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(54) Title: MASP-2 INHIBITORS AND METHODS OF USE

(57) **Abstract:** The present disclosure provides, *inter alia*, compounds with MASP-2 inhibitory activity, compositions of such compounds, and methods of making and using such compounds.

MASP-2 INHIBITORS AND METHODS OF USE

STATEMENT REGARDING SEQUENCE LISTING

The Sequence Listing associated with this application is provided in text format in lieu of a paper copy, and is hereby incorporated by reference into the specification. The name of the text file containing the Sequence Listing is 700128_423WO_SEQUENCE_LISTING.txt. The text file is 6.0 KB, was created on December 3, 2020, and is being submitted electronically via EFS-Web.

TECHNICAL FIELD

The present disclosure is directed generally to compositions and methods that are useful in the field of medicine. More specifically, the disclosure provides synthetic inhibitors of mannan-binding lectin-associated serine protease-2 (MASP-2), including inhibitors that selectively inhibit MASP-2 over thrombin, compositions thereof, and methods for the manufacture and use thereof.

BACKGROUND

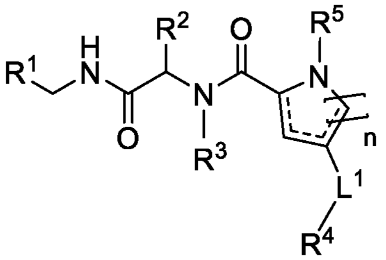
The complement system plays a role in the inflammatory response and becomes activated because of tissue damage or microbial infection. Complement activation must be tightly regulated to ensure selective targeting of invading microorganisms and avoid self-inflicted damage (Ricklin et al., Nat. Immunol. 11 :785-797, 2010). Currently, it is widely accepted that the complement system can be activated through three distinct pathways: the classical pathway, the lectin pathway, and the alternative pathway. The classical pathway is usually triggered by a complex composed of host antibodies bound to a foreign particle (*i.e.*, an antigen) and generally requires prior exposure to an antigen for the generation of a specific antibody response. Since activation of the classical pathway depends on a prior adaptive immune response by the host, the classical pathway is part of the acquired immune system. In contrast, both the lectin and alternative pathways are independent of adaptive immunity and are part of the innate immune system.

Mannan-binding lectin-associated serine protease-2 (MASP-2) has been shown to be required for the function of the lectin pathway, one of the principal complement activation pathways (Vorup-Jensen et al., J. Immunol 165:2093-2100, 2000; Ambrus et al., J Immunol. 170: 1374-1382, 2003; Schwaeble et al., PNAS 108:7523-7528, 2011). Importantly, inhibition of MASP-2 does not appear to interfere with the antibody-dependent classical complement activation pathway, which is a critical component of the acquired immune response to infection. As described in U.S. Patent No. 9,011,860 (assigned to Omeros Corporation), which is hereby incorporated by reference, discloses a fully human monoclonal antibody targeting human MASP-2 has been generated which binds to human MASP-2 with high affinity and blocks the lectin pathway complement activity and is therefore useful to treat various lectin complement pathway-associated diseases and disorders.

MASP-2-dependent complement activation has been implicated as contributing to the pathogenesis of numerous acute and chronic disease states. Therefore, a need exists for compounds that are suitable for administration/treatment of subject suffering from MASP-2 complement pathway-associated diseases and disorders, including diseases that are not suitably or efficiently treated with large molecule biologic inhibitors.

BRIEF SUMMARY

One embodiment provides a compound having the following Structure (I):



(I)

or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein ═══, R^1, R^2, R^3, R^4, R^5, L^1, and n are as defined herein.

Additional embodiments of the present disclosure provide a pharmaceutical composition comprising a compound of Structure (I), or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier or excipient.

The compounds of Structures (I) are useful in the treatment of MASP-2-associated diseases and disorders, and in the manufacture of medicaments for treating MASP-2-associated diseases and disorders. Accordingly, other embodiments of the disclosure provide methods of treating a MASP-2-associated disease and disorder comprising administering to a patient a therapeutically effective amount of a compound of Structure (I), or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof.

These and other aspects, objects and embodiments will become more apparent when read with the detailed description and figures which follow.

DETAILED DESCRIPTION

I. Definitions

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the subject matter of the present disclosure, suitable methods and materials are described below. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

In certain embodiments herein, reference is made to features and aspects of the disclosure, including method steps. All possible combinations of such features and aspects within the embodiments of the disclosure are included, at least to the extent that such combinations are non-contradictory. For example, if an embodiment presents aspects A, B, and C, it is understood that this also discloses embodiments including both aspects A and B, both aspects B and C, and both aspects A and C, as well as an embodiment with aspects A, B, and C.

The terms "a," "an," or "the" not only include aspects with one member, but also include aspects with more than one member. For instance, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise.

Thus, for example, reference to "a cell" includes a plurality of such cells and reference to "the agent" includes reference to one or more agents known to those skilled in the art.

The terms "about" and "approximately" refer to an acceptable degree of error for the quantity measured given the nature or precision of the measurements. Typical, exemplary degrees of error are within ± 20 percent (%); preferably, within ± 10%; and more preferably, within ± c5% of a given value or range of values. Any reference to "about X" specifically indicates at least the values X, 0.95X, 0.96X, 0.97X, 0.98X, 0.99X, 1.01X, 1.02X, 1.03X, 1.04X, and 1.05X. Thus, "about X" is intended to teach and provide written support for a claim limitation of, *e.g.*, "0.98X." Alternatively, in biological systems, the terms "about" and "approximately" may mean values that are within an order of magnitude, preferably within 5-fold, and more preferably within 2-fold of a given value. Numerical quantities given herein are approximate unless stated otherwise, meaning that the term "about" or "approximately" can be inferred when not expressly stated. When "about" is applied to the beginning of a numerical range, it applies to both ends of the range. Thus, "from about 5 to 20%" is equivalent to "from about 5% to about 20%." When "about" is applied to the first value of a set of values, it applies to all values in that set. Thus, "about 7, 9, or 11 mg/kg" is equivalent to "about 7, about 9, or about 11 mg/kg."

The term "MASP-2" refers to mannan-binding lectin-associated serine protease-2. Human MASP-2 protein with UniProt accession code O00187 (SEQ ID NO:1). The Serine Protease Domain ('B-chain' = Mannan-binding lectin serine protease 2 B chain, based on UniProtKB - O00187 (MASP-2_HUMAN)) includes residues 445 to 686 (or consists of residues 445 to 686).

The term "MASP-2-dependent complement activation" refers to MASP-2-dependent activation of the lectin pathway, which occurs under physiological conditions (*i.e.*, in the presence of Ca^{++}) leading to the formation of the lectin pathway C3 convertase C4b2a and upon accumulation of the C3 cleavage product C3b subsequently to the C5 convertase C4b2a(C3b)n.

The term "MASP-2-dependent complement-associated disease or disorder" refers to a disease or disorder that is associated with MASP-2-dependent complement activation.

The term "MASP-2-associated disease or disorder" refers to a disease or disorder that is associated with activation or activity of MASP-2, including MASP-2-dependent complement-associated disease or disorders, and wherein inhibition of MASP-2 is or is expected to be therapeutically beneficial.

The term "lectin pathway" refers to complement activation that occurs via the specific binding of serum and non-serum carbohydrate-binding proteins including mannan-binding lectin (MBL), CL-11 and the ficolins (H-ficolin, M-ficolin, or L-ficolin).

The term "classical pathway" refers to complement activation that is triggered by an antibody bound to a foreign particle and requires binding of the recognition molecule Clq.

Amino acid residues are abbreviated as follows: alanine (Ala; A), asparagine (Asn; N), aspartic acid (Asp; D), arginine (Arg; R), cysteine (Cys; C), glutamic acid (Glu; E), glutamine (Gln; Q), glycine (Gly; G), histidine (His; H), isoleucine (Ile), leucine (Leu), lysine (Lys; K), methionine (Met; M), phenylalanine (Phe; F), proline (Pro; P), serine (Ser; S), threonine (Thr; T), tryptophan (Trp; W), tyrosine (Tyr; Y), and valine (Val; V).

In the broadest sense, the naturally occurring amino acids can be divided into groups based upon the chemical characteristic of the side chain of the respective amino acids. By "hydrophobic" amino acid is meant either His, Leu, Met, Phe, Trp, Tyr, Val, Ala, Cys or Pro. By "hydrophilic" amino acid is meant either Gly, Asn, Gln, Ser, Thr, Asp, Glu, Lys, Arg or His. This grouping of amino acids can be further sub-classed as follows: by "uncharged hydrophilic" amino acid is meant either Ser, Thr, Asn or Gln. By "acidic" amino acid is meant either Glu or Asp. By "basic" amino acid is meant either Lys, Arg or His.

The term "conservative amino acid substitution" is illustrated by a substitution among amino acids within each of the following groups:

(1) glycine, alanine, valine, leucine, and isoleucine;

(2) phenylalanine, tyrosine, and tryptophan;

(3) serine and threonine;

(4) aspartate and glutamate;

(5) glutamine and asparagine; and

(6) lysine, arginine and histidine.

The term "a subject" includes all mammals, including without limitation, humans, non-human primates, dogs, cats, horses, sheep, goats, cows, rabbits, pigs, and rodents.

"Mammal" includes humans and both domestic animals such as laboratory animals and household pets, (*e.g.*, cats, dogs, swine, cattle, sheep, goats, horses, rabbits), and non-domestic animals such as wildlife and the like.

The terms "small molecule" and "small organic molecule" refers to a small carbon-containing molecule that has a molecular weight of about 2500 daltons or lower. In some embodiments, a small molecule has a molecular weight of about 2000 daltons or lower. In some embodiments, a small molecule has a molecular weight of about 1500 daltons or lower. In some embodiments, a small molecule has a molecular weight of about 1000 daltons or lower. In some embodiments, a small molecule has a molecular weight of about 750 daltons or lower. In some embodiments, a small molecule has a molecular weight of about 500 daltons or lower. In some embodiments, a small molecule has a molecular weight of about 50 daltons or greater. In some embodiments, a small molecule has a molecular weight of about 75 daltons or greater. In some embodiments, a small molecule has a molecular weight of about 100 daltons or greater. In some embodiments, a small molecule has a molecular weight of about 150 daltons or greater. In some embodiments, a small molecule has a molecular weight of about 250 daltons or greater. In some emboiments, small molecules may have a molecular weight in the range from about 50 daltons to about 500 daltons, from about 50 daltons to about 750 daltons, from about 50 daltons to about 1000 daltons, from about 50 daltons to about 1500 daltons, from about 50 daltons to about 2000 daltons, or from about 50 daltons to about 2500 daltons. When the term "compound" is used herein, the term is explicitly intended to include small molecule compounds as defined herein (including any of the embodiments thereof).

As used herein, the terms "disease" and "condition" may be used interchangeably or may be different in that the particular malady or condition may not have a known causative agent (so that etiology has not yet been worked out) and it is therefore not yet recognized as a disease but only as an undesirable condition or syndrome, wherein a more or less specific set of symptoms have been identified by clinicians. In some embodiments, a disease is a pathological condition of an organ, a body part, or a system resulting from various causes, such as infection, genetic defect, or environmental stress that is characterized by an identifiable group of symptoms.

"Therapeutically effective amount," "effective amount," or "effective dose" refers to that amount of a compound of the disclosure that, when administered to a mammal (*e.g.*, a human), is sufficient to effect treatment, as defined below, of a disease or condition in the mammal, preferably a human. The amount of a compound of the disclosure which constitutes a "therapeutically effective amount" will vary depending on the compound, the condition and its severity, the manner of administration, and the age of the mammal to be treated, but can be determined routinely by one of ordinary skill in the art having regard to his own knowledge and to this disclosure.

The term "subcutaneous administration" refers to administration of a formulation under all layers of the skin of a subject.

The term "histidine" specifically includes L-histidine unless otherwise specified.

The term "isotonic" refers to a formulation that has essentially the same osmotic pressure as human blood. Isotonic formulations will generally have an osmotic pressure from about 250 to about 350 mOsmol/L. Isotonicity can be measured using a vapor pressure or freezing point depression osmometer, for example.

The term "hypertonic" refers to a formulation with an osmotic pressure above that of human (*i.e.*, greater than 350 mOsm/L).

The term "hydrogen-bonding" is a partially electrostatic attraction between a hydrogen (H) which is bound to a more electronegative atom such as nitrogen

(N) or oxygen (O) and another adjacent atom bearing a lone pair of electrons. For example, when it is stated that the nitrogen acts as a "hydrogen bond donor" it means that a hydrogen (H) bound to a nitrogen (N) is donated by the nitrogen as it electrostatically attracted to or accepted by an adjacent atom bearing a lone pair of electrons such as an oxygen. Similarly, when it is stated that an oxygen acts as a "hydrogen bond acceptor," it means that a hydrogen (H) bound to a more electronegative atom such as nitrogen (N) is electrostatically attracted to or "accepted by" an adjacent atom such as oxygen bearing a lone pair of electrons. Sometimes the hydrogen bonded atoms are called out without explicitly stating the origin and presence of an intermediate hydrogen atom. The term "hydrogen bonding" is used wherever LigPlot+ software predicts a hydrogen bonding interaction using its algorithm and applied parameters of 3.35 Å for maximum distance between hydrogen bond donor and acceptor. Not all hydrogen bonds may actually be in place simultaneously; this is evident for atoms that are shown to form 4 putative hydrogen bonds, where however, at any given time only 3 hydrogen bonds are chemically possible. In general, although crystal structures such as the co-crystal structural information herein does not directly show or detect hydrogen bonding, the software used to describe the co-crystal does predict such H-bonding exists. Therefore, throughout the disclosure when a H-bond is present and described, it may be said to be "predicted" by software to be present.

The term ionic bonding includes a type of chemical bond that involves the electrostatic attraction between oppositely charged ions, and is the primary interaction occurring in ionic compounds.

The term "van der Waals" interaction includes weak, short-range electrostatic attractive forces between uncharged molecules, arising from the interaction of permanent or transient electric dipole moments. As determined by LigPlot+ software employing models derived from the corresponding crystallographic MASP-2 compound co-structures, such interactions include all contacts that are computed using non-bonded contact parameters between hydrophobic to any contacts for interactions with a maximum contact distance of 3.90 Å.

The term "π–π interaction" or "π–π stacking" interaction includes attractive, non-covalent interactions between aromatic rings that are oriented either roughly parallel or roughly perpendicular (such as in "edge-face" interactions) to each other, since they contain π-bonds.

Typically, the active site of serine proteases such as MASP-2 is shaped as a cleft where the polypeptide substrate or inhibitor binds. Schechter and Berger labeled amino acid residues from the N to C terminus of the polypeptide substrate as follows: Pi,..., P3, P2, P1, P1', P2', P3',..., Pj) and their respective binding sub-sites Si,..., S3, S2, S1, S1', S2', S3',..., Sj. The cleavage is catalyzed between P1 and P1' (Schechter, I. & Berger, A. On the size of the active site in proteases. I. Papain. Biochem. Biophys. Res. Commun. 27 (1967)).

The term "binding site" is an area on the protein wherein a small molecule can interact with, such as a region on the surface of MASP-2. The binding site or region may not or only partially overlap with the active site, but nevertheless render the MASP-2 molecule less active or inactive.

The term "or" refers to an alternative and should in general be construed non-exclusively. For example, a claim to "a composition comprising A or B" would typically present an aspect with a composition comprising both A and B. "Or" should, however, be construed to exclude those aspects presented that cannot be combined without contradiction (*e.g.*, a composition pH that is between 9 and 10 or between 7 and 8).

The group "A or B" is equivalent to the group "selected from the group consisting of A and B."

The linking term "comprising" or "comprise" is not closed. For example, "a composition comprising A" must include at least the component A, but it may also include one or more other components (*e.g.*, B; B and C; B, C, and D; and the like). The term "comprising" therefore should in general be construed as not excluding additional ingredients. For example, a claim to "a composition comprising A" would cover compositions that include A and B; A, B, and C; A, B, C, and D; A, B, C, D, and E; and the like.

The term "hypertonic" refers to a formulation with an osmotic pressure above that of human (*i.e.*, greater than 350 mOsm/KglHhO).

The term "agent" refers to a compound or mixture of compounds that, when added to a composition, tend to produce an effect on the composition's properties. For example, a composition comprising a thickening agent is likely to be more viscous than an otherwise identical comparative composition that lacks the thickening agent.

A "synthetic" compound means a compound that is not naturally occurring and that has been synthesized by humans. Reference to a compound herein may be understood to include reference to synthetic compounds, unless the context indicates otherwise.

The expressions, "ambient temperature" and "room temperature," as used herein, are understood in the art, and refer generally to a temperature, *e.g.*, a reaction temperature, that is about the temperature of the room in which the reaction is carried out, *e.g.*, a temperature from about 20 °C to about 30 °C.

At various places in the present specification, certain features of the compounds are disclosed in groups or in ranges. It is specifically intended that such a disclosure include each and every individual sub-combination of the members of such groups and ranges. For example, the terms "C_{1-6} alkyl" and "C_1-C_6 alkyl" are specifically intended to individually disclose (without limitation) methyl, ethyl, C_3 alkyl, C_4 alkyl, C_5 alkyl, and C_6 alkyl.

The term "substituted" means that an atom or group of atoms formally replaces hydrogen as a "substituent" attached to another group. The term "substituted", unless otherwise indicated, refers to any level of substitution, *e.g.*, mono-, di-, tri-, tetra-, penta-, or higher substitution, where such substitution is permitted (*e.g.*, results in a stable compound). The substituents are independently selected, and substitution may be at any chemically accessible position. It is to be understood that substitution at a given atom is limited by valency. The phrase "optionally substituted" means substituted or unsubstituted. The term "substituted" means that at least hydrogen atom is replaced with a substituent. A single divalent substituent, *e.g.*, oxo, can replace two hydrogen atoms.

The terms "C_{n-m}" and "C_n-C_m" where n and m are integers indicates a group that contains from n to m carbon atoms. Examples include C_{1-4}, C_{1-6}, and the like. The term is intended to expressly disclose every member in the range, *i.e.*, C_n, C_{n+1}, C_{n+2} … C_{m-2}, C_{m-1}, C_m. For example, C_{1-6} is intended to disclose C_1, C_2, C_3, C_4, C_5, and C_6. As used herein, "C_{n-m}" means the same as "C_n-C_m".

The term "n-membered," where n is an integer (*e.g.*, 6-membered), typically describes the number of ring-forming atoms in a moiety where the number of ring-forming atoms is n. The term "n-m membered" wherein n and m are integers (*e.g.*, 6-10 membered) describes a range where the number of ring forming atoms is from n to m. For example, piperidinyl is an example of a 6-membered heterocyclyl ring, pyrazolyl is an example of a 5-membered heteroaryl ring, pyridyl is an example of a 6-membered heteroaryl ring and 1,2,3,4-tetrahydro-naphthalene is an example of a 10-membered cycloalkyl group.

"Alkyl" refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing no unsaturation, having from one to twelve carbon atoms, preferably one to eight carbon atoms, more preferably one to six carbon atoms, which is attached to the rest of the molecule by a single bond, *e.g.*, methyl, ethyl, n-propyl, 1-methylethyl (iso-propyl), n-butyl, n-pentyl, 1,1-dimethylethyl (t-butyl), 3-methylhexyl, 2-methylhexyl, and the like. In certain specific embodiments, an alkyl group may be optionally substituted by one of the following groups: alkyl, alkenyl, halo, haloalkenyl, cyano, nitro, aryl, cycloalkyl, heterocyclyl, heteroaryl, oxo, trimethylsilanyl, $-OR^{100}$, $-OC(O)R^{100}$, $-N(R^{100})_2$, $-C(O)R^{100}$, $-C(O)OR^{100}$, $-C(O)N(R^{100})_2$, $-N(R^{20})C(O)OR^{102}$, $-N(R^{100})C(O)R^{102}$, $-N(R^{102})S(O)_pR^{102}$ (where p is 1 to 2), $-S(O)_pOR^{102}$ (where p is 1 to 2), $-S(O)_tR^{102}$ (where t is 0 to 2), and $-S(O)_pN(R^{100})_2$ (where p is 1 to 2) where each R^{100} is independently hydrogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroarylalkyl; and each R^{102} is alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl.

