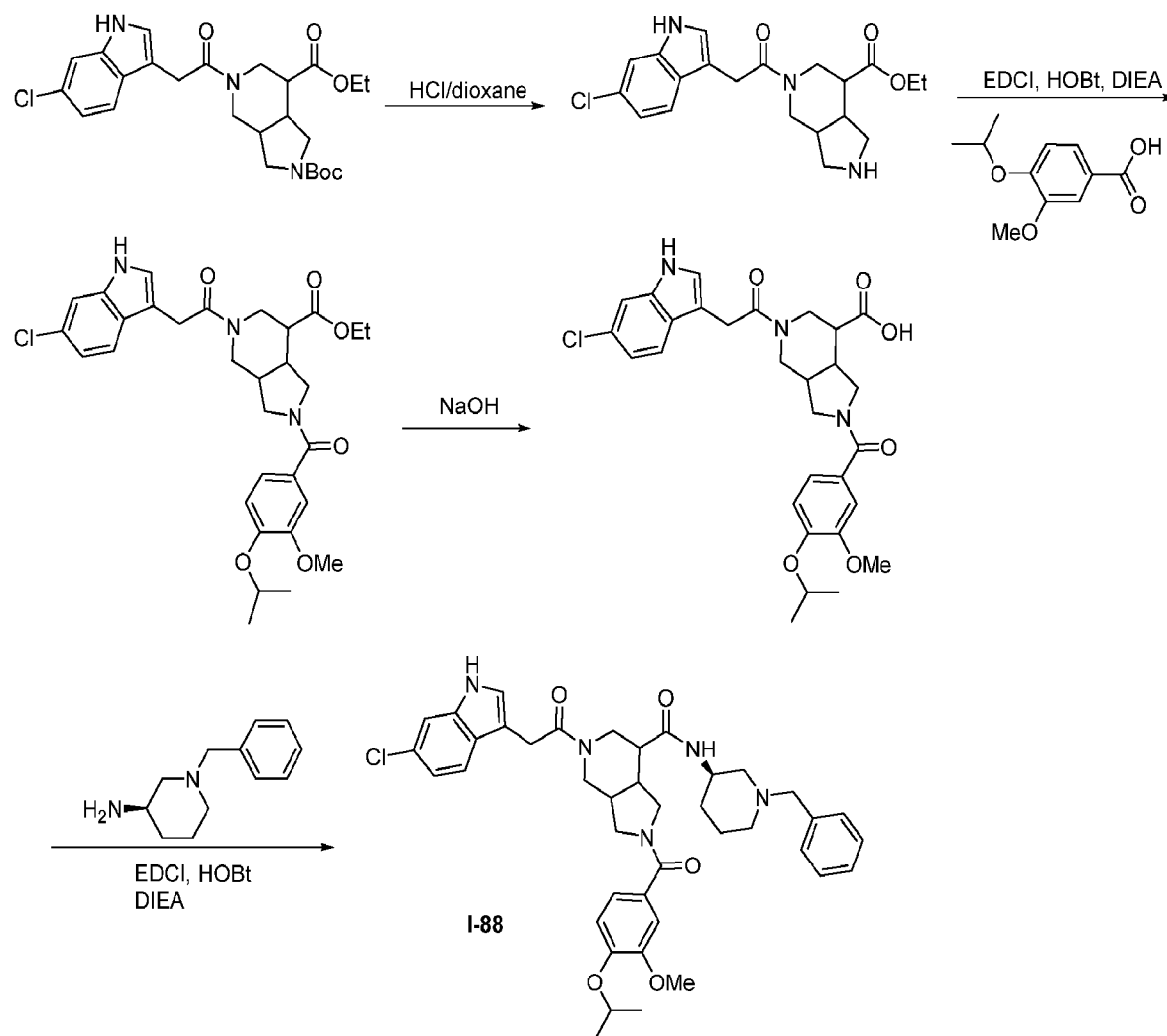
#	¹ H NMR Chromatography conditions, if applicable	LCMS
I-42	¹ H NMR (400 MHz, CD ₃ OD) δ 8.62 – 8.21 (m, 2H), 7.60 – 6.84 (m, 9H), 4.59 – 3.46 (m, 13H), 3.25 – 2.88 (m, 2H), 2.78 – 2.45 (m, 8H), 2.36 – 2.01 (m, 1H), 1.77 – 1.49 (m, 3H).	m/z = 686.4 [M+H] ⁺
I-43	¹ H NMR (400 MHz, CD ₃ OD) δ 8.44 – 8.12 (m, 1H), 7.63 – 6.39 (m, 13H), 4.53 – 3.81 (m, 5H), 3.74 – 3.38 (m, 4H), 3.22 – 2.81 (m, 2H), 2.77 – 1.96 (m, 8H), 1.83 – 1.42 (m, 4H), 1.27 – 1.05 (m, 1H).	m/z = 693.3 [M+H] ⁺
I-44	¹ H NMR (400 MHz, CD ₃ OD) δ 8.92 – 8.39 (m, 2H), 7.69 – 6.91 (m, 9H), 4.63 – 3.39 (m, 10H), 3.29 – 2.78 (m, 3H), 2.73 – 2.59 (m, 5H), 2.54 – 2.05 (m, 3H), 1.86 – 1.52 (m, 4H), 1.34 – 1.22 (m, 4H).	m/z = 696.3 [M+H] ⁺
I-45	¹ H NMR (400 MHz, CD ₃ OD) δ 7.97 – 6.87 (m, 12H), 4.60 – 3.34 (m, 10H), 3.30 – 1.93 (m, 12H), 1.78 – 1.48 (m, 3H).	m/z = 709.4 [M+H] ⁺
I-46	¹ H NMR (400 MHz, CD ₃ OD) δ 7.64 – 6.88 (m, 12H), 4.84 – 3.33 (m, 9H), 3.29 – 1.89 (m, 12H), 1.85 – 1.55 (m, 3H), 1.45 – 1.30 (m, 6H).	m/z = 730.4 [M+H] ⁺
I-47	¹ H NMR (400 MHz, CD ₃ OD) δ 8.47 – 6.58 (m, 12H), 4.77 – 4.16 (m, 2H), 4.16 – 3.34 (m, 9H), 3.27 – 2.47 (m, 8H), 2.46 – 1.58 (m, 4H), 1.58 – 0.84 (m, 3H).	m/z = 707.3 [M+H] ⁺
I-48	¹ H NMR (400 MHz, CD ₃ OD) δ 7.87 – 6.77 (m, 13H), 4.67 – 3.37 (m, 11H), 3.28 – 2.28 (m, 11H), 1.96 – 1.42 (m, 4H).	m/z = 708.4 [M+H] ⁺
I-49	¹ H NMR (400 MHz, CD ₃ OD) δ 8.10 – 6.86 (m, 13H), 4.53 – 4.26 (m, 1H), 4.13 – 3.93 (m, 2H), 3.85 – 3.71 (m, 4H), 3.69 – 3.40 (m, 2H), 3.24 – 2.81 (m, 2H), 2.76 – 2.42 (m, 7H), 2.03 – 1.25 (m, 7H).	m/z = 684.3 [M+H] ⁺
I-50	¹ H NMR (400 MHz, CD ₃ OD) δ 7.65 – 6.90 (m, 14H), 4.60 – 3.40 (m, 6H), 3.25 – 2.80 (m, 3H), 2.80 – 2.39 (m, 7H), 2.26 – 1.53 (m, 4H), 1.38 – 1.22 (m, 2H).	m/z = 654.3 [M+H] ⁺
I-51	¹ H NMR (400 MHz, CD ₃ OD) δ 7.70 – 6.79 (m, 9H), 4.60 – 3.47 (m, 6H), 2.77 – 2.21 (m, 10H), 1.78 – 1.18 (m, 19H).	m/z = 660.3 [M+H] ⁺
I-52	¹ H NMR (400 MHz, CD ₃ OD) δ 7.65 – 6.97 (m, 13H), 4.57 – 3.39 (m, 6H), 3.27 – 2.83 (m, 2H), 2.80 – 2.39 (m, 10H), 2.16 – 1.21 (m, 8H), 0.96 – 0.85 (m, 6H).	m/z = 710.3 [M+H] ⁺
I-53	¹ H NMR (400 MHz, CD ₃ OD) δ 7.62 – 6.61 (m, 12H), 4.73 – 3.37 (m, 9H), 3.25 – 2.97 (m, 4H), 2.77 – 2.36 (m, 8H), 1.85 – 1.52 (m, 3H), 1.45 – 1.23 (m, 3H).	m/z = 695.3 [M+H] ⁺
I-54	¹ H NMR (400 MHz, CD ₃ OD) δ 8.20 – 6.66 (m, 12H), 4.59 – 3.82 (m, 7H), 3.75 – 3.33 (m, 4H), 3.28 – 2.47 (m, 9H), 2.46 – 2.13 (m, 2H), 2.10 – 1.21 (m, 6H), 1.16 – 0.76 (m, 4H).	m/z = 767.4 [M+H] ⁺
I-55	¹ H NMR (400 MHz, CD ₃ OD) δ 8.18 – 7.75 (m, 2H), 7.39 (m, 2H), 7.25 – 7.11 (m, 5H), 7.06 (m, 1H), 4.60 – 3.64 (m, 8H), 3.55 – 3.44 (m, 2H), 3.22 – 2.81 (m, 2H), 2.77 – 2.57 (m, 7H), 2.37 – 1.99 (m, 1H), 1.86 – 1.51 (m, 4H), 1.37 – 1.24 (m, 3H).	m/z = 658.3 [M+H] ⁺

#	¹ H NMR Chromatography conditions, if applicable	LCMS
I-56	¹ H NMR (400 MHz, CD ₃ OD) δ 7.59 – 6.82 (m, 9H), 6.45 – 6.37 (m, 1H), 4.65 – 3.64 (m, 7H), 3.63 – 3.41 (m, 2H), 3.15 – 2.50 (m, 9H), 2.39 – 2.09 (m, 4H), 1.80 – 1.33 (m, 5H).	m/z = 658.3 [M+H] ⁺
I-57	¹ H NMR (400 MHz, CD ₃ OD) δ 8.94 – 8.52 (m, 2H), 7.66 – 6.90 (m, 10H), 4.62 – 3.35 (m, 8H), 3.26 – 2.18 (m, 10H), 1.77 – 1.28 (m, 5H).	m/z = 656.3 [M+H] ⁺
I-58	¹ H NMR (400 MHz, CD ₃ OD) δ 8.53 – 6.87 (m, 12H), 4.61 – 4.21 (m, 2H), 4.20 – 3.74 (m, 3H), 3.73 – 3.37 (m, 4H), 3.22 – 2.93 (m, 1H), 2.85 – 2.55 (m, 10H), 1.78 – 1.33 (m, 6H), 1.28 – 1.15 (m, 2H).	m/z = 683.3 [M+H] ⁺
I-59	¹ H NMR (400 MHz, CD ₃ OD) δ 9.34 – 8.87 (m, 3H), 7.89 – 6.83 (m, 13H), 4.58 – 3.42 (m, 8H), 3.28 – 2.01 (m, 11H), 1.90 – 1.37 (m, 4H).	m/z = 732.3 [M+H] ⁺
I-60	¹ H NMR (400 MHz, CD ₃ OD) δ 8.85 – 6.67 (m, 11H), 4.64 – 3.37 (m, 10H), 3.21 – 2.34 (m, 13H), 1.74 – 1.44 (m, 3H).	m/z = 670.4 [M+H] ⁺
I-61	¹ H NMR (400 MHz, CD ₃ OD) δ 8.07 – 6.79 (m, 14H), 4.57 – 3.37 (m, 10H), 3.26 – 2.83 (m, 2H), 2.76 – 2.01 (m, 8H), 1.75 – 1.45 (m, 3H).	m/z = 693.4 [M+H] ⁺
I-62	¹ H NMR (400 MHz, CD ₃ OD) δ 8.13 – 6.67 (m, 12H), 4.59 – 4.01 (m, 2H), 3.98 – 3.41 (m, 4H), 3.26 – 2.31 (m, 10H), 2.23 – 1.97 (m, 1H), 1.80 – 1.49 (m, 3H), 1.40 – 1.03 (m, 4H).	m/z = 695.3 [M+H] ⁺
I-63	¹ H NMR (400 MHz, CD ₃ OD) δ 8.87 – 8.73 (m, 1H), 8.59 – 8.49 (m, 1H), 8.14 – 8.02 (m, 1H), 7.87 – 6.87 (m, 14H), 4.63 – 3.44 (m, 8H), 3.27 – 2.40 (m, 10H), 2.38 – 2.19 (m, 1H), 2.01 – 1.40 (m, 4H).	m/z = 731.5 [M+H] ⁺
I-64	¹ H NMR (400 MHz, CD ₃ OD) δ 9.23 – 8.95 (m, 1H), 8.74 – 8.39 (m, 1H), 7.97 – 6.84 (m, 11H), 4.63 – 3.92 (m, 9H), 3.23 – 2.41 (m, 9H), 2.39 – 2.19 (m, 1H), 2.12 – 1.41 (m, 4H).	m/z = 695.3 [M+H] ⁺
I-65	¹ H NMR (400 MHz, CD ₃ OD) δ 7.81 – 6.79 (m, 12H), 4.62 – 3.36 (m, 8H), 3.27 – 2.38 (m, 10H), 2.32 – 2.11 (m, 1H), 1.98 – 1.41 (m, 4H).	m/z = 709.3 [M+H] ⁺
I-66	¹ H NMR (400 MHz, CD ₃ OD) δ 7.60 – 6.69 (m, 12H), 4.55 – 3.84 (m, 8H), 3.71 – 3.36 (m, 3H), 3.13 – 2.88 (m, 5H), 2.78 – 2.17 (m, 9H), 1.82 – 1.33 (m, 4H).	m/z = 777.4 [M+H] ⁺
I-67	¹ H NMR (400 MHz, CD ₃ OD) δ 7.62 – 6.71 (m, 13H), 4.55 – 3.82 (m, 6H), 3.72 – 3.37 (m, 3H), 3.29 – 2.38 (m, 11H), 2.38 – 1.96 (m, 1H), 1.79 – 1.33 (m, 7H).	m/z = 698.2 [M+H] ⁺
I-68	¹ H NMR (400 MHz, CD ₃ OD) δ 8.25 – 6.76 (m, 15H), 4.65 – 3.40 (m, 9H), 3.28 – 2.78 (m, 2H), 2.76 – 2.49 (m, 7H), 1.77 – 1.50 (m, 5H), 1.44 – 1.27 (m, 2H).	m/z = 737.3 [M+H] ⁺
I-69	¹ H NMR (400 MHz, CD ₃ OD) δ 8.46 – 6.53 (m, 12H), 4.60 – 3.82 (m, 8H), 3.68 – 3.44 (m, 3H), 3.36 – 3.34 (m, 2H), 3.30 – 2.79 (m, 3H), 2.57 – 1.71 (m, 13H), 0.96 – 0.20 (m, 5H).	m/z = 781.4 [M+H] ⁺

#	¹ H NMR Chromatography conditions, if applicable	LCMS
I-70	¹ H NMR (400 MHz, CD ₃ OD) δ 8.23 – 6.91 (m, 15H), 4.65 – 3.37 (m, 9H), 3.12 – 1.36 (m, 15H).	m/z = 737.4 [M+H] ⁺
I-71	¹ H NMR (400 MHz, CD ₃ OD) δ 7.62 – 6.67 (m, 15H), 4.57 – 4.12 (m, 2H), 4.12 – 3.35 (m, 10H), 3.21 – 2.41 (m, 9H), 1.79 – 1.46 (m, 4H).	m/z = 734.4 [M+H] ⁺
I-72	¹ H NMR (400 MHz, CD ₃ OD) δ 8.45 – 6.88 (m, 12H), 4.57 – 3.37 (m, 7H), 3.27 – 1.93 (m, 11H), 1.86 – 1.11 (m, 5H).	m/z = 711.4 [M+H] ⁺
I-73	¹ H NMR (400 MHz, CD ₃ OD) δ 7.65 – 6.88 (m, 12H), 4.58 – 3.36 (m, 10H), 3.28 – 2.80 (m, 4H), 2.78 – 2.24 (m, 8H), 1.99 – 1.40 (m, 5H).	m/z = 725.4 [M+H] ⁺
I-74	¹ H NMR (400 MHz, CD ₃ OD) δ 8.11 – 6.79 (m, 15H), 4.60 – 3.46 (m, 8H), 3.25 – 2.46 (m, 9H), 2.40 – 1.34 (m, 5H).	m/z = 720.4 [M+H] ⁺
I-75	¹ H NMR (400 MHz, CD ₃ OD) δ 7.59 – 6.88 (m, 12H), 4.62 – 3.41 (m, 8H), 3.20 – 2.45 (m, 10H), 2.41 – 1.30 (m, 7H).	m/z = 711.3 [M+H] ⁺
I-76	¹ H NMR (400 MHz, CD ₃ OD) δ 7.91 – 6.81 (m, 12H), 4.56 – 3.02 (m, 13H), 2.79 – 2.12 (m, 10H), 1.63 – 1.35 (m, 8H).	m/z = 725.3 [M+H] ⁺
I-77	¹ H NMR (400 MHz, CD ₃ OD) δ 7.60 – 6.67 (m, 12H), 4.60 – 4.38 (m, 1H), 4.36 – 4.16 (m, 5H), 4.07 – 3.81 (m, 2H), 3.73 – 3.34 (m, 3H), 3.29 – 2.36 (m, 11H), 2.35 – 1.91 (m, 1H), 1.87 – 1.37 (m, 4H).	m/z = 712.2 [M+H] ⁺
I-78	¹ H NMR (400 MHz, CD ₃ OD) δ 8.47 – 6.83 (m, 12H), 4.62 – 3.38 (m, 9H), 3.25 – 2.19 (m, 14H), 1.81 – 1.41 (m, 4H).	m/z = 669.4 [M+H] ⁺
I-79	¹ H NMR (400 MHz, CD ₃ OD) δ 9.00 – 8.49 (m, 2H), 8.26 – 7.94 (m, 1H), 7.77 – 6.84 (m, 14H), 4.59 – 3.33 (m, 8H), 3.28 – 2.76 (m, 3H), 2.75 – 2.23 (m, 8H), 2.22 – 1.97 (m, 1H), 1.83 – 1.54 (m, 3H).	m/z = 731.3 [M+H] ⁺
I-80	¹ H NMR (400 MHz, CD ₃ OD) δ 9.08 – 8.85 (m, 1H), 8.53 – 6.97 (m, 13H), 6.89 – 6.50 (m, 1H), 4.58 – 3.33 (m, 8H), 3.28 – 2.74 (m, 3H), 2.73 – 2.55 (m, 5H), 2.54 – 2.21 (m, 2H), 2.13 – 1.42 (m, 4H), 1.36 – 1.29 (m, 1H).	m/z = 705.3 [M+H] ⁺
I-81	¹ H NMR (400 MHz, CD ₃ OD) δ 7.64 – 6.85 (m, 9H), 6.35 – 6.20 (m, 1H), 4.70 – 3.34 (m, 9H), 3.27 – 2.79 (m, 2H), 2.74 – 2.54 (m, 6H), 2.35 – 1.96 (m, 2H), 1.77 – 1.49 (m, 4H), 1.41 – 1.30 (m, 1H), 1.19 – 0.87 (m, 4H).	m/z = 685.4 [M+H] ⁺
I-82	¹ H NMR (400 MHz, CD ₃ OD) δ 7.68 – 6.68 (m, 12H), 4.62 – 3.44 (m, 11H), 3.20 – 2.24 (m, 11H), 2.01 – 1.36 (m, 4H).	m/z = 768.4 [M+H] ⁺
I-83	¹ H NMR (400 MHz, CD ₃ OD) δ 7.60 – 6.79 (m, 11H), 4.58 – 3.34 (m, 11H), 3.27 – 2.22 (m, 12H), 2.05 – 1.15 (m, 11H).	m/z = 754.5 [M+H] ⁺

#	¹ H NMR Chromatography conditions, if applicable	LCMS
I-84	¹ H NMR (400 MHz, CD ₃ OD) δ 7.86 – 6.79 (m, 12H), 4.82 – 3.96 (m, 7H), 3.94 – 3.38 (m, 5H), 3.28 – 2.32 (m, 9H), 2.29 – 1.61 (m, 4H), 1.60 – 1.23 (m, 8H).	m/z = 766.3 [M+H] ⁺
I-85	¹ H NMR (400 MHz, CD ₃ OD) δ 7.84 – 6.73 (m, 13H), 4.62 – 3.38 (m, 7H), 3.24 – 2.92 (m, 2H), 2.84 – 2.20 (m, 9H), 1.83 – 1.61 (m, 3H), 1.51 – 1.28 (m, 9H).	m/z = 752.4 [M+H] ⁺
I-86	¹ H NMR (400 MHz, CD ₃ OD) δ 7.64 – 6.80 (m, 12H), 4.80 – 4.55 (m, 1H), 4.55 – 4.16 (m, 2H), 4.15 – 3.87 (m, 2H), 3.84 – 3.43 (m, 3H), 3.41 – 3.35 (m, 3H), 3.27 – 3.11 (m, 1H), 3.10 – 3.06 (m, 1H), 3.05 – 2.77 (m, 1H), 2.74 – 2.55 (m, 5H), 2.22 – 0.85 (m, 14H). First eluting diastereomer purified by prep-HPLC on an Agilent 10 Prep-C18 column (21.2 mm I.D. × 25 cm, 10 μm), using H ₂ O/MeOH 0.1%TFA at a flow rate of 20 mL/min (wave length 214 nm). Rt = 10.5 min.	m/z = 766.5 [M+H] ⁺
I-87	¹ H NMR (400 MHz, CD ₃ OD) δ 7.63 – 6.87 (m, 12H), 4.80 – 4.60 (m, 1H), 4.55 – 3.36 (m, 11H), 3.27 – 2.96 (m, 2H), 2.89 – 2.42 (m, 8H), 1.87 – 1.44 (m, 10H), 1.39 – 1.26 (m, 1H). Second eluting diastereomer purified by prep-HPLC on an Agilent 10 Prep-C18 column (21.2 mm I.D. × 25 cm, 10 μm), using H ₂ O/MeOH 0.1%TFA at a flow rate of 20 mL/min (wave length 214 nm). Rt = 12.7 min.	m/z = 766.5 [M+H] ⁺

Synthesis of N-((R)-1-benzylpiperidin-3-yl)-5-(2-(6-chloro-1H-indol-3-yl)acetyl)-2-(4-isopropoxy-3-methoxybenzoyl)octahydro-1H-pyrrolo[3,4-c]pyridine-7-carboxamide I-88



[00482] Step 1: ethyl 5-(2-(6-chloro-1H-indol-3-yl)acetyl)octahydro-1H-pyrrolo[3,4-c]pyridine-7-carboxylate hydrochloride

[00483] To a solution of the product of 2-(tert-butyl) 7-ethyl 5-(2-(6-chloro-1H-indol-3-yl)acetyl)octahydro-2H-pyrrolo[3,4-c]pyridine-2,7-dicarboxylate (3.5 g, 7.14 mmol; see synthesis of I-1) in DCM (40 mL) was added a solution of HCl in dioxane (4M, 20 mL). The resulting mixture was stirred for 3 h. The solvent was removed under vacuum to afford the product (3.0 g, quant.). LCMS $m/z = 390.2$ $[M+H]^+$.

[00484] Step 2: ethyl 5-(2-(6-chloro-1H-indol-3-yl)acetyl)-2-(4-isopropoxy-3-methoxybenzoyl)octahydro-1H-pyrrolo[3,4-c]pyridine-7-carboxylate

[00485] A mixture of ethyl 5-(2-(6-chloro-1H-indol-3-yl)acetyl)octahydro-1H-pyrrolo[3,4-c]pyridine-7-carboxylate hydrochloride (1.74 g, 4.1 mmol), 4-isopropoxy-3-methoxybenzoic acid (1.03 g, 4.92 mmol), EDCI (1.18 g, 6.15 mmol), HOBt (830 mg, 6.15 mmol) and DIEA (1.06 g, 8.2 mmol) in DMF (10 mL) was stirred overnight. The reaction mixture was diluted with water and extracted with EtOAc three times. The combined organic layers were washed with water and brine, dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by column chromatography (2.5% MeOH/DCM) to give the product (2.1 g, 88%) as a white solid. LCMS *m/z* = 582.3 [M+H]⁺.

[00486] *Step 3: 5-(2-(6-chloro-1H-indol-3-yl)acetyl)-2-(4-isopropoxy-3-methoxybenzoyl)octahydro-1H-pyrrolo[3,4-c]pyridine-7-carboxylic acid*

[00487] To a solution of ethyl 5-(2-(6-chloro-1H-indol-3-yl)acetyl)-2-(4-isopropoxy-3-methoxybenzoyl) octahydro-1H-pyrrolo[3,4-c]pyridine-7-carboxylate (2.1 g, 3.61 mmol) in MeOH (20 mL) was added an aqueous solution of NaOH (1M, 7.2 mL). The resulting mixture was stirred for 3 h. The solvent was removed under vacuum and the residue obtained diluted with water. The pH was adjusted to ~1 by addition of 1M HCl and the aqueous layer extracted with EtOAc three times. The combined organic layers were washed with water and brine, dried over Na₂SO₄ and concentrated to afford the product (1.7 g, 85% yield) as a white solid. LCMS *m/z* = 554.2 [M+H]⁺.

[00488] *Step 4: N-((R)-1-benzylpiperidin-3-yl)-5-(2-(6-chloro-1H-indol-3-yl)acetyl)-2-(4-isopropoxy-3-methoxybenzoyl)octahydro-1H-pyrrolo[3,4-c]pyridine-7-carboxamide (I-88)*

[00489] To a solution of 5-(2-(6-chloro-1H-indol-3-yl)acetyl)-2-(4-isopropoxy-3-methoxybenzoyl)octahydro-1H-pyrrolo[3,4-c]pyridine-7-carboxylic acid (50 mg, 0.09 mmol) in DMA (1 mL) was added (R)-1-benzylpiperidin-3-amine (21 mg, 0.11 mmol), EDCI (26 mg, 0.14 mmol), HOBt (18 mg, 0.14 mmol) and DIPEA (44 mg, 0.27 mmol). The resulting mixture was stirred for 14 h. Water was added and the aqueous layer was extracted with EtOAc three times. The combined organic layers were washed with water and brine and dried over Na₂SO₄. The solvent was removed and the residue purified by prep-TLC (6% MeOH/DCM) to afford **I-88** (30 mg, 46%) as a white solid. LCMS *m/z* = 726.3 [M+H]⁺; ¹H NMR (400 MHz, CD₃OD) δ 7.59 – 6.69 (m, 12H), 4.75 – 4.30 (m, 2H), 3.92 – 3.46 (m, 12H), 3.22 – 2.48 (m, 7H), 2.34 – 1.65 (m, 5H), 1.41 – 1.26 (m, 8H).

[00490] The compounds listed in **Table 3** were synthesized using analogous methods to those shown for **I-88**, using the appropriate commercially available reagents and/or intermediates. Final examples were obtained as a mixture of diastereomers (or enantiomers where applicable) or separated by preparative chiral HPLC as indicated.