"Alkenyl" refers to a straight or branched hydrocarbon chain radical group consisting solely of carbon and hydrogen atoms, containing at least one double bond, having from two to twelve carbon atoms, preferably two to eight carbon atoms and which is attached to the rest of the molecule by a single bond, *e.g.*, ethenyl, prop-1-enyl, but-1-enyl, pent-1-enyl, penta-1,4-dienyl, and the like. In certain embodiments, an alkyl group may be optionally substituted by one of the following groups: alkyl, alkenyl, halo, haloalkenyl, cyano, nitro, aryl, cycloalkyl, heterocyclyl, heteroaryl, oxo, trimethylsilanyl, $-OR^{100}$, $-OC(O)R^{100}$, $-N(R^{100})_2$, $-C(O)R^{100}$, $-C(O)OR^{100}$, $-C(O)N(R^{100})_2$, $-N(R^{20})C(O)OR^{102}$, $-N(R^{100})C(O)R^{102}$, $-N(R^{102})S(O)_pR^{102}$ (where p is 1 to 2), $-S(O)_pOR^{102}$ (where p is 1 to 2), $-S(O)_tR^{102}$ (where t is 0 to 2), and $-S(O)_pN(R^{100})_2$ (where p is 1 to 2) where each R^{100} is independently hydrogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroarylalkyl; and each R^{102} is alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl.

"Alkynyl" refers to a straight-chain or branched hydrocarbon group corresponding to an alkyl group as defined above having one or more triple carbon-carbon bonds. An alkynyl group formally corresponds to an alkyne with one C-H bond replaced by the point of attachment of the alkyl group to the remainder of the compound. The term "C_{n-m} alkynyl" and "C_n-C_m alkynyl" refer to an alkynyl group having n to m carbons. Example alkynyl groups include, but are not limited to, ethynyl, propyn-1-yl, propyn-2-yl and the like. In some embodiments, the alkynyl moiety contains 2 to 6, 2 to 4, or 2 to 3 carbon atoms. Unless indicated otherwise, alkynyl groups are optionally substituted.

"Alkylene" or "alkylene chain" refers to a straight or branched divalent hydrocarbon chain linking the rest of the molecule to a radical group or linking two parts of the molecule, consisting solely of carbon and hydrogen, containing no unsaturation and having from one to twelve carbon atoms, *e.g.*, methylene, ethylene, propylene, n-butylene, and the like. The alkylene chain may optionally contain one or more heteroatoms wherein a carbon in the alkylene chain is replaced with a heteroatom selected from oxygen, nitrogen or sulfur. The alkylene chain is attached to the rest of the molecule through a single bond and to the radical group through a single bond or is attached to two parts of the molecule through a single bond at each point of attachment. In some embodiments, an alkyl group may be optionally substituted by one of the following groups: alkyl, alkenyl, halo, haloalkenyl, cyano, nitro, aryl, cycloalkyl, heterocyclyl, heteroaryl, oxo, trimethylsilanyl, $-OR^{100}$, $-OC(O)R^{100}$, $-N(R^{100})_2$, $-C(O)R^{100}$, $-C(O)OR^{100}$, $-C(O)N(R^{100})_2$, $-N(R^{20})C(O)OR^{102}$, $-N(R^{100})C(O)R^{102}$, $-N(R^{102})S(O)_pR^{102}$ (where p is 1 to 2), $-S(O)_pOR^{102}$ (where p is 1 to 2), $-S(O)_tR^{102}$ (where t is 0 to 2), and $-S(O)_pN(R^{100})_2$ (where p is 1 to 2) where each R^{100} is independently hydrogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroarylalkyl; and each R^{102} is alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl.

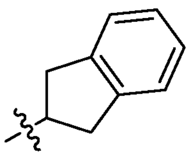
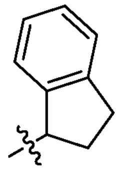
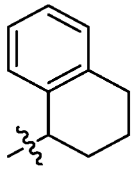
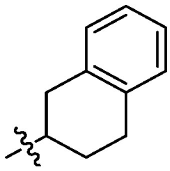
The term "hydroxyalkyl" refers to an alkyl group as defined above in which one or more of the hydrogen atoms has been replaced by a hydroxy group (*i.e.*, -OH). The term "C_{n-m} hydroxyalkyl" refers to a C_{n-m} alkyl group having n to m carbon atoms and from at least one hydroxy group. In some embodiments, the hydroxyalkyl group comprises one hydroxy group. In certain aspects, the hydroxyalkyl group comprises two or more hydroxy groups (*e.g.*, a "dihydroxyalkyl"), each on the same or a different carbon atom(s). In certain aspects, the hydroxyalkyl group has 1, 2, 3, 4, 5, 6, or more hydroxy groups. Examples may include, but are not limited to, hydroxymethyl, 2-hydroxyethyl, and 1-hydroxyethyl.

"Aminylalkyl" refers to an alkyl group as defined above in which one or more hydrogen atoms have been replaced by an aminyl group (*i.e.*, $-NR^{100}R^{101}$ wherein R^{100} and R^{101} are each independently hydrogen, alkyl, alkenyl, or alkynyl as defined herein). In some embodiments, the aminylalkyl comprises one aminyl group. In some embodiments, the aminyl group is $-NH_2$.

"Carboxyalkyl" refers to an alkyl group as defined above in which one or more hydrogen atoms have been replaced by a carboxy group (*i.e.*, -C(O)OH). In some embodiments, the carboxyalkyl comprises one carboxy group.

"Phosphonalkyl" refers to an alkyl group as defined above in which one or more hydrogen atoms have been replaced by a phosphonate group (e.g., $-P(=O)(OR)_2$, wherein R is hydrogen, alkyl, aryl, heteroaryl, arylalkyl, or heteroarylalkyl). In some embodiments, a phosphonalkyl group is $-(CH_2)_nP(=O)(OR)_2$ wherein R is, at each occurrence, independently hydrogen, alkyl, aryl, heteroaryl, arylalkyl, or heteroarylalkyl. In some more specific embodiments, R is, at each occurrence, independently hydrogen or alkyl. In some embodiments, the phosphonalkyl comprises one phosphonate group.

"Aryl" refers to a hydrocarbon ring system radical comprising hydrogen, 6 to 18 carbon atoms and at least one aromatic ring. For purposes of this disclosure, the aryl radical may be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which may include fused or bridged ring systems. Aryl radicals include, but are not limited to, aryl radicals derived from aceanthrylene, acenaphthylene, acephenanthrylene, anthracene, azulene, benzene, chrysene, fluoranthene, fluorene, *as*-indacene, *s*-indacene, indane, indene, naphthalene, phenalene, phenanthrene, pleiadene, pyrene, and triphenylene. In some embodiments, an aryl group may be optionally substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, halo, haloalkyl, haloalkenyl, cyano, nitro, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, $-R^{101}-OR^{100}$, $-R^{101}OC(O)R^{100}$, $-R^{101}-N(R^{100})_2$, $-R^{101}-N(R^{100})-R^{103}-OR^{100}$, $-R^{101}-C(O)R^{100}$, $-R^{101}-C(O)OR^{100}$, $-R^{101}-C(O)N(R^{100})_2$, $-R^{101}-N(R^{100})C(O)OR^{102}$, $-R^{101}-N(R^{100})C(O)R^{102}$, $-R^{101}-N(R^{100})S(O)_pR^{102}$ (where p is 1 to 2), $-R^{101}-N{=}C(OR^{100})R^{100}$, $-R^{101}-S(O)_pOR^{102}$ (where p is 1 to 2), $-R^{101}-S(O)_tR^{102}$ (where t is 0 to 2), and $-R^{101}-S(O)_pN(R^{100})_2$ (where p is 1 to 2) where each R^{100} is independently hydrogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroarylalkyl; each R^{101} is independently a direct bond or a straight or branched alkylene chain; each R^{102} is alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroarylalkyl, and each R^{103} is a direct bond or a straight or branched alkylene chain. In some embodiments an aryl group has the following structure:

 ;  ;  or  .

"Arylalkyl" or "aralkyl" refers to a group of formula -alkylene–aryl wherein the alkylene group and aryl groups are as defined herein, respectively. In some embodiments, arylalkyl is C_{6-10} aryl-C_{1-3} alkyl. In some embodiments, arylalkyl is C_{6-10}

aryl-C_{1-4} alkyl. In some embodiments, arylalkyl is C_{6-10} aryl-C_{1-3} alkyl. In some embodiments, arylalkyl is phenyl-C_{1-3} alkyl. Examples include, but are not limited to, benzyl, 1-phenylethyl, 4-methylbenzyl, and 1,1,-dimethyl-1-phenylmethyl. In some embodiments, arylalkyl is optionally substituted benzyl.

"Aryloxy" refers to a group with the formula -O-aryl wherein aryl is a group as defined above. In some embodiments, the aryloxy group is -O-C_{6-10} aryl. In some embodiments, the aryloxy is a substituted or unsubstituted phenyloxy (*i.e.*, -O-C_6 aryl).

"Arylalkoxy" refers to a group with the formula -alkoxy-aryl wherein alkoxy and aryl are groups as defined above, respectively. In some embodiments, arylalkoxy is C_{6-10} aryl-C_{1-3} alkoxy. In some embodiments, arylalkoxy is C_{6-10} aryl-C_{1-4} alkoxy. In some embodiments, arylalkoxy is C_{6-10} aryl-C_{1-3} alkoxy. In some embodiments, arylalkoxy is phenyl-C_{1-3} alkoxy (*e.g.*, methoxy).

"Cycloalkyl" refers to a stable non-aromatic monocyclic or polycyclic hydrocarbon radical consisting solely of carbon and hydrogen atoms, which may include fused or bridged ring systems, having from three to fifteen carbon atoms, preferably having from three to ten carbon atoms, and which is saturated or unsaturated and attached to the rest of the molecule by a single bond. Monocyclic radicals include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Polycyclic radicals include, for example, adamantyl, norbornyl, decalinyl, and the like. In some embodiments, a cycloalkyl group may be optionally substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, halo, haloalkyl, haloalkenyl, cyano, nitro, oxo, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, $-R^{101}-OR^{100}$, $-R^{101}-OC(O)-R^{100}$, $-R^{101}-N(R^{100})-R^{103}-OR^{100}$, $-R^{101}-N(R^{100})_2$, $-R^{101}-C(O)R^{100}$, $-R^{101}-C(O)OR^{100}$, $-R^{101}-C(O)N(R^{100})_2$, $-R^{101}-N(R^{100})C(O)OR^{102}$, $-R^{101}-N(R^{100})C(O)R^{102}$, $-R^{101}-N(R^{100})S(O)_pR^{102}$ (where p is 1 to 2), $-R^{101}-N{=}C(OR^{100})R^{100}$, $-R^{101}-S(O)_pOR^{102}$ (where p is 1 to 2), $-R^{101}-S(O)_tR^{102}$ (where t is 0 to 2), and $-R^{101}-S(O)_pN(R^{100})_2$ (where p is 1 to 2) where each R^{100} is independently hydrogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroarylalkyl; each R^{101} is independently a direct bond or a straight or branched alkylene chain; each R^{102} is alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroarylalkyl, and each R^{103} is a direct bond or a straight or branched alkylene chain.

"Cycloalkylalkyl" refers to a radical of the formula -$R^{100}R^{101}$ where R^{100} is an alkylene chain as defined above and R^{101} is a cycloalkyl radical as defined above. When specifically stated in the specification, the alkylene chain and/or the cycloalkyl radical may be optionally substituted as defined above for optionally substituted alkylene chain and optionally substituted cycloalkyl.

"Alkoxy" refers to a radical group having the following formula "-O-alkyl," wherein the alkyl group is as defined herein above. Example alkoxy groups include methoxy, ethoxy, propoxy (*e.g.*, *n*-propoxy and isopropoxy), *t*-butoxy, and the like. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms. Unless indicated otherwise, alkoxy groups are optionally substituted.

"Alkoxyalkyl" refers to a radical having the following formula "-alkylene-O-alkyl," wherein the alkylene and alkyl groups are as defined herein above, respectively. In some embodiments, the alkoxyalkyl group comprises one -O-alkyl group. In some embodiments, the alkoxyalkyl group comprises two or more alkoxy groups. Examples may include, but are not limited to, methoxymethyl, ethoxymethyl, 3-ethoxyethyl, and 1-methoxyethyl. Unless indicated otherwise, alkoxyalkyl groups are optionally substituted.

"Oxo" refers to a =O group. For example, an oxo connected to a carbon atom forms a carbonyl group (*i.e.*, C=O). Alternatively, when an oxo group is attached to a heteroatom, for example, a sulfoxide, sulfone group, an *N*-oxide group is formed.

"Sulfido" refers to a =S group.

"Amino" refers to a -NH_2 group.

"Carbamyl" refers to a –C(O)NH_2 group.

"Carboxy" refers to a -C(O)OH group.

"Carbonyl" refers to a C(=O) group, which also may be written as C(O).

"Cyano" or "nitrile" refers to a –C≡N group, which also may be written as -CN.

"Nitro" refers to a -NO_2 group.

"Hydroxy" or "hydroxyl" refers to an -OH group.

"Halo" or "halogen" refers to bromo, chloro, fluoro or iodo.

"Haloalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more halo radicals, as defined above, *e.g.*, trifluoromethyl, difluoromethyl, trichloromethyl, 2,2,2-trifluoroethyl, 1-fluoromethyl-2-fluoroethyl, 3-bromo-2-fluoropropyl, 1-bromomethyl-2-bromoethyl, and the like. The alkyl part of the haloalkyl radical may be optionally substituted as defined above for an alkyl group.

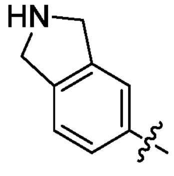
The term "haloalkoxy", employed alone or in combination with other terms, refers to a group of formula -O-haloalkyl, wherein the haloalkyl group is as defined above. Example haloalkoxy groups include trifluoromethoxy, difluoromethoxy, pentafluoroethoxy, and the like.

"Heterocyclyl" refers to a stable 3- to 18-membered non-aromatic ring radical which consists of two to twelve carbon atoms and from one to six heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur. Unless stated otherwise specifically in the specification, the heterocyclyl radical may be a monocyclic, bicyclic, tricyclic, or tetracyclic ring system, which may include fused, bridged, and spiro ring systems; and the nitrogen, carbon, or sulfur atoms in the heterocyclyl radical may be optionally oxidized; the nitrogen atom may be optionally quaternized; and the heterocyclyl radical may be partially or fully saturated. Examples of such heterocyclyl radicals include, but are not limited to, azetidinyl, 3-azabicyclo[3.1.0]hexan-3-yl, 1-azaspiro[3.3]heptan-1-yl, 5-azaspiro[2.3]hexan-5-yl, 2-oxa-6-azaspiro[3.3]heptan-6-yl, 1-oxa-6-azaspiro[3.4]octan-6-yl, 1-oxa-6-azaspiro[3.3]heptan-6-yl, 6-oxa-1-azaspiro[3.3]heptan-1-yl, 6-azaspiro[3.4]octan-6-yl, 7-oxa-2-azaspiro[3.5]nonan-2-yl, 2,6-diazaspiro[3.3]heptan-2-yl, dioxolanyl, dioxinyl, thienyl[1,3]dithianyl, decahydroisoquinolyl, imidazolinyl, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidinyl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl, quinuclidinyl, thiazolidinyl, 1,2,4-thiadiazol-5(4H)-ylidene, tetrahydrofuryl, trioxanyl, trithianyl, triazinanyl, tetrahydropyranyl, thiomorpholinyl, thiamorpholinyl, 1-oxo-thiomorpholinyl, and 1,1-dioxo-thiomorpholinyl. In certain embodiments, a heterocyclyl group may be optionally substituted by one or more substituents selected from the group consisting of alkyl, alkenyl, halo, haloalkyl, haloalkenyl, cyano, oxo, thioxo, nitro, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, $-R^{101}-OR^{100}$, $-R^{101}-OC(O)-R^{100}$, $-R^{101}-N(R^{100})-R^{103}-OR^{100}$, $-R^{101}-N(R^{100})_2$, $-R^{101}-C(O)R^{100}$, $-R^{101}-C(O)OR^{100}$, $-R^{101}-C(O)N(R^{100})_2$, $-R^{101}-N(R^{100})C(O)OR^{102}$, $-R^{101}-N(R^{100})C(O)R^{102}$, $-R^{101}-N(R^{100})S(O)_pR^{102}$ (where p is 1 to 2), $-R^{101}-N{=}C(OR^{100})R^{102}$, $-R^{101}-S(O)_pOR^{102}$ (where p is 1 to 2), $-R^{101}-S(O)_tR^{102}$ (where t is 0 to 2), and $-R^{101}-S(O)_pN(R^{100})_2$ (where p is 1 to 2) where each R^{100} is independently hydrogen, alkyl, alkenyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroarylalkyl; each R^{101} is independently a direct bond or a straight or branched alkylene chain; each R^{102} is alkyl, alkenyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroarylalkyl, and each R^{103} is a direct bond or a straight or branched alkylene chain.

"Heterocyclylalkyl" refers to a radical of the formula $-R^{100}R^{101}$ where R^{100} is an alkylene chain as defined above and R^{101} is a heterocyclyl radical as defined above, and if the heterocyclyl is a nitrogen-containing heterocyclyl, the heterocyclyl may be attached to the alkyl radical at the nitrogen atom. In some embodiments, the alkylene chain of the heterocyclylalkyl radical may be optionally substituted as defined above for an optionally substituted alkylene chain. In some embodiments, the heterocyclyl part of the heterocyclylalkyl radical may be optionally substituted as defined above for an optionally substituted heterocyclyl group.

"Heteroaryl" refers to a 4- to 14-membered ring system radical comprising hydrogen atoms, one to thirteen carbon atoms, one to six heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, and at least one aromatic ring. For purposes of this disclosure, the heteroaryl radical may be a monocyclic, bicyclic, tricyclic, or tetracyclic ring system, which may include fused or bridged ring systems; and the nitrogen, carbon, or sulfur atoms in the heteroaryl radical may be optionally oxidized; the nitrogen atom may be optionally quaternized. Examples include, but are not limited to, azepinyl, acridinyl, benzimidazolyl, benzthiazolyl, benzindolyl, benzodioxolyl, benzofuranyl, benzooxazolyl, benzothiazolyl, benzothiadiazolyl, benzo[b][1,4]dioxepinyl, 1,4-benzodioxanyl, benzonaphthofuranyl, benzoxazolyl, benzodioxolyl, benzodioxinyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzothienyl (benzothiophenyl), benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridinyl, benzoxazolinonyl, benzimidazolthionyl, carbazolyl, cinnolinyl, dibenzofuranyl, dibenzothiophenyl, furanyl, furanonyl, isothiazolyl, imidazolyl, indazolyl, indolyl, indazolyl, isoindolyl, indolinyl, isoindolinyl, isoquinolyl, indolizinyl, isoxazolyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, oxiranyl, 1-oxidopyridinyl, 1-oxidopyrimidinyl, 1-oxidopyrazinyl, 1-oxidopyridazinyl, 1-phenyl-1H-pyrrolyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, pteridinonyl, purinyl, pyrrolyl, pyrazolyl, pyridinyl, pyridinonyl, pyrazinyl, pyrimidinyl, pryrimidinonyl, pyridazinyl, pyrrolyl, pyrido[2,3-d]pyrimidinonyl, quinazolinyl, quinazolinonyl, quinoxalinyl, quinoxalinonyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, thiazolyl, thiadiazolyl, thieno[3,2-d]pyrimidin-4-onyl, thieno[2,3-d]pyrimidin-4-onyl, triazolyl, tetrazolyl, triazinyl, and thiophenyl (*i.e.* thienyl). In certain embodiments, a heteroaryl group may be optionally substituted by one or more substituents selected from the group consisting of alkyl, alkenyl, halo, haloalkyl, haloalkenyl, cyano, oxo, thioxo, nitro, thioxo, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, $-R^{101}-OR^{100}$, $-R^{101}-OC(O)-R^{100}$, $-R^{101}-N(R^{100})-R^{103}-OR^{100}$, $-R^{101}-N(R^{100})_2$, $-R^{101}-C(O)R^{100}$, $-R^{101}-C(O)OR^{100}$, $-R^{101}-C(O)N(R^{100})_2$, $-R^{101}-N(R^{100})C(O)OR^{102}$, $-R^{101}-N(R^{100})C(O)R^{100})C(O)R^{102}$, $-R^{101}-N(R^{100})S(O)_pR^{102}$ (where p is 1 to 2), $-R^{101}-N{=}C(OR^{100})R^{100}$, $-R^{101}-S(O)_pOR^{102}$ (where p is 1 to 2), $-R^{101}-S(O)_tR^{102}$ (where t is 0 to 2), and $-R^{101}-S(O)_pN(R^{100})_2$ (where p is 1 to 2) where each R^{100} is independently hydrogen, alkyl, alkenyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroarylalkyl; each R^{101} is independently a direct bond or a straight or branched alkylene chain; each R^{102} is alkyl, alkenyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl, and each R^{103} is a direct bond or a straight or branched alkylene chain. Preferably, the optional substituents on an optionally substituted bicyclic heteroaryl group for R^1 herein are halo.

Preferably, the optional substituents on an optionally substituted monocyclic heteroaryl group for R^1 herein are alkyl. The term "heteroaryl" includes, *e.g.*, the following structures:



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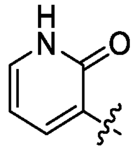

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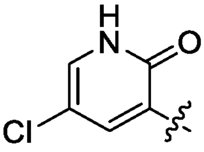

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"N-heteroaryl" refers to a heteroaryl radical as defined above containing at least one nitrogen. The point of attachment of the N-heteroaryl to the rest of the molecule can be through a nitrogen atom or a carbon atom in the N-heteroaryl. When specifically stated in the specification, an N-heteroaryl radical may be optionally substituted as described above for an optionally substituted heteroaryl radical.

"Heteroarylalkyl" refers to a radical of the formula —$R^{100}R^{101}$ where R^{100} is an alkylene chain as defined above and R^{101} is a heteroaryl radical as defined above. When specifically stated in the specification, the heteroaryl part of the heteroarylalkyl radical may be optionally substituted as defined above for an optionally substituted heteroaryl group. In some specific embodiments, the alkylene chain part of the heteroarylalkyl radical may be optionally substituted as defined above for an optionally substituted alkylene chain.

The compounds and methods of the present disclosure are also meant to encompass all pharmaceutically acceptable compounds of Structures (I) being isotopically-labelled by having one or more atoms replaced by an atom having a different atomic mass or mass number.

Examples of isotopes that can be incorporated into the disclosed compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, chlorine, and iodine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, ^{36}Cl, ^{123}I, and ^{125}I, respectively. These radio-labelled compounds could be useful to help determine or measure the effectiveness of the compounds, by characterizing, for example, the site or mode of action or binding affinity. Certain isotopically-labelled compounds of Structures (I), for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, *i.e.*, ^{3}H, and carbon-14, *i.e.*, ^{14}C, are particularly useful for this purpose in view of their ease of incorporation and ready means of detection.

Substitution with heavier isotopes such as deuterium, *i.e.*, ^{2}H, may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements, and hence may be preferred in some circumstances. In one embodiment, the compounds of Structures (I) are enriched with deuterium. Such deuterated compounds can be achieved by methods known to one skilled in the art, such as exchanging protons with deuterium or by synthesizing the molecule with enriched starting materials.

Substitution with positron emitting isotopes, such as ^{11}C, ^{18}F, ^{15}O, and ^{13}N, can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy. Isotopically-labeled compounds of Structures (I) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the Examples and Preparations as set out below using an appropriate isotopically-labeled reagent in place of the non-labeled reagent previously employed.

This disclosure is also meant to encompass the *in vivo* metabolic products of the disclosed compounds. Such products may result from, for example, the oxidation, reduction, hydrolysis, amidation, esterification, and the like of an administered compound, primarily due to enzymatic processes. Accordingly, this disclosure includes compounds produced by a process comprising contacting a compound of this disclosure with a mammal for a period of time sufficient to yield a metabolic product thereof. Such products are typically are identified by administering a radio-labelled compound in a detectable dose to an animal, such as rat, mouse, guinea pig, monkey, or to human, allowing sufficient time for metabolism to occur, and isolating its conversion products from the urine, blood, or other biological samples.

"Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

"Optional" or "optionally" means that the subsequently described event of circumstances may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. For example, "optionally substituted aryl" means that the aryl radical may or may not be substituted and that the description includes both substituted aryl radicals and aryl radicals having no substitution ("unsubstituted"). When a functional group is described as "optionally substituted," and in turn, substituents on the functional group are also "optionally substituted" and so on, for the purposes of this disclosure, such iterations are limited to five, preferably such iterations are limited to two.

"Pharmaceutically acceptable carrier, diluent or excipient" includes without limitation any adjuvant, carrier, excipient, glidant, sweetening agent, diluent, preservative, dye/colorant, flavor enhancer, surfactant, wetting agent, dispersing agent, suspending agent, stabilizer, isotonic agent, solvent, or emulsifier which has been approved by the United States Food and Drug Administration as being acceptable for use in humans or domestic animals.

"Pharmaceutically acceptable salt" includes both acid and base addition salts.

"Pharmaceutically acceptable acid addition salt" refers to those salts which retain the biological effectiveness and properties of the free bases, which are not biologically or otherwise undesirable, and which are formed with inorganic acids such as, but are not limited to, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and organic acids such as, but not limited to, acetic acid, 2,2-dichloroacetic acid, adipic acid, alginic acid, ascorbic acid, aspartic acid, benzenesulfonic acid, benzoic acid, 4-acetamidobenzoic acid, camphoric acid, camphor-10-sulfonic acid, capric acid, caproic acid, caprylic acid, carbonic acid, cinnamic acid, citric acid, cyclamic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, 2-hydroxyethanesulfonic acid, formic acid, fumaric acid, galactaric acid, gentisic acid, glucoheptonic acid, gluconic acid, glucuronic acid, glutamic acid, glutaric acid, 2-oxo-glutaric acid, glycerophosphoric acid, glycolic acid, hippuric acid, isobutyric acid, lactic acid, lactobionic acid, lauric acid, maleic acid, malic acid, malonic acid, mandelic acid, methanesulfonic acid, mucic acid, naphthalene-1,5-disulfonic acid, naphthalene-2-sulfonic acid, 1-hydroxy-2-naphthoic acid, nicotinic acid, oleic acid, orotic acid, oxalic acid, palmitic acid, pamoic acid, propionic acid, pyroglutamic acid, pyruvic acid, salicylic acid, 4-aminosalicylic acid, sebacic acid, stearic acid, succinic acid, tartaric acid, thiocyanic acid, p-toluenesulfonic acid, trifluoroacetic acid, undecylenic acid, and the like.

"Pharmaceutically acceptable base addition salt" refers to those salts which retain the biological effectiveness and properties of the free acids, which are not biologically or otherwise undesirable. These salts are prepared from addition of an inorganic base or an organic base to the free acid. Salts derived from inorganic bases include, but are not limited to, the sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts, and the like. Preferred inorganic salts are the ammonium, sodium, potassium, calcium, and magnesium salts. Salts derived from organic bases include, but are not limited to, salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as ammonia, isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, diethanolamine, ethanolamine, deanol, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, benethamine, benzathine, ethylenediamine, glucosamine, methylglucamine, theobromine, triethanolamine, tromethamine, purines, piperazine, piperidine, N-ethylpiperidine, polyamine resins and the like. Particularly preferred organic bases are isopropylamine, diethylamine, ethanolamine, trimethylamine, dicyclohexylamine, choline, and caffeine.

Often crystallizations produce a solvate of the compound of the disclosure (*e.g.*, a compound of Structure (I)). As used herein, the term "solvate" refers to an aggregate that comprises one or more molecules of a compound of the disclosure with one or more molecules of solvent. The solvent may be water, in which case the solvate may be a hydrate. Alternatively, the solvent may be an organic solvent. Thus, the compounds of the present disclosure may exist as a hydrate, including a monohydrate, dihydrate, hemihydrate, sesquihydrate, trihydrate, tetrahydrate, and the like, as well as the corresponding solvated forms. The compound of the disclosure may be true solvates, while in other cases, the compound of the disclosure may merely retain adventitious water or be a mixture of water plus some adventitious solvent.

A "pharmaceutical composition" refers to a formulation of a compound of the disclosure and a medium generally accepted in the art for the delivery of the biologically active compound to mammals, *e.g.*, humans. Such a medium includes all pharmaceutically acceptable carriers, diluents, or excipients therefor.

"Treating" or "treatment" as used herein covers the treatment of the disease or condition of interest in a mammal, preferably a human, having the disease or condition of interest, and includes:

(a) preventing the disease or condition from occurring in a mammal, in particular, when such mammal is predisposed to the condition but has not yet been diagnosed as having it;

(b) inhibiting the disease or condition, *i.e.*, arresting the disease or condition's development;

(c) relieving (or ameliorating) the disease or condition, *i.e.*, causing regression of the disease or condition; or

(d) relieving (or ameliorating) the symptoms resulting from the disease or condition, *e.g.*, without addressing the underlying disease or condition.

As used herein, the terms "disease" and "condition" may be used interchangeably or may be different in that the particular malady or condition may not have a known causative agent (so that etiology has not yet been worked out) and it is therefore not yet recognized as a disease but only as an undesirable condition or syndrome, wherein a more or less specific set of symptoms have been identified by clinicians.

The compounds of the disclosure, or their pharmaceutically acceptable salts may contain one or more stereocenter and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (*R*)- or (*S*)- or, as (*D*)- or (*L*)- for amino acids. The present disclosure is meant to include all such possible isomers, as well as their racemic and optically pure forms. Optically active (+) and (−), (*R*)- and (*S*)-, or (*D*)- and (*L*)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques, for example, chromatography and fractional crystallization. Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high-pressure liquid chromatography (HPLC). When the compounds described herein contain olefinic double bonds or other centres giving rise to geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers. Likewise, all tautomeric forms are also intended to be included.

A "stereoisomer" refers to a compound made up of the same atoms bonded by the same bonds but having different three-dimensional structures, which are not interchangeable. The present disclosure contemplates various stereoisomers and mixtures thereof and includes enantiomers, which refers to two stereoisomers whose molecules are non-superimposable mirror images of one another. See, *e.g.*, Smith, M. B. and J. March, March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, 6th edition (Wiley, 2007), for a detailed description of the structure and properties of enantiomers and stereoisomers.

A "tautomer" refers to a proton shift from one atom of a molecule to another atom of the same molecule. The present disclosure includes tautomers of any said compounds.

The use of parentheses and brackets in substituent groups is used herein to conserve space. Accordingly, the use of parenthesis in a substituent group indicates that the group enclosed within the parentheses is attached directly to the atom preceding the parenthesis. The use of brackets in a substituent group indicates that the group enclosed within the brackets is also attached directly to the atom preceding the parenthesis.

The chemical naming protocol and structure diagrams used herein are a modified form of the I.U.P.A.C. nomenclature system, using ChemBioDraw Ultra

Version 14.0 software program. For complex chemical names employed herein, a substituent group is named before the group to which it attaches. For example, cyclopropylethyl comprises an ethyl backbone with cyclopropyl substituent. In chemical structure diagrams, all bonds are identified, except for some carbon atoms, which are assumed to be bonded to sufficient hydrogen atoms to complete the valency.

At certain places, the definitions or embodiments may refer to specific rings (*e.g.*, an azetidine ring, a pyridine ring, *etc.*). Unless otherwise indicated, these rings can be attached to any ring member provided that the valency of the atom is not exceeded.

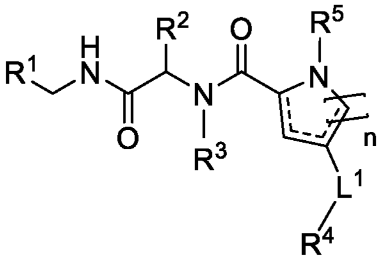
When any two groups or two instances of the same substituent group are "independently selected" from a list of alternatives, the groups may be the same or different. For example, if R^a and R^b are independently selected from the group consisting of alkyl, fluoro, amino, and hydroxyalkyl, then a molecule with two R^a groups and two R^b groups could have all groups be alkyl group (*e.g.*, four different alkyl groups). Alternatively, the first R^a could be alkyl, the second R^a could be fluoro, the first R^b could be hydroxyalkyl, and the second R^b could be amino (or any other substituents taken from the group). Alternatively, both R^a and the first R^b could be fluoro, while the second R^b could be alkyl (*i.e.*, some pairs of substituent groups may be the same, while other pairs may be different). Unless otherwise indicated, if two or more groups having the same definition are present, but the definition provides for alternatives, it should be understood that each occurrence of the same group is independently selected from the possible alternatives. For example, if two or more R^a groups are present in a compound, and the definition of R^a provides that R^a can be A, B, or C, then it should be understood that each R^a group present in the compound is independently chosen from A, B, and C, so that the R^a groups present in the compound can be the same or different.

Compounds, and salts thereof, including pharmaceutically acceptable salts, can be found together with other substances such as water and solvents (*e.g.*, hydrates and solvates) or can be isolated. When in the solid state, the compounds described herein, and salts thereof may occur in various forms and may, *e.g.*, take the form of solvates, including hydrates. The compounds may be in any solid-state form, such as a polymorph or solvate, so unless clearly indicated otherwise, reference to compounds and salts thereof should be understood as encompassing any solid-state form of the compound.

In some embodiments, the compounds described herein or salts thereof, are substantially isolated. "Substantially isolated" means the compound is at least partially or substantially separated from the environment in which it was formed or detected. Partial separation can include, *e.g.*, a composition enriched in the compounds of the disclosure. Substantial separation can include compositions containing at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 97%, or at least about 99% by weight of the compounds of the disclosure, or salt thereof.

II. Compounds

In certain aspects, the present disclosure provides a compound having the following Structure (I):



(I)

or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein:

---- at each occurrence, independently represents a double or single bond;

R^1 is a substituted or unsubstituted aryl or a substituted or unsubstituted heteroaryl;

R^2 is hydrogen, alkyl, alkoxy, haloalkyl, hydroxyalkyl, haloalkoxy, or cycloalkyl;

R^3 is hydrogen, alkyl, haloalkyl, or cycloalkyl, or R^2 and R^3, together with the carbon and nitrogen to which they are attached, respectively, form an optionally substituted 4-7 membered heterocyclyl;

R^4 is a substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocyclyl;

R^5 is hydrogen, alkyl, haloalkyl, cycloalkyl, phosphonalkyl, $(CH_2)_mC(=O)OR^6$, $C(=O)R^6$, $C(=O)OR^6$, $(CH_2)_mNR^6S(O)_2R^7$, or $C(=O)NR^6R^7$;

R^6 and R^7 are, at each occurrence, independently hydrogen, alkyl, haloalkyl, cycloalkyl, or arylalkyl;

L^1 is a direct bond, $-CR^{8a}R^{8b}-$, $-S(O)_t-$, NR^{8c}, or -O-;

R^{8a} and R^{8b} are each independently hydrogen, alkyl, or R^{8a} and R^{8b}, together with the carbon to which they are attached form an optionally substituted 3-6 membered cycloalkyl;

R^{8c} is hydrogen, alkyl, haloalkyl, (C=O)alkyl, (C=O)Oalkyl, (C=O)cycloalkyl, (C=O)Ocycloalkyl, (C=O)aryl, (C=O)Oaryl, (C=O)heteroaryl, (C=O)Oheteroaryl, (C=O)heterocyclyl, (C=O)O heterocyclyl, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted heterocyclyl, a substituted or unsubstituted arylalkyl, a substituted or unsubstituted heteroarylalkyl, a substituted or unsubstituted cycloalkylalkyl, or a substituted or unsubstituted heterocyclylalkyl;

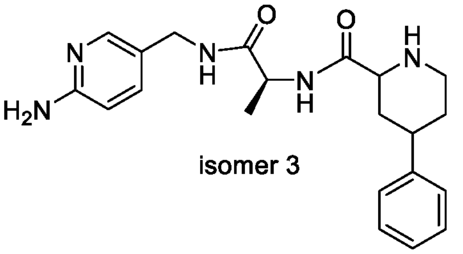
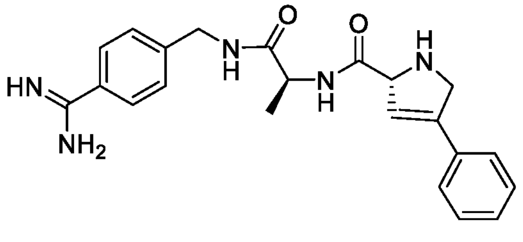
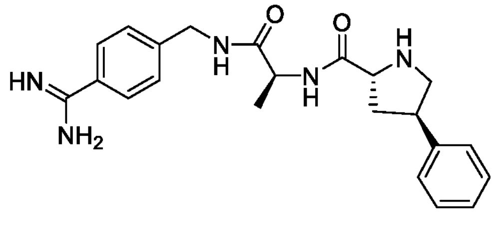
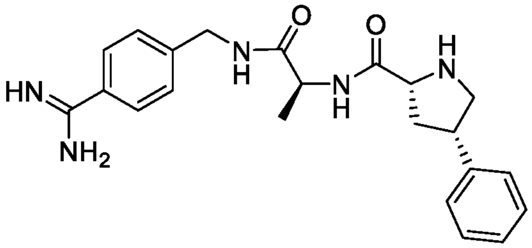
n is 1 or 2;

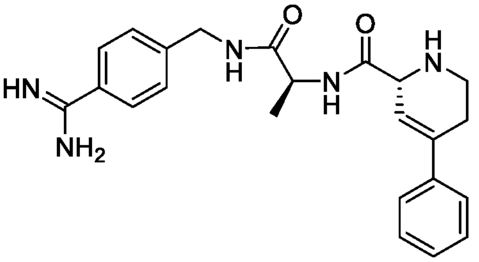
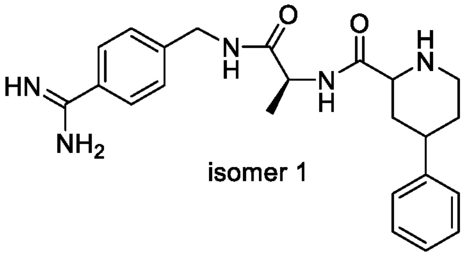
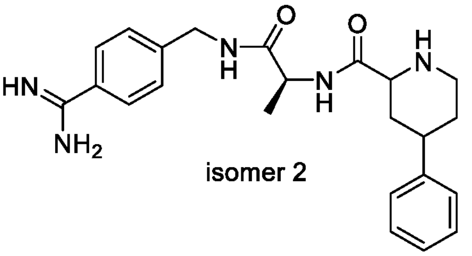
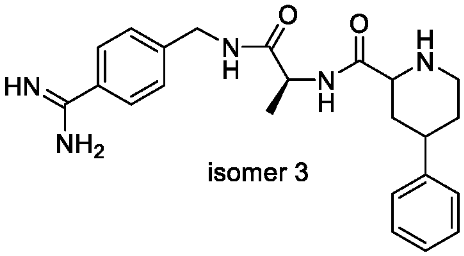
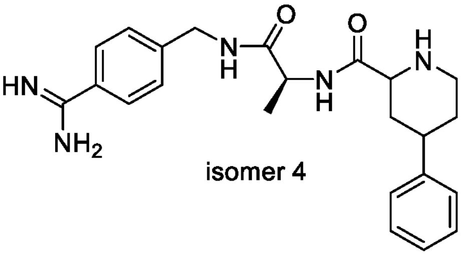
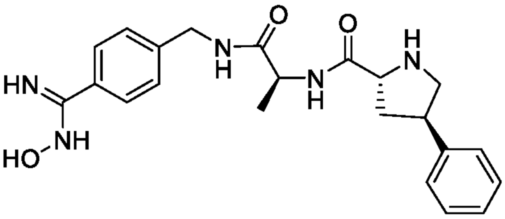
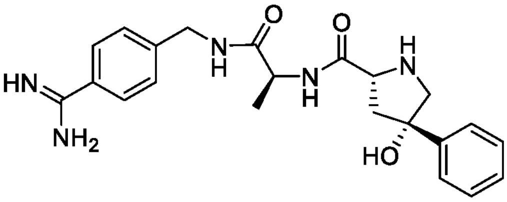
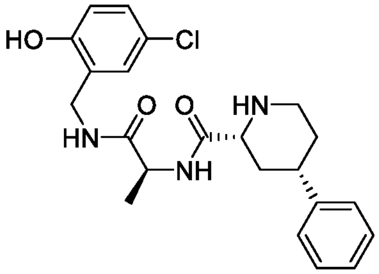
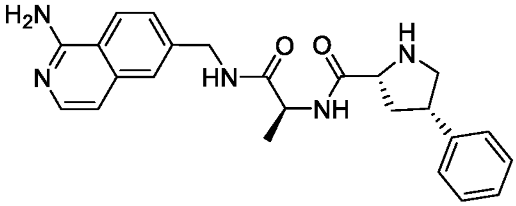
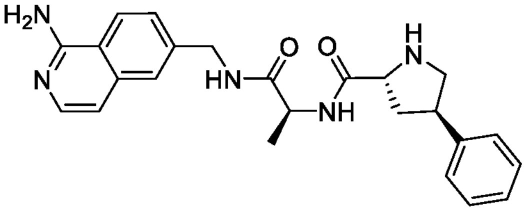
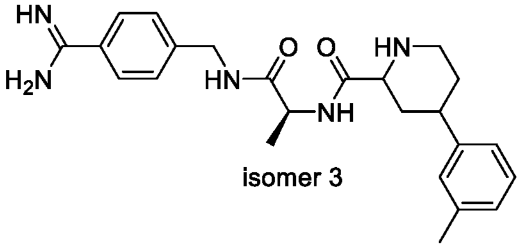
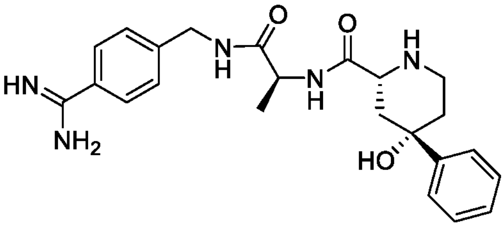
m is 1, 2, 3, 4, 5, or 6; and