Table 3. Compounds made by a method analogous to I-88

#	¹ H NMR Chromatography conditions, if applicable	LCMS
I-89	¹ H NMR (400 MHz, CD ₃ CD) δ 7.76 – 6.62 (m, 12H), 4.78 – 4.54 (m, 1H), 4.53 – 4.09 (m, 2H), 4.08 – 3.75 (m, 6H), 3.73 – 3.37 (m, 4H), 3.22 – 2.94 (m, 3H), 2.79 – 2.27 (m, 4H), 2.24 – 1.81 (m, 2H), 1.80 – 1.46 (m, 3H), 1.44 – 1.28 (m, 8H).	m/z = 740.4 [M+H] ⁺
I-90	¹ H NMR (400 MHz, CD ₃ OD) δ 7.74 – 6.63 (m, 12H), 4.78 – 4.30 (m, 2H), 4.26 – 3.77 (m, 8H), 3.76 – 3.60 (m, 3H), 3.58 – 3.37 (m, 3H), 3.26 – 2.72 (m, 5H), 2.71 – 1.80 (m, 5H), 1.78 – 1.49 (m, 2H), 1.41 – 1.22 (m, 8H).	m/z = 754.4 [M+H] ⁺
I-91	¹ H NMR (400 MHz, CD ₃ OD) δ 8.58 – 6.55 (m, 11H), 4.78 – 3.37 (m, 11H), 3.25 – 2.97 (m, 2H), 2.91 – 2.26 (m, 8H), 2.24 – 1.98 (m, 1H), 1.87 – 1.50 (m, 4H), 1.47 – 1.27 (m, 10H).	m/z = 743.3 [M+H] ⁺
I-92	¹ H NMR (400 MHz, CD ₃ OD) δ 7.64 – 6.63 (m, 12H), 4.76 – 3.73 (m, 12H), 3.72 – 3.57 (m, 1H), 3.50 (d, J = 6.4 Hz, 1H), 3.40 (s, 1H), 3.29 – 2.98 (m, 2H), 2.88 – 2.42 (m, 6H), 2.30 – 1.98 (m, 1H), 1.48 – 0.86 (m, 10H), 0.68 (d, J = 6.2 Hz, 1H).	m/z = 758.3 [M+H] ⁺
I-93	¹ H NMR (400 MHz, CD ₃ OD) δ 7.64 – 6.59 (m, 7H), 4.76 – 3.77 (m, 9H), 3.74 – 3.37 (m, 3H), 3.25 – 2.42 (m, 8H), 2.38 – 1.46 (m, 10H), 1.44 – 1.23 (m, 10H), 1.20 – 0.90 (m, 3H).	m/z = 734.4 [M+H] ⁺
I-94	¹ H NMR (400 MHz, CD ₃ OD) δ 8.58 – 6.52 (m, 7H), 4.79 – 3.36 (m, 11H), 3.27 – 2.38 (m, 8H), 2.37 – 1.44 (m, 8H), 1.44 – 1.08 (m, 13H), 1.08 – 0.62 (m, 3H).	m/z = 816.5 [M+H] ⁺
I-95	¹ H NMR (400 MHz, CD ₃ OD) δ 7.71 – 6.57 (m, 7H), 4.76 – 3.34 (m, 11H), 3.27 – 2.88 (m, 2H), 2.88 – 2.70 (m, 2H), 2.69 – 1.95 (m, 4H), 1.80 – 1.45 (m, 2H), 1.40 – 1.26 (m, 9H), 1.25 – 0.96 (m, 3H), 0.93 – 0.84 (m, 7H), 0.80 – 0.70 (m, 3H).	m/z = 722.4 [M+H] ⁺
I-96	¹ H NMR (400 MHz, CD ₃ OD) δ 7.69 – 6.60 (m, 7H), 4.78 – 4.23 (m, 3H), 4.22 – 3.89 (m, 2H), 3.87 – 3.78 (m, 3H), 3.76 – 3.33 (m, 3H), 3.25 – 2.98 (m, 2H), 2.95 – 2.67 (m, 3H), 2.67 – 1.98 (m, 4H), 1.82 – 1.41 (m, 2H), 1.41 – 1.29 (m, 8H), 1.28 – 0.96 (m, 4H), 0.93 – 0.84 (m, 6H), 0.81 – 0.70 (m, 3H).	m/z = 722.4 [M+H] ⁺
I-97	¹ H NMR (400 MHz, CD ₃ OD) δ 7.66 – 6.60 (m, 7H), 4.79 – 3.76 (m, 9H), 3.75 – 3.36 (m, 3H), 3.28 – 2.44 (m, 8H), 2.41 – 1.93 (m, 1H), 1.83 – 1.46 (m, 3H), 1.43 – 1.26 (m, 9H), 1.20 (m, 2H), 1.04 – 0.84 (m, 5H), 0.84 – 0.69 (m, 2H).	m/z = 708.4 [M+H] ⁺
I-98	¹ H NMR (400 MHz, CD ₃ OD) δ 7.66 – 6.59 (m, 12H), 4.78 – 4.35 (m, 2H), 4.33 – 3.96 (m, 2H), 3.95 – 3.38 (m, 8H), 3.26 – 2.75 (m, 5H),	m/z = 742.3 [M+H] ⁺

#	¹ H NMR Chromatography conditions, if applicable	LCMS
	2.72 – 2.15 (m, 5H), 1.90 – 1.60 (m, 2H), 1.43 – 1.19 (m, 9H).	
I-99	¹ H NMR (400 MHz, CD ₃ OD) δ 7.73 – 6.49 (m, 12H), 4.67 – 3.78 (m, 9H), 3.73 – 3.42 (m, 4H), 3.29 – 3.05 (m, 4H), 2.73 – 2.29 (m, 5H), 2.11 – 1.66 (m, 3H), 1.41 – 1.30 (m, 6H).	m/z = 728.3 [M+H] ⁺
I-100	¹ H NMR (400 MHz, CD ₃ OD) δ 7.70 – 6.46 (m, 12H), 4.74 – 3.78 (m, 9H), 3.74 – 3.34 (m, 5H), 3.28 – 3.05 (m, 2H), 3.01 – 2.81 (m, 4H), 2.68 – 2.44 (m, 4H), 2.10 – 1.72 (m, 3H), 1.42 – 1.22 (m, 7H). First eluting diastereomer purified by chiral prep-HPLC on a UniChiral CNZ-5H column (5 cm I.D. × 25 cm), using MeOH 0.1% DEA at a flow rate of 90 mL/min (wave length 254 nm). Rt = 12.5 min	m/z = 742.3 [M+H] ⁺
I-101	¹ H NMR (400 MHz, CD ₃ OD) δ 7.68 – 6.47 (m, 12H), 4.76 – 3.79 (m, 9H), 3.76 – 3.33 (m, 5H), 3.28 – 3.05 (m, 2H), 3.01 – 2.81 (m, 4H), 2.70 – 2.48 (m, 4H), 2.08 – 1.75 (m, 3H), 1.42 – 1.24 (m, 7H). Second eluting diastereomer purified by chiral prep-HPLC on a UniChiral CNZ-5H column (5 cm I.D. × 25 cm), using MeOH 0.1% DEA at a flow rate of 90 mL/min (wave length 254 nm). Rt = 13.9 min	m/z = 742.4 [M+H] ⁺
I-102	¹ H NMR (400 MHz, CD ₃ OD) δ 7.63 – 6.61 (m, 12H), 4.77 – 3.38 (m, 17H), 3.27 – 1.94 (m, 10H), 1.40 – 1.33 (m, 3H), 1.24 – 1.05 (m, 3H), 0.79 – 0.67 (m, 1H).	m/z = 758.4 [M+H] ⁺
I-103	¹ H NMR (400 MHz, CD ₃ OD) δ 7.65 – 6.60 (m, 12H), 4.65 (m, 3H), 4.21 – 3.69 (m, 6H), 3.69 – 3.38 (m, 4H), 3.26 – 3.15 (m, 1H), 3.12 – 2.74 (m, 5H), 2.69 – 2.50 (m, 4H), 2.31 – 1.67 (m, 3H), 1.45 – 0.89 (m, 10H).	m/z = 756.4 [M+H] ⁺
I-104	¹ H NMR (400 MHz, CD ₃ OD) δ 7.83 – 6.58 (m, 7H), 4.78 – 3.35 (m, 11H), 3.25 – 2.16 (m, 8H), 2.12 – 1.44 (m, 8H), 1.43 – 0.71 (m, 16H).	m/z = 816.4 [M+H] ⁺
I-105	¹ H NMR (400 MHz, CD ₃ OD) δ 7.67 – 6.57 (m, 12H), 4.78 – 3.34 (m, 15H), 3.28 – 1.92 (m, 9H), 1.45 – 1.03 (m, 8H), 0.79 – 0.67 (m, 1H).	m/z = 758.4 [M+H] ⁺
I-106	¹ H NMR (400 MHz, CD ₃ OD) δ 7.79 – 6.44 (m, 12H), 4.74 – 3.39 (m, 15H), 3.29 – 2.98 (m, 2H), 2.87 – 2.42 (m, 5H), 2.31 – 1.96 (m, 1H), 1.42 – 1.12 (m, 9H), 0.72 – 0.67 (m, 1H).	m/z = 758.4 [M+H] ⁺
I-107	¹ H NMR (400 MHz, CD ₃ OD) δ 7.68 – 6.65 (m, 7H), 4.71 – 3.77 (m, 9H), 3.72 – 3.34 (m, 6H), 3.28 – 2.94 (m, 4H), 2.83 – 2.58 (m, 5H), 2.32 – 1.96 (m, 1H), 1.68 – 1.58 (m, 6H), 1.43 – 1.27 (m, 10H), 1.24 – 1.04 (m, 5H), 0.93 – 0.83 (m, 2H), 0.65 – 0.63 (m, 1H).	m/z = 764.5 [M+H] ⁺
I-108	¹ H NMR (400 MHz, CD ₃ OD) δ 7.81 – 6.44 (m, 7H), 4.81 – 4.41 (m, 3H), 4.39 – 4.08 (m, 1H), 4.07 – 3.79 (m, 5H), 3.73 – 3.52 (m, 2H), 3.47 – 3.36 (m, 1H), 3.24 – 2.94 (m, 3H), 2.80 – 2.61 (m, 4H), 2.57 – 2.14 (m, 2H), 1.70 – 1.56 (m, 5H), 1.41 – 1.35 (m, 9H), 1.23 – 1.05 (m, 5H), 0.92 – 0.81 (m, 4H).	m/z = 764.5 [M+H] ⁺
I-109	¹ H NMR (400 MHz, CD ₃ OD) δ 7.64 – 6.59 (m, 12H), 4.78 – 3.36 (m, 12H), 3.27 – 2.51 (m, 6H), 2.48 – 1.96 (m, 2H), 1.84 – 1.55 (m, 3H), 1.43 – 1.22 (m, 7H).	m/z = 728.4 [M+H] ⁺

#	¹ H NMR Chromatography conditions, if applicable	LCMS
I-110	¹ H NMR (400 MHz, CD ₃ OD) δ 7.63 – 6.57 (m, 12H), 4.77 – 3.73 (m, 8H), 3.70 – 2.86 (m, 9H), 2.83 – 2.29 (m, 6H), 1.42 – 1.16 (m, 6H). First eluting diastereomer purified by chiral prep-HPLC on a UniChiral CND-5H column (2.21 cm I.D. × 25 cm), using Hexane/EtOH (70/30) at a flow rate of 25 mL/min (wave length 254 nm). Rt = 9.1 min	m/z = 753.4 [M+H] ⁺
I-111	¹ H NMR (400 MHz, CD ₃ OD) δ 7.64 – 6.40 (m, 12H), 4.76 – 4.16 (m, 3H), 4.02 – 3.34 (m, 9H), 3.28 – 2.22 (m, 10H), 1.41 – 1.24 (m, 7H). Second eluting diastereomer purified by chiral prep-HPLC on a UniChiral CND-5H column (2.21 cm I.D. × 25 cm), using Hexane/EtOH (70/30) at a flow rate of 25 mL/min (wave length 254 nm). Rt = 15.0 min	m/z = 753.4 [M+H] ⁺
I-112	¹ H NMR (400 MHz, CD ₃ OD) δ 7.64 – 6.62 (m, 7H), 4.79 – 3.77 (m, 9H), 3.72 – 3.38 (m, 3H), 3.26 – 2.50 (m, 8H), 1.78 – 1.50 (m, 7H), 1.43 – 0.74 (m, 17H).	m/z = 748.4 [M+H] ⁺
I-113	¹ H NMR (400 MHz, CD ₃ OD) δ 7.64 – 6.62 (m, 7H), 4.80 – 3.77 (m, 9H), 3.73 – 3.39 (m, 3H), 3.25 – 2.18 (m, 8H), 1.79 – 1.53 (m, 7H), 1.45 – 0.72 (m, 17H).	m/z = 748.4 [M+H] ⁺
I-114	¹ H NMR (400 MHz, CD ₃ OD) δ 7.63 – 7.49 (m, 1H), 7.43 – 6.62 (m, 6H), 4.76 – 3.37 (m, 12H), 3.26 – 2.17 (m, 10H), 1.80 – 1.45 (m, 3H), 1.43 – 1.27 (m, 10H), 1.07 – 0.68 (m, 7H).	m/z = 708.5 [M+H] ⁺
I-115	¹ H NMR (400 MHz, CD ₃ OD) δ 8.48 – 6.57 (m, 11H), 4.77 – 3.36 (m, 12H), 3.26 – 2.96 (m, 2H), 2.90 – 2.40 (m, 7H), 2.35 – 2.14 (m, 1H), 2.03 – 1.46 (m, 3H), 1.43 – 1.15 (m, 7H).	m/z = 758.4 [M+H] ⁺
I-116	¹ H NMR (400 MHz, CD ₃ OD) δ 7.64 – 6.61 (m, 7H), 4.76 – 3.38 (m, 14H), 3.25 – 2.85 (m, 2H), 2.81 – 2.39 (m, 6H), 2.11 – 1.83 (m, 2H), 1.81 – 0.96 (m, 20H).	m/z = 764.5 [M+H] ⁺
I-117	¹ H NMR (400 MHz, CD ₃ OD) δ 7.63 – 6.63 (m, 12H), 4.80 – 3.36 (m, 16H), 3.26 – 2.45 (m, 7H), 2.351.47 (m, 4H)1.45 – 1.27 (m, 8H). First eluting diastereomer purified by chiral prep-HPLC on a UniChiral CND-5H column (3 cm I.D. × 25 cm), using Hexane/EtOH (70/30) at a flow rate of 45 mL/min (wave length 254 nm). Rt = 10.3 min	m/z = 726.4 [M+H] ⁺
I-118	¹ H NMR (400 MHz, CD ₃ OD) δ 7.64 – 6.69 (m, 12H), 4.76 – 3.37 (m, 16H), 3.27 – 2.45 (m, 6H), 2.36 – 1.48 (m, 3H), 1.44 – 1.26 (m, 8H). Second eluting diastereomer purified by chiral prep-HPLC on a UniChiral CND-5H column (3 cm I.D. × 25 cm), using Hexane/EtOH (70/30) at a flow rate of 45 mL/min (wave length 254 nm). Rt = 13.8 min	m/z = 726.4 [M+H] ⁺

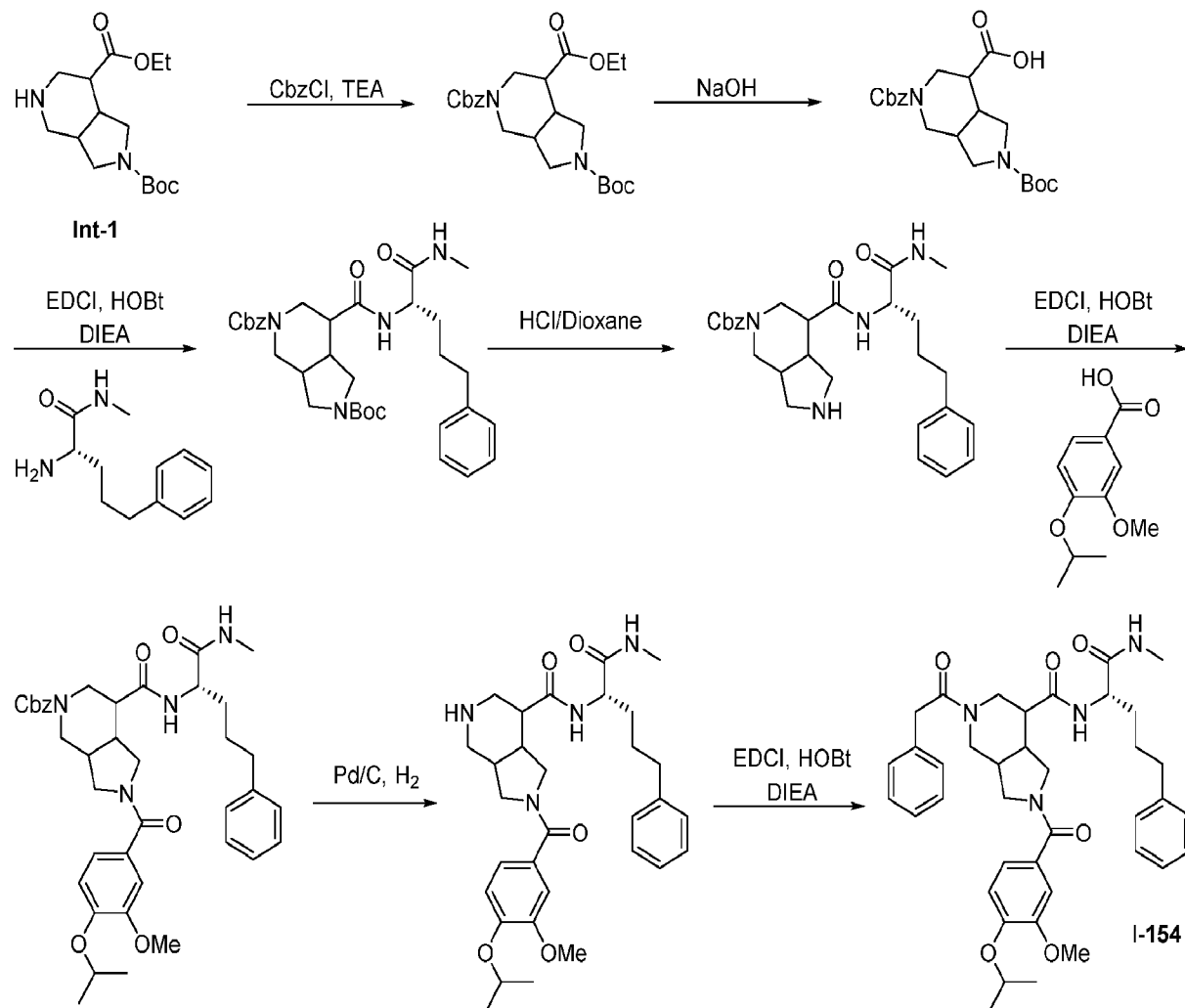
#	¹ H NMR Chromatography conditions, if applicable	LCMS
I-119	¹ H NMR (400 MHz, CD ₃ OD) δ 7.66 – 6.90 (m, 12H), 4.65 – 4.46 (m, 1H), 4.14 – 3.80 (m, 6H), 3.73 – 3.37 (m, 2H), 3.26 – 2.79 (m, 4H), 2.76 – 2.22 (m, 4H), 2.22 – 1.62 (m, 1H), 1.57 – 1.37 (m, 4H), 1.35 – 1.28 (m, 9H).	m/z = 685.3 [M+H] ⁺
I-120	¹ H NMR (400 MHz, CD ₃ OD) δ 7.66 – 6.55 (m, 12H), 4.78 – 3.38 (m, 11H), 3.17 – 2.81 (m, 4H), 2.75 – 2.48 (m, 5H), 2.44 – 2.02 (m, 1H), 1.41 – 1.30 (m, 8H).	m/z = 714.3 [M+H] ⁺
I-121	¹ H NMR (400 MHz, CD ₃ OD) δ 7.65 – 6.47 (m, 11H), 4.76 – 4.14 (m, 3H), 4.11 – 3.37 (m, 8H), 3.27 – 2.38 (m, 10H), 2.27 – 1.61 (m, 1H), 1.41 – 1.22 (m, 6H).	m/z = 730.3 [M+H] ⁺
I-122	¹ H NMR (400 MHz, CD ₃ OD) δ 7.65 – 6.50 (m, 12H), 4.80 – 4.36 (m, 2H), 4.36 – 3.93 (m, 1H), 3.92 – 3.60 (m, 6H), 3.59 – 3.34 (m, 2H), 3.21 – 2.78 (m, 4H), 2.77 – 2.31 (m, 6H), 1.46 – 1.20 (m, 8H).	m/z = 714.3 [M+H] ⁺
I-123	¹ H NMR (400 MHz, CD ₃ OD) δ 7.64 – 6.41 (m, 11H), 4.69 – 3.77 (m, 8H), 3.77 – 3.37 (m, 3H), 3.25 – 2.39 (m, 10H), 2.38 – 1.50 (m, 2H), 1.43 – 1.22 (m, 8H).	m/z = 730.2 [M+H] ⁺
I-124	¹ H NMR (400 MHz, CD ₃ OD) δ 8.52 – 6.62 (m, 7H), 4.74 – 3.75 (m, 8H), 3.74 – 3.37 (m, 3H), 3.28 – 2.76 (m, 3H), 2.76 – 2.41 (m, 5H), 2.38 – 1.71 (m, 1H), 1.42 – 1.09 (m, 11H).	m/z = 638.3 [M+H] ⁺
I-125	¹ H NMR (400 MHz, CD ₃ OD) δ 7.68 – 6.60 (m, 7H), 4.65 – 3.78 (m, 8H), 3.73 – 3.35 (m, 3H), 3.25 – 2.88 (m, 2H), 2.84 – 2.17 (m, 6H), 2.10 – 1.57 (m, 1H), 1.36 – 1.28 (m, 10H).	m/z = 638.3 [M+H] ⁺
I-126	¹ H NMR (400 MHz, CD ₃ OD) δ 8.55 – 6.50 (m, 11H), 4.78 – 4.00 (m, 4H), 3.99 – 3.77 (m, 5H), 3.74 – 3.37 (m, 3H), 3.27 – 2.41 (m, 10H), 1.87 – 1.54 (m, 3H), 1.42 – 1.24 (m, 8H).	m/z = 743.3 [M+H] ⁺
I-127	¹ H NMR (400 MHz, CD ₃ OD) δ 7.59 – 6.55 (m, 11H), 4.79 – 3.36 (m, 13H), 3.29 – 2.28 (m, 11H), 2.21 – 1.46 (m, 5H), 1.42 – 1.30 (m, 7H).	m/z = 758.4 [M+H] ⁺
I-128	¹ H NMR (400 MHz, CD ₃ OD) δ 7.72 – 6.42 (m, 11H), 4.78 – 4.12 (m, 4H), 4.11 – 3.34 (m, 9H), 3.23 – 1.52 (m, 14H), 1.37 – 1.26 (m, 7H).	m/z = 758.4 [M+H] ⁺
I-129	¹ H NMR (400 MHz, CD ₃ OD) δ 7.87 – 6.63 (m, 7H), 4.743.36 (m, 13H), 3.262.25 (m, 10H), 1.770.62 (m, 21H).	m/z = 764.5 [M+H] ⁺
I-130	¹ H NMR (400 MHz, CD ₃ OD) δ 7.66 – 6.61 (m, 7H), 4.76 – 3.99 (m, 4H), 3.97 – 3.37 (m, 11H), 3.28 – 2.76 (m, 3H), 2.75 – 1.65 (m, 7H), 1.61 – 0.87 (m, 17H).	m/z = 750.4 [M+H] ⁺
I-131	¹ H NMR (400 MHz, CD ₃ OD) δ 7.66 – 6.61 (m, 7H), 4.76 – 3.99 (m, 4H), 3.97 – 3.37 (m, 11H), 3.28 – 2.76 (m, 3H), 2.75 – 1.65 (m, 7H), 1.61 – 0.87 (m, 17H).	m/z = 750.4 [M+H] ⁺
I-132	¹ H NMR (400 MHz, CD ₃ OD) δ 7.70 – 6.58 (m, 7H), 4.79 – 3.77 (m, 9H), 3.76 – 3.35 (m, 3H), 3.30 – 2.98 (m, 2H), 2.96 – 2.41 (m, 6H), 1.86 – 1.45 (m, 9H), 1.42 – 1.26 (m, 9H), 1.17 – 0.87 (m, 3H).	m/z = 734.4 [M+H] ⁺
I-133	¹ H NMR (400 MHz, CD ₃ OD) δ 7.71 – 6.60 (m, 11H), 4.76 – 3.95 (m, 4H), 3.95 – 3.36 (m, 8H), 3.26 – 2.82 (m, 3H), 2.82 – 1.56 (m, 12H), 1.43 – 1.22 (m, 8H).	m/z = 810.4 [M+H] ⁺
I-134	¹ H NMR (400 MHz, CD ₃ OD) δ 7.74 – 6.59 (m, 11H), 4.78 – 3.35 (m,	m/z = 810.4

#	¹ H NMR Chromatography conditions, if applicable	LCMS
	12H), 3.24 – 2.37 (m, 10H), 2.33 – 1.45 (m, 5H), 1.43 – 1.19 (m, 7H).	[M+H] ⁺
I-135	¹ H NMR (400 MHz, CD ₃ OD) δ 7.66 – 6.60 (m, 7H), 4.78 – 4.24 (m, 3H), 3.90 (m, 2H), 3.86 (m, 1H), 3.82 (m, 3H), 3.75 – 3.35 (m, 4H), 3.24 – 2.96 (m, 3H), 2.96 – 2.78 (m, 1H), 2.77 – 2.48 (m, 5H), 1.69 (m, 5H), 1.51 (m, 1H), 1.43 – 1.28 (m, 7H), 1.27 – 1.05 (m, 5H), 1.03 – 0.76 (m, 3H).	m/z = 764.5 [M+H] ⁺
I-136	¹ H NMR (400 MHz, CD ₃ OD) δ 7.72 – 6.04 (m, 12H), 4.75 – 3.98 (m, 3H), 3.96 – 3.36 (m, 8H), 3.26 – 2.88 (m, 2H), 2.84 – 2.17 (m, 7H), 1.41 – 1.22 (m, 6H).	m/z = 740.4 [M+H] ⁺
I-137	¹ H NMR (400 MHz, CD ₃ OD) δ 7.67 – 6.52 (m, 12H), 4.76 – 3.92 (m, 4H), 3.91 – 3.36 (m, 8H), 3.28 – 2.85 (m, 3H), 2.84 – 2.08 (m, 8H), 1.42 – 1.19 (m, 7H).	m/z = 738.3 [M+H] ⁺
I-138	¹ H NMR (400 MHz, CD ₃ OD) δ 8.77 – 8.51 (m, 2H), 8.00 – 6.65 (m, 9H), 4.79 – 3.79 (m, 9H), 3.73 – 3.39 (m, 3H), 3.24 – 2.12 (m, 11H), 1.92 – 1.57 (m, 3H), 1.45 – 1.23 (m, 7H).	m/z = 743.4 [M+H] ⁺
I-139	¹ H NMR (400 MHz, CD ₃ OD) δ 7.70 – 6.63 (m, 10H), 4.76 – 3.34 (m, 12H), 3.26 – 2.86 (m, 4H), 2.85 – 2.42 (m, 5H), 1.96 – 1.63 (m, 3H), 1.46 – 1.14 (m, 9H).	m/z = 783.4 [M+H] ⁺
I-140	¹ H NMR (400 MHz, CD ₃ OD) δ 7.66 – 6.64 (m, 7H), 4.75 – 3.38 (m, 12H), 3.26 – 2.36 (m, 9H), 1.75 – 1.01 (m, 25H).	m/z = 762.4 [M+H] ⁺
I-141	¹ H NMR (400 MHz, CD ₃ OD) δ 7.72 – 6.58 (m, 7H), 4.80 – 3.36 (m, 13H), 3.23 – 2.42 (m, 8H), 1.77 – 1.05 (m, 25H).	m/z = 762.4 [M+H] ⁺
I-142	¹ H NMR (400 MHz, CD ₃ OD) δ 7.65 – 6.61 (m, 7H), 4.78 – 3.39 (m, 12H), 3.25 – 2.97 (m, 2H), 2.85 – 2.52 (m, 5H), 2.08 – 1.08 (m, 24H).	m/z = 764.4 [M+H] ⁺
I-143	¹ H NMR (400 MHz, CD ₃ OD) δ 7.90 – 6.59 (m, 10H), 4.72 – 3.37 (m, 13H), 3.27 – 2.91 (m, 3H), 2.90 – 2.56 (m, 7H), 1.83 – 1.61 (m, 3H), 1.44 – 1.33 (m, 6H), 1.22 – 1.18 (m, 2H).	m/z = 783.5 [M+H] ⁺
I-144	¹ H NMR (400 MHz, CD ₃ OD) δ 7.68 – 6.57 (m, 11H), 4.75 – 3.79 (m, 9H), 3.73 – 3.41 (m, 3H), 3.28 – 2.79 (m, 3H), 2.78 – 2.54 (m, 6H), 2.44 – 2.00 (m, 2H), 1.73 – 1.50 (m, 3H), 1.41 – 1.29 (m, 8H).	m/z = 760.4 [M+H] ⁺
I-145	¹ H NMR (400 MHz, CD ₃ OD) δ 7.52 – 6.55 (m, 12H), 4.77 – 4.52 (m, 3H), 4.52 – 4.30 (m, 2H), 4.11 – 4.93 (m, 1H), 4.92 – 3.79 (m, 5H), 3.75 – 3.56 (m, 2H), 3.55 – 3.35 (m, 2H), 3.27 – 3.02 (m, 2H), 2.85 – 2.72 (m, 3H), 2.65 – 2.23 (m, 4H), 1.45 – 1.28 (m, 7H), 1.23 – 0.84 (m, 3H). First eluting diastereomer purified by chiral prep-HPLC on a CHIRALPAK IF column (0.46 cm I.D. × 15 cm), using n-Hexane/EtOH 0.1% DEA (60/40) at a flow rate of 1.0 mL/min (wave length 210 nm). Rt = 8.2 min	m/z = 758.4 [M+H] ⁺
I-146	¹ H NMR (400 MHz, CD ₃ OD) δ 7.55 – 6.60 (m, 12H), 4.66 – 4.12 (m, 6H), 4.05 – 3.75 (m, 6H), 3.70 – 3.58 (m, 1H), 3.52 – 3.35 (m, 3H), 3.26 – 3.01 (m, 2H), 2.84 – 2.47 (m, 6H), 1.40 – 1.97 (m, 9H), 1.46 – 1.35 (m, 9H), 0.71 – 0.66 (m, 2H).	m/z = 758.3 [M+H] ⁺

#	¹ H NMR Chromatography conditions, if applicable	LCMS
	Second eluting diastereomer purified by chiral prep-HPLC on a CHIRALPAK IF column (0.46 cm I.D. × 15 cm), using n-Hexane/EtOH 0.1% DEA (60/40) at a flow rate of 1.0 mL/min (wave length 210 nm). Rt = 10.5 min	
I-147	¹ H NMR (400 MHz, CD ₃ OD) δ 8.07 – 6.76 (m, 12H), 4.80 – 3.98 (m, 6H), 3.97 – 3.58 (m, 7H), 3.55 – 3.33 (m, 2H), 3.29 – 1.63 (m, 8H), 1.37 – 0.88 (m, 9H). First eluting diastereomer purified by prep-HPLC on an Agilent 10 Prep-C18 column (21.2 mm I.D. × 25 cm, 10 μm), using H ₂ O/ACN 0.1% TFA at a flow rate of 20 mL/min (wave length 214 nm). Rt = 12.9 min	m/z = 758.4 [M+H] ⁺
I-148	¹ H NMR (400 MHz, CD ₃ OD) δ 7.62 – 6.88 (m, 12H), 4.67 – 4.23 (m, 5H), 4.13 – 3.68 (m, 8H), 3.63 – 3.33 (m, 2H), 3.28 – 2.58 (m, 5H), 2.54 – 2.13 (m, 3H), 1.38 – 1.27 (m, 6H), 1.23 – 1.06 (m, 3H). Second eluting diastereomer purified by prep-HPLC on an Agilent 10 Prep-C18 column (21.2 mm I.D. × 25 cm, 10 μm), using H ₂ O/ACN 0.1% TFA at a flow rate of 20 mL/min (wave length 214 nm). Rt = 13.9 min	m/z = 758.4 [M+H] ⁺
I-149	¹ H NMR (400 MHz, CD ₃ OD) δ 7.92 – 6.63 (m, 14H), 4.80 – 3.45 (m, 11H), 3.27 – 2.07 (m, 8H), 1.77 – 1.18 (m, 11H) 1H), 1.80 – 1.52 (m, 2H), 1.48 – 0.86 (m, 9H).	m/z = 752.5 [M+H] ⁺
I-150	¹ H NMR (400 MHz, CD ₃ OD) δ 8.58 – 6.67 (m, 16H), 4.79 – 3.39 (m, 12H), 3.23 – 1.96 (m, 9H), 1.88 – 1.33 (m, 9H).	m/z = 762.4 [M+H] ⁺
I-151	¹ H NMR (400 MHz, CD ₃ OD) δ 8.78 – 8.71 (m, 1H), 8.70 – 8.61 (m, 0.5H), 8.40 – 8.29 (m, 0.5H), 7.61 – 6.65 (m, 13H), 4.79 – 3.75 (m, 8H), 3.70 – 3.35 (m, 3H), 3.29 – 2.94 (m, 2H), 2.84 – 2.39 (m, 5H), 2.22 – 2.00 (m, 1H), 1.87 – 1.49 (m, 3H), 1.42 – 1.31 (m, 5H), 1.29 – 1.23 (m, 3H).	m/z = 763.4 [M+H] ⁺
I-152	¹ H NMR (400 MHz, CD ₃ OD) δ 7.68 – 6.41 (m, 11H), 4.77 – 4.13 (m, 3H), 4.11 – 3.33 (m, 9H), 3.28 – 1.51 (m, 14H), 1.44 – 1.21 (m, 7H). First eluting diastereomer purified by chiral prep-HPLC on a UniChiral CND-5H column (21.2mm I.D. × 250 mm), using ACN/IPA/DEA = 95/5/0.1, at a flow rate of 20 mL/min (wave length 254 nm). Rt = 5.7 min.	m/z = 758.4 [M+H] ⁺
I-153	¹ H NMR (400 MHz, CD ₃ OD) δ 7.63 – 6.50 (m, 11H), 4.77 – 3.38 (m, 13H), 3.27 – 2.28 (m, 10H), 2.20 – 1.47 (m, 4H), 1.42 – 1.27 (m, 6H). Second eluting diastereomer purified by chiral prep-HPLC on a UniChiral CND-5H column (21.2mm I.D. × 250 mm), using ACN/IPA/DEA = 95/5/0.1, at a flow rate of 20 mL/min (wave length	m/z = 758.4 [M+H] ⁺

#	¹ H NMR Chromatography conditions, if applicable	LCMS
	254 nm). Rt = 6.3 min.	
I-261	¹ H NMR (400 MHz, CD ₃ OD) δ 7.64 – 6.55 (m, 9H), 4.79 – 3.37 (m, 13H), 3.28 – 2.52 (m, 8H), 2.38 – 1.78 (m, 1H), 1.44 – 1.25 (m, 6H). First eluting enantiomer purified by chiral prep-HPLC on a UniChiral CND-5H column (21.2mm I.D. × 250 mm), using n-Hexane/EtOH = 70/30, at a flow rate of 20 mL/min (wave length 254 nm). Rt = 14.9 min.	m/z = 659.4 [M+H] ⁺
I-262	¹ H NMR (400 MHz, CD ₃ OD) δ 7.64 – 6.54 (m, 9H), 4.74 – 3.39 (m, 13H), 3.27 – 2.47 (m, 8H), 2.43 – 1.93 (m, 1H), 1.42 – 1.28 (m, 6H). Second eluting enantiomer purified by chiral prep-HPLC on a UniChiral CND-5H column (21.2mm I.D. × 250 mm), using n-Hexane/EtOH = 70/30, at a flow rate of 20 mL/min (wave length 254 nm). Rt = 17.9 min.	m/z = 659.4 [M+H] ⁺

Synthesis of 2-(4-isopropoxy-3-methoxybenzoyl)-N-((S)-1-(methylamino)-1-oxo-5-phenylpentan-2-yl)-5-(2-phenylacetyl)octahydro-1H-pyrrolo[3,4-c]pyridine-7-carboxamide I-154



[00491] Step 1: 5-benzyl 2-(tert-butyl) 7-ethyl hexahydro-2H-pyrrolo[3,4-c]pyridine-2,5,7(3H)-tricarboxylate

[00492] To a solution of **Int-1** (5 g, 16.7 mmol) in DCM (50 mL) was added Et₃N (3.4 g, 33.5 mmol). After stirring for 30 min, CbzCl (3.1 g, 18.4 mmol) was added and stirring continued for 4 h. The reaction was quenched with water and extracted with EtOAc three times. The combined organic layers were washed with water, brine, and dried over Na₂SO₄. The solvent was removed *in vacuo* and the residue purified by column chromatography (20% EtOAc/PE) to afford the product (5.7 g, 79%) as a white solid. LCMS *m/z* = 333.3 [M-Boc+H]⁺; ¹H NMR (400 MHz,

CD₃OD) δ 7.39 – 7.26 (m, 5H), 5.13 (d, J = 3.9 Hz, 2H), 4.31 – 3.47 (m, 4H), 3.46 – 3.32 (m, 3H), 3.30 (d, J = 1.6 Hz, 1H), 3.24 – 1.58 (m, 5H), 1.46 (s, 9H), 1.29 – 1.23 (m, 3H).

[00493] Step 2: 5-((benzyloxy)carbonyl)-2-(tert-butoxycarbonyl)octahydro-1H-pyrrolo[3,4-c]pyridine-7-carboxylic acid

[00494] To a solution of 5-benzyl 2-(tert-butyl) 7-ethyl hexahydro-2H-pyrrolo[3,4-c]pyridine-2,5,7(3H)-tricarboxylate (5.7 g, 13.2 mmol) in MeOH (60 mL) was added aqueous NaOH (1M, 20 mL). The mixture was stirred at room temperature for 3h, then diluted with water and the pH adjusted to ~3 by addition of 1M HCl. The aqueous layer was extracted with EtOAc three times. The combined organic layers were washed with water, brine and dried over Na₂SO₄. Concentration afforded the product (4.7 g, 88%) as a white solid. LCMS m/z = 305.3 [M-Boc+H]⁺.

[00495] Step 3: 5-benzyl 2-(tert-butyl) 7-(((S)-1-(methylamino)-1-oxo-5-phenylpentan-2-yl)carbamoyl)hexahydro-2H-pyrrolo[3,4-c]pyridine-2,5(3H)-dicarboxylate To a solution of 5-((benzyloxy)carbonyl)-2-(tert-butoxycarbonyl)octahydro-1H-pyrrolo[3,4-c]pyridine-7-carboxylic acid (4.5 g, 11.1 mmol) in DMA (50 mL) was added (S)-2-amino-N-methyl-5-phenylpentanamide (3.4 g, 16.7 mmol), EDCI (3.2 g, 16.7 mmol), HOBT (1.7 g, 12.2 mmol) and DIEA (2.9 g, 22.3 mmol). The resulting mixture was stirred at room temperature overnight. The reaction was quenched with water and extracted with EtOAc three times. The combined organic layers were washed with water, brine and dried over Na₂SO₄. The solvent was removed and the residue purified by column chromatography (5% MeOH/DCM) to afford the product (5.3 g, 80%) as a white solid. LCMS m/z = 493.4 [M-Boc+H]⁺.

[00496] Step 4: benzyl 7-(((S)-1-(methylamino)-1-oxo-5-phenylpentan-2-yl)carbamoyl)octahydro-5H-pyrrolo[3,4-c]pyridine-5-carboxylate hydrochloride

[00497] To a solution of 5-benzyl 2-(tert-butyl) 7-(((S)-1-(methylamino)-1-oxo-5-phenylpentan-2-yl)carbamoyl)hexahydro-2H-pyrrolo[3,4-c]pyridine-2,5(3H)-dicarboxylate (5.3 g, 8.9 mmol) in DCM (25 mL) was added a solution of HCl in dioxane (4M, 25mL). The resulting mixture was stirred at room temperature for 1 h. The solvent was removed to afford the product (7.8 g, quant.). LCMS m/z = 493.4 [M+H]⁺.

[00498] Step 5: benzyl 2-(4-isopropoxy-3-methoxybenzoyl)-7-(((S)-1-(methylamino)-1-oxo-5-phenylpentan-2-yl)carbamoyl)octahydro-5H-pyrrolo[3,4-c]pyridine-5-carboxylate

[00499] A mixture of benzyl 7-(((S)-1-(methylamino)-1-oxo-5-phenylpentan-2-yl)carbamoyl)octahydro-5H-pyrrolo[3,4-c]pyridine-5-carboxylate hydrochloride (5.1 g, 9.8 mmol), 4-isopropoxy-3-methoxybenzoic acid (2.47 g, 11.7 mmol), EDCI (2.8 g, 14.7 mmol), HOBt (2.0 g, 14.7 mmol) and DIEA (3.87 g, 30 mmol) in DMF (20 mL) was stirred overnight. The reaction mixture was diluted with water and extracted with EtOAc three times. The combined organic layers were washed with water and brine, dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by column chromatography (5% MeOH/DCM) to give the product (6.7 g, quant.) as a colorless oil. LCMS *m/z* = 685.4 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD) δ 7.46 – 6.78 (m, 13H), 5.49 (s, 1H), 5.14 (d, *J* = 2.7 Hz, 2H), 4.67 – 4.47 (m, 1H), 4.34 – 4.11 (m, 2H), 3.83 (d, *J* = 7.0 Hz, 4H), 3.59 (d, *J* = 3.7 Hz, 2H), 3.46 – 3.34 (m, 1H), 2.98 (d, *J* = 53.8 Hz, 1H), 2.76 – 2.46 (m, 7H), 2.40 (t, *J* = 7.3 Hz, 1H), 1.62 (d, *J* = 33.2 Hz, 3H), 1.39 – 1.21 (m, 8H).

[00500] Step 6: 2-(4-isopropoxy-3-methoxybenzoyl)-N-((S)-1-(methylamino)-1-oxo-5-phenylpentan-2-yl)octahydro-1H-pyrrolo[3,4-c]pyridine-7-carboxamide

[00501] To a solution of benzyl 2-(4-isopropoxy-3-methoxybenzoyl)-7-(((S)-1-(methylamino)-1-oxo-5-phenylpentan-2-yl)carbamoyl)octahydro-5H-pyrrolo[3,4-c]pyridine-5-carboxylate (6.7 g, 9.8 mmol) in MeOH (70 mL) was added Pd/C (10%, 600 mg). The resulting mixture was stirred under H₂ at room temperature overnight. The solution was filtered through celite and the filtrate concentrated to afford the product (5.2 g, 97%). LCMS *m/z* = 551.4 [M+H]⁺; ¹H NMR (400 MHz, CD₃OD) δ 7.29 – 6.81 (m, 8H), 4.74 – 4.48 (m, 1H), 4.37 – 4.15 (m, 1H), 3.90 – 3.81 (m, 3H), 3.78 – 3.35 (m, 4H), 3.06 – 2.82 (m, 3H), 2.78 – 2.16 (m, 9H), 1.89 – 1.38 (m, 4H), 1.34 – 1.24 (m, 6H).

[00502] Step 7: 2-(4-isopropoxy-3-methoxybenzoyl)-N-((S)-1-(methylamino)-1-oxo-5-phenylpentan-2-yl)-5-(2-phenylacetyl)octahydro-1H-pyrrolo[3,4-c]pyridine-7-carboxamide (I-154)

[00503] A mixture of 2-(4-isopropoxy-3-methoxybenzoyl)-N-((S)-1-(methylamino)-1-oxo-5-phenylpentan-2-yl)octahydro-1H-pyrrolo[3,4-c]pyridine-7-carboxamide (55 mg, 0.1 mmol), 2-phenylacetic acid (16 mg, 0.12 mmol), EDCI (23 mg, 0.12 mmol), HOBt (20 mg, 0.15 mmol) and DIEA (32 mg, 0.25 mmol) in DMA (1.0 mL) was stirred at room temperature overnight. The reaction mixture was diluted with water and extracted with EtOAc three times. The combined organic layers were washed with water and brine, dried over Na₂SO₄ and concentrated *in vacuo*.

The residue was purified by prep-HPLC to afford **I-154** (24.2 mg, 37%) as a white solid. LCMS $m/z = 669.4$ $[M+H]^+$; 1H NMR (400 MHz, CD_3OD) δ 7.43 – 6.79 (m, 13H), 4.69 – 3.76 (m, 9H), 3.74 – 3.34 (m, 3H), 3.28 – 2.87 (m, 2H), 2.87 – 2.49 (m, 6H), 2.48 – 2.17 (m, 2H), 2.03 – 1.48 (m, 4H), 1.40 – 1.26 (m, 7H).

[00504] The compounds listed in **Table 4** were synthesized using analogous methods to those shown for **I-154**, using the appropriate commercially available reagents and/or intermediates. Final examples were obtained as a mixture of diastereomers or separated by preparative HPLC or preparative TLC as indicated.

Table 4. Compounds made by a method analogous to I-154

#	1H NMR Chromatography conditions, if applicable	LCMS
I-155	1H NMR (400 MHz, CD_3OD) δ 8.61 – 8.24 (m, 1H), 7.87 – 7.63 (m, 1H), 7.48 – 6.68 (m, 10H), 4.84 – 3.35 (m, 11H), 3.29 – 2.10 (m, 11H), 2.08 – 1.43 (m, 4H), 1.40 – 1.22 (m, 8H).	$m/z = 670.4$ $[M+H]^+$
I-156	1H NMR (400 MHz, CD_3OD) δ 7.65 – 6.71 (m, 12H), 4.77 – 3.78 (m, 10H), 3.76 – 3.34 (m, 6H), 3.28 – 2.48 (m, 6H), 2.37 – 1.47 (m, 3H), 1.45 – 1.24 (m, 8H).	$m/z = 743.4$ $[M+H]^+$
I-157	1H NMR (400 MHz, CD_3OD) δ 7.08 – 6.93 (m, 1H), 6.86 – 6.30 (m, 12H), 4.15 – 3.28 (m, 6H), 3.26 – 2.85 (m, 3H), 2.79 – 2.38 (m, 5H), 2.35 – 1.81 (m, 10H), 1.32 – 0.95 (m, 3H), 0.84 – 0.71 (m, 7H).	$m/z = 722.5$ $[M+H]^+$
I-158	1H NMR (400 MHz, CD_3OD) δ 8.99 – 8.84 (m, 1H), 8.53 – 8.33 (m, 1H), 8.20 – 7.89 (m, 2H), 7.88 – 7.53 (m, 2H), 7.29 – 6.72 (m, 8H), 4.74 – 4.31 (m, 2H), 4.31 – 3.98 (m, 1H), 3.88 – 3.35 (m, 9H), 2.84 – 2.17 (m, 8H), 2.05 – 0.98 (m, 12H).	$m/z = 706.5$ $[M+H]^+$
I-159	1H NMR (400 MHz, CD_3OD) δ 7.75 – 6.81 (m, 13H), 4.65 – 3.81 (m, 8H), 3.80 – 3.33 (m, 7H), 2.82 – 2.38 (m, 8H), 1.75 – 1.49 (m, 3H), 1.37 – 1.27 (m, 8H).	$m/z = 708.5$ $[M+H]^+$
I-160	1H NMR (400 MHz, CD_3OD) δ 9.34 – 9.11 (m, 1H), 8.20 – 7.72 (m, 5H), 7.29 – 6.79 (m, 8H), 4.72 – 3.80 (m, 7H), 3.78 – 3.34 (m, 5H), 2.89 – 2.28 (m, 8H), 2.08 – 1.55 (m, 3H), 1.37 – 1.26 (m, 8H).	$m/z = 706.4$ $[M+H]^+$
I-161	1H NMR (400 MHz, CD_3OD) δ 7.56 – 7.55 (m, 1H), 7.30 – 7.01 (m, 12H), 6.49 – 6.41 (m, 1H), 5.34 – 4.92 (m, 2H), 4.73 – 3.35 (m, 11H), 3.23 – 2.90 (m, 2H), 2.80 – 1.97 (m, 8H), 1.78 – 1.53 (m, 4H), 1.40 – 1.27 (m, 8H).	$m/z = 708.5$ $[M+H]^+$
I-162	1H NMR (400 MHz, CD_3OD) δ 7.42 – 6.64 (m, 12H), 4.67 – 4.05 (m, 4H), 3.88 – 3.34 (m, 8H), 2.79 – 2.47 (m, 7H), 2.43 – 1.95 (m, 4H), 1.82 – 1.35 (m, 4H), 1.35 – 1.20 (m, 9H).	$m/z = 708.4$ $[M+H]^+$

#	¹ H NMR Chromatography conditions, if applicable	LCMS
I-163	¹ H NMR (400 MHz, CD ₃ OD) δ 8.57 – 6.81 (m, 10H), 4.70 – 3.35 (m, 15H), 3.23 – 2.36 (m, 9H), 1.85 – 1.22 (m, 11H).	m/z = 687.4 [M+H] ⁺
I-164	¹ H NMR (400 MHz, CD ₃ OD) δ 8.56 – 8.28 (m, 1H), 7.81 – 7.66 (m, 1H), 7.41 – 6.83 (m, 10H), 4.66 – 3.82 (m, 7H), 3.79 – 3.33 (m, 4H), 3.28 – 2.78 (m, 6H), 2.76 – 2.36 (m, 8H), 1.74 – 1.54 (m, 3H), 1.35 – 1.27 (m, 8H).	m/z = 684.4 [M+H] ⁺
I-165	¹ H NMR (400 MHz, CD ₃ OD) δ 8.99 – 8.84 (m, 2H), 8.25 – 8.07 (m, 2H), 7.93 – 7.75 (m, 1H), 7.27 – 7.02 (m, 7H), 7.02 – 6.83 (m, 1H), 4.69 – 3.78 (m, 8H), 3.70 – 3.37 (m, 5H), 2.83 – 2.49 (m, 7H), 1.85 – 1.50 (m, 3H), 1.36 – 1.28 (m, 8H).	m/z = 707.4 [M+H] ⁺
I-166	¹ H NMR (400 MHz, CD ₃ OD) δ 8.28 – 8.17 (m, 1H), 7.29 – 6.80 (m, 8H), 4.66 – 4.19 (m, 3H), 3.90 – 3.77 (m, 3H), 3.75 – 3.34 (m, 4H), 3.29 – 3.08 (m, 1H), 3.06 – 1.95 (m, 12H), 1.86 – 1.50 (m, 3H), 1.38 – 1.19 (m, 7H).	m/z = 660.4 [M+H] ⁺
I-167	¹ H NMR (400 MHz, CD ₃ OD) δ 8.82 – 8.81 (m, 1H), 8.35 – 8.25 (m, 1H), 8.04 – 7.97 (m, 1H), 7.84 – 7.73 (m, 2H), 7.53 – 7.52 (m, 1H), 7.23 – 6.83 (m, 8H), 4.70 – 3.36 (m, 12H), 3.26 – 3.13 (m, 2H), 2.78 – 2.20 (m, 8H), 1.68 – 1.57 (m, 3H), 1.34 – 1.26 (m, 9H).	m/z = 720.5 [M+H] ⁺
I-168	¹ H NMR (400 MHz, CD ₃ OD) δ 7.81 – 6.76 (m, 14H), 4.69 – 3.72 (m, 7H), 3.66 – 3.33 (m, 4H), 3.22 – 2.59 (m, 7H), 2.51 – 1.99 (m, 2H), 1.79 – 1.52 (m, 3H), 1.35 – 1.27 (m, 8H).	m/z = 721.5 [M+H] ⁺
I-169	¹ H NMR (400 MHz, CD ₃ OD) δ 7.26 – 6.85 (m, 8H), 4.63 – 4.51 (m, 1H), 4.34 – 4.32 (m, 1H), 4.22 – 4.15 (m, 1H), 3.84 – 3.34 (m, 12H), 3.25 – 3.12 (m, 1H), 2.74 – 2.61 (m, 7H), 2.44 – 2.33 (m, 1H), 2.11 – 2.08 (m, 1H), 2.08 – 2.04 (m, 1H), 1.71 – 1.50 (m, 5H), 1.40 – 1.21 (m, 12H).	m/z = 677.5 [M+H] ⁺
I-170	¹ H NMR (400 MHz, CD ₃ OD) δ 7.56 – 7.55 (m, 1H), 7.30 – 7.01 (m, 12H), 6.49 – 6.41 (m, 1H), 5.23 – 4.85 (m, 2H), 4.67 – 4.52 (m, 1H), 4.36 – 4.22 (m, 1H), 4.20 – 3.97 (m, 1H), 3.88 – 3.82 (m, 3H), 3.78 – 3.71 (m, 1H), 3.62 – 3.36 (m, 4H), 3.23 – 2.90 (m, 2H), 2.73 – 2.57 (m, 6H), 2.45 – 2.36 (m, 1H), 2.20 – 2.00 (m, 1H), 1.78 – 1.40 (m, 4H), 1.36 – 1.27 (m, 8H).	m/z = 708.4 [M+H] ⁺
I-171	¹ H NMR (400 MHz, CD ₃ OD) δ 7.30 – 6.71 (m, 9H), 6.04 – 5.93 (m, 1H), 4.69 – 4.47 (m, 1H), 4.38 – 3.79 (m, 6H), 3.77 – 3.33 (m, 4H), 3.30 – 3.08 (m, 2H), 2.78 – 2.37 (m, 8H), 2.20 – 2.04 (m, 3H), 1.83 – 1.53 (m, 3H), 1.39 – 1.22 (m, 7H).	m/z = 658.5 [M+H] ⁺
I-172	¹ H NMR (400 MHz, CD ₃ OD) δ 8.04 – 6.81 (m, 12H), 4.67 – 4.02 (m, 4H), 3.91 – 3.67 (m, 4H), 3.66 – 3.34 (m, 4H), 3.22 – 2.70 (m, 3H), 2.70 – 2.46 (m, 5H), 2.45 – 1.92 (m, 1H), 1.85 – 1.50 (m, 3H), 1.50 – 1.12 (m, 9H).	m/z = 728.4 [M+H] ⁺
I-173	¹ H NMR (400 MHz, CD ₃ OD) δ 9.63 – 8.23 (m, 12H), 6.22 – 5.57 (m, 4H), 5.49 – 5.31 (m, 4H), 5.31 – 4.90 (m, 5H), 4.36 – 3.91 (m, 9H), 3.47 – 2.99 (m, 3H), 2.96 – 2.69 (m, 10H).	m/z = 726.5 [M+H] ⁺