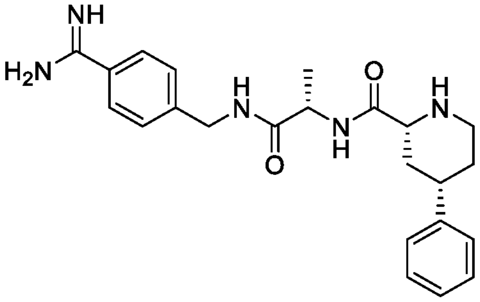
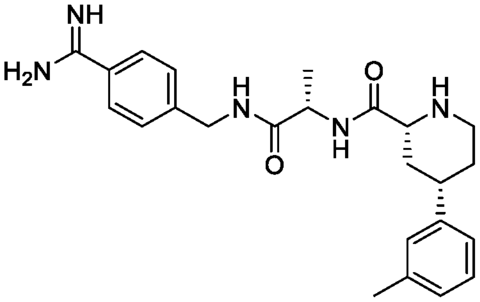
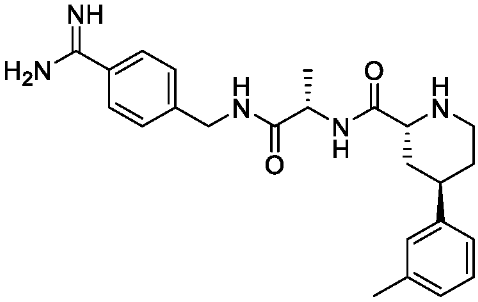
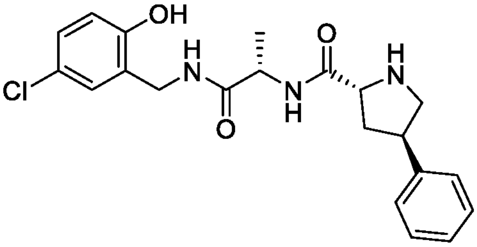
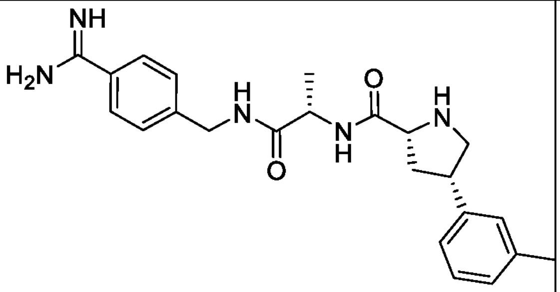
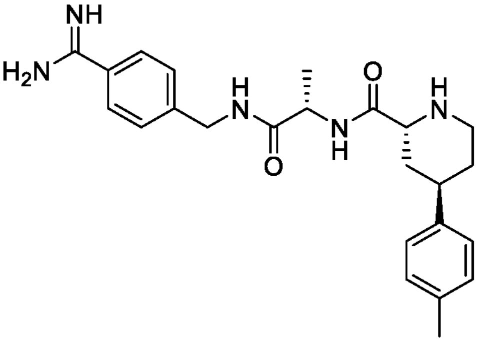
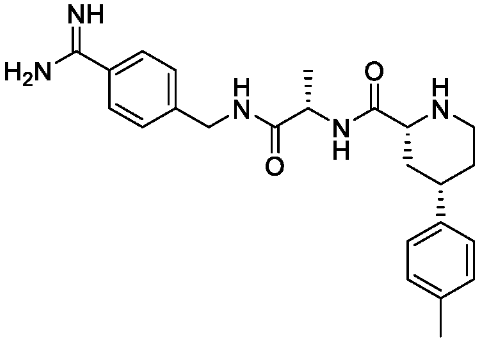
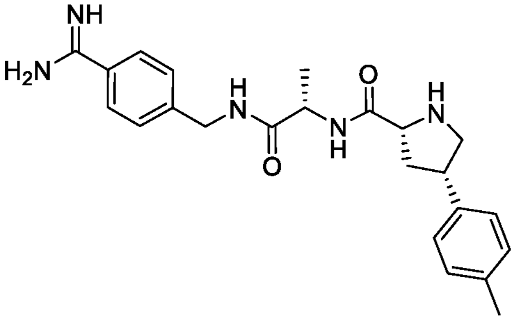
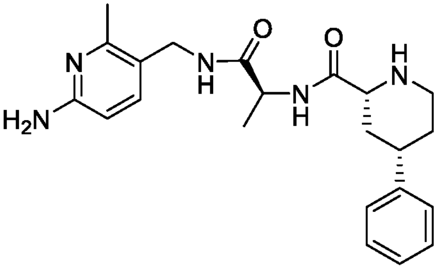
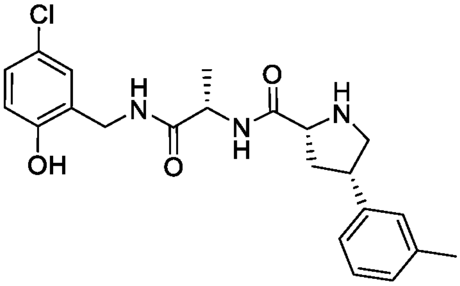
t is 0, 1, or 2,

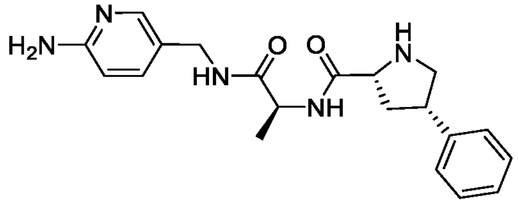
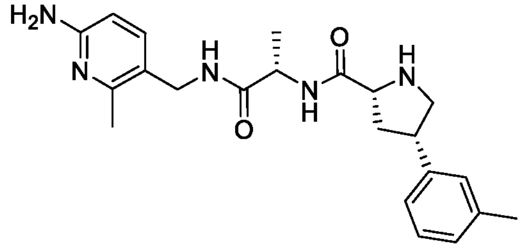
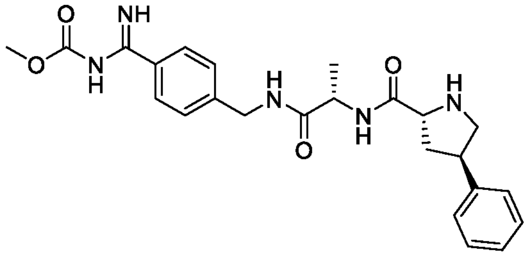
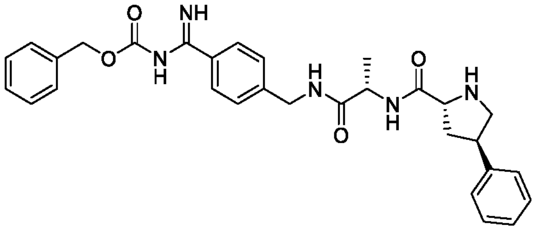
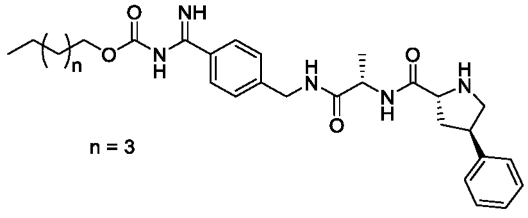
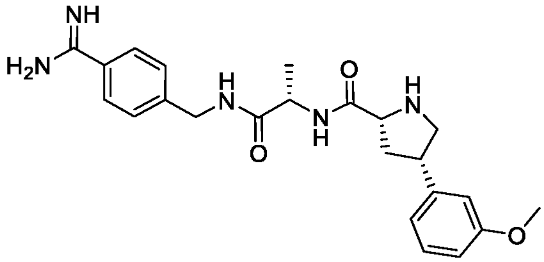
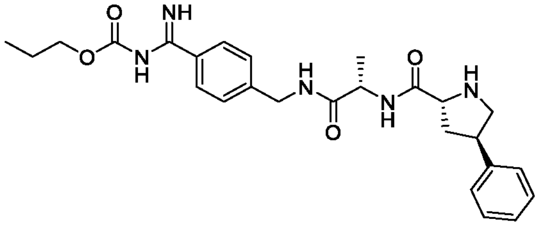
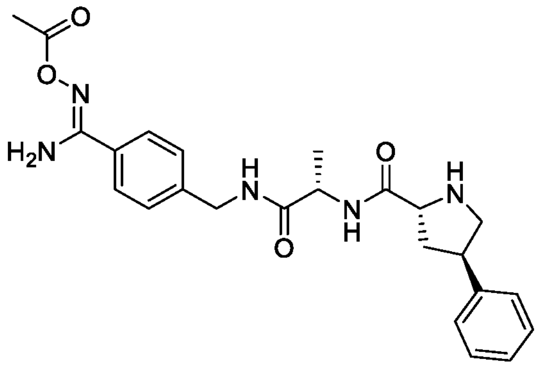
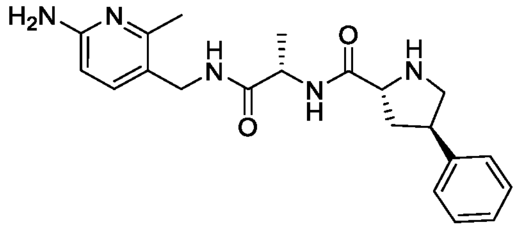
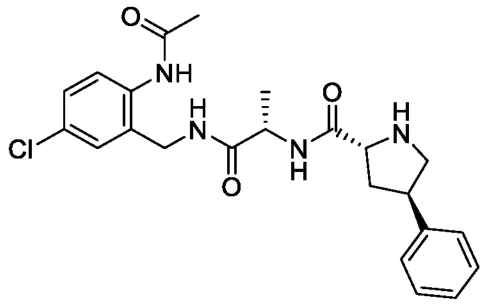
provided that the compound of Structure (I) does not have a structure in Table A below:

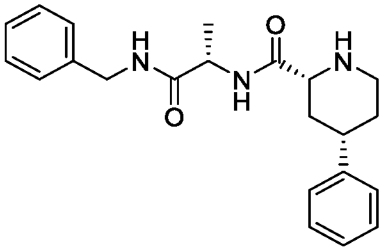
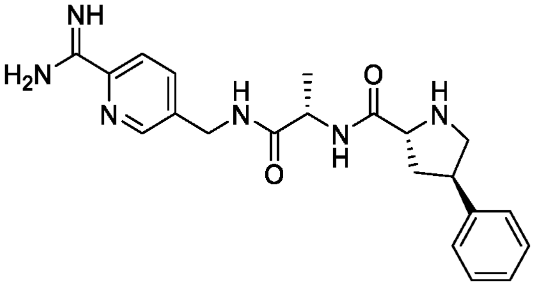
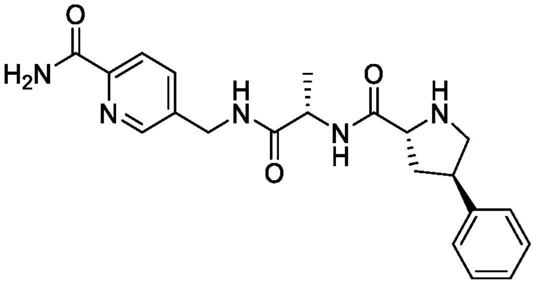
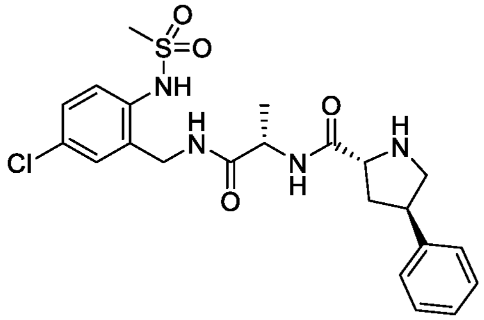
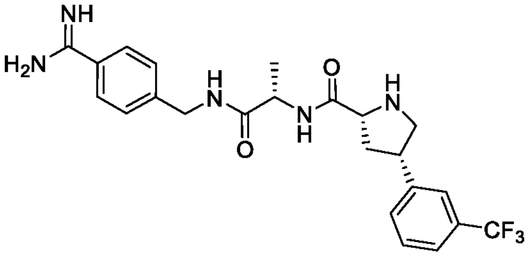
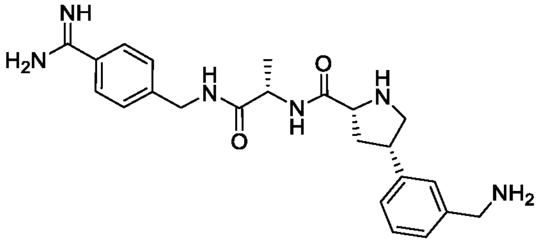
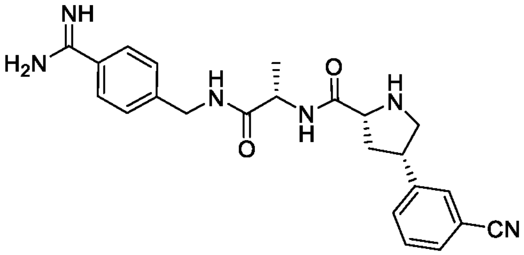
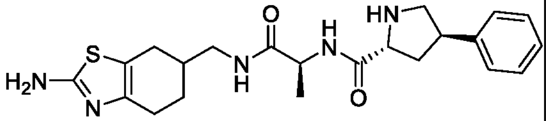
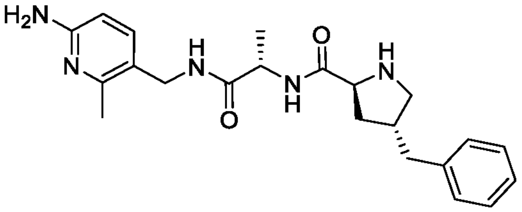
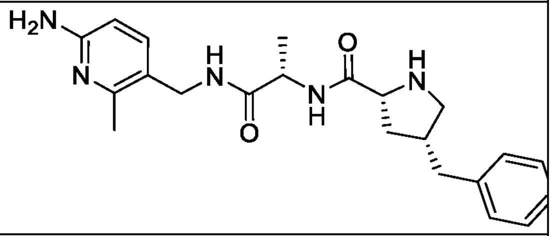
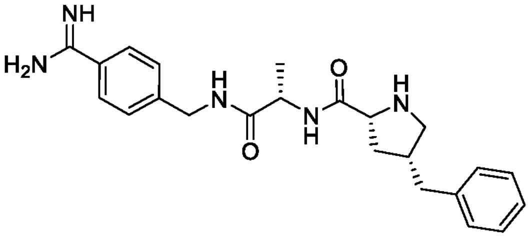
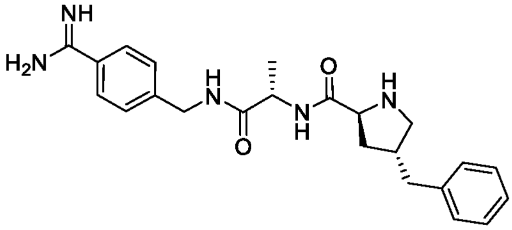
Table A. Compounds not included in Structure (I)

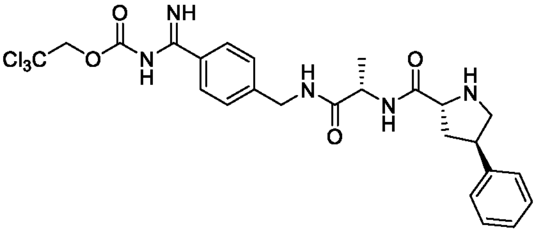
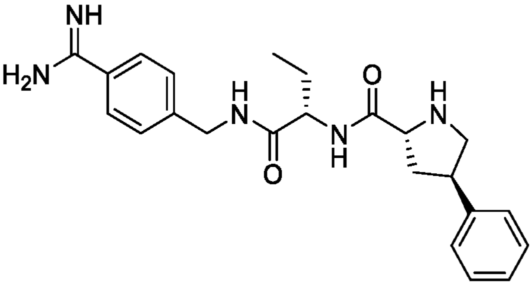
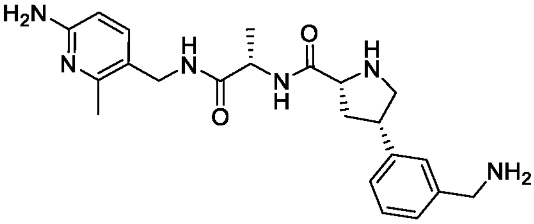
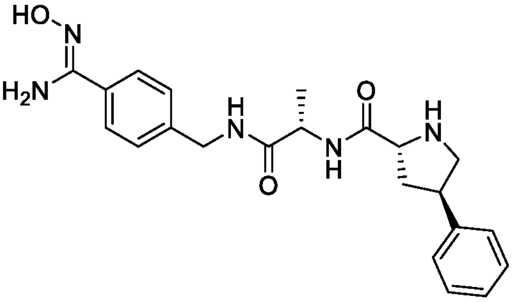
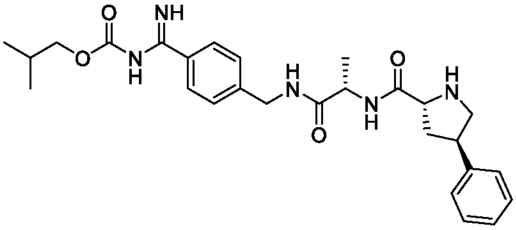
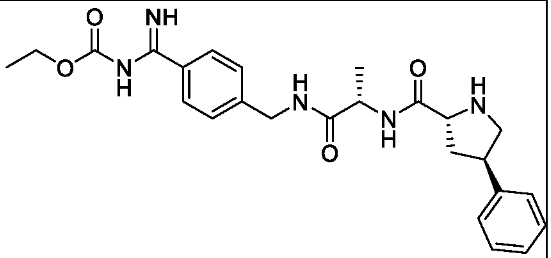
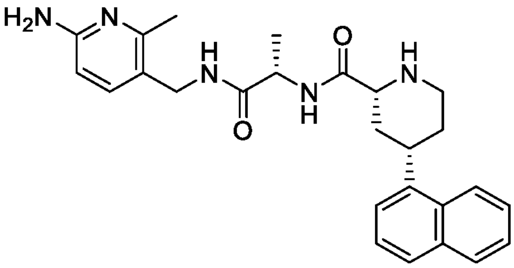
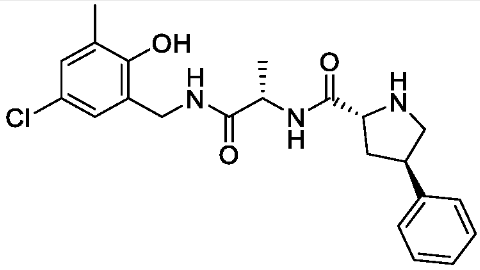
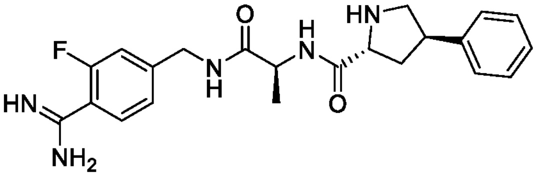
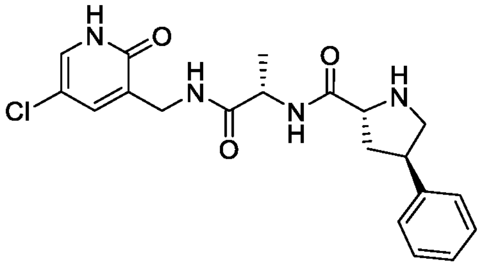
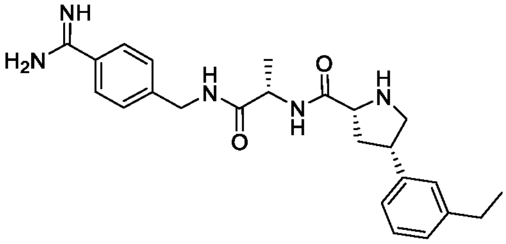
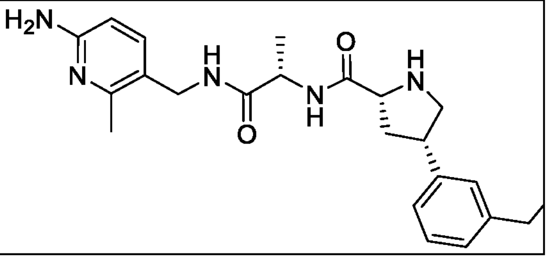
	
	