#	¹ H NMR Chromatography conditions, if applicable	LCMS
I-174	¹ H NMR (400 MHz, CD ₃ OD) δ 7.64 – 7.50 (m, 1H), 7.34 – 6.82 (m, 12H), 6.52 – 6.40 (m, 1H), 5.40 – 4.97 (m, 2H), 4.75 – 3.34 (m, 11H), 3.27 – 2.90 (m, 2H), 2.81 – 1.97 (m, 8H), 1.86 – 1.43 (m, 4H), 1.40 – 1.25 (m, 8H).	m/z = 726.5 [M+H] ⁺
I-175	¹ H NMR (400 MHz, CD ₃ OD) δ 7.53 – 6.67 (m, 12H), 4.72 – 4.24 (m, 2H), 4.23 – 3.60 (m, 7H), 3.60 – 3.34 (m, 2H), 3.28 – 2.79 (m, 2H), 2.78 – 2.48 (m, 9H), 2.48 – 1.92 (m, 2H), 1.86 – 1.43 (m, 3H), 1.40 – 1.18 (m, 10H).	m/z = 722.4 [M+H] ⁺
I-176	¹ H NMR (400 MHz, CD ₃ OD) δ 7.24 – 6.82 (m, 11H), 6.49 – 6.38 (m, 1H), 4.70 – 4.51 (m, 2H), 4.33 – 3.99 (m, 4H), 3.96 – 3.90 (m, 1H), 3.86 – 3.76 (m, 5H), 3.68 – 3.50 (m, 3H), 3.25 – 2.84 (m, 2H), 2.71 – 2.38 (m, 8H), 2.03 – 1.63 (m, 3H), 1.38 – 1.25 (m, 9H).	m/z = 738.5 [M+H] ⁺
I-177	¹ H NMR (400 MHz, CD ₃ OD) δ 7.59 – 6.73 (m, 13H), 4.84 – 3.94 (m, 3H), 3.94 – 3.80 (m, 3H), 3.81 – 3.36 (m, 2H), 3.25 – 2.77 (m, 2H), 2.77 – 2.46 (m, 6H), 2.46 – 1.93 (m, 2H), 1.84 – 1.53 (m, 9H), 1.50 – 1.04 (m, 10H).	m/z = 736.5 [M+H] ⁺
I-178	¹ H NMR (400 MHz, CD ₃ OD) δ 7.43 – 6.72 (m, 13H), 4.76 – 4.18 (m, 3H), 4.16 – 3.73 (m, 7H), 3.61 – 3.38 (m, 2H), 3.13 – 2.90 (m, 2H), 2.77 – 2.37 (m, 8H), 1.77 – 1.24 (m, 11H).	m/z = 708.4 [M+H] ⁺
I-179	¹ H NMR (400 MHz, CD ₃ OD) δ 8.25 – 6.67 (m, 12H), 4.76 – 4.30 (m, 2H), 4.30 – 3.35 (m, 10H), 3.28 – 2.93 (m, 2H), 2.80 – 2.15 (m, 8H), 1.90 – 1.21 (m, 11H).	m/z = 709.4 [M+H] ⁺
I-180	¹ H NMR (400 MHz, CD ₃ OD) δ 7.63 – 6.30 (m, 12H), 4.77 – 3.80 (m, 6H), 3.79 – 3.32 (m, 5H), 3.27 – 2.35 (m, 9H), 2.32 – 1.48 (m, 3H), 1.47 – 1.17 (m, 8H).	m/z = 694.5 [M+H] ⁺
I-181	¹ H NMR (400 MHz, CD ₃ OD) δ 9.02 – 6.80 (m, 14H), 4.75 – 3.99 (m, 3H), 3.89 – 3.82 (m, 3H), 3.81 – 3.36 (m, 6H), 2.88 – 2.25 (m, 8H), 2.08 – 1.39 (m, 3H), 1.36 – 1.14 (m, 8H).	m/z = 706.5 [M+H] ⁺
I-182	¹ H NMR (400 MHz, CD ₃ OD) δ 8.15 – 6.69 (m, 12H), 4.73 – 4.08 (m, 3H), 3.92 – 3.40 (m, 8H), 3.01 – 2.32 (m, 8H), 2.09 – 1.19 (m, 12H).	m/z = 695.4 [M+H] ⁺
I-183	¹ H NMR (400 MHz, CD ₃ OD) δ 7.28 – 6.28 (m, 9H), 4.71 – 4.16 (m, 3H), 3.89 – 3.71 (m, 4H), 3.663.53 (m, 2H), 2.82 – 2.49 (m, 8H), 2.44 – 2.24 (m, 4H), 1.81 – 1.50 (m, 3H), 1.34 – 1.24 (m, 10H).	m/z = 659.5 [M+H] ⁺
I-184	¹ H NMR (400 MHz, CD ₃ OD) δ 8.66 – 6.81 (m, 11H), 4.72 – 3.96 (m, 3H), 3.95 – 3.35 (m, 9H), 3.28 – 2.58 (m, 7H), 2.57 – 1.99 (m, 5H), 1.95 – 1.51 (m, 3H), 1.50 – 1.16 (m, 8H).	m/z = 670.5 [M+H] ⁺
I-185	¹ H NMR (400 MHz, CD ₃ OD) δ 7.28 – 6.83 (m, 8H), 4.72 – 3.35 (m, 12H), 2.94 – 2.25 (m, 14H), 1.77 – 1.52 (m, 3H), 1.35 – 1.24 (m, 8H).	m/z = 690.4 [M+H] ⁺

#	¹ H NMR Chromatography conditions, if applicable	LCMS
I-186	¹ H NMR (400 MHz, CD ₃ OD) δ 7.31 – 6.75 (m, 8H), 4.75 – 4.11 (m, 5H), 4.10 – 3.67 (m, 5H), 3.67 – 3.33 (m, 3H), 3.29 – 2.77 (m, 2H), 2.77 – 2.21 (m, 8H), 2.18 – 1.60 (m, 3H), 1.58 – 1.27 (m, 7H).	m/z = 661.4 [M+H] ⁺
I-187	¹ H NMR (400 MHz, CD ₃ OD) δ 8.30 – 6.72 (m, 9H), 4.68 – 3.36 (m, 12H), 2.84 – 2.24 (m, 11H), 1.87 – 1.20 (m, 11H).	m/z = 660.4 [M+H] ⁺
I-188	¹ H NMR (400 MHz, CD ₃ OD) δ 7.28 – 6.83 (m, 8H), 4.72 – 3.35 (m, 12H), 2.94 – 2.25 (m, 14H), 1.77 – 1.52 (m, 3H), 1.35 – 1.24 (m, 8H).	m/z = 674.5 [M+H] ⁺
I-189	¹ H NMR (400 MHz, CD ₃ OD) δ 7.27 – 5.78 (m, 10H), 4.69 – 4.19 (m, 4H), 3.91 – 3.35 (m, 8H), 2.75 – 2.21 (m, 11H), 1.76 – 1.49 (m, 3H), 1.34 – 1.24 (m, 8H).	m/z = 658.5 [M+H] ⁺
I-190	¹ H NMR (400 MHz, CD ₃ OD) δ 7.78 – 6.81 (m, 12H), 4.63 – 4.11 (m, 4H), 3.86 – 3.77 (m, 3H), 3.72 – 3.37 (m, 4H), 2.79 – 2.36 (m, 7H), 1.93 – 1.42 (m, 4H), 1.40 – 1.20 (m, 10H).	m/z = 712.4 [M+H] ⁺
I-191	¹ H NMR (400 MHz, CD ₃ OD) δ 7.74 – 6.77 (m, 12H), 4.65 – 4.07 (m, 4H), 3.99 – 3.33 (m, 8H), 2.80 – 2.35 (m, 11H), 1.92 – 1.43 (m, 3H), 1.41 – 1.08 (m, 8H).	m/z = 708.5 [M+H] ⁺
I-192	¹ H NMR (400 MHz, CD ₃ OD) δ 8.79 – 8.67 (m, 1H), 8.60 – 8.45 (m, 1H), 8.06 – 7.85 (m, 2H), 7.29 – 6.81 (m, 9H), 4.68 – 3.75 (m, 7H), 3.73 – 3.34 (m, 3H), 3.27 – 2.83 (m, 4H), 2.78 – 2.40 (m, 11H), 2.38 – 1.91 (m, 2H), 1.88 – 1.47 (m, 3H), 1.45 – 1.29 (m, 6H).	m/z = 698.5 [M+H] ⁺
I-193	¹ H NMR (400 MHz, CD ₃ OD) δ 8.10 – 7.70 (m, 1H), 7.29 – 6.80 (m, 8H), 4.74 – 4.16 (m, 4H), 3.88 – 3.79 (m, 3H), 3.71 – 3.34 (m, 4H), 3.28 – 2.83 (m, 1H), 2.81 – 2.34 (m, 11H), 1.86 – 1.37 (m, 4H), 1.35 – 1.20 (m, 7H).	m/z = 660.4 [M+H] ⁺
I-194	¹ H NMR (400 MHz, CD ₃ OD) δ 9.13 – 8.88 (m, 1H), 8.54 – 8.34 (m, 2H), 7.96 – 7.88 (m, 1H), 7.25 – 6.92 (m, 8H), 4.73 – 4.16 (m, 3H), 3.79 – 3.33 (m, 8H), 2.88 – 2.42 (m, 8H), 1.84 – 1.50 (m, 4H), 1.34 – 1.27 (m, 8H). First eluting diastereomer purified by Prep-TLC (6% MeOH/DCM). R _f = 0.45	m/z = 696.4 [M+H] ⁺
I-195	¹ H NMR (400 MHz, CD ₃ OD) δ 9.24 – 8.88 (m, 1H), 8.57 – 8.32 (m, 2H), 7.97 – 7.88 (m, 1H), 7.28 – 6.81 (m, 8H), 4.80 – 4.15 (m, 4H), 3.87 – 3.33 (m, 7H), 3.06 – 2.35 (m, 9H), 2.07 – 1.51 (m, 3H), 1.35 – 1.23 (m, 8H). Second eluting diastereomer purified by Prep-TLC (6% MeOH/DCM). R _f = 0.4	m/z = 696.4 [M+H] ⁺

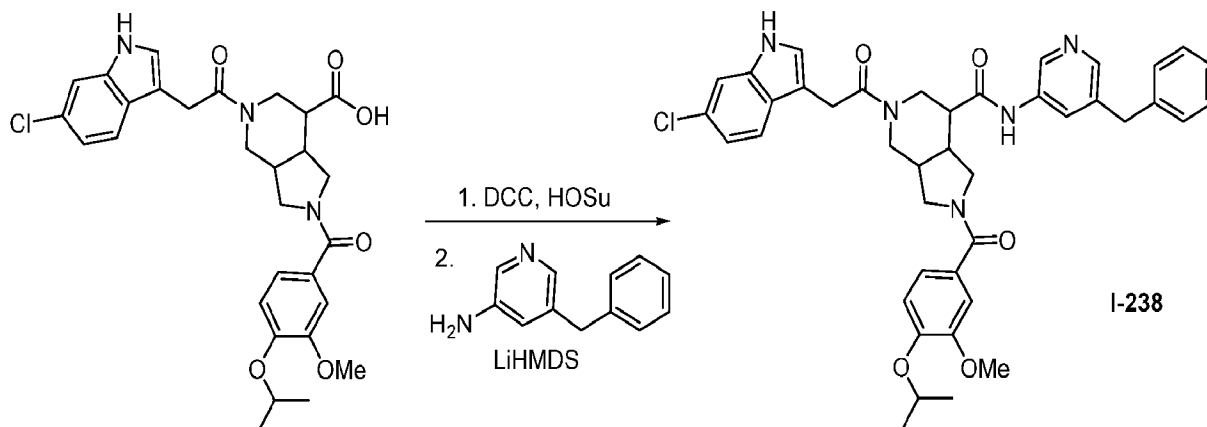
#	¹ H NMR Chromatography conditions, if applicable	LCMS
I-196	¹ H NMR (400 MHz, CD ₃ OD) δ 9.03 – 8.73 (m, 2H), 7.31 – 6.78 (m, 8H), 4.74 – 4.10 (m, 3H), 3.91 – 3.36 (m, 9H), 3.27 – 2.92 (m, 1H), 2.84 – 2.37 (m, 8H), 1.84 – 1.56 (m, 3H), 1.38 – 1.23 (m, 9H).	m/z = 691.3 [M+H] ⁺
I-197	¹ H NMR (400 MHz, CD ₃ OD) δ 7.30 – 6.49 (m, 9H), 4.66 – 4.14 (m, 3H), 3.89 – 3.56 (m, 6H), 3.52 – 3.33 (m, 2H), 2.81 – 2.54 (m, 7H), 1.84 – 1.48 (m, 3H), 1.39 – 1.21 (m, 11H).	m/z = 679.4 [M+H] ⁺
I-198	¹ H NMR (400 MHz, CD ₃ OD) δ 7.75 – 6.93 (m, 9H), 6.30 – 6.13 (m, 1H), 4.74 – 4.36 (m, 2H), 4.35 – 3.97 (m, 2H), 3.93 – 3.75 (m, 4H), 3.72 – 3.35 (m, 4H), 3.26 – 2.97 (m, 2H), 2.76 – 2.49 (m, 7H), 1.80 – 1.54 (m, 4H), 1.41 – 1.23 (m, 8H)	m/z = 659.5 [M+H] ⁺
I-199	¹ H NMR (400 MHz, CD ₃ OD) δ 8.43 – 6.43 (m, 12H), 4.74 – 3.33 (m, 12H), 3.25 – 2.34 (m, 8H), 2.04 – 1.47 (m, 3H), 1.45 – 1.19 (m, 8H).	m/z = 694.5 [M+H] ⁺
I-200	¹ H NMR (400 MHz, CD ₃ OD) δ 7.37 – 6.70 (m, 12H), 4.75 – 4.25 (m, 3H), 4.20 – 3.76 (m, 9H), 3.70 – 3.35 (m, 3H), 3.24 – 2.96 (m, 2H), 2.94 – 2.51 (m, 7H), 2.46 – 2.36 (m, 1H), 1.77 – 1.55 (m, 3H), 1.40 – 1.24 (m, 8H).	m/z = 738.5 [M+H] ⁺
I-201	¹ H NMR (400 MHz, CD ₃ OD) δ 7.50 – 6.73 (m, 12H), 4.80 – 3.90 (m, 4H), 3.88 – 3.47 (m, 4H), 3.69 – 3.35 (m, 3H), 3.28 – 2.49 (m, 9H), 2.44 – 2.29 (m, 4H), 1.91 – 1.45 (m, 4H), 1.42 – 1.23 (m, 8H).	m/z = 722.4 [M+H] ⁺
I-202	¹ H NMR (400 MHz, CD ₃ OD) δ 8.56 – 8.40 (m, 2H), 7.44 – 6.87 (m, 10H), 4.67 – 4.13 (m, 3H), 4.07 – 3.45 (m, 9H), 3.24 – 2.81 (m, 2H), 2.76 – 2.40 (m, 7H), 1.83 – 1.42 (m, 4H), 1.37 – 1.22 (m, 8H).	m/z = 670.4 [M+H] ⁺
I-203	¹ H NMR (400 MHz, CD ₃ OD) δ 7.91 – 6.65 (m, 12H), 4.77 – 4.06 (m, 3H), 4.04 – 3.34 (m, 9H), 3.29 – 2.72 (m, 3H), 2.71 – 2.21 (m, 7H), 1.63 (m, 3H), 1.40 – 1.23 (m, 8H).	m/z = 733.5 [M+H] ⁺
I-204	¹ H NMR (400 MHz, CD ₃ OD) δ 7.83 – 6.80 (m, 12H), 4.77 – 3.79 (m, 9H), 3.76 – 3.34 (m, 4H), 3.29 – 2.86 (m, 2H), 2.75 – 2.57 (m, 6H), 2.46 – 2.30 (m, 1H), 1.78 – 1.52 (m, 3H), 1.40 – 1.28 (m, 7H), 0.94 – 0.86 (m, 1H).	m/z = 743.4 [M+H] ⁺
I-205	¹ H NMR (400 MHz, CD ₃ OD) δ 7.88 – 6.35 (m, 11H), 4.75 – 3.39 (m, 12H), 3.27 – 2.50 (m, 9H), 2.44 – 2.20 (m, 1H), 1.82 – 1.21 (m, 11H).	m/z = 743.4 [M+H] ⁺
I-206	¹ H NMR (400 MHz, CD ₃ OD) δ 9.20 – 9.05 (m, 1H), 8.25 – 8.10 (m, 1H), 7.29 – 6.82 (m, 8H), 4.68 – 3.35 (m, 12H), 2.82 – 2.36 (m, 8H), 1.77 – 1.50 (m, 3H), 1.38 – 1.21 (m, 8H).	m/z = 662.4 [M+H] ⁺
I-207	¹ H NMR (400 MHz, CD ₃ OD) δ 7.30 – 6.80 (m, 8H), 4.68 – 3.74 (m, 11H), 3.72 – 3.36 (m, 5H), 3.23 – 2.30 (m, 9H), 1.88 – 1.52 (m, 7H), 1.37 – 1.23 (m, 8H).	m/z = 663.5 [M+H] ⁺

#	¹ H NMR Chromatography conditions, if applicable	LCMS
I-208	¹ H NMR (400 MHz, CD ₃ OD) δ 9.01 – 8.74 (m, 1H), 8.36 – 8.20 (m, 1H), 7.85 – 7.69 (m, 1H), 7.29 – 6.81 (m, 8H), 4.72 – 4.12 (m, 3H), 3.94 – 3.33 (m, 9H), 3.28 – 3.02 (m, 1H), 2.89 – 2.36 (m, 8H), 1.84 – 1.53 (m, 3H), 1.40 – 1.20 (m, 8H).	m/z = 681.4 [M+H] ⁺
I-209	¹ H NMR (400 MHz, CD ₃ OD) δ 8.04 – 7.86 (m, 1H), 7.70 – 7.40 (m, 2H), 7.29 – 6.82 (m, 8H), 4.83 – 4.10 (m, 5H), 4.04 – 3.34 (m, 9H), 3.28 – 2.92 (m, 2H), 2.80 – 2.36 (m, 7H), 1.83 – 1.55 (m, 3H), 1.42 – 1.19 (m, 7H).	m/z = 686.4 [M+H] ⁺
I-210	¹ H NMR (400 MHz, CD ₃ OD) δ 9.28 – 8.67 (m, 3H), 8.20 – 7.52 (m, 5H), 7.30 – 6.82 (m, 8H), 4.70 – 3.36 (m, 12H), 2.85 – 2.35 (m, 8H), 1.82 – 1.56 (m, 2H), 1.45 – 1.22 (m, 8H).	m/z = 732.5 [M+H] ⁺
I-211	¹ H NMR (400 MHz, CD ₃ OD) δ 8.69 – 8.44 (m, 2H), 7.30 – 6.82 (m, 8H), 4.74 – 3.34 (m, 12H), 3.27 – 2.98 (m, 1H), 2.87 – 2.33 (m, 11H), 1.86 – 1.58 (m, 3H), 1.37 – 1.23 (m, 7H).	m/z = 671.4 [M+H] ⁺
I-212	¹ H NMR (400 MHz, CD ₃ OD) δ 8.81 – 8.64 (m, 1H), 8.12 – 8.05 (m, 1H), 7.86 – 7.46 (m, 2H), 7.28 – 6.82 (m, 8H), 4.71 – 3.78 (m, 9H), 3.68 – 3.36 (m, 3H), 3.26 – 2.92 (m, 2H), 2.84 – 2.57 (m, 6H), 2.51 – 1.98 (m, 2H), 1.75 – 1.52 (m, 3H), 1.39 – 1.26 (m, 8H).	m/z = 709.4 [M+H] ⁺
I-213	¹ H NMR (400 MHz, CDCl ₃) δ 7.76 – 7.62 (m, 1H), 7.37 – 6.94 (m, 10H), 6.88 – 6.74 (m, 1H), 6.61 – 6.50 (m, 1H), 4.63 – 4.20 (m, 2H), 4.04 – 3.27 (m, 10H), 3.25 – 2.45 (m, 8H), 2.06 – 1.50 (m, 5H), 1.45 – 1.29 (m, 7H).	m/z = 694.5 [M+H] ⁺
I-214	¹ H NMR (400 MHz, CD ₃ OD) δ 8.59 – 6.76 (m, 11H), 4.72 – 3.39 (m, 12H), 3.21 – 2.33 (m, 11H), 1.83 – 1.52 (m, 3H), 1.42 – 1.21 (m, 10H).	m/z = 684.5 [M+H] ⁺
I-215	¹ H NMR (400 MHz, CD ₃ OD) δ 7.28 – 6.22 (m, 11H), 4.66 – 4.18 (m, 4H), 3.87 – 3.79 (m, 3H), 3.79 – 3.58 (m, 5H), 3.49 – 3.33 (m, 2H), 2.76 – 2.36 (m, 8H), 1.82 – 1.54 (m, 3H), 1.35 – 1.25 (m, 9H).	m/z = 658.4 [M+H] ⁺
I-216	¹ H NMR (400 MHz, CD ₃ OD) δ 7.87 – 7.68 (m, 1H), 7.35 – 6.82 (m, 9H), 4.73 – 4.46 (m, 2H), 4.43 – 4.20 (m, 1H), 4.19 – 3.92 (m, 4H), 3.87 – 3.34 (m, 8H), 3.27 – 2.38 (m, 9H), 1.77 – 1.47 (m, 3H), 1.37 – 1.25 (m, 8H).	m/z = 687.4 [M+H] ⁺
I-217	¹ H NMR (400 MHz, CD ₃ OD) δ 7.28 – 6.67 (m, 12H), 4.70 – 3.33 (m, 13H), 3.27 – 2.93 (m, 2H), 2.79 – 2.36 (m, 10H), 1.79 – 1.52 (m, 3H), 1.39 – 1.23 (m, 8H).	m/z = 722.5 [M+H] ⁺
I-218	¹ H NMR (400 MHz, CD ₃ OD) δ 7.96 – 6.45 (m, 13H), 4.72 – 3.36 (m, 16H), 3.26 – 2.15 (m, 13H), 1.81 – 1.17 (m, 11H).	m/z = 766.5 [M+H] ⁺
I-219	¹ H NMR (400 MHz, CD ₃ OD) δ 7.47 – 6.70 (m, 12H), 4.75 – 3.39 (m, 11H), 3.27 – 2.33 (m, 13H), 1.82 – 1.52 (m, 3H), 1.45 – 1.18 (m, 9H).	m/z = 722.5 [M+H] ⁺

#	¹ H NMR Chromatography conditions, if applicable	LCMS
I-220	¹ H NMR (400 MHz, CD ₃ OD) δ 7.74 – 6.57 (m, 12H), 4.65 – 3.97 (m, 4H), 3.96 – 3.65 (m, 6H), 3.63 – 3.36 (m, 2H), 3.24 – 2.77 (m, 2H), 2.76 – 2.36 (m, 7H), 2.33 – 1.93 (m, 1H), 1.64 (m, 4H), 1.35 – 1.19 (m, 7H).	m/z = 742.3 [M+H] ⁺
I-221	¹ H NMR (400 MHz, CD ₃ OD) δ 7.35 – 6.85 (m, 12H), 4.72 – 3.35 (m, 12H), 3.27 – 2.82 (m, 2H), 2.81 – 2.24 (m, 8H), 1.89 – 1.42 (m, 4H), 1.35 – 1.22 (m, 7H).	m/z = 742.3 [M+H] ⁺
I-222	¹ H NMR (400 MHz, CD ₃ OD) δ 7.63 – 6.76 (m, 12H), 4.75 – 3.37 (m, 11H), 3.30 – 3.00 (m, 2H), 2.99 – 2.24 (m, 8H), 2.01 – 1.46 (m, 4H), 1.43 – 1.19 (m, 8H).	m/z = 742.3 [M+H] ⁺
I-223	¹ H NMR (400 MHz, CD ₃ OD) δ 7.68 – 6.69 (m, 13H), 4.73 – 3.76 (m, 9H), 3.75 – 3.32 (m, 3H), 3.26 – 2.90 (m, 2H), 2.77 – 2.45 (m, 6H), 2.43 – 2.34 (m, 1H), 2.32 – 1.85 (m, 1H), 1.79 – 1.38 (m, 4H), 1.38 – 1.22 (m, 7H).	m/z = 708.4 [M+H] ⁺
I-224	¹ H NMR (400 MHz, CD ₃ OD) δ 8.53 – 8.33 (m, 2H), 7.81 – 7.66 (m, 1H), 7.47 – 6.83 (m, 9H), 4.75 – 3.80 (m, 9H), 3.79 – 3.38 (m, 4H), 2.77 – 2.54 (m, 7H), 2.46 – 2.34 (m, 1H), 1.73 – 1.44 (m, 4H), 1.39 – 1.25 (m, 8H).	m/z = 670.4 [M+H] ⁺
I-225	¹ H NMR (400 MHz, CD ₃ OD) δ 7.67 – 6.64 (m, 12H), 4.77 – 3.79 (m, 9H), 3.77 – 3.63 (m, 3H), 3.62 – 3.36 (m, 3H), 3.27 – 3.02 (m, 2H), 2.97 – 2.79 (m, 1H), 2.77 – 2.55 (m, 6H), 2.44 – 2.37 (m, 1H), 2.24 – 2.00 (m, 1H), 1.86 – 1.50 (m, 4H), 1.41 – 1.26 (m, 8H).	m/z = 756.5 [M+H] ⁺
I-226	¹ H NMR (400 MHz, CD ₃ OD) δ 7.74 – 6.31 (m, 12H), 4.77 – 4.11 (m, 4H), 4.08 – 3.38 (m, 6H), 3.26 – 2.81 (m, 2H), 2.81 – 2.07 (m, 9H), 2.07 – 1.55 (m, 3H), 1.54 – 1.16 (m, 12H).	m/z = 756.5 [M+H] ⁺
I-227	¹ H NMR (400 MHz, CD ₃ OD) δ 7.97 – 6.38 (m, 11H), 4.75 – 3.90 (m, 4H), 3.87 – 3.40 (m, 7H), 3.20 – 2.52 (m, 8H), 2.46 – 1.51 (m, 5H), 1.42 – 1.17 (m, 10H).	m/z = 776.4 [M+H] ⁺
I-228	¹ H NMR (400 MHz, CD ₃ OD) δ 7.64 – 6.79 (m, 12H), 4.66 – 4.08 (m, 3H), 3.89 – 3.34 (m, 8H), 3.29 – 2.34 (m, 12H), 1.85 – 1.46 (m, 3H), 1.43 – 1.17 (m, 8H).	m/z = 708.4 [M+H] ⁺
I-229	¹ H NMR (400 MHz, CD ₃ OD) δ 7.31 – 6.54 (m, 12H), 4.74 – 3.97 (m, 4H), 3.96 – 3.69 (m, 8H), 3.67 – 3.36 (m, 3H), 3.27 – 2.78 (m, 3H), 2.79 – 1.91 (m, 8H), 1.75 – 1.43 (m, 3H), 1.39 – 1.23 (m, 7H).	m/z = 738.4 [M+H] ⁺
I-230	¹ H NMR (400 MHz, CD ₃ OD) δ 8.65 – 8.31 (m, 3H), 7.28 – 6.88 (m, 8H), 4.73 – 3.35 (m, 14H), 3.25 – 2.33 (m, 10H), 1.80 – 1.54 (m, 3H), 1.38 – 1.26 (m, 8H).	m/z = 671.5 [M+H] ⁺
I-231	¹ H NMR (400 MHz, CD ₃ OD) δ 7.59 – 6.69 (m, 12H), 4.83 – 3.38 (m, 12H), 3.29 – 2.21 (m, 14H), 2.02 – 1.58 (m, 3H), 1.49 – 1.21 (m, 8H).	m/z = 722.5 [M+H] ⁺

#	¹ H NMR Chromatography conditions, if applicable	LCMS
I-232	¹ H NMR (400 MHz, CD ₃ OD) δ 8.41 (m, 1H), 7.27 – 6.84 (m, 9H), 4.68 – 4.19 (m, 4H), 3.87 – 3.77 (m, 4H), 3.70 – 3.57 (m, 2H), 2.78 – 2.58 (m, 7H), 2.48 – 2.36 (m, 2H), 1.74 – 1.57 (m, 2H), 1.36 – 1.22 (m, 9H). First eluting diastereomer purified by prep-HPLC on an Agilent 10 Prep-C18 column (21.2 mm I.D. × 25 cm, 10 μm), using H ₂ O/ACN 0.1%TFA at a flow rate of 20 mL/min (wave length 214 nm). Rt = 10.1 min	m/z = 680.4 [M+H] ⁺
I-233	¹ H NMR (400 MHz, CD ₃ OD) δ 8.48 – 8.33 (m, 1H), 7.32 – 6.93 (m, 9H), 4.79 – 4.15 (m, 4H), 3.86 – 3.80 (m, 3H), 3.69 – 3.57 (m, 3H), 3.50 – 3.42 (m, 1H), 2.81 – 2.55 (m, 8H), 1.78 – 1.58 (m, 4H), 1.36 – 1.28 (m, 8H). Second eluting diastereomer purified by prep-HPLC on an Agilent 10 Prep-C18 column (21.2 mm I.D. × 25 cm, 10 μm), using H ₂ O/ACN 0.1%TFA at a flow rate of 20 mL/min (wave length 214 nm). Rt = 11.8 min	m/z = 680.4 [M+H] ⁺
I-234	¹ H NMR (400 MHz, CD ₃ OD) δ 7.57 – 6.47 (m, 12H), 4.75 – 3.72 (m, 11H), 3.66 – 3.33 (m, 3H), 3.23 – 2.68 (m, 5H), 2.66 – 2.36 (m, 5H), 2.01 – 1.53 (m, 4H), 1.45 – 1.20 (m, 9H), 0.62 – 0.55 (m, 2H), 0.37 – 0.28 (m, 2H).	m/z = 778.5 [M+H] ⁺
I-235	¹ H NMR (400 MHz, CD ₃ OD) δ 7.61 – 6.49 (m, 12H), 4.65 – 4.23 (m, 2H), 4.20 – 3.74 (m, 9H), 3.73 – 3.34 (m, 3H), 3.21 – 2.85 (m, 2H), 2.82 – 2.15 (m, 8H), 2.07 – 1.44 (m, 4H), 1.40 – 1.23 (m, 8H).	m/z = 738.4 [M+H] ⁺
I-236	¹ H NMR (400 MHz, CD ₃ OD) δ 7.83 – 6.37 (m, 13H), 4.72 – 4.14 (m, 3H), 3.92 – 3.74 (m, 3H), 3.67 – 3.42 (m, 1H), 3.27 – 2.22 (m, 11H), 1.85 – 1.27 (m, 11H), 1.27 – 0.72 (m, 6H).	m/z = 734.5 [M+H] ⁺
I-237	¹ H NMR (400 MHz, CD ₃ OD) δ 7.99 – 6.52 (m, 12H), 4.79 – 3.78 (m, 9H), 3.74 – 3.35 (m, 4H), 3.26 – 2.14 (m, 11H), 1.77 – 1.53 (m, 3H), 1.33 (m, 6H).	m/z = 786.3 [M+H] ⁺

Synthesis of N-(5-benzylpyridin-3-yl)-5-(2-(6-chloro-1H-indol-3-yl)acetyl)-2-(4-isopropoxy-3-methoxybenzoyl)octahydro-1H-pyrrolo[3,4-c]pyridine-7-carboxamide **I-238**



[00505] Step 1: To a solution of 5-(2-(6-chloro-1H-indol-3-yl)acetyl)-2-(4-isopropoxy-3-methoxybenzoyl)octahydro-1H-pyrrolo[3,4-c]pyridine-7-carboxylic acid (100 mg, 0.18 mmol; see synthesis of **I-88**) in DCM (3 mL) was added DCC (31.0 mg, 0.27 mmol) and HOSu (42 mg, 0.36 mmol). The mixture was stirred for 8 h. The resulting mixture was filtered and concentrated to afford the active ester as a white solid. LCMS $m/z = 651.2$ $[M+H]^+$.

[00506] Step 2: To a solution of 5-benzylpyridin-3-amine (50 mg, 0.077 mmol) in THF (5 mL) was added LiHMDS (2M in THF, 0.153 mmol) dropwise at 0°C. After stirring for 30 min, the active ester was added to the mixture and stirred **I-238** (5 mg, 10%) as a white solid. LCMS $m/z = 720.3$ $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 9.20 – 8.89 (m, 1H), 8.46 – 8.30 (m, 1H), 8.20 – 7.80 (m, 1H), 7.63 – 6.72 (m, 12H), 4.77 – 4.42 (m, 1H), 4.38 – 4.05 (m, 3H), 4.02 – 3.88 (m, 2H), 3.87 – 3.55 (m, 6H), 3.55 – 3.33 (m, 2H), 3.25 – 3.09 (m, 1H), 2.96 – 1.99 (m, 4H), 1.46 – 1.20 (m, 8H).

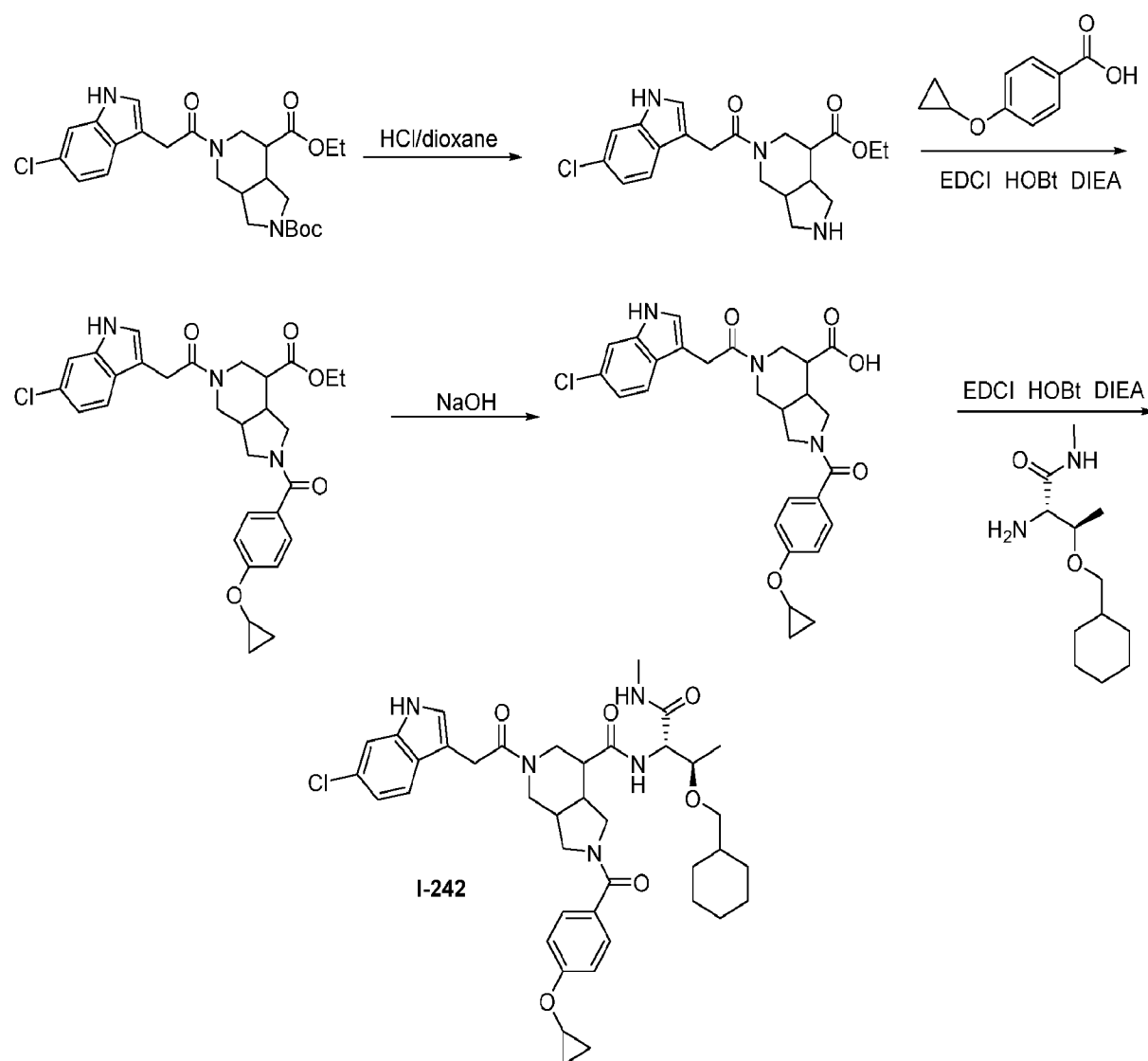
[00507] The compounds listed in **Table 5** were synthesized using analogous methods to those shown for **I-238**, using the appropriate commercially available reagents and/or intermediates. Final examples were obtained as a mixture of diastereomers.

Table 5. Compounds made by a method analogous to I-229

#	^1H NMR	LCMS
I-239	^1H NMR (400 MHz, CD_3OD) δ 9.07 – 6.28 (m, 15H), 4.79 – 4.19 (m, 3H), 4.19 – 3.35 (m, 11H), 3.27 – 3.00 (m, 1H), 2.96 – 1.99 (m, 4H), 1.45 – 1.18 (m, 7H).	$m/z = 720.3$ $[M+H]^+$

#	¹ H NMR	LCMS
I-240	¹ H NMR (400 MHz, CD ₃ OD) δ 8.51 – 8.29 (m, 1H), 8.08 – 7.68 (m, 2H), 7.57 – 7.26 (m, 4H), 7.24 – 6.69 (m, 8H), 4.81 – 4.29 (m, 2H), 4.27 – 3.70 (m, 7H), 3.60 – 3.47 (m, 2H), 3.27 – 2.24 (m, 5H), 1.42 – 1.25 (m, 7H).	m/z = 722.3 [M+H] ⁺
I-241	¹ H NMR (400 MHz, CD ₃ OD) δ 9.25 – 8.90 (m, 1H), 8.32 – 8.06 (m, 1H), 7.72 – 6.75 (m, 13H), 4.80 – 4.23 (m, 4H), 4.06 – 3.35 (m, 10H), 3.23 – 3.03 (m, 1H), 2.90 – 2.61 (m, 2H), 2.57 – 2.34 (m, 1H), 1.68 – 0.98 (m, 8H).	m/z = 720.4 [M+H] ⁺

Synthesis of 5-(2-(6-chloro-1H-indol-3-yl)acetyl)-N-((2S,3R)-3-(cyclohexylmethoxy)-1-(methylamino)-1-oxobutan-2-yl)-2-(4-cyclopropoxybenzoyl)octahydro-1H-pyrrolo[3,4-c]pyridine-7-carboxamide I-242



[00508] *Step 1: ethyl 5-(2-(6-chloro-1H-indol-3-yl)acetyl)octahydro-1H-pyrrolo[3,4-c]pyridine-7-carboxylate*

[00509] To a solution of 2-(tert-butyl) 7-ethyl 5-(2-(6-chloro-1H-indol-3-yl)acetyl)octahydro-2H-pyrrolo[3,4-c]pyridine-2,7-dicarboxylate (500 mg, 1.02 mmol; see synthesis of **I-1**) in DCM (10 mL) was added HCl (4M in dioxane, 10 mL). The resulting mixture was stirred for 2 h. The solvent was removed to afford the product (500 mg, quant.). LCMS $m/z = 390.2$ $[M+H]^+$.

[00510] *Step 2: ethyl 5-(2-(6-chloro-1H-indol-3-yl)acetyl)-2-(4-cyclopropoxybenzoyl)octahydro-1H-pyrrolo[3,4-c]pyridine-7-carboxylate*

[00511] In a similar manner to the procedure reported in **Step 1** of the preparation of **I-1**, the coupling of ethyl 5-(2-(6-chloro-1H-indol-3-yl)acetyl)octahydro-1H-pyrrolo[3,4-c]pyridine-7-carboxylate and 4-cyclopropoxybenzoic acid gave the product (413 mg, 76%) after column chromatography (2.5% MeOH/DCM) as a white solid.

[00512] *Step 3: 5-(2-(6-chloro-1H-indol-3-yl)acetyl)-2-(4-cyclopropoxybenzoyl)octahydro-1H-pyrrolo[3,4-c]pyridine-7-carboxylic acid*

[00513] To a solution of ethyl 5-(2-(6-chloro-1H-indol-3-yl)acetyl)-2-(4-cyclopropoxybenzoyl)octahydro-1H-pyrrolo[3,4-c]pyridine-7-carboxylate (413 mg, 0.753 mmol) in MeOH (5 mL) was added aqueous NaOH (1M, 3 mL). The resulting mixture was stirred for 3 h. The solvent was removed under vacuum, the residue diluted with water and the pH adjusted to ~1 by addition of 1M HCl. The aqueous layer was extracted with EtOAc three times. The combined organic layers were washed with water, brine and dried over Na₂SO₄. Removal of the solvent afforded the product (381.0 mg, 97%) as a white solid. LCMS $m/z = 522.3$ $[M+H]^+$.

[00514] *Step 4: 5-(2-(6-chloro-1H-indol-3-yl)acetyl)-N-((2S,3R)-3-(cyclohexylmethoxy)-1-(methylamino)-1-oxobutan-2-yl)-2-(4-cyclopropoxybenzoyl)octahydro-1H-pyrrolo[3,4-c]pyridine-7-carboxamide*

[00515] In a similar manner to the procedure in **Step 1** of the preparation of **I-1**, the coupling of 5-(2-(6-chloro-1H-indol-3-yl)acetyl)-2-(4-cyclopropoxybenzoyl)octahydro-1H-pyrrolo[3,4-c]pyridine-7-carboxylic acid and (2S,3R)-2-amino-3-(cyclohexylmethoxy)-N-methylbutanamide gave **I-242** (40 mg, 51%) after column chromatography (2.8% MeOH/DCM) as a white solid. LCMS $m/z = 732.4$ $[M+H]^+$; ¹H NMR (400 MHz, CD₃OD) δ 8.06 – 6.94 (m, 8H), 4.68 – 3.35 (m,

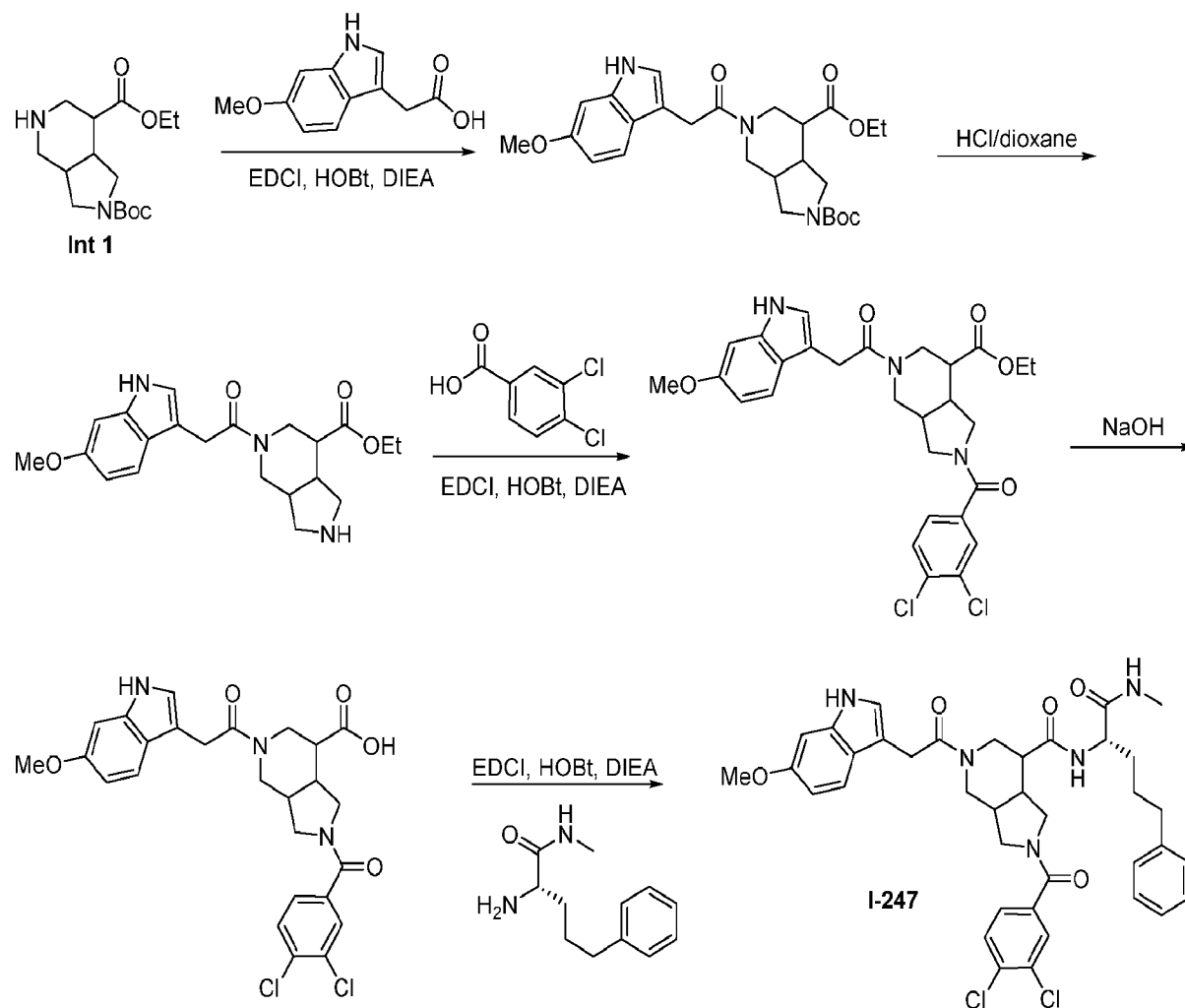
10H), 3.27 – 2.07 (m, 9H), 1.80 – 1.58 (m, 5H), 1.57 – 1.39 (m, 1H), 1.38 – 1.06 (m, 7H), 1.04 – 0.72 (m, 7H).

[00516] The compounds listed in **Table 6** were synthesized using analogous methods to those shown for **I-242**, using the appropriate commercially available reagents and/or intermediates. Final examples were obtained as a mixture of diastereomers.

Table 6. Compounds made by a method analogous to I-242

#	¹ H NMR	LCMS
I-243	¹ H NMR (400 MHz, CD ₃ OD) δ 7.65 – 6.93 (m, 12H), 4.82 – 4.26 (m, 5H), 4.25 – 3.33 (m, 8H), 3.27 – 2.73 (m, 2H), 2.71 – 2.37 (m, 2H), 1.37 – 1.28 (m, 2H), 1.20 – 1.15 (m, 4H), 1.06 – 0.83 (m, 2H), 0.83 – 0.64 (m, 3H).	m/z = 730.4 [M+H] ⁺
I-244	¹ H NMR (400 MHz, CD ₃ OD) δ 7.74 – 6.87 (m, 12H), 4.73 – 3.34 (m, 13H), 3.28 – 1.98 (m, 6H), 1.27 – 1.14 (m, 2H), 0.92 – 0.63 (m, 5H).	m/z = 730.4 [M+H] ⁺
I-245	¹ H NMR (400 MHz, CD ₃ OD) δ 7.68 – 6.89 (m, 12H), 4.69 – 4.27 (m, 4H), 4.21 – 3.35 (m, 8H), 3.26 – 1.97 (m, 6H), 1.37 – 0.61 (m, 7H).	m/z = 730.4 [M+H] ⁺
I-246	¹ H NMR (400 MHz, CD ₃ OD) δ 7.67 – 6.88 (m, 12H), 4.79 – 3.35 (m, 12H), 3.26 – 1.88 (m, 6H), 1.28 – 0.61 (m, 7H)	m/z = 730.4 [M+H] ⁺

Synthesis of 2-(3,4-dichlorobenzoyl)-5-(2-(6-methoxy-1H-indol-3-yl)acetyl)-N-((S)-1-(methylamino)-1-oxo-5-phenylpentan-2-yl)octahydro-1H-pyrrolo[3,4-c]pyridine-7-carboxamide I-247



[00517] Step 1: 2-(tert-butyl) 7-ethyl 5-(2-(6-methoxy-1H-indol-3-yl)acetyl)octahydro-2H-pyrrolo[3,4-c]pyridine-2,7-dicarboxylate

[00518] To a solution of **Int-1** (400 mg, 1.34 mmol) in DMA (10 mL) was added 2-(6-methoxy-1H-indol-3-yl)acetic acid (330 mg, 1.61 mmol), EDCI (385 mg, 2.01 mmol), HOBT (217 mg, 1.61 mmol) and DIPEA (520 mg, 4.02 mmol). The resulting mixture was stirred overnight. Water was added and the mixture was extracted with EtOAc three times. The combined organic layers were washed with water, brine and dried over Na₂SO₄. The solvent was then removed and the crude purified by column chromatography (2% MeOH/DCM) to afford the product (410 mg, 63%) as a white solid. LCMS *m/z* = 486 [M+H]⁺; ¹H NMR (400 MHz, CD₃OD) δ 7.46 (dd, *J* = 21.3, 8.6 Hz,

1H), 7.07 – 6.99 (m, 1H), 6.92 – 6.85 (m, 1H), 6.69 (td, J = 8.5, 3.9 Hz, 1H), 4.60 (s, 1H), 4.31 (dt, J = 16.2, 12.8 Hz, 1H), 4.20 – 3.94 (m, 3H), 3.80 (d, J = 4.9 Hz, 3H), 3.73 (t, J = 13.9 Hz, 1H), 3.31 (dq, J = 4.2, 2.9, 2.2 Hz, 3H), 3.05 (s, 3H), 2.92 (s, 3H), 1.45 – 1.36 (m, 9H), 1.28 – 1.17 (m, 3H).

[00519] **Step 2: ethyl 5-(2-(6-methoxy-1H-indol-3-yl)acetyl)octahydro-1H-pyrrolo[3,4-c]pyridine-7-carboxylate hydrochloride** To a solution of 2-(tert-butyl) 7-ethyl 5-(2-(6-methoxy-1H-indol-3-yl)acetyl)octahydro-2H-pyrrolo[3,4-c]pyridine-2,7-dicarboxylate (410 mg, 0.84 mmol) in DCM (3 mL) was added HCl (4M in dioxane, 3 mL). The resulting mixture was stirred for 3 h. The solvent was removed to afford the target compound (443 mg, quant.). LCMS m/z = 386 [M+H]⁺.

[00520] **Step 3: ethyl 2-(3,4-dichlorobenzoyl)-5-(2-(6-methoxy-1H-indol-3-yl)acetyl)octahydro-1H-pyrrolo[3,4-c]pyridine-7-carboxylate**

[00521] In a similar manner to the procedure in **Step 1**, the coupling of ethyl 5-(2-(6-methoxy-1H-indol-3-yl)acetyl)octahydro-1H-pyrrolo[3,4-c]pyridine-7-carboxylate hydrochloride and 3,4-dichlorobenzoic acid gave the desired product (86 mg, 26%) after column chromatography (2% MeOH/DCM) as a white solid. LCMS m/z = 558 [M+H]⁺; ¹H NMR (400 MHz, CD₃OD) δ 8.30 – 6.46 (m, 7H), 4.54 – 4.08 (m, 1H), 4.08 – 3.83 (m, 1H), 3.82 – 3.61 (m, 4H), 3.61 – 3.34 (m, 2H), 3.28 – 3.12 (m, 1H), 3.12 – 2.88 (m, 1H), 2.81 – 2.32 (m, 2H), 2.30 – 1.19 (m, 6H), 1.18 – 0.61 (m, 3H).

[00522] **Step 4: 2-(3,4-dichlorobenzoyl)-5-(2-(6-methoxy-1H-indol-3-yl)acetyl)octahydro-1H-pyrrolo[3,4-c]pyridine-7-carboxylic acid** To a solution of ethyl 2-(3,4-dichlorobenzoyl)-5-(2-(6-methoxy-1H-indol-3-yl)acetyl)octahydro-1H-pyrrolo[3,4-c]pyridine-7-carboxylate (86 mg, 0.15 mmol) in MeOH (3 mL) was added aqueous NaOH (1M, 3 mL). The mixture was stirred at room temperature for 5 h then the solvent was removed under vacuum. The residue obtained was diluted with water and the pH adjusted to ~1 by addition of 1M HCl. The aqueous layer was extracted with EtOAc three times and the combined organic layers were washed with water, brine and dried over Na₂SO₄. Removal of the solvent afforded the product (48 mg, 59%) as a white solid. LCMS m/z = 530 [M+H]⁺.

[00523] **Step 5: 2-(3,4-dichlorobenzoyl)-5-(2-(6-methoxy-1H-indol-3-yl)acetyl)-N-((S)-1-(methylamino)-1-oxo-5-phenylpentan-2-yl)octahydro-1H-pyrrolo[3,4-c]pyridine-7-**

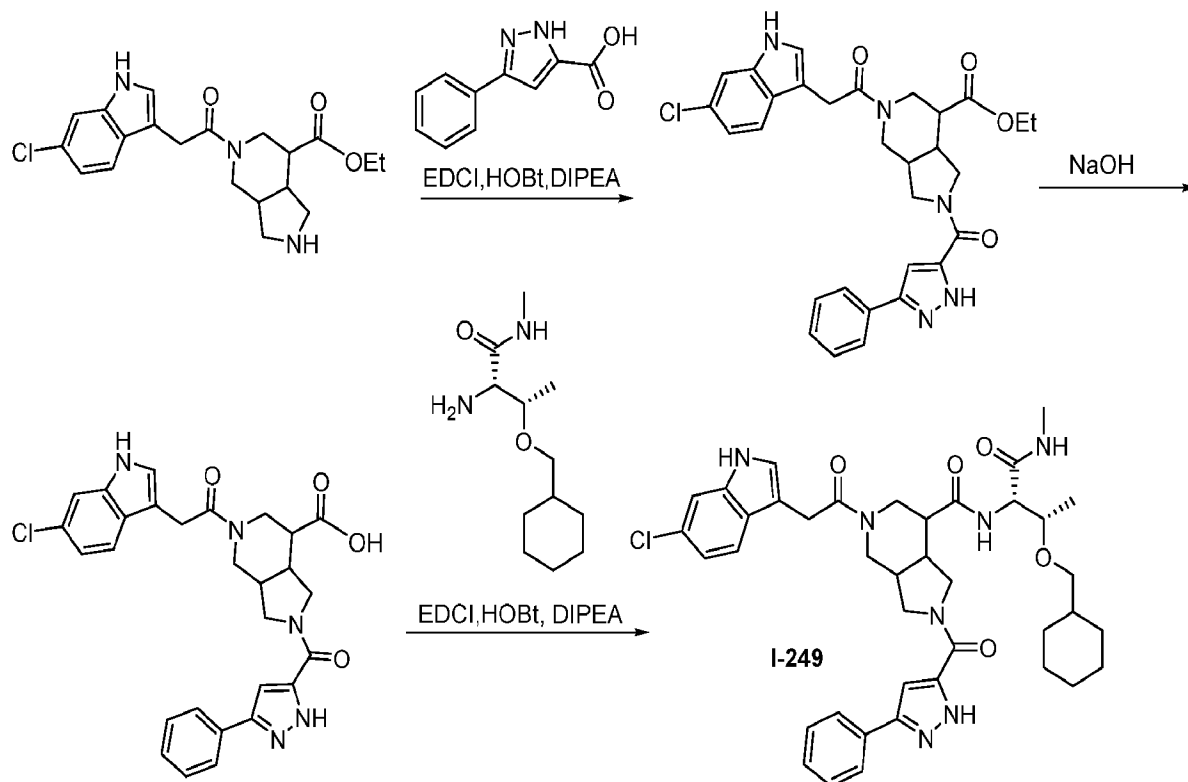
carboxamide In a similar manner to the procedure in **Step 1**, the coupling of 2-(3,4-dichlorobenzoyl)-5-(2-(6-methoxy-1H-indol-3-yl)acetyl)octahydro-1H-pyrrolo[3,4-c]pyridine-7-carboxylic acid and (S)-2-amino-N-methyl-5-phenylpentanamide gave **I-247** (10 mg, 15%) after column chromatography (2% MeOH/DCM) as a white solid. LC-MS $m/z = 718.3$ $[M+H]^+$; 1H NMR (400 MHz, CD_3OD) δ 7.77 – 6.60 (m, 12H), 4.66 – 4.01 (m, 3H), 4.01 – 3.70 (m, 5H), 3.69 – 3.44 (m, 2H), 3.43 – 3.33 (m, 1H), 3.29 – 2.14 (m, 11H), 2.06 – 1.31 (m, 5H).

[00524] The compounds listed in **Table 7** were synthesized using analogous methods to those shown for **I-247**, using the appropriate commercially available reagents and/or intermediates. Final examples were obtained as a mixture of diastereomers.

Table 7. Compounds made by a method analogous to I-247

Example	1H NMR	LCMS
I-248	1H NMR (400 MHz, CD_3OD) δ 8.56 – 6.39 (m, 12H), 4.60 – 4.20 (m, 2H), 4.19 – 3.98 (m, 1H), 3.98 – 3.64 (m, 5H), 3.62 – 3.36 (m, 2H), 3.31 – 2.78 (m, 4H), 2.76 – 2.60 (m, 5H), 2.57 – 2.36 (m, 2H), 2.03 – 1.33 (m, 5H), 1.25 – 0.74 (m, 1H).	$m/z = 751.2$ $[M+H]^+$

Synthesis of 5-(2-(6-chloro-1H-indol-3-yl)acetyl)-N-((2S,3S)-3-(cyclohexylmethoxy)-1-(methylamino)-1-oxobutan-2-yl)-2-(3-phenyl-1H-pyrazole-5-carbonyl)octahydro-1H-pyrrolo[3,4-c]pyridine-7-carboxamide I-249



[00525] Step 1: ethyl 5-(2-(6-chloro-1H-indol-3-yl)acetyl)-2-(3-phenyl-1H-pyrazole-5-carbonyl)octahydro-1H-pyrrolo[3,4-c]pyridine-7-carboxylate

[00526] To a solution of ethyl 5-(2-(6-chloro-1H-indol-3-yl)acetyl)octahydro-1H-pyrrolo[3,4-c]pyridine-7-carboxylate (358 mg, 0.92 mmol; see synthesis of **I-242**) in DMF (5.0 mL) was added 3-phenyl-1H-pyrazole-5-carboxylic acid (207 mg, 1.1 mmol), EDCI (264 mg, 1.38 mmol), HOBT (186 mg, 1.38 mmol) and DIPEA (593 mg, 4.59 mmol). The resulting mixture was stirred for 14 h. Water was then added and the aqueous extracted with EtOAc three times. The combined organic layers were washed with water and brine and dried over Na₂SO₄. The solvent was removed and the crude purified by column chromatography (2% MeOH/DCM) to give ethyl 5-(2-(6-chloro-1H-indol-3-yl)acetyl)-2-(3-phenyl-1H-pyrazole-5-carbonyl)octahydro-1H-pyrrolo[3,4-c]pyridine-7-carboxylate (350 mg, 68%) as a yellow solid.