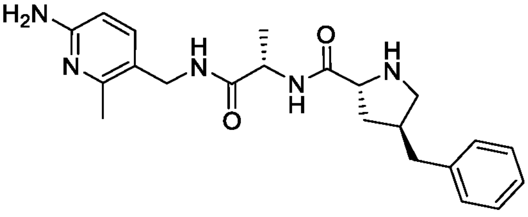
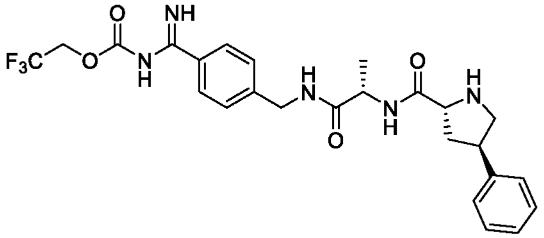
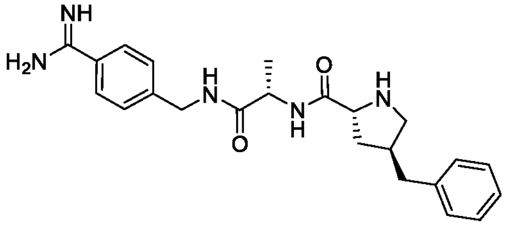
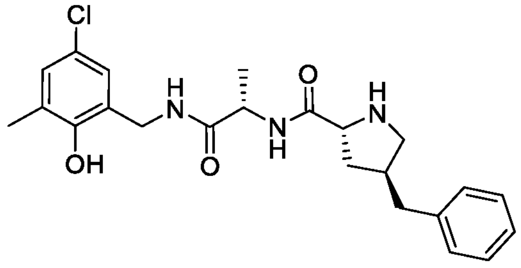
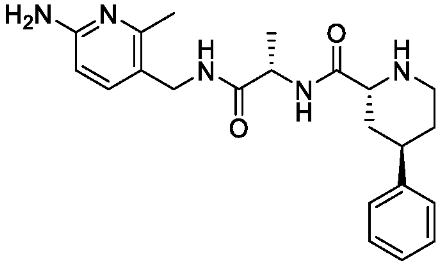
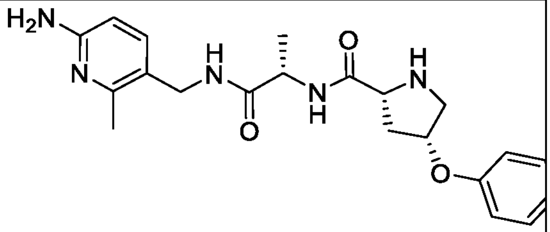
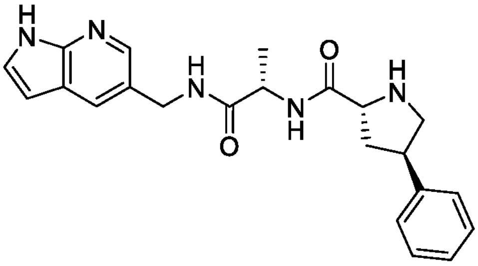
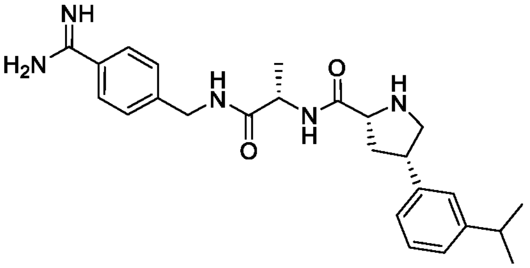
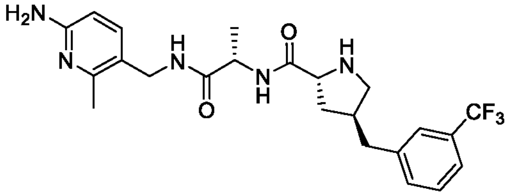
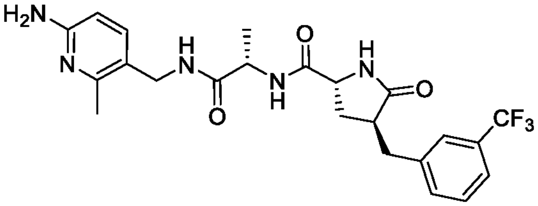
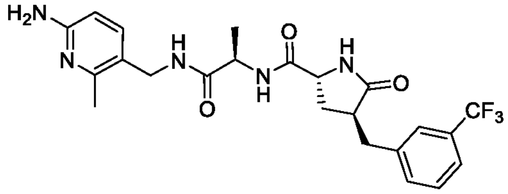
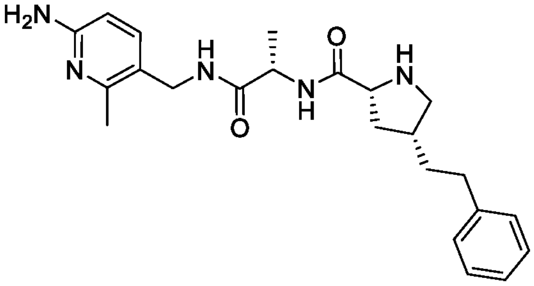
	 isomer 1
 isomer 2	 isomer 3
 isomer 4	
	
	
 isomer 3	

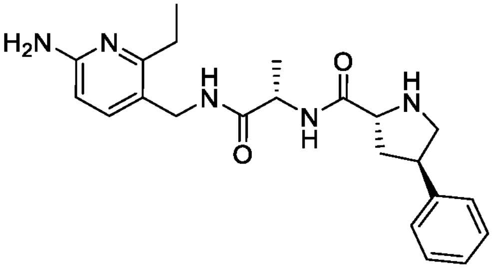
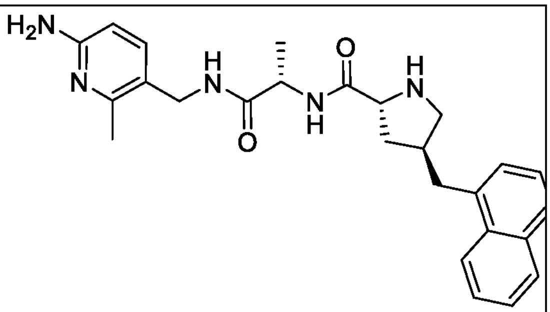
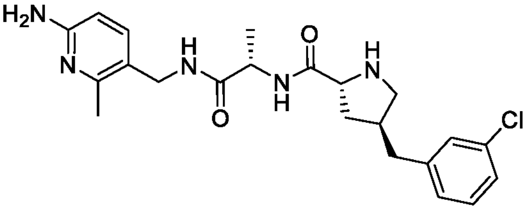
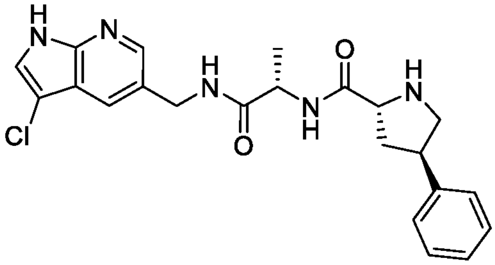
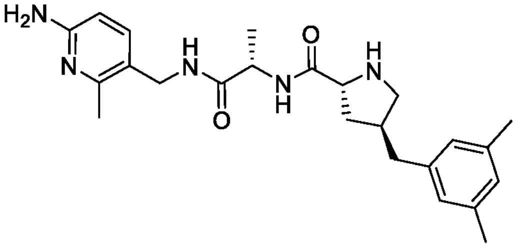
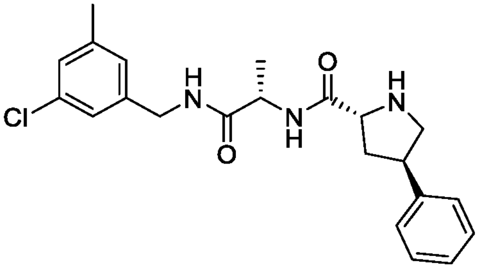
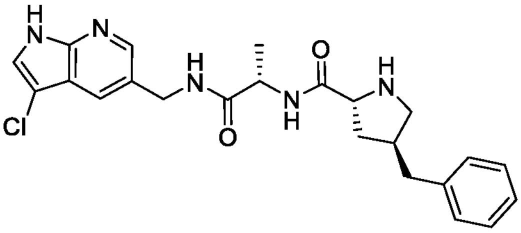
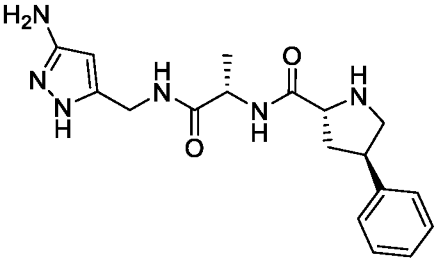
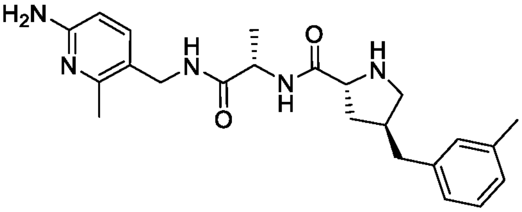
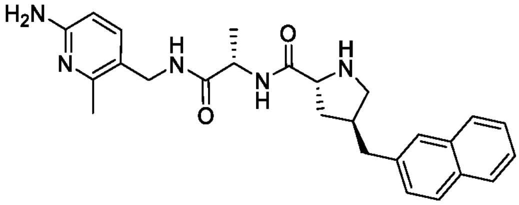
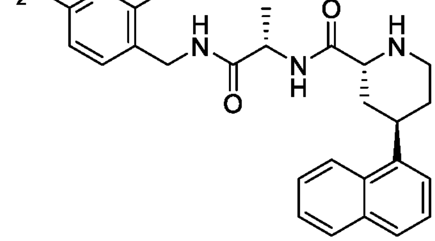
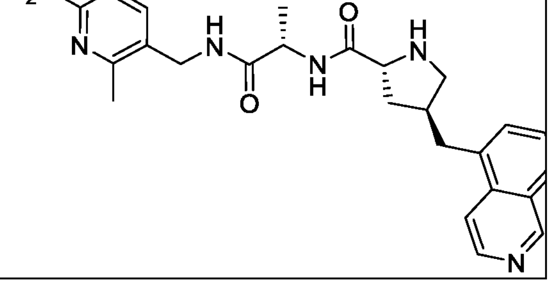
	
	
	
	
	

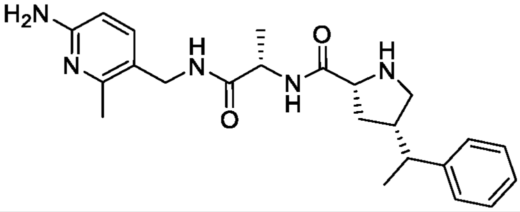
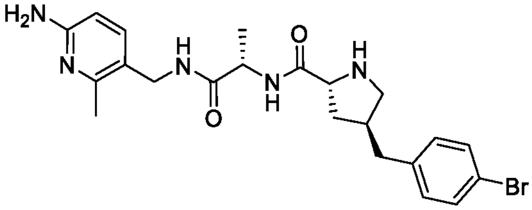
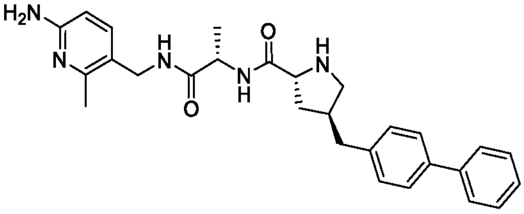
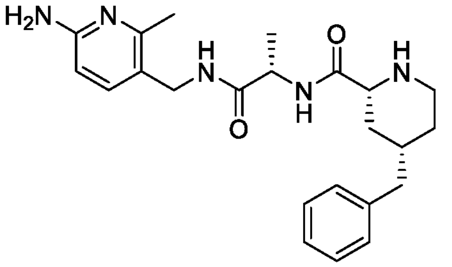
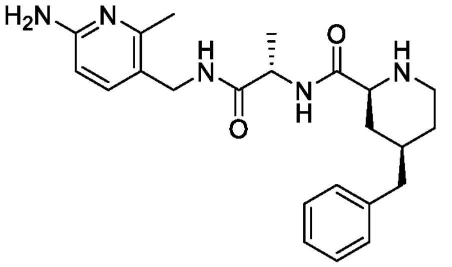
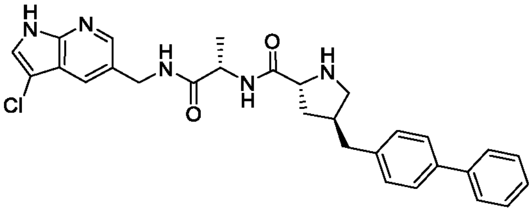
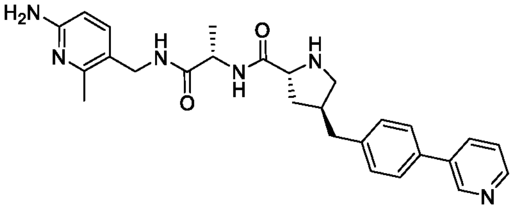
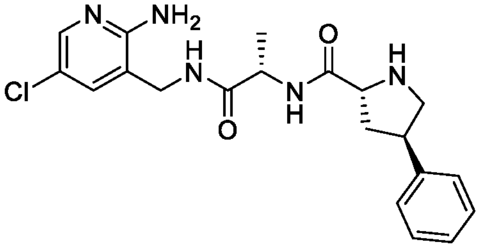
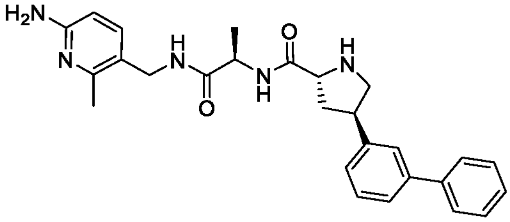
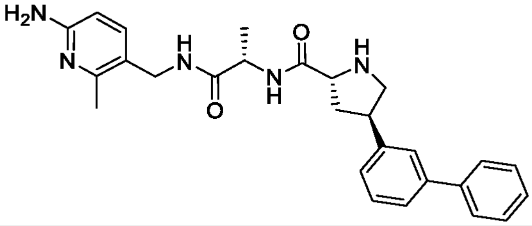
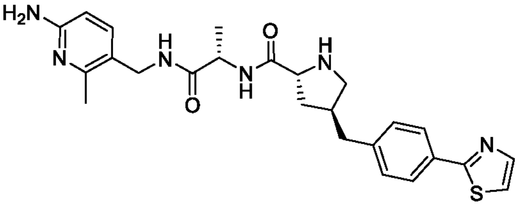
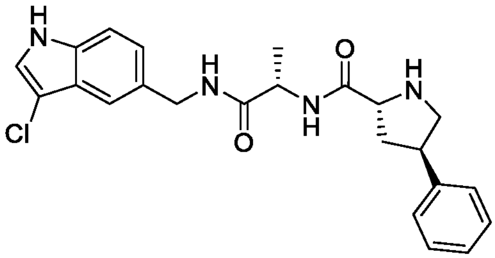
	
	
	
	
	

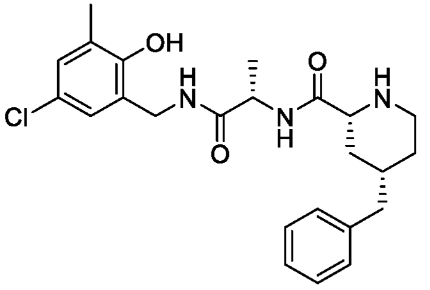
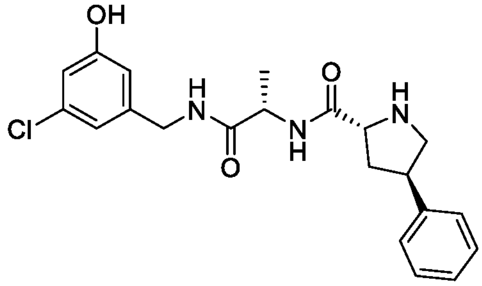
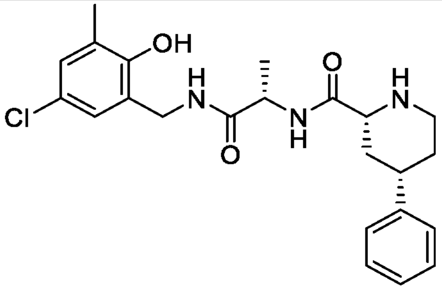
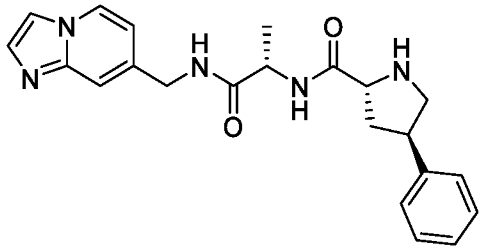
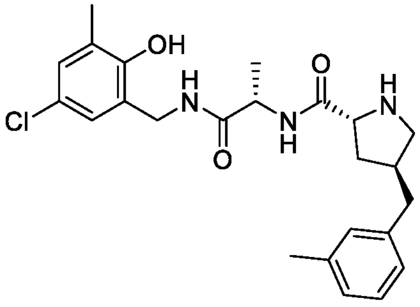
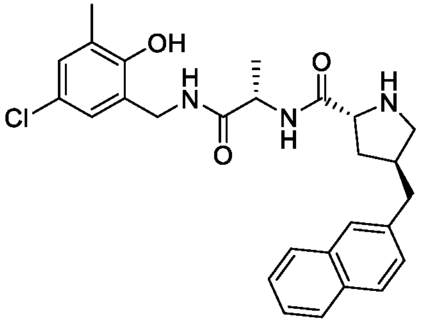
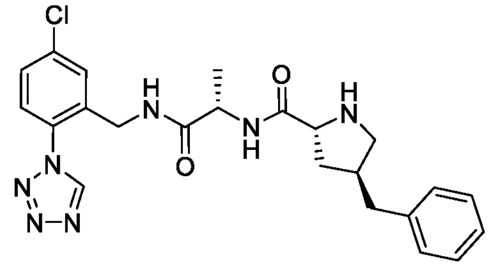
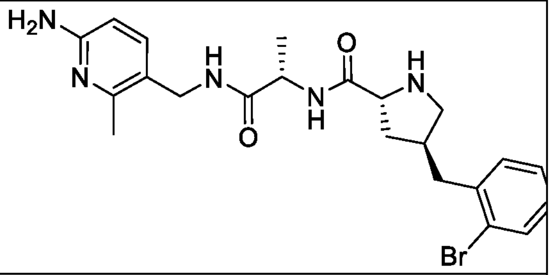
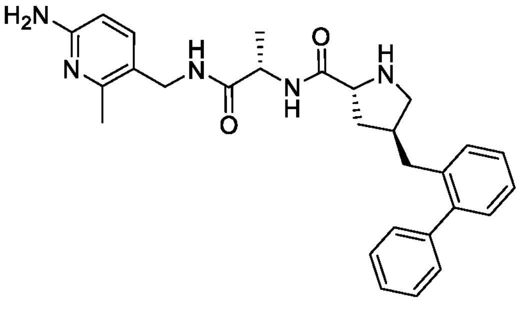
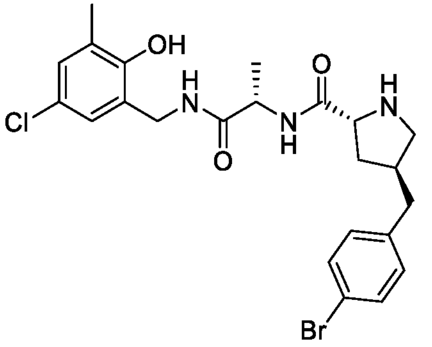
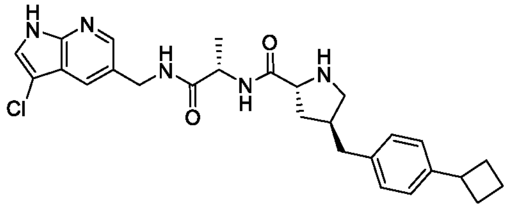
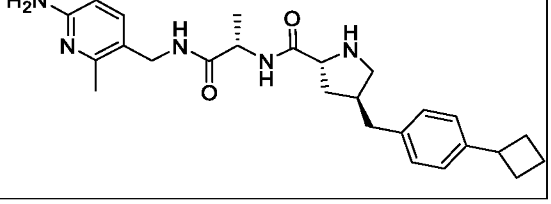
	
	
	
	
	
	

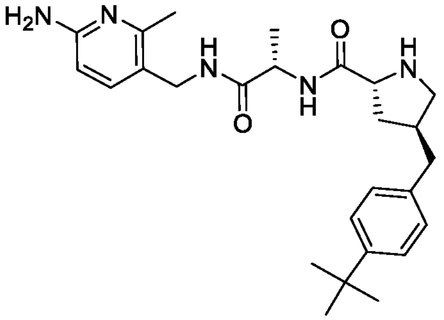
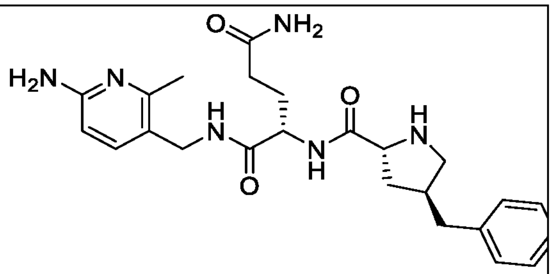
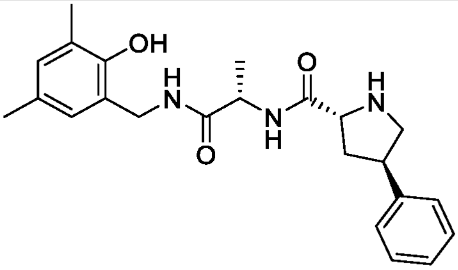
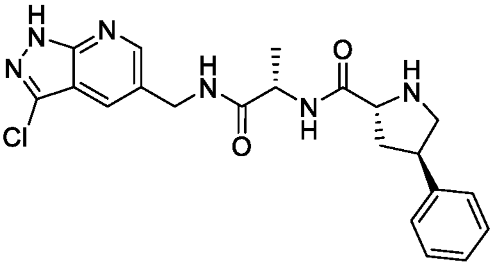
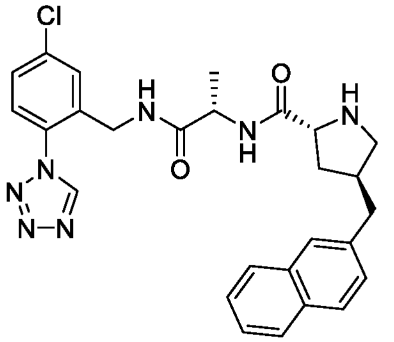
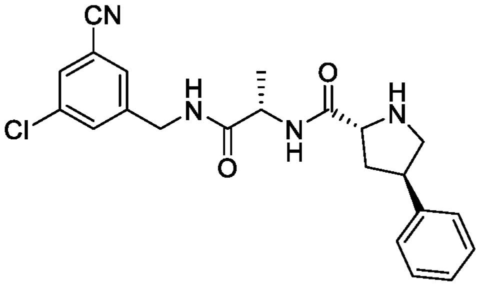
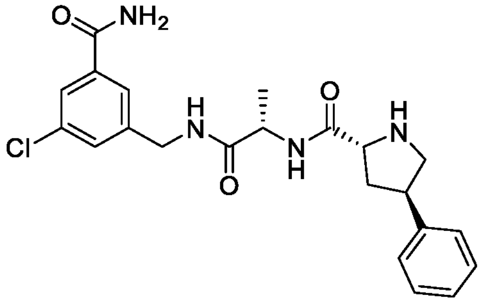
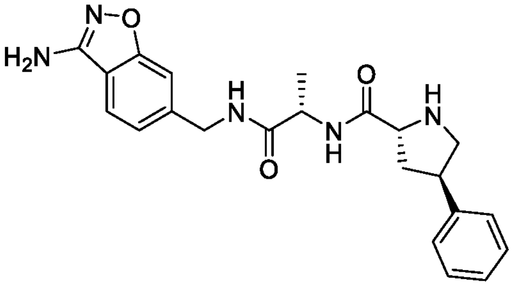
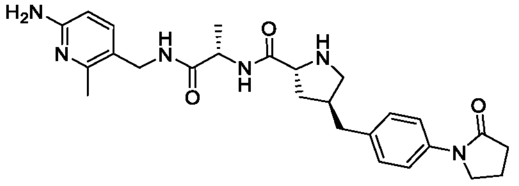
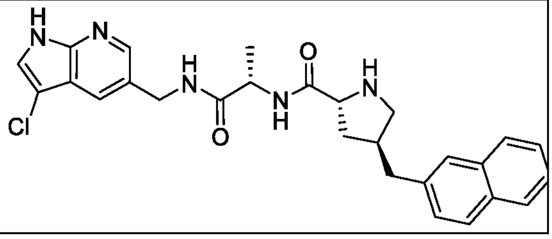
	
	
	
	
	
	

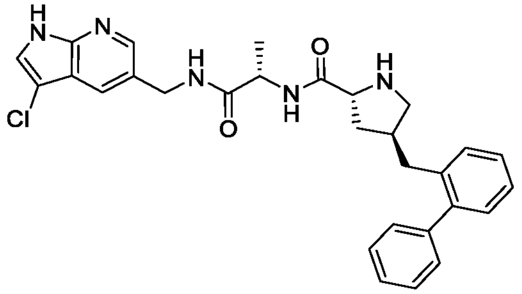
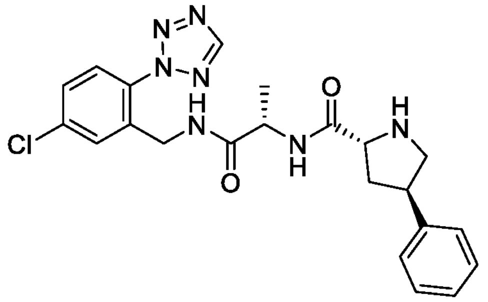
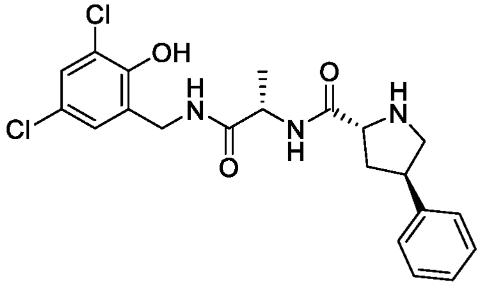
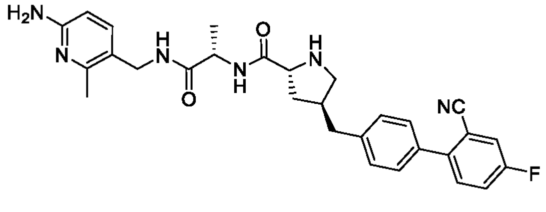
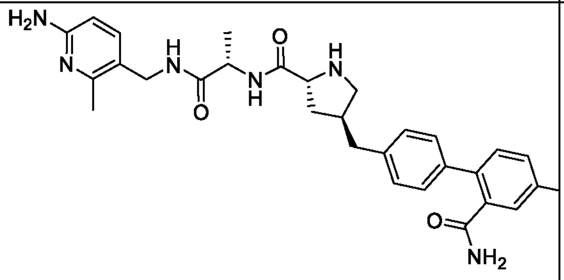
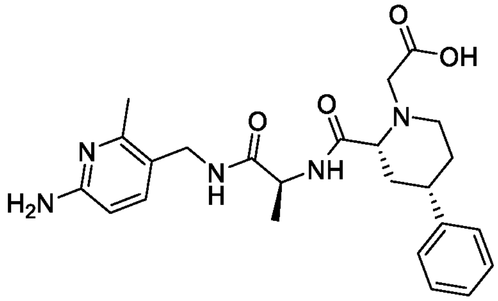
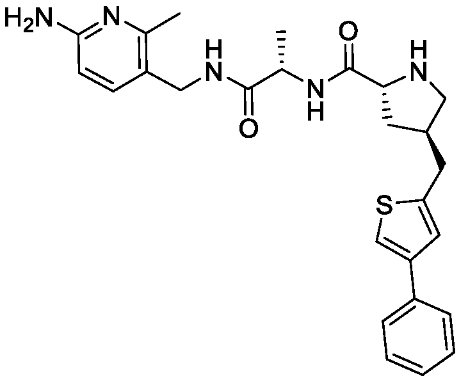
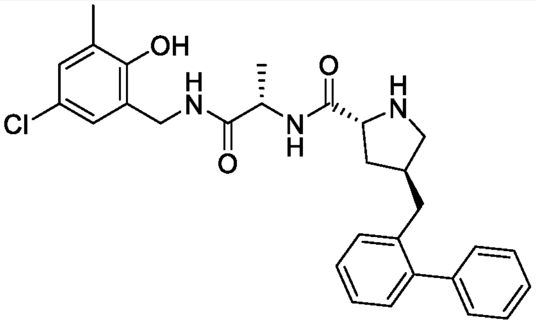
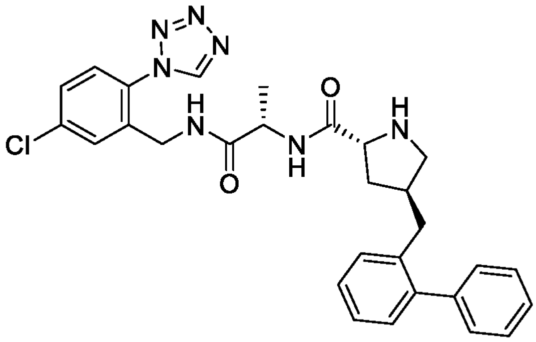
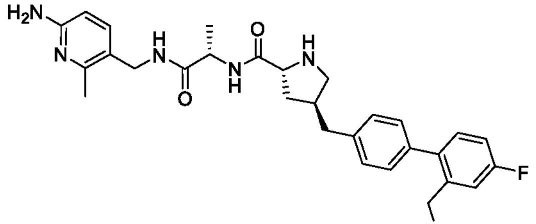
	
	
	
	
	
	

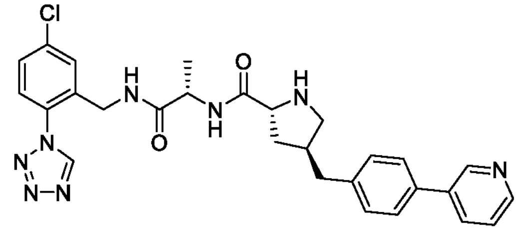
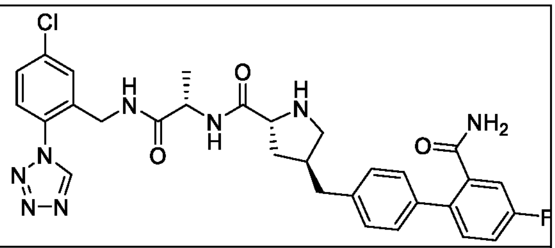
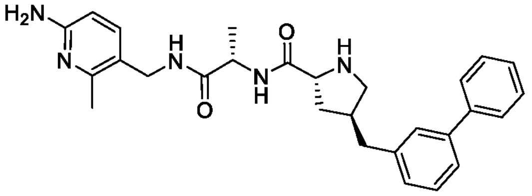
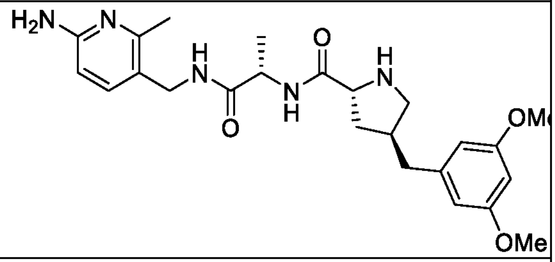
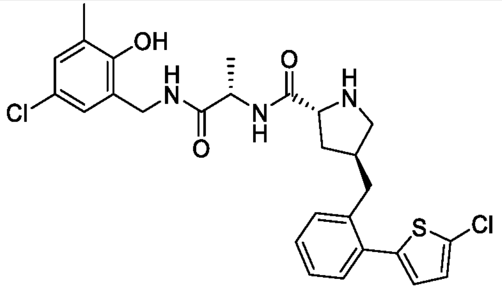
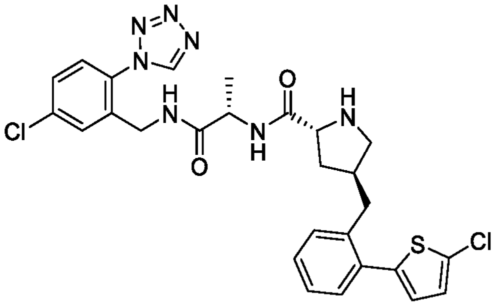
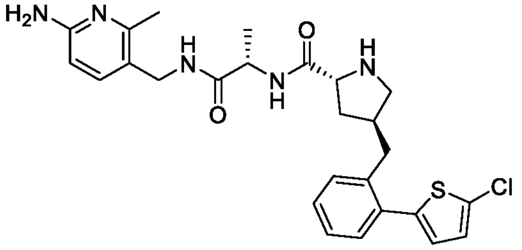
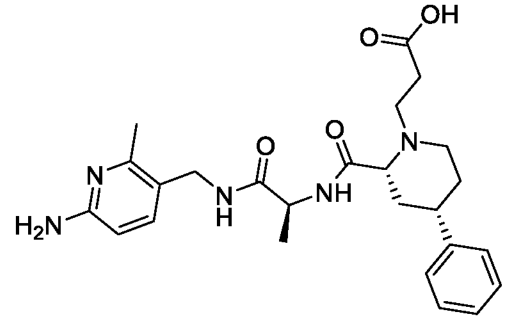
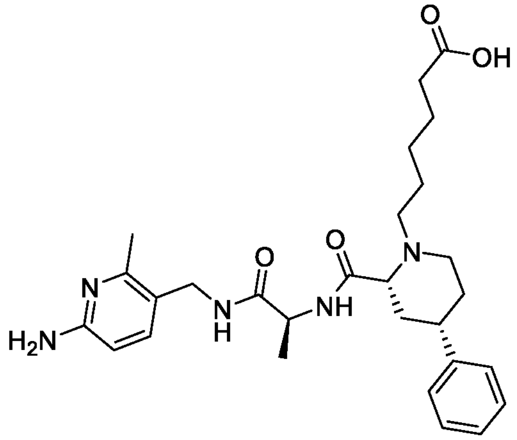
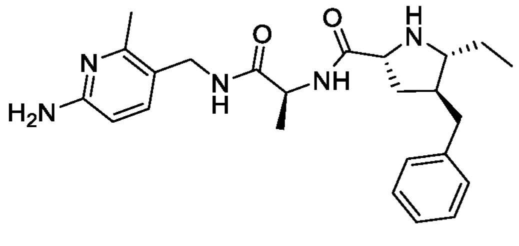
	
	
	
	
	
	

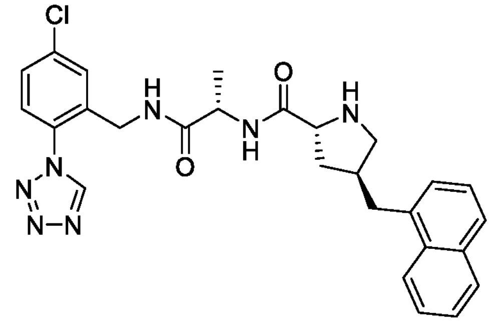
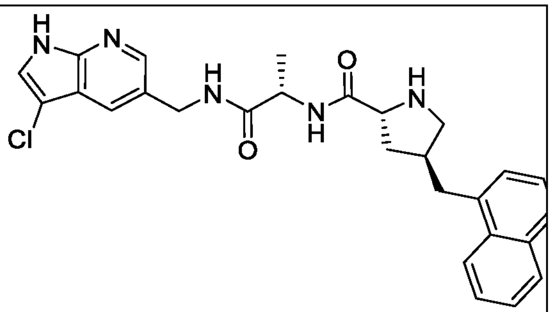
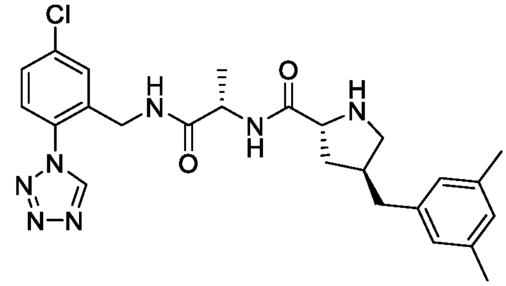
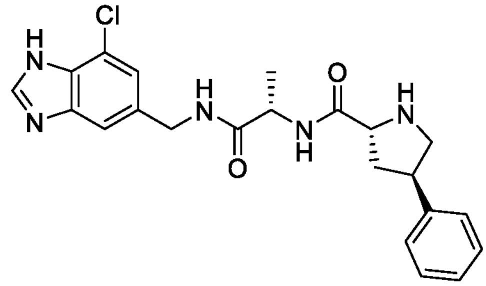
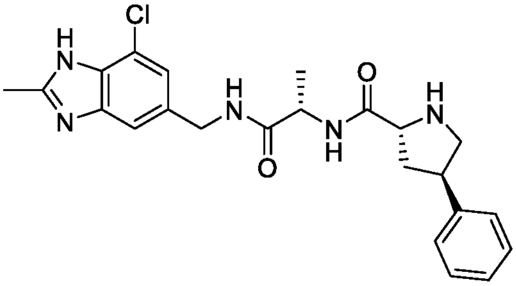
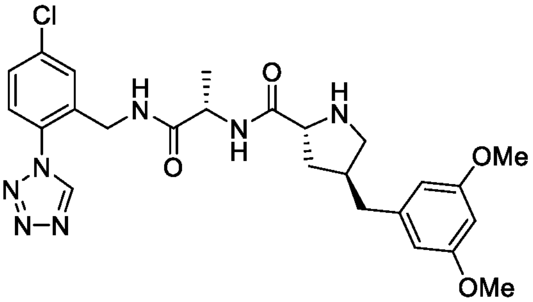
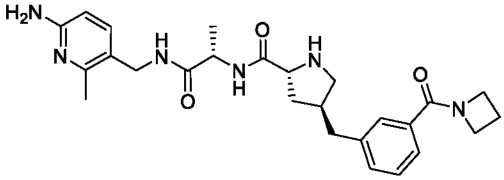
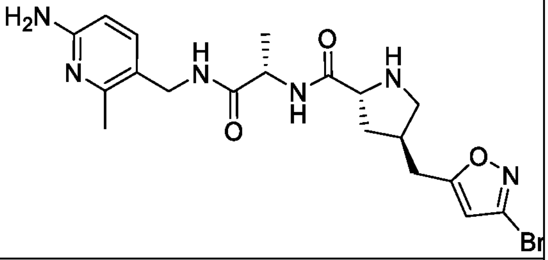
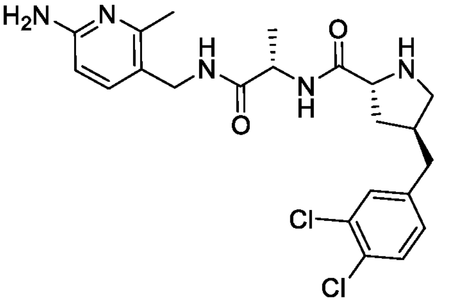
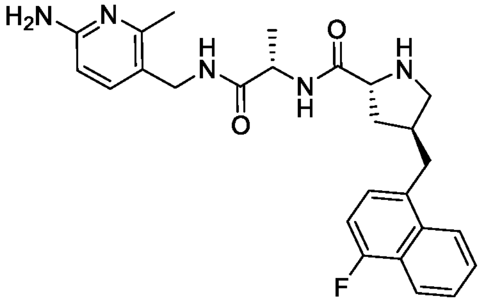
	
	
	
	
	
	