[00527] Step 2: 5-(2-(6-chloro-1H-indol-3-yl)acetyl)-2-(3-phenyl-1H-pyrazole-5-carbonyl)octahydro-1H-pyrrolo[3,4-c]pyridine-7-carboxylic acid

[00528] To the solution of ethyl 5-(2-(6-chloro-1H-indol-3-yl)acetyl)-2-(3-phenyl-1H-pyrazole-5-carbonyl)octahydro-1H-pyrrolo[3,4-c]pyridine-7-carboxylate (350 mg, 0.62 mmol) in a mixture of THF and H₂O (5.0 mL/1.0 mL) was added NaOH (75 mg, 1.87 mmol) and the solution was stirred for 4 h. The pH was adjusted to 2 by addition of 1N HCl then concentrated to give the product (450 mg, quant.) as a white solid. LCMS m/z = 532.1 [M+H]⁺.

[00529] *Step 3: 5-(2-(6-chloro-1H-indol-3-yl)acetyl)-N-((2S,3S)-3-(cyclohexylmethoxy)-1-(methylamino)-1-oxobutan-2-yl)-2-(3-phenyl-1H-pyrazole-5-carbonyl)octahydro-1H-pyrrolo[3,4-c]pyridine-7-carboxamide*

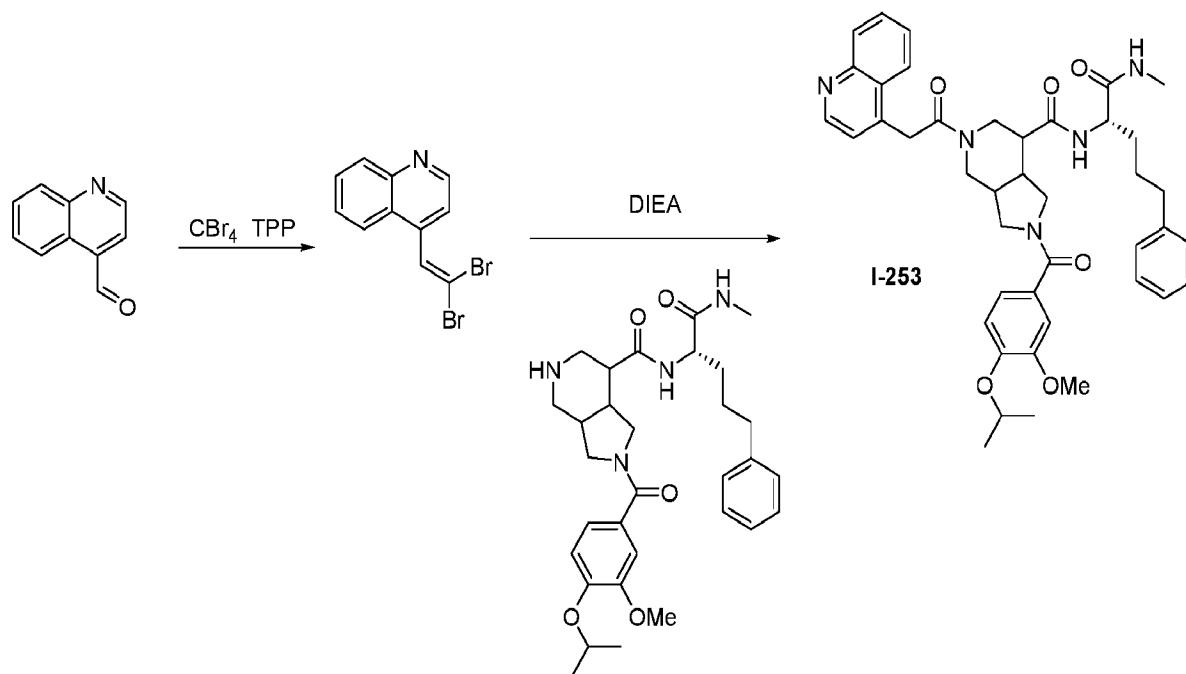
[00530] In a similar manner reported for synthesis of the product of **Step 1**, the coupling of 5-(2-(6-chloro-1H-indol-3-yl)acetyl)-2-(3-phenyl-1H-pyrazole-5-carbonyl)octahydro-1H-pyrrolo[3,4-c]pyridine-7-carboxylic acid and (2S,3S)-2-amino-3-(cyclohexylmethoxy)-N-methylbutanamide afforded **I-249** (20 mg, 28%) as a white solid after prep-TLC (6% MeOH/DCM). LCMS m/z = 742.3 [M+H]⁺; ¹H NMR (400 MHz, CD₃OD) δ 8.00 – 6.80 (m, 10H), 4.65 – 3.40 (m, 11H), 3.25 – 2.46 (m, 9H), 1.79 – 1.54 (m, 5H), 1.26 – 0.73 (m, 10H).

[00531] The compounds listed in **Table 8** were synthesized using analogous methods to those shown for **I-249**, using the appropriate commercially available reagents and/or intermediates. Final examples were obtained as a mixture of diastereomers.

Table 8. Compounds made by a method analogous to I-249

Example	¹ H NMR Chromatography conditions, if applicable	LCMS
I-250	¹ H NMR (400 MHz, CD ₃ OD) δ 8.07 – 6.74 (m, 15H), 4.71 – 3.45 (m, 13H), 3.29 – 2.03 (m, 9H), 1.48 – 1.37 (m, 1H), 1.29 – 1.03 (m, 3H)	m/z = 736.5 [M+H] ⁺
I-251	¹ H NMR (400 MHz, CD ₃ OD) δ 8.00 – 6.73 (m, 10H), 4.67 – 3.42 (m, 11H), 3.24 – 2.21 (m, 10H), 1.82 – 1.39 (m, 6H), 1.22 – 0.83 (m, 7H).	m/z = 742.4 [M+H] ⁺
I-252	¹ H NMR (400 MHz, CD ₃ OD) δ 7.91 – 6.73 (m, 15H), 4.69 – 4.33 (m, 4H), 4.28 – 3.72 (m, 6H), 3.70 – 3.47 (m, 2H), 3.23 – 2.74 (m, 3H), 2.71 – 2.44 (m, 4H), 2.44 – 1.85 (m, 1H), 1.25 – 0.83 (m, 4H).	m/z = 736.5 [M+H] ⁺

Synthesis of 2-(4-isopropoxy-3-methoxybenzoyl)-N-((S)-1-(methylamino)-1-oxo-5-phenylpentan-2-yl)-5-(2-(quinolin-4-yl)acetyl)octahydro-1H-pyrrolo[3,4-c]pyridine-7-carboxamide I-253



[00532] Step 1: 4-(2,2-dibromovinyl)quinoline

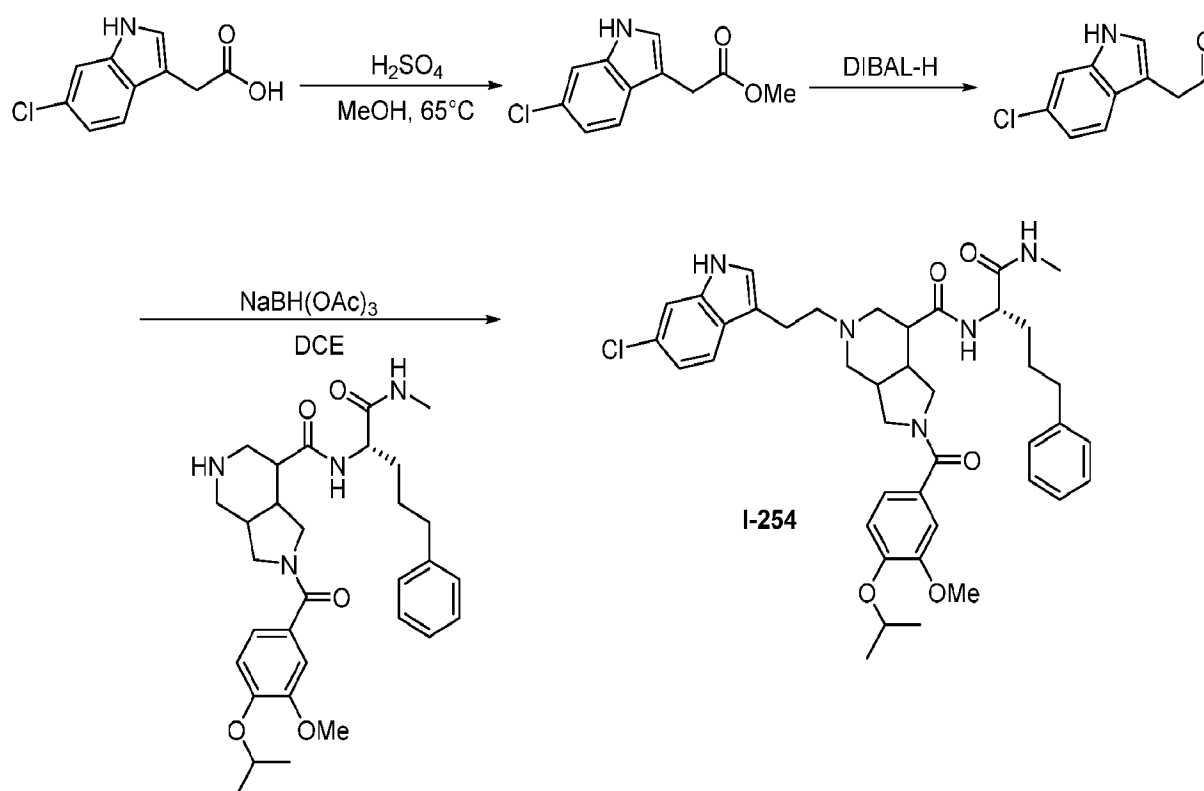
[00533] A mixture of quinoline-4-carbaldehyde (500mg, 3.18 mmol), carbon tetrabromide (3.16 g, 9.54 mmol) and triphenylphosphine (5.19 g, 19.08 mmol) in DCM (10 mL) was stirred at room temperature for 1.5 h under an atmosphere of N₂. Water was added and the aqueous extracted with EtOAc. The combined organic layers were washed with water, brine and dried over Na₂SO₄. The solvent was removed and the residue purified by column chromatography (6% MeOH/DCM) to afford 4-(2,2-dibromovinyl)quinoline (45.5 mg, 4.6 %) as a brown solid.

[00534] Step 2: 2-(4-isopropoxy-3-methoxybenzoyl)-N-((S)-1-(methylamino)-1-oxo-5-phenylpentan-2-yl)-5-(2-(quinolin-4-yl)acetyl)octahydro-1H-pyrrolo[3,4-c]pyridine-7-carboxamide

[00535] To a solution of 4-(2,2-dibromovinyl)quinoline (25 mg, 0.08 mmol) in DMF (1.5 ml) and H₂O (0.5 mL) was added 2-(4-isopropoxy-3-methoxybenzoyl)-N-((S)-1-(methylamino)-1-oxo-5-phenylpentan-2-yl)octahydro-1H-pyrrolo[3,4-c]pyridine-7-carboxamide (45 mg, 0.08 mmol; see synthesis of **I-154**) and DIEA (31 mg, 0.24 mmol). The resulting mixture was stirred at room temperature for 4 h. Water was added and the aqueous extracted with EtOAc three times. The

combined organic layers were washed with water, brine and dried over Na_2SO_4 . The solvent was removed and the residue purified by prep-HPLC to afford the product (31 mg, 48%) as a yellow solid. LCMS $m/z = 720.4$ $[\text{M}+\text{H}]^+$ ^1H NMR (400 MHz, CD_3OD) δ 9.22 – 9.00 (m, 1H), 8.45 – 7.83 (m, 5H), 7.29 – 6.83 (m, 8H), 4.72 – 3.37 (m, 13H), 3.22 – 2.00 (m, 9H), 1.92 – 1.18 (m, 11H).

Synthesis of 5-(2-(6-chloro-1H-indol-3-yl)ethyl)-2-(4-isopropoxy-3-methoxybenzoyl)-N-((S)-1-(methylamino)-1-oxo-5-phenylpentan-2-yl)octahydro-1H-pyrrolo[3,4-c]pyridine-7-carboxamide I-254



[00536] Step 1: methyl 2-(6-chloro-1H-indol-3-yl)acetate

[00537] To a solution of 2-(6-chloro-1H-indol-3-yl)acetic acid (210 mg, 1.0 mmol) in MeOH (5.0 mL) was added con. H_2SO_4 (3 mL). The mixture was heated at 65°C for 1h. The mixture was poured into ice-water and the aqueous extracted with EtOAc three times. The combined organic layers were washed with water, brine and dried over Na_2SO_4 . The solvent was removed and the residue purified by column chromatography (20% EtOAc/PE) to afford methyl 2-(6-chloro-1H-indol-3-yl)acetate (121 mg, 54%) as a white solid.

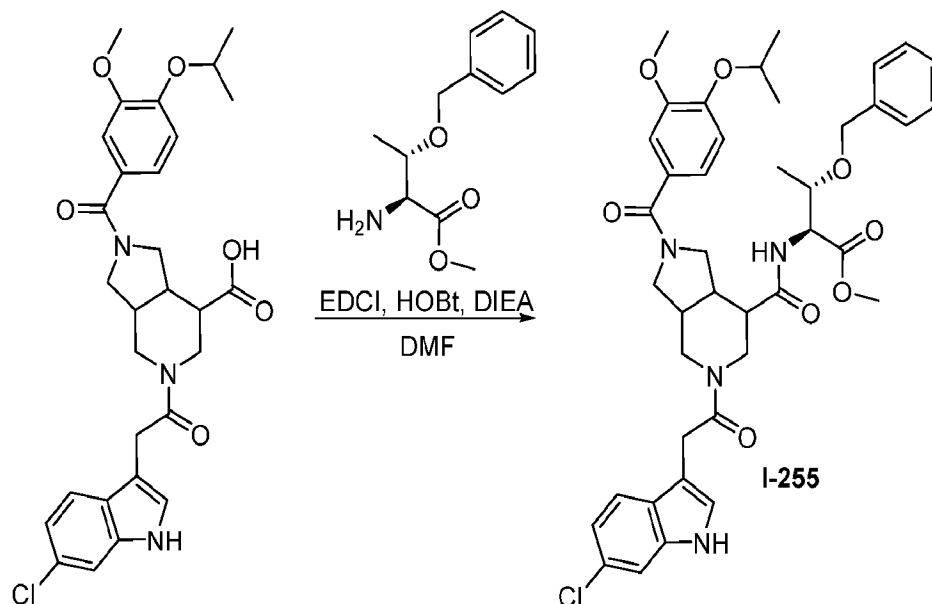
[00538] Step 2: 2-(6-chloro-1H-indol-3-yl)acetaldehyde

[00539] To a solution of methyl 2-(6-chloro-1H-indol-3-yl)acetate (121 mg, 0.54 mmol) in DCM (1.0 mL) at -78°C was added DIBAL-H (4M in Toluene, 0.2mL). The resulting mixture was stirred at -78°C under N₂ for 3 h. The reaction mixture was quenched with saturated aq. NH₄Cl and the aqueous extracted with EtOAc three times. The combined organic layers were washed with water, brine and dried over Na₂SO₄. The solvent was removed and the residue purified by column chromatography (33% EtOAc/PE) to afford 2-(6-chloro-1H-indol-3-yl)acetaldehyde (26 mg, 25% yield) as a white solid.

[00540] *Step 3: 5-(2-(6-chloro-1H-indol-3-yl)ethyl)-2-(4-isopropoxy-3-methoxybenzoyl)-N-((S)-1-(methylamino)-1-oxo-5-phenylpentan-2-yl)octahydro-1H-pyrrolo[3,4-c]pyridine-7-carboxamide*

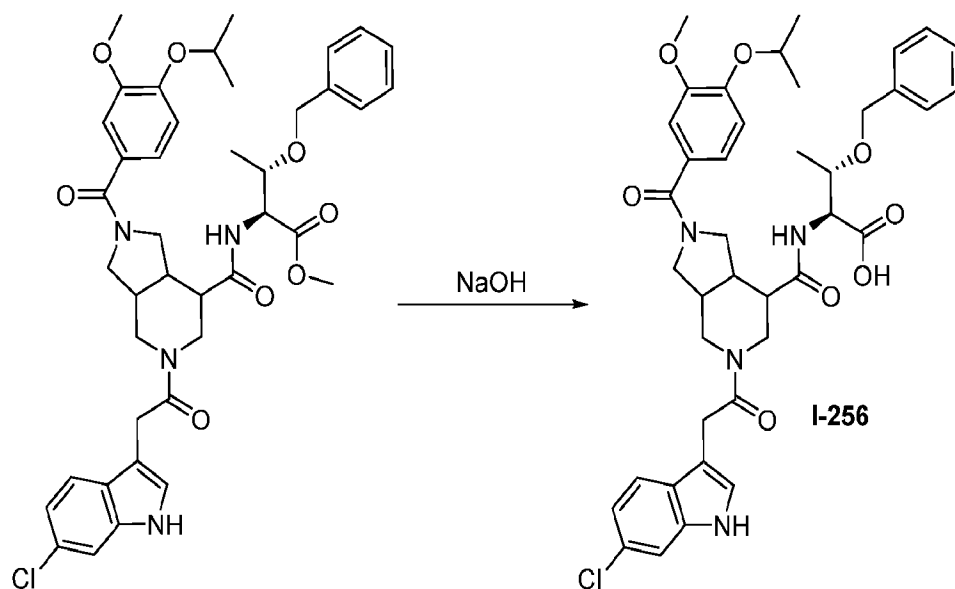
[00541] To 2-(4-isopropoxy-3-methoxybenzoyl)-N-((S)-1-(methylamino)-1-oxo-5-phenylpentan-2-yl)octahydro-1H-pyrrolo[3,4-c]pyridine-7-carboxamide (50 mg, 0.09 mmol; see synthesis of **I-154**) and 2-(6-chloro-1H-indol-3-yl)acetaldehyde (12.0 mg, 0.06 mmol) in DCE (2.0 mL) was added NaBH(OAc)₃ (38.5mg, 0.18 mmol) and the mixture stirred at room temperature overnight. The reaction mixture was concentrated *in vacuo* and the residue purified by prep-HPLC to afford the product (11.2 mg, 25.4%) as a white solid. LCMS *m/z* =728.5 [M+H]⁺; ¹H NMR (400 MHz, CD₃OD) δ 7.59 – 6.74 (m, 12H), 4.68 – 3.91 (m, 3H), 3.87 – 3.79 (m, 3H), 3.72 – 3.34 (m, 4H), 2.96 – 2.89 (m, 2H), 2.82 – 2.76 (m, 1H), 2.75 – 2.51 (m, 8H), 2.49 – 2.39 (m, 2H), 1.79 – 1.50 (m, 4H), 1.36 – 1.28 (m, 8H).

Synthesis of methyl (2S,3S)-3-(benzyloxy)-2-(5-(2-(6-chloro-1H-indol-3-yl)acetyl)-2-(4-isopropoxy-3-methoxybenzoyl)octahydro-1H-pyrrolo[3,4-c]pyridine-7-carboxamido)butanoate I-255



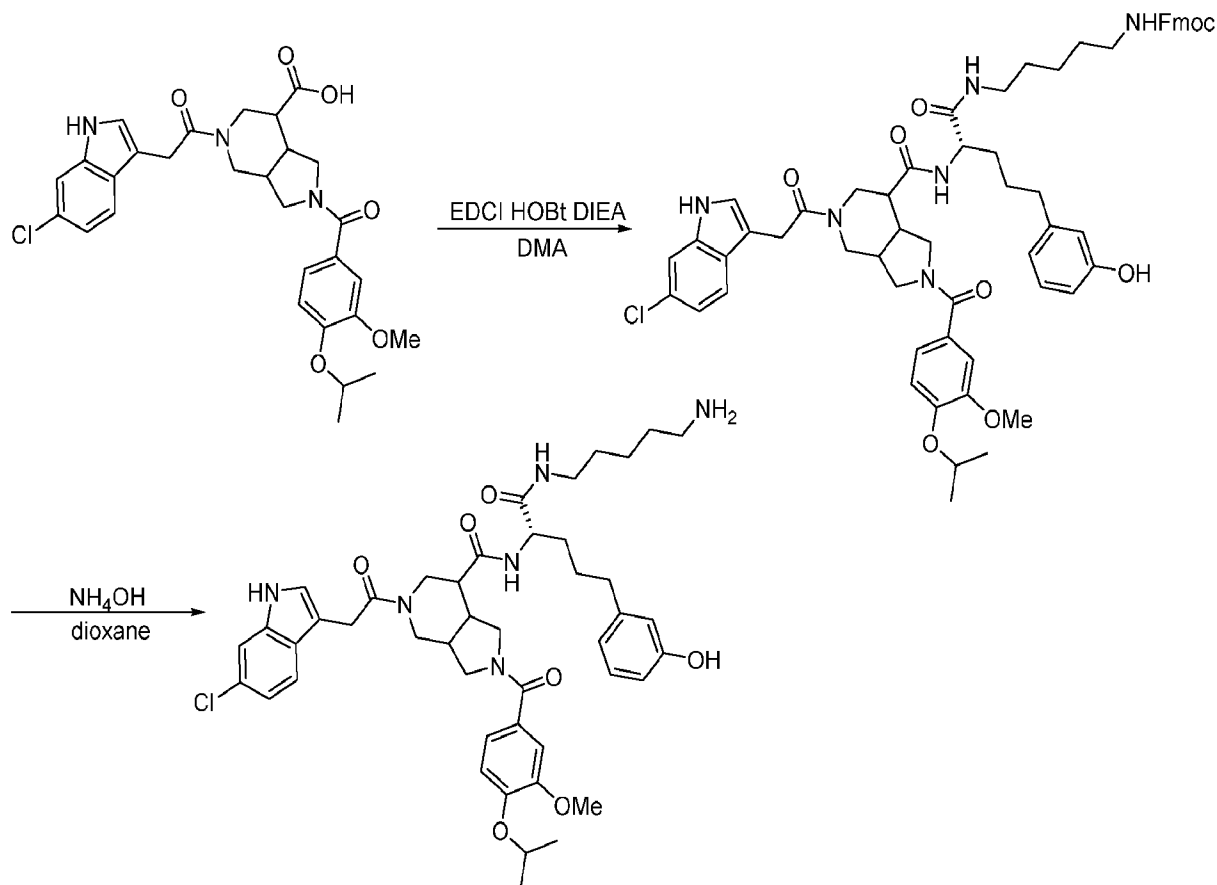
[00542] A mixture of methyl O-benzyl-L-allothreoninate (60.45 mg, 0.271 mmol), 5-(2-(6-chloro-1H-indol-3-yl)acetyl)-2-(4-isopropoxy-3-methoxybenzoyl)octahydro-1H-pyrrolo[3,4-c]pyridine-7-carboxylic acid (100 mg, 0.181 mmol) (**I-88, Step 3**), EDCI (52.0 mg, 0.271 mmol), HOBt (36.6 mg, 0.271 mmol) and DIEA (70.0 mg, 0.542 mmol) in DMF (5 mL) was stirred at room temperature overnight. Water was added and the aqueous extracted with EtOAc three times. The combined organic layers were washed with water and brine and dried over Na₂SO₄. The residue obtained after concentration was purified by prep-HPLC to afford methyl (2S,3S)-3-(benzyloxy)-2-(5-(2-(6-chloro-1H-indol-3-yl)acetyl)-2-(4-isopropoxy-3-methoxybenzoyl)octahydro-1H-pyrrolo[3,4-c]pyridine-7-carboxamido)butanoate (80 mg, 58%) as a white solid. LCMS m/z = 759.4 [M+H]⁺; ¹H NMR (400 MHz, CD₃OD) δ 8.75 – 6.58 (m, 12H), 4.79 – 4.47 (m, 3H), 4.40 – 3.98 (m, 2H), 3.98 – 3.60 (m, 8H), 3.59 – 3.35 (m, 3H), 3.17 – 2.97 (m, 2H), 2.83 – 1.98 (m, 4H), 1.62 – 1.19 (m, 8H), 1.15 – 1.05 (m, 1H), 0.94 – 0.67 (m, 2H).

Synthesis of O-benzyl-N-(5-(2-(6-chloro-1H-indol-3-yl)acetyl)-2-(4-isopropoxy-3-methoxybenzoyl)octahydro-1H-pyrrolo[3,4-c]pyridine-7-carbonyl)-L-allothreonine I-256



[00543] To a solution of **I-255** in MeOH (5 mL) was added aqueous NaOH (1 M, 2 mL). The resulting mixture was stirred for 3 h then solvent was removed under vacuum. The residue obtained was diluted with water and the pH adjusted to ~1 by addition of 1 M HCl. The aqueous layer was extracted with EtOAc three times and the combined organic layers were washed with water, brine, dried over Na₂SO₄ and concentrated to afford O-benzyl-N-(5-(2-(6-chloro-1H-indol-3-yl)acetyl)-2-(4-isopropoxy-3-methoxybenzoyl)octahydro-1H-pyrrolo[3,4-c]pyridine-7-carbonyl)-L-allothreonine (500 mg, 90%) as a white solid. LCMS $m/z = 745.4$ $[M+H]^+$; ¹H NMR (400 MHz, CD₃OD) δ 7.78 – 6.64 (m, 12H), 4.80 – 4.39 (m, 3H), 4.38 – 3.95 (m, 2H), 3.94 – 3.68 (m, 5H), 3.67 – 3.37 (m, 3H), 3.24 – 2.96 (m, 1H), 2.92 – 2.16 (m, 3H), 1.45 – 1.37 (m, 3H), 1.36 – 1.10 (m, 8H), 0.97 – 0.67 (m, 2H). LCMS $m/z = 745.4$ $[M+H]^+$.

Synthesis of N-((S)-1-((5-aminopentyl)amino)-5-(3-hydroxyphenyl)-1-oxopentan-2-yl)-5-(2-(6-chloro-1H-indol-3-yl)acetyl)-2-(4-isopropoxy-3-methoxybenzoyl)octahydro-1H-pyrrolo[3,4-c]pyridine-7-carboxamide I-257 and I-258



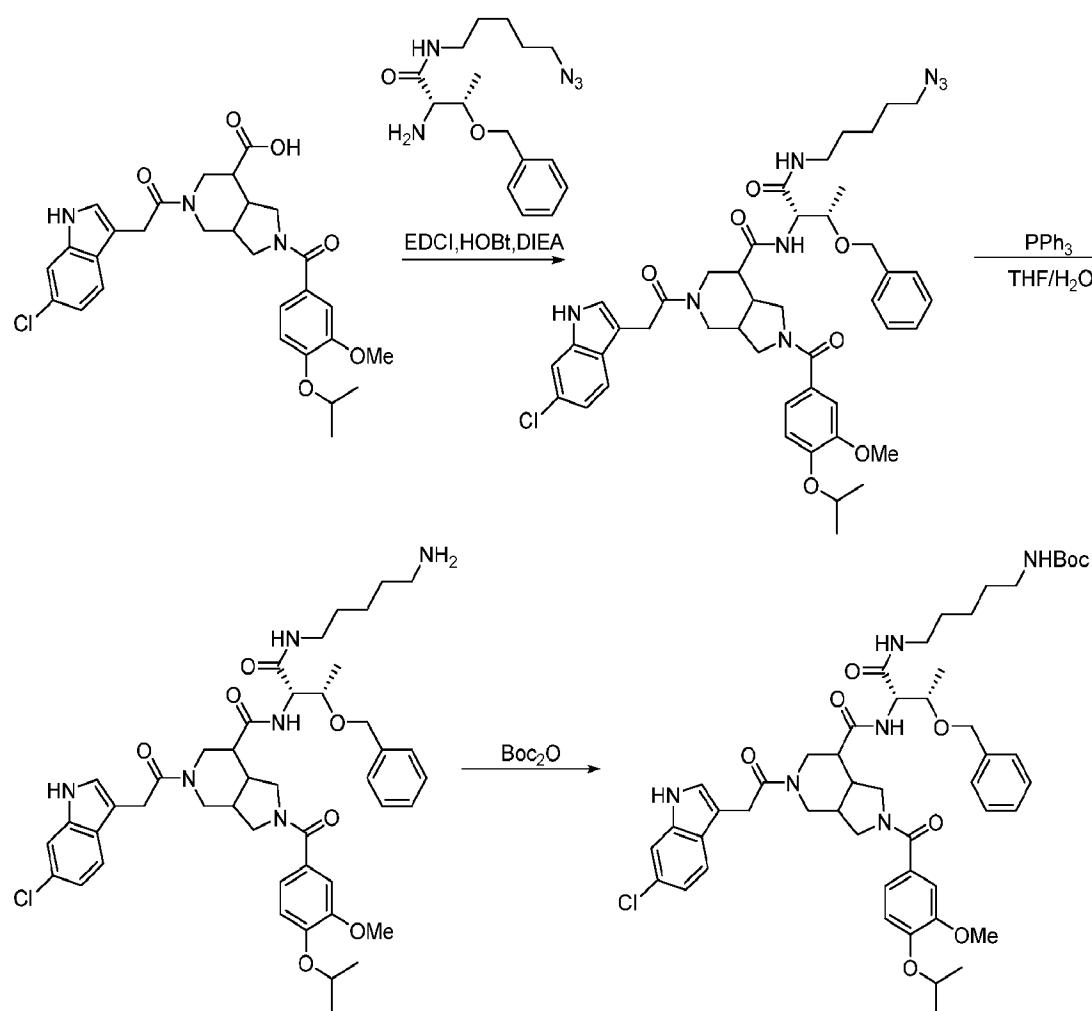
[00544] *Step 1: (9H-fluoren-9-yl)methyl (5-((2S)-2-(5-(2-(6-chloro-1H-indol-3-yl)acetyl)-2-(4-isopropoxy-3-methoxybenzoyl)octahydro-1H-pyrrolo[3,4-c]pyridine-7-carboxamido)-5-(3-hydroxyphenyl)pentanamido)pentyl)carbamate*

[00545] Made using the same procedure reported for preparation of **I-255** using (9H-fluoren-9-yl)methyl (S)-(5-(2-amino-5-(3-hydroxyphenyl)pentanamido)pentyl)carbamate. Two diastereomers (30 mg each) were obtained after silica gel column (50% EtOAc/PE). LCMS $m/z = 1051.3$ $[M+H]^+$.

[00546] *Step 2: N-((S)-1-((5-aminopentyl)amino)-5-(3-hydroxyphenyl)-1-oxopentan-2-yl)-5-(2-(6-chloro-1H-indol-3-yl)acetyl)-2-(4-isopropoxy-3-methoxybenzoyl)octahydro-1H-pyrrolo[3,4-c]pyridine-7-carboxamide*

[00547] To a solution of the first eluting diastereomer from Step 1 (40 mg, 0.038 mmol) in dioxane (1 mL) was added aq. NH_4OH (1 mL) and the mixture was heated at 65 °C in a sealed tube overnight. The solvent was removed under reduced pressure and the residue was purified by prep-HPLC to afford **I-257** (5.4 mg, 19%) as colorless solid. LCMS $m/z = 829.5$ $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, CD_3OD) δ 7.62 – 6.48 (m, 11H), 4.70 – 3.75 (m, 9H), 3.69 – 3.35 (m, 3H), 3.22 – 2.74 (m, 6H), 2.69 – 2.04 (m, 5H), 1.79 – 1.49 (m, 7H), 1.43 – 1.25 (m, 10H). The second eluting diastereomer of from Step 1 was treated in the same fashion to afford **I-258** (10.8 mg, 38%) as a colorless solid. LCMS $m/z = 829.5$ $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, CD_3OD) δ 7.72 – 6.46 (m, 11H), 4.78 – 4.42 (m, 2H), 4.36 – 4.01 (m, 2H), 3.97 – 3.42 (m, 8H), 3.26 – 2.78 (m, 7H), 2.66 – 2.10 (m, 5H), 1.74 – 1.22 (m, 16H).

Synthesis of tert-butyl (5-((2S,3S)-3-(benzyloxy)-2-(5-(2-(6-chloro-1H-indol-3-yl)acetyl)-2-(4-isopropoxy-3-methoxybenzoyl)octahydro-1H-pyrrolo[3,4-c]pyridine-7-carboxamido)butanamido)pentyl)carbamate I-259 and I-260



[00548] *Step 1: N-((2S,3S)-1-((5-azidopentyl)amino)-3-(benzyloxy)-1-oxobutan-2-yl)-5-(2-(6-chloro-1H-indol-3-yl)acetyl)-2-(4-isopropoxy-3-methoxybenzoyl)octahydro-1H-pyrrolo[3,4-c]pyridine-7-carboxamide* Made using the procedure reported for I-257/I-258, Step 1, using (2S,3S)-2-amino-N-(5-azidopentyl)-3-(benzyloxy)butanamide to give the titled product (100 mg, 20%) as a yellow solid. LCMS $m/z = 855.3 [M+H]^+$.

[00549] *Step 2: N-((2S,3S)-1-((5-aminopentyl)amino)-3-(benzyloxy)-1-oxobutan-2-yl)-5-(2-(6-chloro-1H-indol-3-yl)acetyl)-2-(4-isopropoxy-3-methoxybenzoyl)octahydro-1H-pyrrolo[3,4-c]pyridine-7-carboxamide*

[00550] To a solution of N-((2S,3S)-1-((5-azidopentyl)amino)-3-(benzyloxy)-1-oxobutan-2-yl)-5-(2-(6-chloro-1H-indol-3-yl)acetyl)-2-(4-isopropoxy-3-methoxybenzoyl)octahydro-1H-pyrrolo[3,4-c]pyridine-7-carboxamide (270 mg, 0.31 mmol) in a mixture of THF (2 mL) and H₂O (1 mL) was added PPh₃ (162 mg, 0.62 mmol). The resulting mixture was stirred at room temperature for 14 hours. The solvent was removed and the residue purified by prep-HPLC to afford the titled product (174 mg, 68%) as a white solid. LCMS $m/z = 829.5 [M+H]^+$.

[00551] *Step 3: tert-butyl (5-((2S,3S)-3-(benzyloxy)-2-(5-(2-(6-chloro-1H-indol-3-yl)acetyl)-2-(4-isopropoxy-3-methoxybenzoyl)octahydro-1H-pyrrolo[3,4-c]pyridine-7-carboxamido)butanamido)pentyl)carbamate* To a solution of N-((2S,3S)-1-((5-aminopentyl)amino)-3-(benzyloxy)-1-oxobutan-2-yl)-5-(2-(6-chloro-1H-indol-3-yl)acetyl)-2-(4-isopropoxy-3-methoxybenzoyl)octahydro-1H-pyrrolo[3,4-c]pyridine-7-carboxamide (25 mg, 0.03 mmol) in DCM (1 mL) was added Boc₂O (6.5 mg, 0.03 mmol) and Et₃N (9 mg, 0.06 mmol). The resulting mixture was stirred at room temperature overnight. The solvent was removed *in vacuo* and the residue purified by prep-HPLC on an Agilent 10 Prep-C18 column (21.2 mm I.D. × 25 cm, 10 μm), using H₂O/ACN 0.1%TFA, at a flow rate of 20 mL/min (wave length 214 nm) to afford the first eluting (R_t = 9.3 min) diastereomer (16 mg, 57%) **I-259** as a white solid; ¹H NMR (400 MHz, CD₃OD) δ 7.63 – 6.66 (m, 12H), 4.73 – 4.31 (m, 5H), 4.15 – 3.36 (m, 9H), 3.26 – 2.90 (m, 6H), 2.87 – 1.99 (m, 5H), 1.43 (s, 9H), 1.39 – 1.13 (m, 15H). LCMS $m/z = 929.6 [M+H]^+$, and the second eluting (R_t = 10.5 min) diastereomer (10 mg, 35%) **I-260** also as a white solid; ¹H NMR (400 MHz, CD₃OD) δ 7.67 – 6.63 (m, 12H), 4.75 – 3.35 (m, 16H), 3.28 – 2.93 (m, 7H), 2.85 – 2.44 (m, 3H), 2.29 – 1.97 (m, 1H), 1.42 (s, 9H), 1.38 – 1.18 (m, 11H), 0.93 – 0.67 (m, 2H). LCMS $m/z = 929.6 [M+H]^+$.

Example A1: Caliper Assay

[00552] Inhibition of CDK2/Cyclin E1 activity in the presence of compounds of the present disclosure was evaluated using a Caliper LabChip® EZ Reader mobility shift assay. In the assay, activated CDK2/Cyclin E1 catalyzes the phosphorylation of a fluorescently tagged peptide 5-FAM-QSPKKG-CONH₂ (PerkinElmer, FL Peptide 18) which induces a difference in capillary electrophoresis mobility. The peptide substrate and product were measured, and the conversion ratio was used to determine the inhibition (as % activity and IC₅₀ values) of CDK2/Cyclin E1. Reactions contained 50 mM HEPES pH 7.5, 10 mM MgCl₂, 1 mM EDTA, 2mM DTT, 0.01% Brij35, 0.5 mg/mL BSA, 0.1% DMSO, 2.5 nM CDK2/Cyclin E1(14-475), 100 μM ATP, and 1.5 μM fluorescent peptide substrate.

[00553] Dose titrations of inhibitors in 100% DMSO were combined with 3.25 nM CDK2/Cyclin E1(14-475) and 130 μM of ATP in reaction buffer. The mixtures were incubated for 30 minutes before the addition of fluorescent peptide substrate to initiate the kinase reaction. The final conditions were 2.5nM CDK2/Cyclin E1(14-475), 100 μM ATP, and 1.5 μM fluorescent peptide. The reactions were stopped after 100 minutes with the addition of EDTA (6 mM final EDTA concentration). The stopped reactions were analyzed on a Caliper LabChip® EZ Reader II. The conversion ratios were normalized to yield % activity, plotted against compound concentration, and fit to a four-parameter equation to determine the IC₅₀ for each compound.

[00554] The results of the Caliper Assay are reported in **Table X**, below. Compounds with an IC₅₀ less than or equal to 0.5 μM are designated as “A”. Compounds with an IC₅₀ greater than 0.5 μM and less than or equal to 5.0 μM are designated as “B”. Compounds with an IC₅₀ greater than 5.0 μM and less than or equal to 10.0 μM are designated as “C”. Compounds with an IC₅₀ greater than 10.0 μM are designated as “D”.

Example A2: BrdU Cell Proliferation Assay

[00555] A BrdU assay was used as a measure of proliferation based on the DNA replication process of proliferating cells. BrdU, a pyrimidine analog, is added to the cell culture and incorporated into the DNA of proliferating cells. The presence of the BrdU analog was then measured through a

colorimetric ELISA. After fixation and permeabilization of cells, peroxidase-conjugated antibody recognizing BrdU is added and allowed to incubate, followed by thorough washing to remove unbound antibody. In order to quantify the amount of bound antibody, peroxidase substrate is added and produces a color that can be measured at 450 nm.

[00556] On day -1, Kuramochi cells (Sekisui XenoTech JCRB0098) were seeded at 2,000 cells/well in columns 2-12 of a 96 well plate (Corning, CLS3596) in 150uL media and allowed to adhere overnight at 37 degree with 5% CO₂. In order to assess specificity of the compounds, Kuramochi RB^{KO} cells were also plated and treated, as RB^{KO} cells were not expected to show a proliferative response to CCNE/CDK specific inhibitors.

[00557] On day 0, the source plate was prepared by adding 10mM compounds and performing 3-fold serial dilutions for a 4-point dose response of each compound. Using a multichannel pipette, 2uL of the contents of the source plate were stamped into an intermediate plate with 500uL of RPMI 1640 Media, GlutaMAX Supplement (Life Technologies, 61870127) in each well of a Nunc 96 DeepWell™ plate, non-treated 96 DeepWell plate, 2 mL/well, sterile, natural, 60/cs (Sigma Z717274) and mixed thoroughly. 50uL from row A of this intermediate plate were added to rows A-H of one plate of previously seeded Kuramochi cells, and each subsequent row of the intermediate plate was added to a full plate of cells.

[00558] On day 4, the plates were developed using the BrdU ELISA Cell Proliferation Assay according to manufacturer's instructions (Roche, 11647229001). Briefly, BrdU was diluted 1:100 in Gibco®, Opti-MEM® and 20 µL/well was added, shaken for 10 minutes at 350rpm, and then returned to the incubator for 1 hour. Following incubation, the medium was discarded, and the cells were fixed by adding 200 µL of Fix/Denature solution. The anti-BrdU peroxidase antibody was diluted 1:1000 in OptiMEM, added at 100 µL/well, and incubated while shaking (350rpm) for one hour. Three washes with PBS were performed to remove any unbound antibody, followed by the addition of 100 µL of substrate solution to each well. µL/well of 1M sulfuric acid solution was then added to halt the reaction, and plates were read out using an Envision spectrophotometer (Perkin Elmer) set to read 450nm absorbance. Background absorbance values from empty wells were subtracted from all samples and then normalized to DMSO treated wells.

[00559] The results of the BrdU cell proliferation assay are reported in **Table X**, below. Compounds with an IC₅₀ less than or equal to 0.5 µM are designated as "A". Compounds with an IC₅₀ greater

than 0.5 μM and less than or equal to 5.0 μM are designated as “B”. Compounds with an IC_{50} greater than 5.0 μM and less than or equal to 10.0 μM are designated as “C”. Compounds with an IC_{50} greater than 10.0 μM are designated as “D”.

Example A3: HotSpot™ Kinase Inhibition Assay

[00560] Inhibition of a select panel of CDK2/CCNE1 activities in the presence of compounds of the present disclosure was evaluated using the HotSpot™ assay (proprietary to Reaction Biology Corporation). In the assay, activated CDK2/Cyclin E1 catalyzes the transfer of radioactive phosphate to amino acid residues of peptide or protein substrates, which are detected radiometrically. After subtraction of background derived from control reactions containing inactive enzyme, kinase activity data is expressed as the percent remaining kinase activity in test samples compared to reactions without inhibitor present. Reactions contained 20mM HEPES pH 7.5, 10 mM MgCl_2 , 1 mM EGTA, 2mM DTT, 0.02% Brij35, 0.02 mg/mL BSA, 0.1 mM Na_3VO_4 , 1% DMSO, 1.5 nM CDK2/Cyclin E1(14-475), 10 μM ATP, and 20 μM Histone H1 protein isolated from calf thymus (Sigma).

[00561] CDK2/Cyclin E1(14-75) and Histone H1 were mixed in reaction buffer. To this mixture, was added dose titrations of inhibitor compounds in 100% DMSO by acoustic transfer. The compound mixtures were incubated for 20 minutes, then the kinase reactions were initiated by the addition of a mixture of ATP and ^{33}P ATP for final concentrations of 10 μM total ATP, 20 μM Histone H1, and 1.5 nM CDK2/Cyclin E1(14-475). The reactions were carried out for 120 minutes, then spotted on a P81 ion exchange filter paper, and extensively washed with 0.75% phosphoric acid. The resulting radioactive counts were normalized to yield % activity, plotted against compound concentration, and fit to a four-parameter equation to determine the IC_{50} for each compound.

[00562] The results of the HotSpot™ assay are reported in **Table X**, below. Compounds with an IC_{50} less than or equal to 1.0 μM are designated as “A”. Compounds with an IC_{50} greater than 1.0 μM and less than or equal to 10 μM are designated as “B”. Compounds with an IC_{50} greater than 10 μM and less than or equal to 100 μM are designated as “C”. Compounds with an IC_{50} greater than 100 μM are designated as “D”.

Example A4: Incucyte® Cell Proliferation Assay

[00563] Kuramochi cells labeled with mApple-H2B and Kuramochi RB1-/- cells labeled with NucLight green (Sartorius, 4475) were co-plated on 384-well assay-ready plates along with test compounds at varying concentrations. Plates were placed in the IncuCyte® Sartorius and scanned at 0 and 72 hours. IncuCyte® software was used to count the number of fluorescent nuclei in each well. The fold change in cell count from 0 to 72 hours in wells treated with increasing compounds concentrations (10pts, 1/2log dilution, 20 μ M top concentration) was normalized to DMSO control wells. The normalized cell counts were fit with dose response curves and a GI₅₀ was calculated.

[00564] The results of the Incucyte® Kuramochi cell viability assay are reported in **Table X**, below. Compounds with a GI₅₀ less than or equal to 1.0 μ M are designated as “A”. Compounds with a GI₅₀ greater than 1.0 μ M and less than or equal to 10.0 μ M are designated as “B”. Compounds with a GI₅₀ greater than 10.0 μ M and less than or equal to 20.0 μ M are designated as “C”. Compounds with a GI₅₀ greater than 20.0 μ M are designated as “D”.

Table X. Assay Results

#	Caliper Assay	BrdU Cell Proliferation Assay	Kinase Inhibition Assay	Incucyte® Cell Proliferation Assay
I-1	A	D		
I-2		D	C	
I-3	D	D		
I-4	D			
I-5	D	D		
I-6	B	D		
I-7	B	C		
I-8	D	D		
I-9	C	D		
I-10	D	D		
I-11	D	D		
I-12	D	D		
I-13	D	C	D	
I-14	D	D		
I-15	D	D		
I-16	D	D		
I-17		D	D	
I-18	D	D		
I-19	D	B	A	
I-20	D	D		
I-21	D	D		
I-22	D	D		
I-23	D	D		

#	Caliper Assay	BrdU Cell Proliferation Assay	Kinase Inhibition Assay	Incucyte® Cell Proliferation Assay
I-24	D	D		
I-25	B	D		
I-26	C	D		
I-27	D	D		
I-28	D	D		
I-29	D	D		
I-30	D	D		
I-31	D	D		
I-32		D	D	
I-33	C			
I-34	C	D		
I-35		D	D	
I-36	D			
I-37	D	D		
I-38	D	D		
I-39	D	D		
I-40	D	D		
I-41	D	D		
I-42		D	D	
I-43	D	D		
I-44	D	D		
I-45	D	D		
I-46	B	D		
I-47	D	D		
I-48	D	D		
I-49		D		
I-50		D	B	
I-51		D		
I-52	C	D		
I-53		D		
I-54	D	D		
I-55	D	D		
I-56	B	D		
I-57	D	D		
I-58	D	D		
I-59	D	D		
I-60	D	D		
I-61	D	D		
I-62		D	D	
I-63		D		
I-64		D	C	
I-65	D	D		
I-66	D	D		
I-67			C	
I-68		D		
I-69	D	D		
I-70	D	D		

#	Caliper Assay	BrdU Cell Proliferation Assay	Kinase Inhibition Assay	Incucyte® Cell Proliferation Assay
I-71	D	D		
I-72	D	D		
I-73	D	D		
I-74	D	D		
I-75	D	D		
I-76		D		
I-77		D	D	
I-78	D	D		
I-79	C	D		
I-80	D	D		
I-81		D	C	
I-82	B	C		
I-83	A	D		
I-84	B	D		
I-85	A	D		
I-86	D	D		
I-87	A	D		
I-88	D	D		
I-89	D	D		
I-90	D	D		
I-91	B	D		
I-92	D	D		
I-93	B	D		
I-94	D	D		
I-95	B	D		
I-96		D		
I-97	B	D		
I-98	B	D		
I-99	B	D		
I-100	A	B		
I-101	D	D		
I-102	B	D		
I-103	B	D		
I-104	D	D		
I-105	D	D		
I-106	A	B		B
I-107	A	B		
I-108	D	D		
I-109	B	D		
I-110	D	D		
I-111	A	D		
I-112	C	D		
I-113	B	D		
I-114	D	D		
I-115	C	D		
I-116	D	D		
I-117	B	D		

#	Caliper Assay	BrdU Cell Proliferation Assay	Kinase Inhibition Assay	Incucyte® Cell Proliferation Assay
I-118	D	D		
I-119		D		
I-120		D		
I-121		D		
I-122			C	
I-123			C	
I-124		D	D	
I-125			C	
I-126	B	D		
I-127	B	D		
I-128	C	B		
I-129	D	D		
I-130	B	D		
I-131	C	B		
I-132	B	D		
I-133	B	D		
I-134	D	D		
I-135	A	B		
I-136	B	D		
I-137	D	D		
I-138	D	D		
I-139	B	D		
I-140	B	D		
I-141	D	C		
I-142	D	D		
I-143	D	D		
I-144	B	D		
I-145	A	B		B
I-146	A	D		C
I-147	D	D		D
I-148	B	D		D
I-149	B	D		
I-150	B	C		
I-151	A	B		
I-152	D	D		
I-153	B	D		
I-154	D	D		
I-155	D	D		
I-156	B	D		
I-157	D	D		
I-158	D	D		
I-159	D	D		
I-160	D	D		
I-161	D	D		
I-162	D	D		
I-163	D	D		
I-164	D	D		

#	Caliper Assay	BrdU Cell Proliferation Assay	Kinase Inhibition Assay	Incucyte® Cell Proliferation Assay
I-165	D	D		
I-166	D	D		
I-167	D	D		
I-168	D	D		
I-169	D	D		
I-170	D	D		
I-171	D	D		
I-172	D	D		
I-173	B	D		
I-174	B	D		
I-175	D	D		
I-176	D	D		
I-177	D	D		
I-178	D	D		
I-179	D	D		
I-180	D	D		
I-181	D	D		
I-182	D	D		
I-183	D	D		
I-184	D	D		
I-185	D	D		
I-186	D	D		
I-187	D	D		
I-188	D	D		
I-189	D	D		
I-190	D	D		
I-191	D	D		
I-192	D	D		
I-193	D	D		
I-194		D		
I-195	D	D		
I-196	D	D		
I-197	D	D		
I-198	D	D		
I-199	D	D		
I-200	C	D		
I-201	B	D		
I-202	D	D		
I-203	B	D		
I-204	B	D		
I-205	B	D		
I-206	D	D		
I-207	D	D		
I-208	D	D		
I-209	D	D		
I-210	D	D		
I-211	D	D		

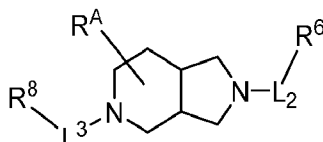
#	Caliper Assay	BrdU Cell Proliferation Assay	Kinase Inhibition Assay	Incucyte® Cell Proliferation Assay
I-212	D	D		
I-213	D	D		
I-214	D	D		
I-215	D	D		
I-216	D	D		
I-217	D	D		
I-218	D	D		
I-219	B	D		
I-220	D	D		
I-221		D	D	
I-222			B	
I-223	D	D		
I-224	D			
I-225	B	D		
I-226	B	C		
I-227	A	D		
I-228	D	D		
I-229	D	D		
I-230	D	D		
I-231	C	D		
I-232	D	D		
I-233	D	D		
I-234	D	D		
I-235			B	
I-236	B	D		
I-237	A	D		
I-238	B	B		
I-239	B	D		
I-240	B	D		
I-241	D	D		
I-242	B	D		
I-243	B	D		
I-244	D	D		
I-245	D	D		
I-246	D	D		
I-247	D	D		
I-248	D	D		
I-249	D	D		
I-250	B	D		
I-251	D	C	D	
I-252	D	D		
I-253	D	D		
I-254	D			
I-255	A	B		
I-256	B	D		
I-257	B	D		
I-258	D	D		

#	Caliper Assay	BrdU Cell Proliferation Assay	Kinase Inhibition Assay	Incucyte [®] Cell Proliferation Assay
I-259	A	B		
I-260	B	D		
I-261	D			D
I-262	D			D

CLAIMS

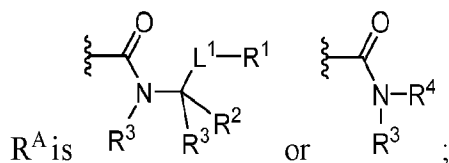
We claim:

1. A compound, wherein the compound is of Formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:



L^1 is a covalent bond or a saturated or unsaturated, straight or branched, optionally substituted bivalent C_{1-6} hydrocarbon chain, wherein 0-2 methylene units of L^1 are independently replaced by -O-, -NR-, -S-, -OC(O)-, -C(O)O-, -C(O)-, -S(O)-, -S(O)₂-, -C(S)-, -NRS(O)₂-, -S(O)₂NR-, -NRC(O)-, -C(O)NR-, -OC(O)NR-, -NRC(O)O-, or -NRC(O)NR-;

R^1 is hydrogen, an optionally substituted C_{1-6} aliphatic group, or an optionally substituted cyclic group selected from a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, a 7-12 membered saturated or partially unsaturated bicyclic carbocyclic ring, phenyl, an 8-10 membered bicyclic aromatic carbocyclic ring, a 3-8 membered saturated or partially unsaturated monocyclic heterocyclic ring (having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur), a 7-12 membered saturated or partially unsaturated bicyclic heterocyclic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), a 5-6 membered monocyclic heteroaromatic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), and an 8-10 membered bicyclic heteroaromatic ring (having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur);

R^2 is hydrogen, an optionally substituted C_{1-6} aliphatic group, -C(O)OR, -C(O)NR₂, or an optionally substituted cyclic group selected from phenyl and a 5-6 membered monocyclic heteroaromatic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur);

each instance of R^3 is independently hydrogen or an optionally substituted C_{1-6} aliphatic group;

R^4 is a cyclic group selected from a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, a 7-12 membered saturated or partially unsaturated bicyclic carbocyclic ring, phenyl, an 8-10 membered bicyclic aromatic carbocyclic ring, a 3-8 membered saturated or partially unsaturated monocyclic heterocyclic ring (having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur), a 7-12 membered saturated or partially unsaturated bicyclic heterocyclic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), a 5-6 membered monocyclic heteroaromatic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), and an 8-10 membered bicyclic heteroaromatic ring (having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur), wherein the cyclic group is optionally substituted with one or more instances of R^5 ;

each instance of R^5 is independently halogen, $-CN$, $-NO_2$, $-OR$, $-SR$, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, $-S(O)R$, $-S(O)NR_2$, $-C(O)R$, $-C(O)OR$, $-C(O)NR_2$, $-C(O)N(R)OR$, $-OC(O)R$, $-OC(O)NR_2$, $-N(R)C(O)OR$, $-N(R)C(O)R$, $-N(R)C(O)NR_2$, $-N(R)C(NR)NR_2$, $-N(R)S(O)_2NR_2$, $-N(R)S(O)_2R$, an optionally substituted C_{1-6} aliphatic group, or an optionally substituted $-C_{1-6}$ aliphatic-Cy group;

L^2 is a saturated or unsaturated, straight or branched, optionally substituted bivalent C_{1-4} hydrocarbon chain, wherein 0-2 methylene units of L^2 are independently replaced by $-O-$, $-NR-$, $-S-$, $-OC(O)-$, $-C(O)O-$, $-C(O)-$, $-S(O)-$, $-S(O)_2-$, $-C(S)-$, $-NRS(O)_2-$, $-S(O)_2NR-$, $-NRC(O)-$, $-C(O)NR-$, $-OC(O)NR-$, $-NRC(O)O-$, or $-NRC(O)NR-$;