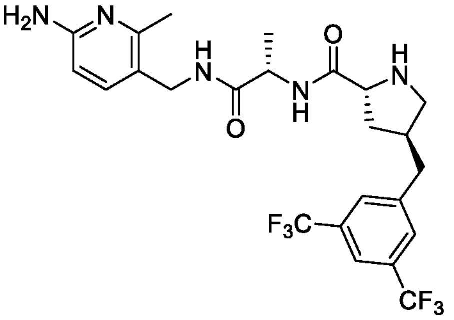
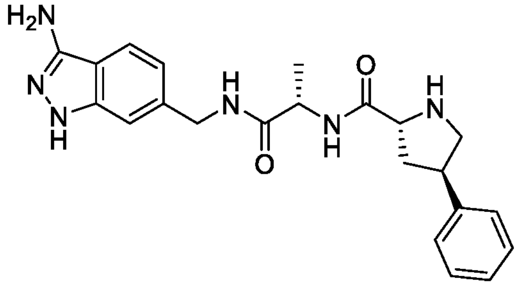
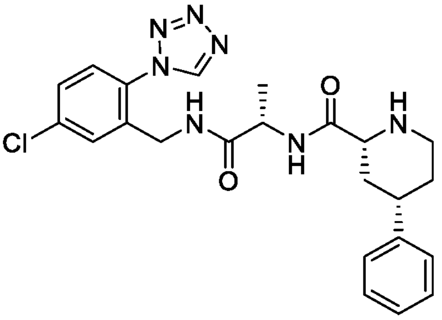
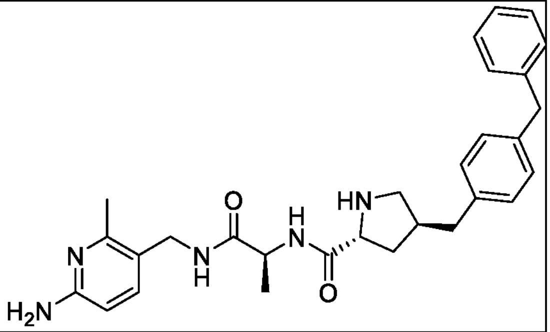
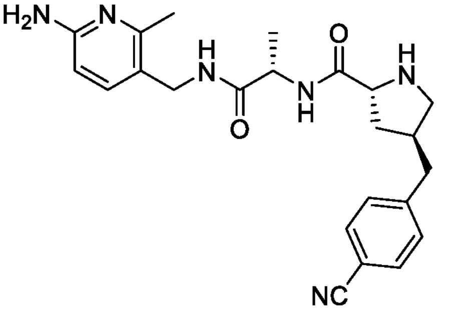
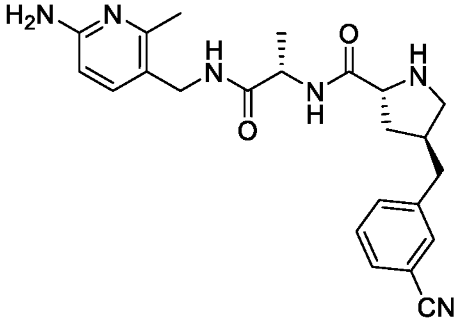
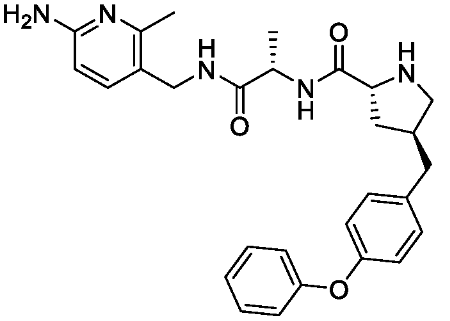
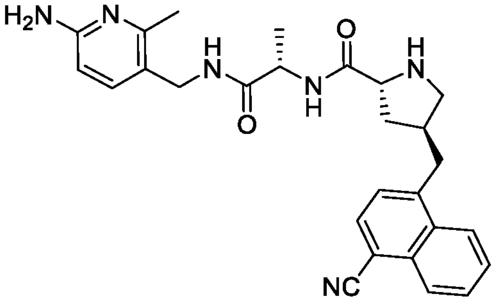
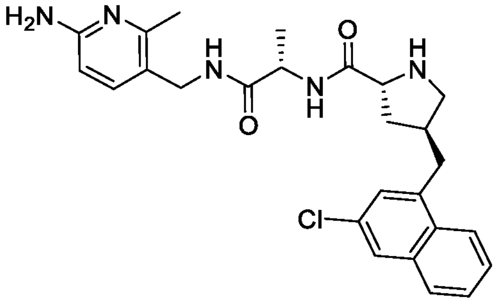
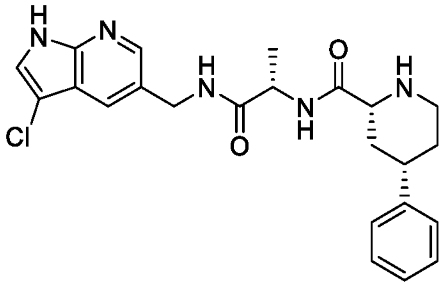
	
	
	
	
	
	

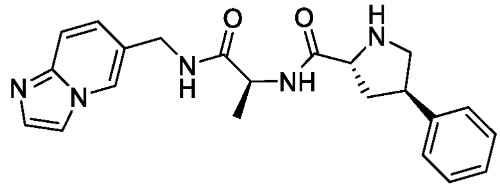
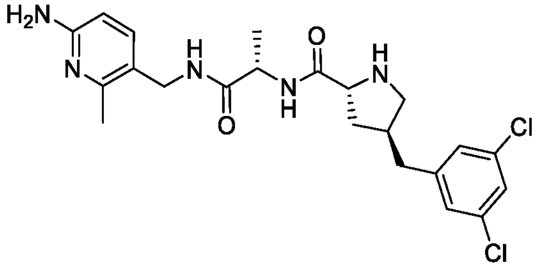
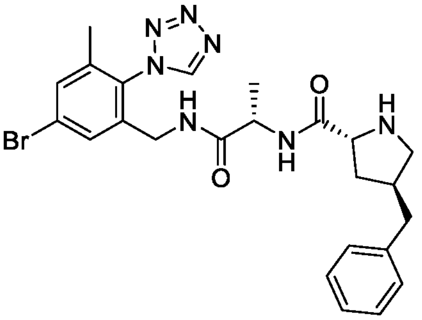
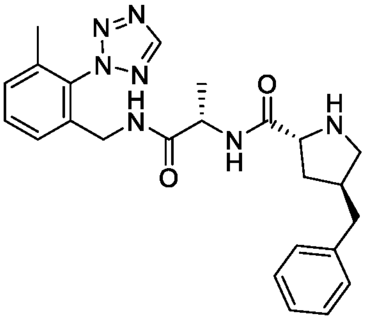
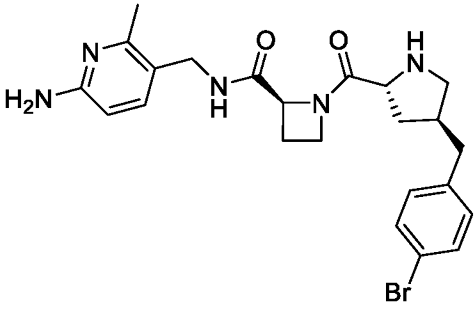
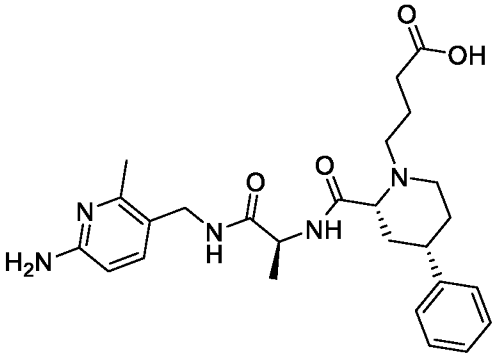
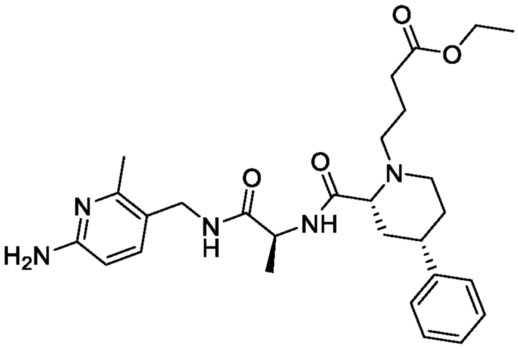
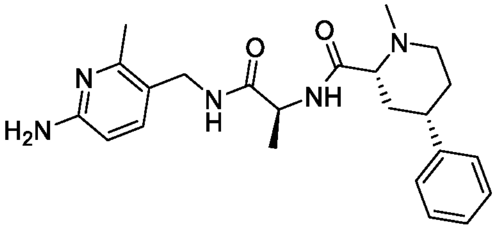
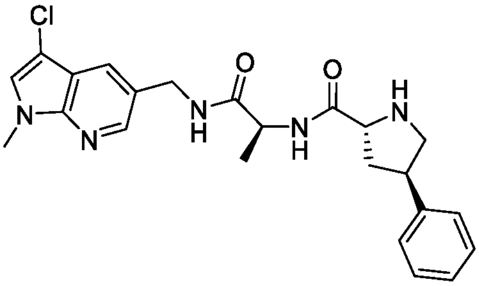
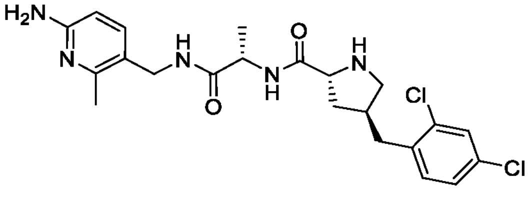
	
	
	
	
	

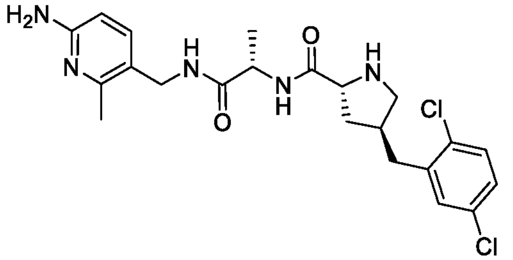
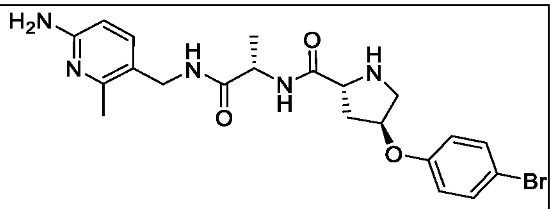
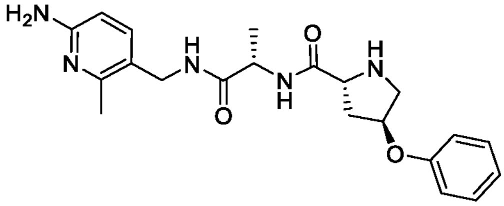
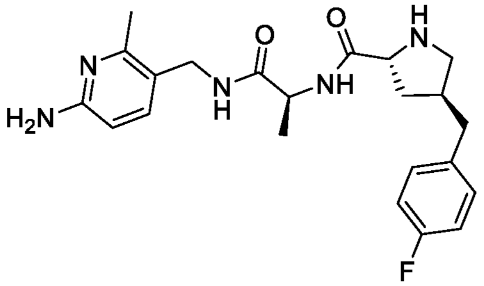
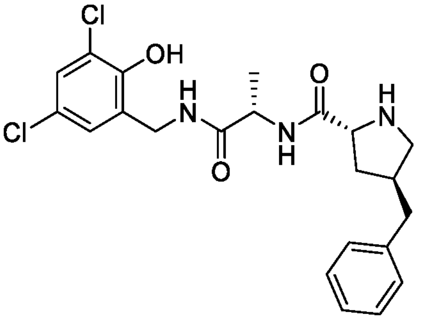
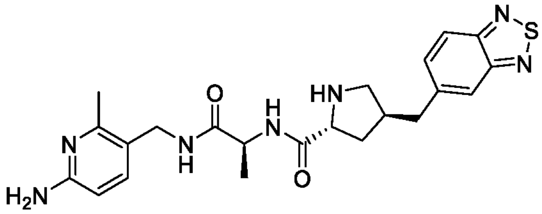
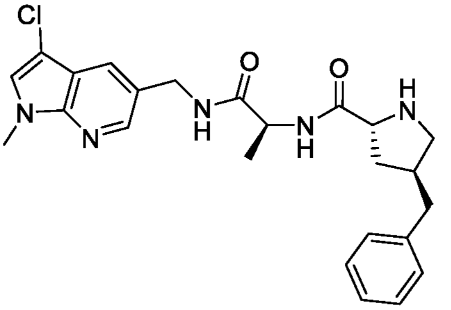
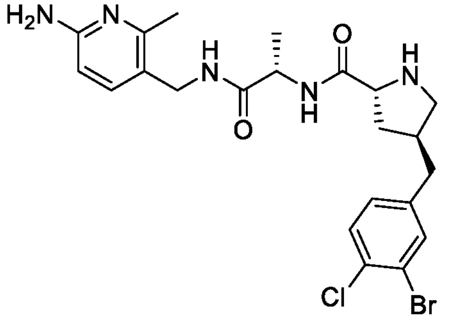
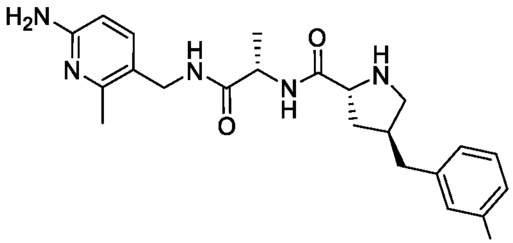
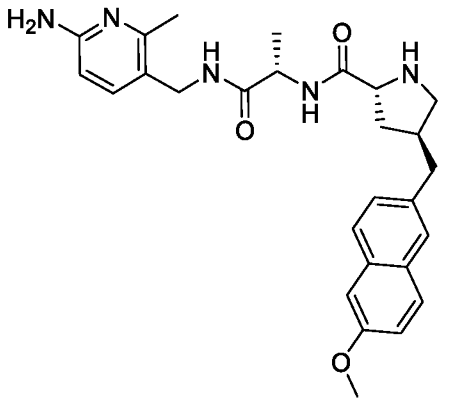
	
	
	
	
	

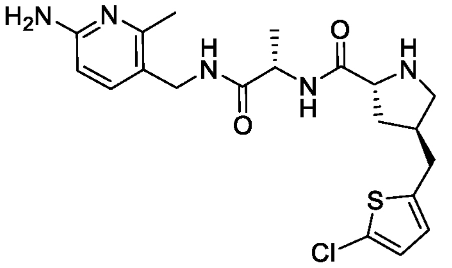
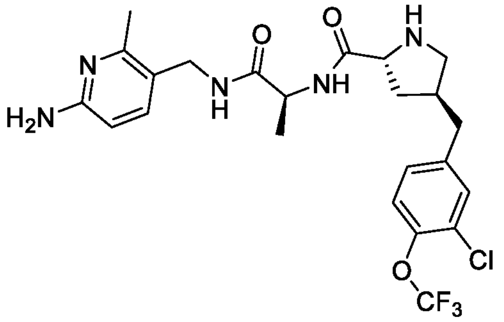
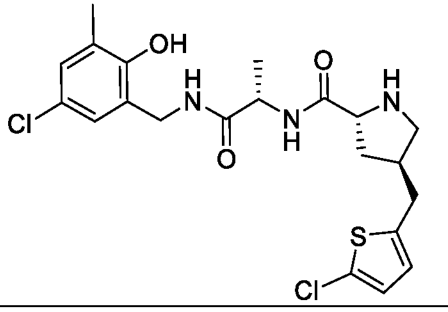
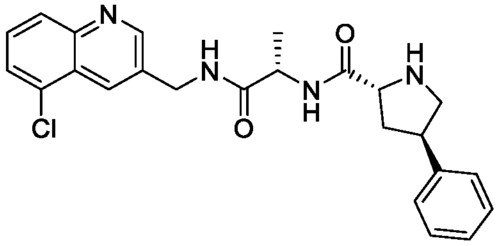
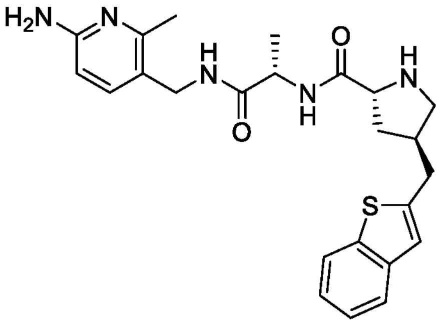
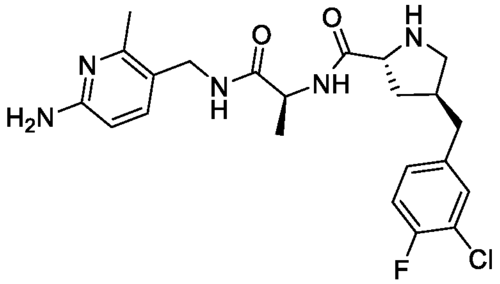
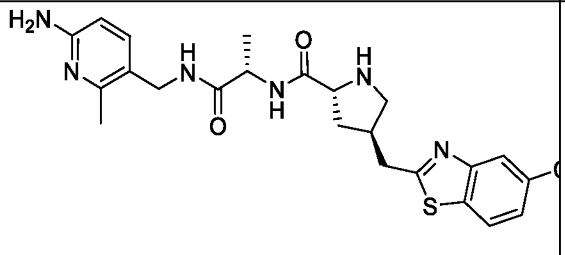
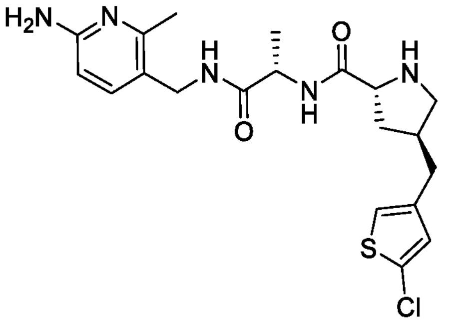
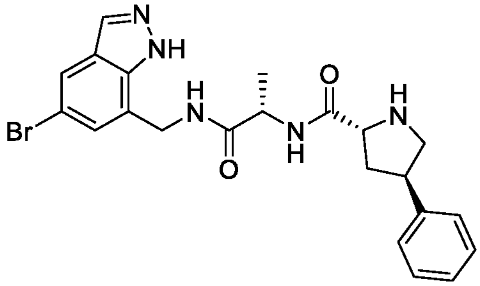
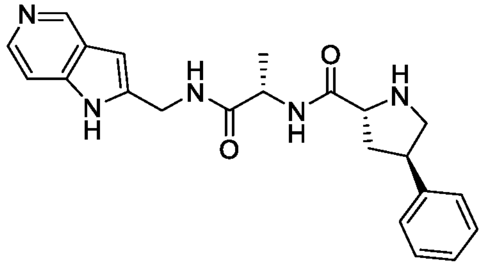
	
	
	
	
	

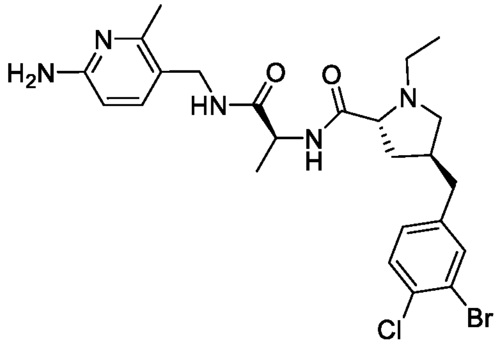
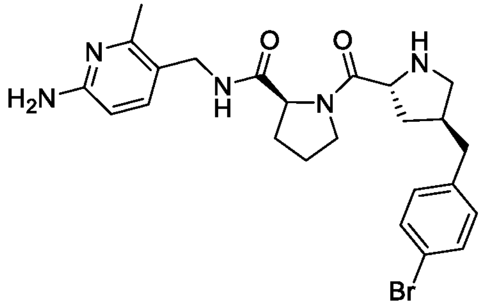
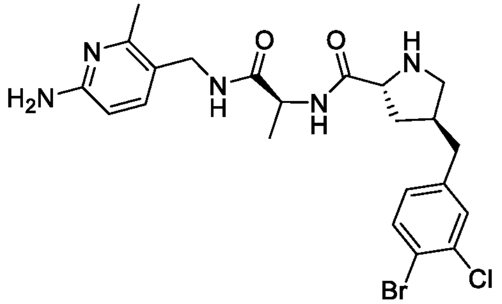
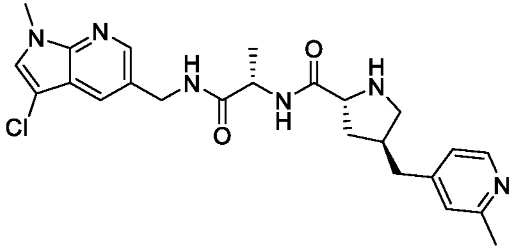
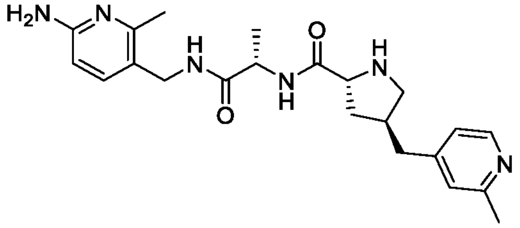
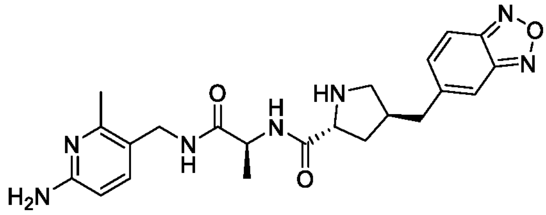
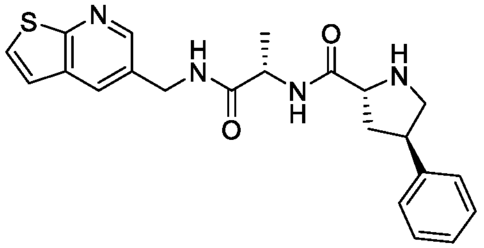
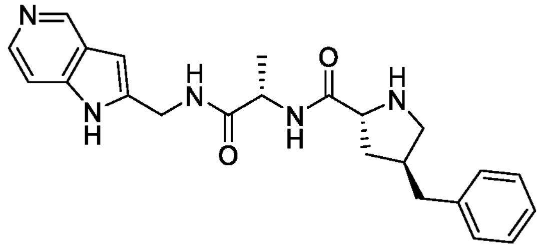
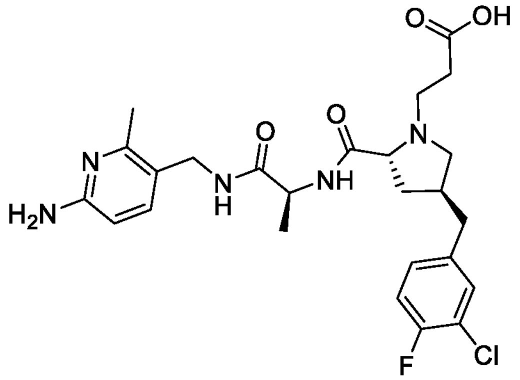
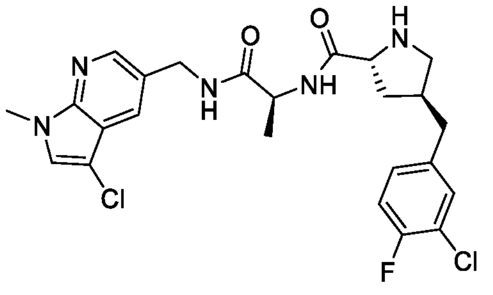
	