R^6 is an optionally substituted C_{1-6} aliphatic group, or a cyclic group selected from a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, a 7-12 membered saturated or partially unsaturated bicyclic carbocyclic ring, phenyl, an 8-10 membered bicyclic aromatic carbocyclic ring, a 3-8 membered saturated or partially unsaturated monocyclic heterocyclic ring (having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur), a 7-12 membered saturated or partially unsaturated bicyclic heterocyclic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), a 5-6 membered monocyclic heteroaromatic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), and an 8-10 membered bicyclic heteroaromatic ring (having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur), wherein the cyclic group is optionally substituted with one or more instances of R^7 ;

each instance of R^7 is independently halogen, $-CN$, $-NO_2$, $-OR$, $-SR$, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, $-S(O)R$, $-S(O)NR_2$, $-C(O)R$, $-C(O)OR$, $-C(O)NR_2$, $-C(O)N(R)OR$, $-OC(O)R$, $-OC(O)NR_2$, $-N(R)C(O)OR$, $-N(R)C(O)R$, $-N(R)C(O)NR_2$, $-N(R)C(O)S(O)_2R$, $-N(R)C(NR)NR_2$, $-N(R)S(O)_2NR_2$, $-N(R)S(O)_2R$, an optionally substituted C_{1-6} aliphatic group, or Cy, or two instances of R^6 on the same carbon atom are taken together to form an oxo group;

L^3 is a saturated or unsaturated, straight or branched, optionally substituted bivalent C_{1-4} hydrocarbon chain, wherein 0-2 methylene units of L^3 are independently replaced by $-O-$, $-NR-$, $-S-$, $-OC(O)-$, $-C(O)O-$, $-C(O)-$, $-S(O)-$, $-S(O)_2-$, $-C(S)-$, $-NRS(O)_2-$, $-S(O)_2NR-$, $-NRC(O)-$, $-C(O)NR-$, $-OC(O)NR-$, $-NRC(O)O-$, or $-NRC(O)NR-$;

R^8 is a cyclic group selected from a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, a 7-12 membered saturated or partially unsaturated bicyclic carbocyclic ring, phenyl, an 8-10 membered bicyclic aromatic carbocyclic ring, a 3-8 membered saturated or partially unsaturated monocyclic heterocyclic ring (having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur), a 7-12 membered saturated or partially unsaturated bicyclic heterocyclic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), a 5-6 membered monocyclic heteroaromatic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), and an 8-10 membered bicyclic heteroaromatic ring (having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur), wherein the cyclic group is optionally substituted with one or more instances of R^9 ;

each instance of R^9 is independently halogen, $-CN$, $-NO_2$, $-OR$, $-SR$, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, $-S(O)R$, $-S(O)NR_2$, $-C(O)R$, $-C(O)OR$, $-C(O)NR_2$, $-C(O)N(R)OR$, $-OC(O)R$, $-OC(O)NR_2$, $-N(R)C(O)OR$, $-N(R)C(O)R$, $-N(R)C(O)NR_2$, $-N(R)C(NR)NR_2$, $-N(R)S(O)_2NR_2$, $-N(R)S(O)_2R$, an optionally substituted C_{1-6} aliphatic group, an optionally substituted C_{1-6} aliphatic-Cy group, or Cy;

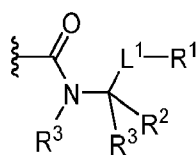
each Cy is independently an optionally substituted cyclic group selected from a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, phenyl, a 3-8 membered saturated or partially unsaturated monocyclic heterocyclic ring (having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur), and a 5-6 membered monocyclic

heteroaromatic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur); and

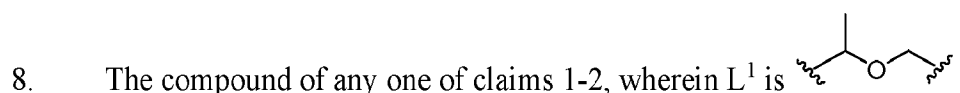
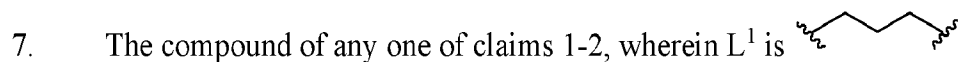
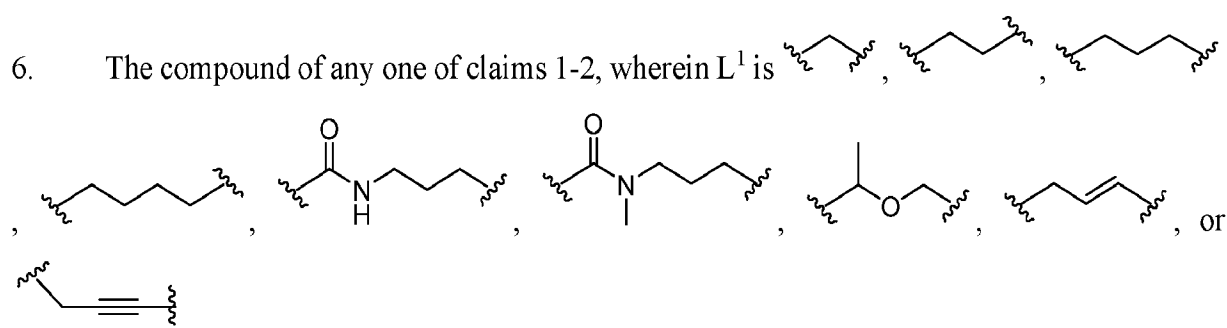
each R is independently hydrogen, or an optionally substituted C₁₋₆ aliphatic group, an optionally substituted phenyl, an optionally substituted 3-7 membered saturated or partially unsaturated carbocyclic ring, an optionally substituted 3-7 membered saturated or partially unsaturated heterocyclic ring (having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur), or an optionally substituted 5-6 membered heteroaryl ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur); or

two R groups on the same nitrogen are taken together with their intervening atoms to form an optionally substituted 4-7 membered saturated, partially unsaturated, or heteroaryl ring (having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur);

wherein the compound is not 5-(2-(6-chloro-1H-indol-3-yl)acetyl)-2-(4-isopropoxy-3-methoxybenzoyl)-N-(1-(methylamino)-1-oxo-5-phenylpentan-2-yl)octahydro-1H-pyrrolo[3,4-c]pyridine-7-carboxamide.



2. The compound of claim 1, wherein R^A is
3. The compound of any one of claims 1-2, wherein L¹ is a covalent bond.
4. The compound of any one of claims 1-2, wherein L¹ is a saturated or unsaturated, straight or branched, optionally substituted bivalent C₁₋₆ hydrocarbon chain, wherein 0-2 methylene units of L¹ are independently replaced by -O-, -NR-, -S-, -OC(O)-, -C(O)O-, -C(O)-, -S(O)-, -S(O)₂-, -C(S)-, -NRS(O)₂-, -S(O)₂NR-, -NRC(O)-, -C(O)NR-, -OC(O)NR-, -NRC(O)O-, or -NRC(O)NR-.
5. The compound of any one of claims 1-2, wherein L¹ is an optionally substituted straight or branched C₁₋₄ alkylene chain, wherein 1-2 methylene units of L¹ are independently replaced by -O-, -NR-, -C(O)O-, or -NRC(O)-.



9. The compound of any one of claims 1-8, wherein R^1 is hydrogen.

10. The compound of any one of claims 1-8, wherein R^1 is an optionally substituted C_{1-6} aliphatic group.

11. The compound of any one of claims 1-8, wherein R^1 is an optionally substituted cyclic group selected from a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, a 7-12 membered saturated or partially unsaturated bicyclic carbocyclic ring, phenyl, an 8-10 membered bicyclic aromatic carbocyclic ring, a 3-8 membered saturated or partially unsaturated monocyclic heterocyclic ring (having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur), a 7-12 membered saturated or partially unsaturated bicyclic heterocyclic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), a 5-6 membered monocyclic heteroaromatic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), and an 8-10 membered bicyclic heteroaromatic ring (having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur).

12. The compound of any one of claims 1-8, wherein R^1 is an optionally substituted cyclic group selected from a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, phenyl, a 3-8 membered saturated or partially unsaturated monocyclic heterocyclic ring (having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur), a 5-6 membered

monocyclic heteroaromatic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), and an 8-10 membered bicyclic heteroaromatic ring (having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur).

13. The compound of any one of claims 1-8, wherein R^1 is an optionally substituted cyclic group selected from phenyl, cyclohexyl, cyclopentyl, cycloheptyl, tetrahydrofuranyl, tetrahydropyranyl, indole, and benzotriazole.

14. The compound of any one of claims 1-8, wherein R^1 is optionally substituted cyclohexyl.

15. The compound of any one of claims 1-8, wherein R^1 is optionally substituted phenyl.

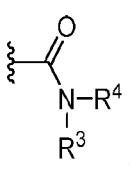
16. The compound of any one of claims 1-15, wherein R^2 is an optionally substituted C_{1-6} aliphatic group, $-C(O)OR$, $-C(O)NR_2$, or an optionally substituted cyclic group selected from phenyl and a 5-6 membered monocyclic heteroaromatic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur).

17. The compound of any one of claims 1-15, wherein R^2 is $C(O)NR_2$.

18. The compound of any one of claims 1-15, wherein R^2 is hydrogen, methyl, $-C(O)NHCH_3$, $-C(O)NH_2$, $-C(O)OCH_3$, or $-C(O)OH$.

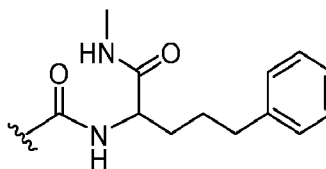
19. The compound of any one of claims 1-15, wherein R^2 is a 5-6 membered monocyclic heteroaromatic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur).

20. The compound of any one of claims 1-15, wherein R^2 is an oxazolyl or pyrimidinyl group.

21. The compound of claim 1, wherein R^A is .

22. The compound of claim 1 or 21, wherein R^4 is a cyclic group selected from a 3-8 membered saturated or partially unsaturated monocyclic heterocyclic ring (having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur), and a 5-6 membered monocyclic heteroaromatic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), wherein the cyclic group is optionally substituted with one or more instances of R^5 .
23. The compound of claim 1 or 21, wherein R^4 is a cyclic group selected from phenyl, pyridine, and piperidine, wherein the cyclic group is optionally substituted with one or more instances of R^5 .
24. The compound of claim 1 or 21-23, wherein R^5 is $-OR$, $-C(O)R$, an optionally substituted C_{1-6} aliphatic group, or an optionally substituted $-C_{1-6}$ aliphatic-Cy group.
25. The compound of claim 1 or 21-23, wherein R^5 is an optionally substituted benzyl group, an optionally substituted benzoyl group, an optionally substituted phenoxy group, or an optionally substituted phenylacetyl group.
26. The compound of any one of claims 1-25, wherein each R^3 is hydrogen.
27. The compound of claim 1, wherein R^A is a substituent of **Table A1** or **Table A2**.
28. The compound of claim 1, wherein R^A is a substituent of **Table A1**.
29. The compound of claim 1, wherein R^A is a substituent of **Table A2**.

30. The compound of claim 1, wherein R^A is



31. The compound of anyone of claims 1-30, wherein L^2 is a saturated, straight, optionally

substituted bivalent C₁₋₄ hydrocarbon chain, wherein 1 methylene unit of L² is replaced by -C(O)-

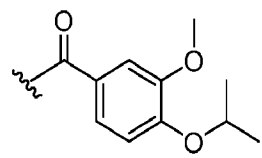
32. The compound of anyone of claims 1-30, wherein L² is -C(O)-.

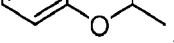
33. The compound of anyone of claims 1-32, wherein R⁶ is a cyclic group selected from a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, a 7-12 membered saturated or partially unsaturated bicyclic carbocyclic ring, phenyl, an 8-10 membered bicyclic aromatic carbocyclic ring, a 3-8 membered saturated or partially unsaturated monocyclic heterocyclic ring (having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur), a 7-12 membered saturated or partially unsaturated bicyclic heterocyclic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), a 5-6 membered monocyclic heteroaromatic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), and an 8-10 membered bicyclic heteroaromatic ring (having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur), wherein the cyclic group is optionally substituted with one or more instances of R⁷.

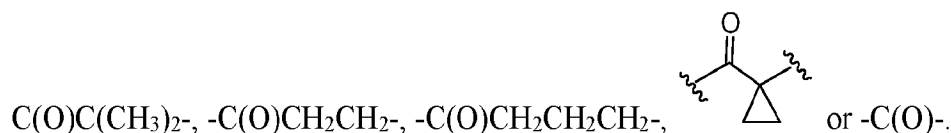
34. The compound of anyone of claims 1-32, wherein R⁶ is a cyclic group selected from phenyl, an 8-10 membered bicyclic aromatic carbocyclic ring, a 5-6 membered monocyclic heteroaromatic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), and an 8-10 membered bicyclic heteroaromatic ring (having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur), wherein the cyclic group is optionally substituted with one or more instances of R⁷.

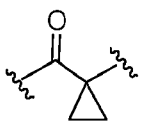
35. The compound of anyone of claims 1-32, wherein R⁶ is a cyclic group selected from cyclohexyl, phenyl, quinoliny, isoquinoliny, quinoxaliny, 2,3-dihydrobenzo[b][1,4]dioxiny, pyrazoly, isoxazoly, imidazoly, thiazoly, pyridiny, pyraziny, pyridaziny, pyrimidiny, 2,3-dihydrobenzo[d]furany, benzofurany, indoly, benzo[1,2,3]triazole, benzimidazoly, imidazo[1,2-a]pyrimidiny, imidazo[1,2-a]pyraziny, indazoly, indoliny, indoliziny, isoindoliny, and 2,3-dihydrobenzo[d]oxazoly, wherein the cyclic group is optionally substituted with one or more instances of R⁷.

36. The compound of anyone of claims 1-35, wherein each R^7 is independently halogen, $-CN$, $-OR$, $-NR_2$, $-S(O)_2NR_2$, $-N(R)C(O)R$, $-N(R)C(O)S(O)_2R$, an optionally substituted C_{1-6} aliphatic group, or Cy, or two instances of R^7 on the same carbon atom are taken together to form an oxo group.
37. The compound of anyone of claims 1-35, wherein each R^7 is independently halogen, $-CN$, $-OR$, $-NR_2$, $-S(O)_2NR_2$, $-N(R)C(O)R$, $-N(R)C(O)S(O)_2R$, an optionally substituted C_{1-6} aliphatic group, or Cy, or two instances of R^7 on the same carbon atom are taken together to form an oxo group.
38. The compound of anyone of claims 1-30, wherein $-L^2-R^6$ is a substituent of **Table B1** or **Table B2**.
39. The compound of anyone of claims 1-30, wherein $-L^2-R^6$ is a substituent of **Table B1**.
40. The compound of anyone of claims 1-30, wherein $-L^2-R^6$ is a substituent of **Table B2**.



41. The compound of anyone of claims 1-30, wherein $-L^2-R^6$ is .
42. The compound of anyone of claims 1-41, wherein L^3 is a saturated, straight, optionally substituted bivalent C_{1-4} hydrocarbon chain, wherein 1 methylene unit of L^3 is replaced by $-O-$, $-NR-$, $-OC(O)-$, $-C(O)O-$, $-C(O)-$, $-NRC(O)-$, or $-C(O)NR$.
43. The compound of anyone of claims 1-41, wherein L^3 is a saturated, straight, optionally substituted bivalent C_{1-4} hydrocarbon chain, wherein 1 methylene unit of L^3 is replaced by $-C(O)-$.
44. The compound of anyone of claims 1-41, wherein L^3 is $-C(O)CH_2-$, $-C(O)C(CH_3)H-$, $-$



45. The compound of anyone of claims 1-41, wherein L^3 is $\text{-C(O)CH}_2\text{-}$,  or $\text{-C(O)C(CH}_3)_2\text{H-}$.

46. The compound of anyone of claims 1-45, wherein R^8 is a cyclic group selected from phenyl, a 3-8 membered saturated or partially unsaturated monocyclic heterocyclic ring (having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur), a 7-12 membered saturated or partially unsaturated bicyclic heterocyclic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), a 5-6 membered monocyclic heteroaromatic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), and an 8-10 membered bicyclic heteroaromatic ring (having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur), wherein the cyclic group is optionally substituted with one or more instances of R^9 .

47. The compound of anyone of claims 1-45, wherein R^8 is an 8-10 membered bicyclic heteroaromatic ring (having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur), optionally substituted with one or more instances of R^9 .

48. The compound of anyone of claims 1-45, wherein R^8 is a cyclic group selected from indolyl, indazolyl, benzimidazolyl, benzofuranyl, phenyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, quinolinyl, isoquinolinyl, pyrazolyl, tetrazolyl, quinoxalinyl, indolizinyl, thiazolyl, oxazolyl, pyrrolyl, imidazo[1,2-a]pyrazinyl, and tetrahydropyranyl wherein the cyclic group is optionally substituted with one or more instances of R^9 .

49. The compound of anyone of claims 1-48, wherein each instance of R^9 is independently halogen, -CN , -OR , or an optionally substituted C_{1-6} aliphatic group.

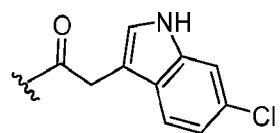
50. The compound of anyone of claims 1-48, wherein each instance of R^9 is independently chloro, bromo, -CN, methyl, or methoxy.

51. The compound of anyone of claims 1-41, wherein $-L^2-R^6$ is a substituent of **Table C1** or **Table C2**.

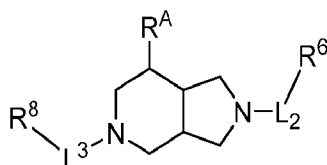
52. The compound of anyone of claims 1-41, wherein $-L^2-R^6$ is a substituent of **Table C1**.

53. The compound of anyone of claims 1-41, wherein $-L^2-R^6$ is a substituent of **Table C2**.

54. The compound of anyone of claims 1-41, wherein $-L^2-R^6$ is



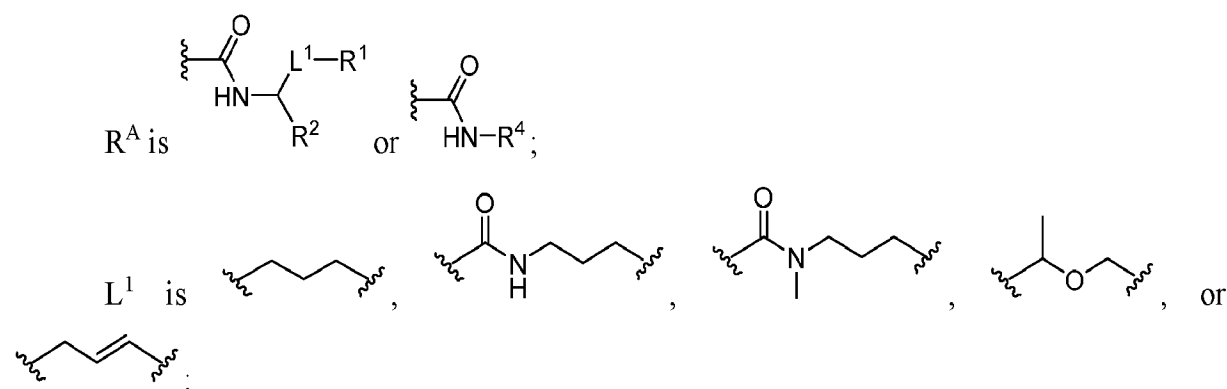
55. The compound of claim 1, wherein the compound of Formula **I** is a compound of Formula **II**:



II

or a pharmaceutically acceptable salt thereof.

56. The compound of claim 1 or claim 55, wherein



R^1 is a C_{1-4} aliphatic group or an optionally substituted cyclic group selected from a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, phenyl, a 3-8 membered saturated or partially unsaturated monocyclic heterocyclic ring (having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur), a 5-6 membered monocyclic heteroaromatic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), and an 8-10 membered bicyclic heteroaromatic ring (having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur);

R^2 is hydrogen, methyl, $-C(O)NHCH_3$, $-C(O)NH_2$, $-C(O)OCH_3$, $-C(O)OH$, or a 5-6 membered monocyclic heteroaromatic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur);

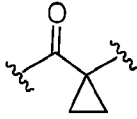
R^4 is a cyclic group selected from a 3-8 membered saturated or partially unsaturated monocyclic heterocyclic ring (having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur), and a 5-6 membered monocyclic heteroaromatic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), wherein the cyclic group is optionally substituted with one or more instances of R^5 ;

each R^5 is independently $-OR$, $-C(O)R$, an optionally substituted C_{1-6} aliphatic group, or an optionally substituted $-C_{1-6}$ aliphatic-Cy group;

L^2 is $-C(O)-$;

R^6 is a cyclic group selected from phenyl, an 8-10 membered bicyclic aromatic carbocyclic ring, a 5-6 membered monocyclic heteroaromatic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), and an 8-10 membered bicyclic heteroaromatic ring (having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur), wherein the cyclic group is optionally substituted with one or more instances of R^7 ;

each R^7 is independently $-OR$, an optionally substituted C_{1-6} aliphatic group, Cy or two instances of R^7 on the same carbon atom are taken together to form an oxo group;

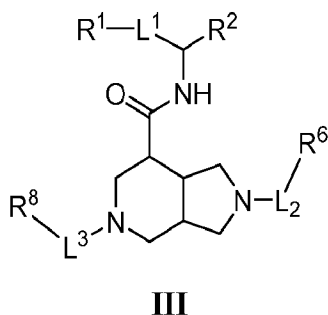
L^3 is $-C(O)CH_2-$,  or $-C(O)C(CH_3)H-$;

R^8 is an 8-10 membered bicyclic heteroaromatic ring (having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur), optionally substituted with one or more instances of R^9 ;

each instance of R^9 is independently halogen, $-CN$, $-OR$, or a C_{1-6} aliphatic group; and

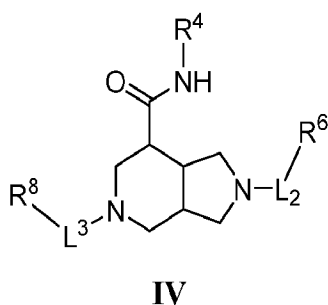
each instance of Cy is independently phenyl or a 5-6 membered monocyclic heteroaromatic ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur).

57. The compound of claim 1, wherein the compound of Formula **I** is a compound of Formula **III**:



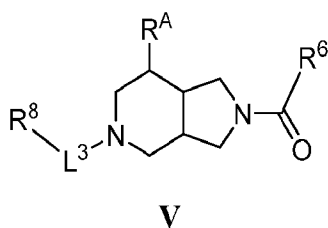
or a pharmaceutically acceptable salt thereof.

58. The compound of claim 1, wherein the compound of Formula **I** is a compound of Formula **IV**:



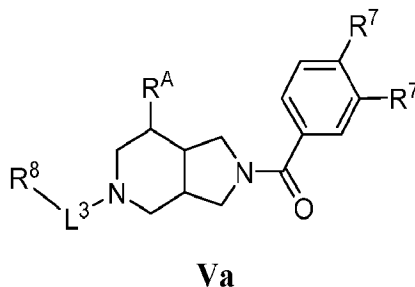
or a pharmaceutically acceptable salt thereof.

59. The compound of claim 1, wherein the compound of Formula **I** is a compound of Formula **V**:



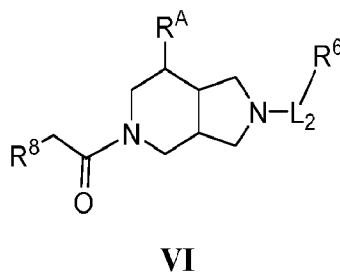
or a pharmaceutically acceptable salt thereof.

60. The compound of claim 1, wherein the compound of Formula **I** is a compound of Formula **Va**:



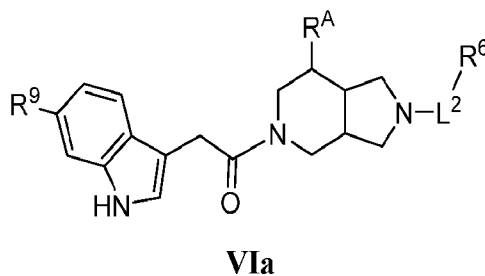
or a pharmaceutically acceptable salt thereof.

61. The compound of claim 1, wherein the compound of Formula **I** is a compound of Formula **VI**:



or a pharmaceutically acceptable salt thereof.

62. The compound of claim 1, wherein the compound of Formula **I** is a compound of Formula **VIa**:



or a pharmaceutically acceptable salt thereof.

63. The compound of claim 1, wherein the compound is one of those in **Table 1** or a pharmaceutically acceptable salt thereof.

64. A pharmaceutically acceptable composition comprising a compound of any of claims 1-

63, and a pharmaceutically acceptable carrier, excipient, vehicle, adjuvant or diluent.

65. The pharmaceutically acceptable composition of claim 64, further comprising an additional therapeutic agent.

66. A method of inhibiting the activity of a cyclin-dependent kinase (CDK) comprising contacting a compound of any one of claims 1-63 with the CDK.

67. A method of treating a disease or disorder associated with CDK2 activity in a patient comprising administering to the patient in need thereof a compound of any one of claims 1-63 or a pharmaceutical composition of any one of claims 64-65.

68. The method of claim 67, wherein the disease or disorder associated with CDK2 activity is selected from cancers, myeloproliferative disorders, autoimmune disorders, inflammatory disorders, viral infections, and fibrotic disorders.

69. The method of claim 67, wherein the disease or disorder associated with CDK2 activity is a cancer.

70. The method of claim 67, wherein the disease or disorder associated with CDK2 activity is a cancer selected from breast cancer, ovarian cancer, bladder cancer, uterine cancer, prostate cancer, lung cancer, esophageal cancer, head and neck cancer, colorectal cancer, kidney cancer, liver cancer, pancreatic cancer, stomach cancer, melanoma and thyroid cancer.

71. The method of claim 67, wherein the disease or disorder associated with CDK2 activity is liver fibrosis.

72. The method of claim 67, wherein the disease or disorder associated with CDK2 activity is Cushing disease.

73. The method of claim 67, wherein the disease or disorder associated with CDK2 activity is

polycystic kidney disease.

74. The method of claim 67, wherein the disease or disorder associated with CDK2 activity is Alzheimer's disease.

75. A method of reducing male fertility comprising administering to the patient in need thereof a compound of any one of claims 1-63 or a pharmaceutical composition of any one of claims 64-65.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 22/34963

A. CLASSIFICATION OF SUBJECT MATTER

IPC - INV. A61K 31/4162, A61K 31/33, A61K 45/00; ADD. A61K 31/00 (2022.01)

CPC - INV. A61K 31/4162, A61K 31/33, A61K 45/00; ADD. A61K 31/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2009/0111794 A1 (Bacani et al.) 30 April 2009 (30.04.2009); para[0276]	1-8, 21-23, 27-30, 55-63
A	US 2017/0037050 A1 (Medshine Discovery Inc.) 09 February 2017 (09.02.2017);	1-8, 21-23, 27-30, 55-63
A	Pubmed Compound Record for Cid 143728706, '1-N-cyclopentyl-7a-hydroxy-3-oxo-2-(2-oxoethyl)-4-N-[4-(trifluoromethyl)phenyl]-1,3a,4,5,6,7-hexahydropyrrolo[3,4-c]pyridine-1,4-dicarboxamide', U.S. National Library of Medicine, 07 December 2019 (07.12.2019), pages 1-8 (https://pubchem.ncbi.nlm.nih.gov/compound/143728706); p2	1-8, 21-23, 27-30, 55-63
A	US 2019/0218230 A1 (Janssen Pharmaceutica NV) 18 July 2019 (18.07.2019); entire document	1-8, 21-23, 27-30, 55-63
A	WO 2009/019286 A1 (Abbott Gmbh & Co. Kg) 12 February 2009 (12.02.2009); entire document	1-8, 21-23, 27-30, 55-63

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"D" document cited by the applicant in the international application

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

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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

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

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

02 September 2022

Date of mailing of the international search report

SEP 26 2022

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents

P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-8300

Authorized officer

Kari Rodriguez

Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 22/34963

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 9-20, 24-26, 31-54, 64-75
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.