	
	
	
	

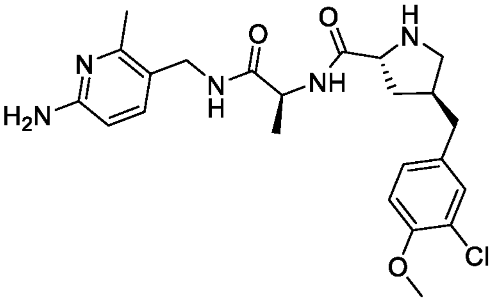
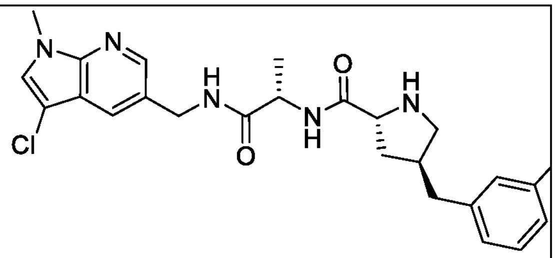
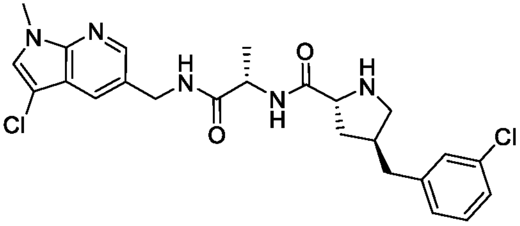
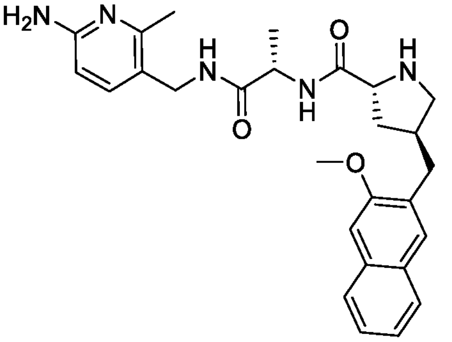
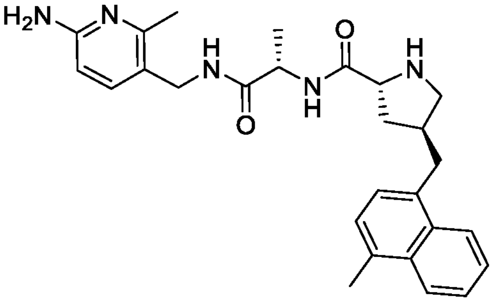
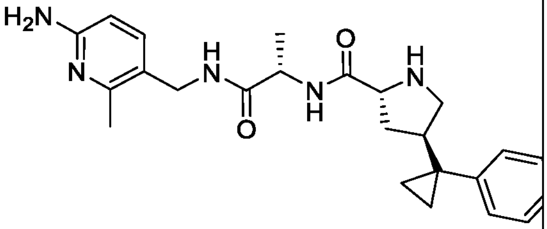
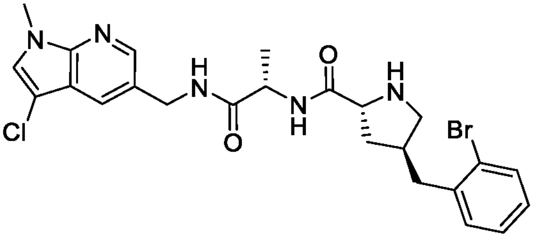
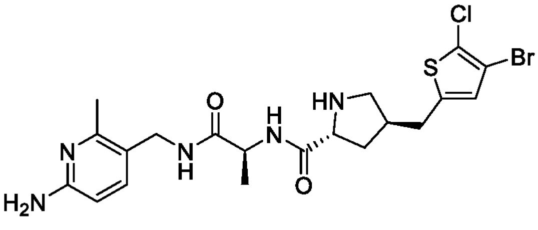
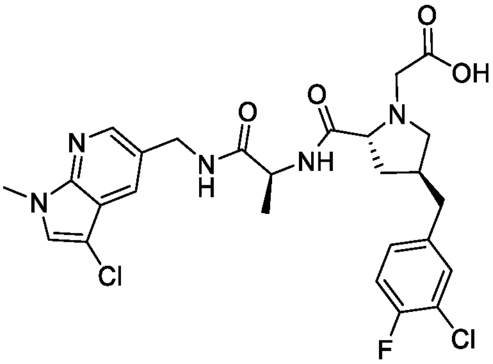
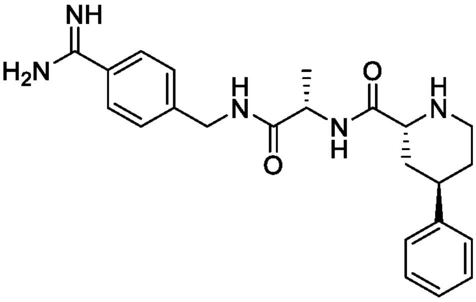
	
	
	
	
	

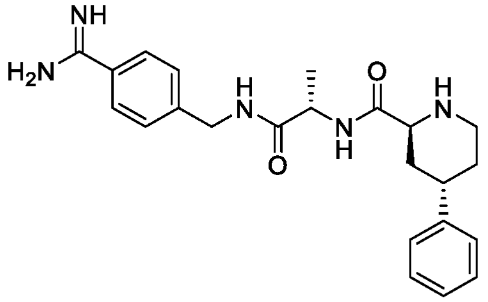
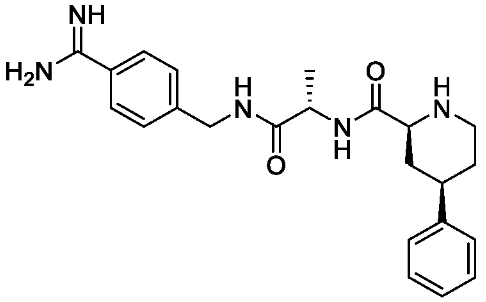
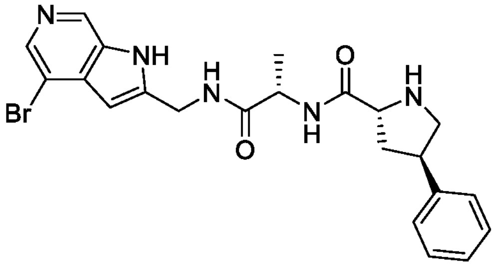
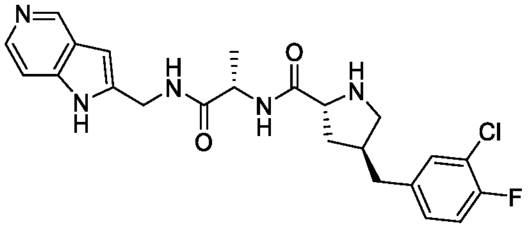
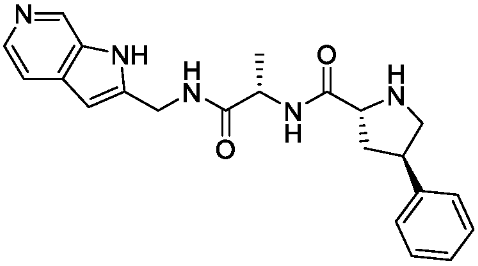
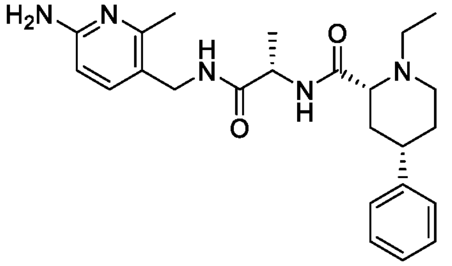
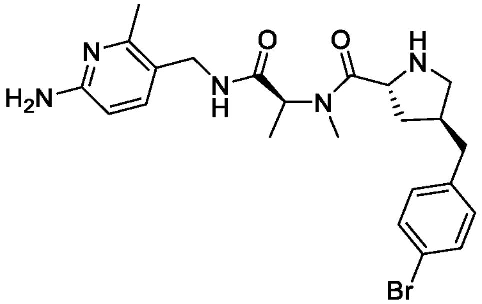
	
	
	
	
	

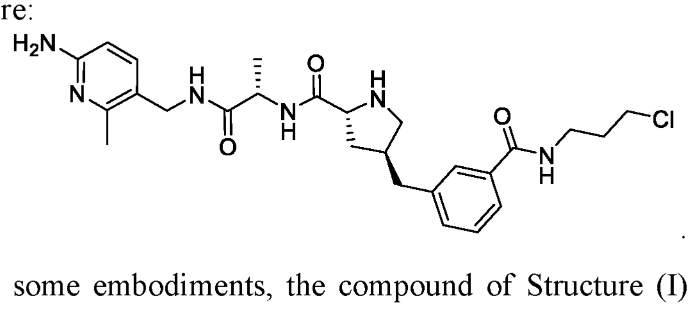
	
	
	
	
	

In some embodiments, the compound of structure (I) does not have the following structure:



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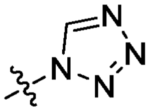
In some embodiments, the compound of Structure (I) does not have a structure of any of the compound of International Application No. PCT/US19/34225, International Application No. PCT/US19/34220, or U.S. Application No. 16/425,791 (*e.g.*, the compounds listed in Table 1 or the Examples of each of the aforementioned applications).

In some embodiments, R^1 is a substituted or unsubstituted aryl. In certain embodiments, R^1 is a substituted or unsubstituted C_6-C_{10} aryl. In some specific embodiments, R^1 is a substituted or unsubstituted phenyl. In certain specific embodiments, R^1 is a substituted phenyl.

In some more specific embodiments, R^1 is phenyl substituted with one or more of R^{1a}, R^{1b}, R^{1c}, R^{1d}, or R^{1e} wherein R^{1a}, R^{1b}, R^{1c}, R^{1d}, and R^{1e} are each independently selected from the group consisting of $C(=NH)NHC(=O)OR^8$, $C(=NOC(=O)R^8)NH_2$, $C(=NOC(=O)OR^8)NH_2$, $C(=NOH)NH_2$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, C_{1-6} haloalkyl, aminylalkyl, hydroxyalkyl, cyano, OR^9, SR^9, $C(O)R^9$, $C(O)NR^9R^{10}$, $C(O)OR^9$, $OC(O)R^9$, $OC(O)OR^9$, $OC(O)NR^9R^{10}$, NR^9R^{10}, $N(R^9)C(O)R^{10}$, $N(R^9)C(O)NR^{10}R^{11}$, $N(R^9)C(O)OR^{10}$, $C(=NR^9)NR^{10}R^{11}$, $C(=NOR^9)NR^{10}R^{11}$, $C(=NOC(O)R^9)NR^{10}R^{11}$, $C(=NR^9)N(R^{10})C(O)OR^{11}$, $N(R^9)C(=NR^{10})NR^{11}R^{12}$, $S(O)R^9$, $S(O)NR^9R^{10}$, $S(O)_2R^9$, $N(R^9)S(O)_2R^{10}$, $S(O)_2NR^9R^{10}$, oxo, substituted or unsubstituted C_{6-10} aryl, substituted or unsubstituted C_{6-10} arylalkyl, substituted or unsubstituted C_{6-10} aryloxy, substituted or unsubstituted C_{6-10} arylalkoxy, substituted or unsubstituted 5-10 membered heteroaryl, substituted or unsubstituted C_{3-10} cycloalkyl, and substituted or unsubstituted 4-10 membered heterocyclyl, wherein R^9, R^{10}, R^{11}, and R^{12}, are, at each occurrence, independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, hydroxyl, C_{1-6} alkoxy, aryl, arylalkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, cycloalkyl, heterocyclyl, heteroarylalkyl, and heteroaryl.

In certain more specific embodiments, R^{1a}, R^{1b}, R^{1c}, R^{1d}, or R^{1e} is optionally substituted with one or more substituents selected from the group consisting of halo, CN, OR^{13}, SR^{13}, $C(O)R^{13}$, $C(O)NR^{13}R^{14}$, $C(O)OR^{13}$, $OC(O)R^{13}$, $OC(O)NR^{13}R^{14}$, $NR^{13}R^{14}$, $NR^{13}C(O)R^{14}$, $NR^{13}C(O)NR^{14}R^{15}$, $NR^{13}C(O)OR^{14}$, $C(=NR^{13})NR^{14}R^{15}$, $NR^{13}C(=NR^{14})NR^{15}R^{16}$, $S(O)R^{13}$, $S(O)NR^{13}R^{14}$, $S(O)_2R^{13}$, $NR^{13}S(O)_2R^{14}$, $S(O)_2NR^{13}R^{14}$ and oxo when R^{1a}, R^{1b}, R^{1c}, R^{1d}, or R^{1e} is a substituted C_{6-10} aryl, a substituted C_{6-10} arylalkyl, a substituted C_{6-10} aryloxy, a substituted C_{6-10} arylalkoxy, a substituted 5-10 membered heteroaryl, a substituted C_{3-10} cycloalkyl, and a substituted 4-10 membered heterocyclyl, wherein R^{13}, R^{14}, R^{15}, and R^{16} are, at each occurrence, independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, hydroxyl, C_{1-6} alkoxy, aryl, arylalkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, cycloalkyl, heterocyclyl, and heteroaryl.

In some embodiments, R^1 is phenyl substituted with at least one substituent selected from the group consisting of halo, haloalkyl, $C(=NR^9)NR^{10}R^{11}$, $C(=NR^9)NR^{10}C(O)OR^{11}$, and 5-10 membered heteroaryl. In certain more specific embodiments, R^1 is substituted with at least one substituent selected from the group consisting of $-C(=NH)NH_2$, chloro, fluoro, $-CHF_2$, and



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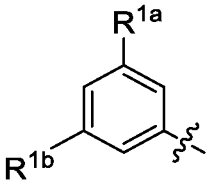
In some embodiments, R^1 has one of the following structures:



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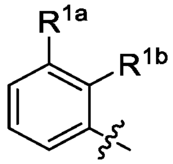

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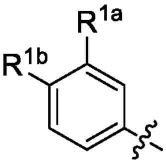

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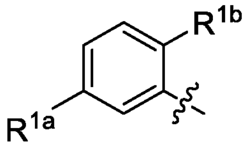

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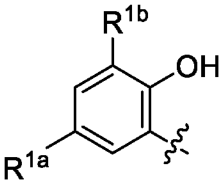

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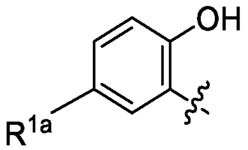

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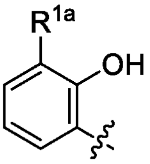

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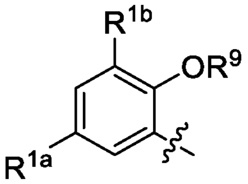

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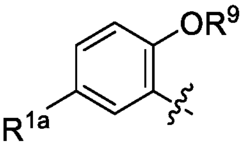

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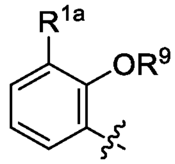

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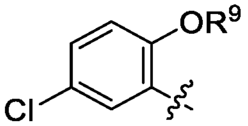

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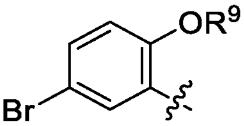

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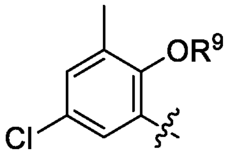

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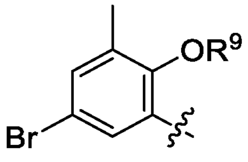

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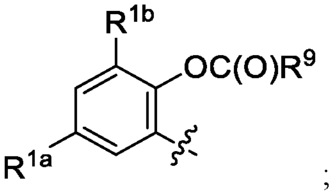

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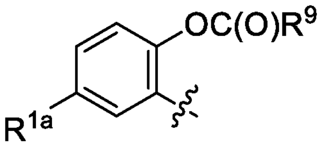

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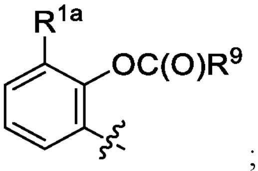

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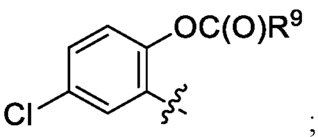

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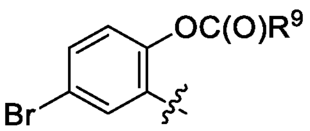

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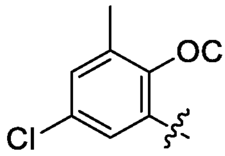

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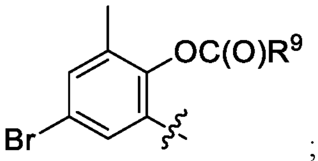

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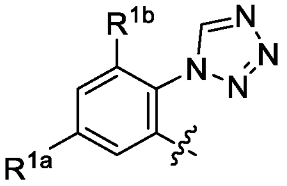

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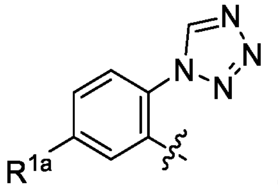

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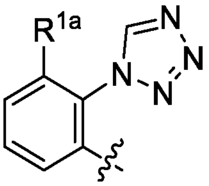
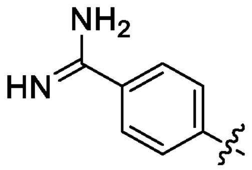


.

In some more specific embodiments, R^1 has one of the following structures:



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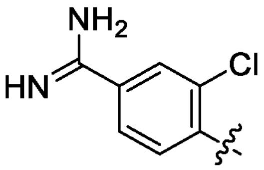

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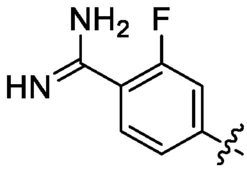

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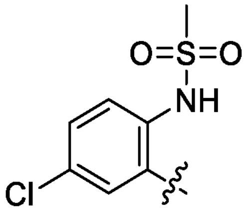

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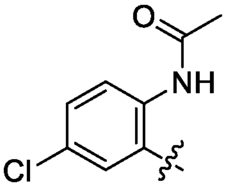

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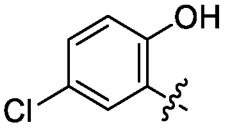

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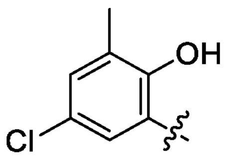

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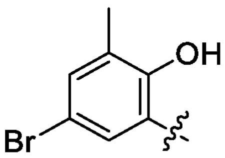

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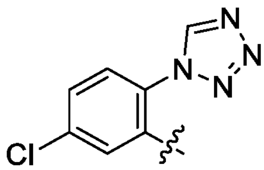

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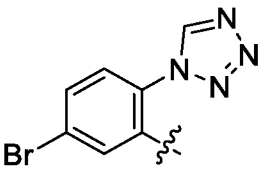

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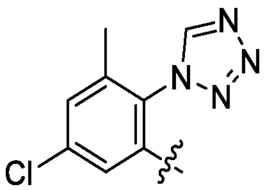

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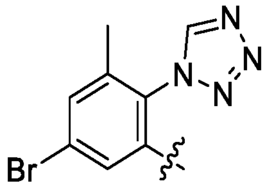
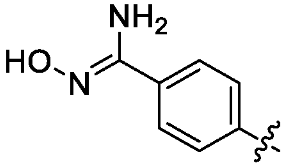
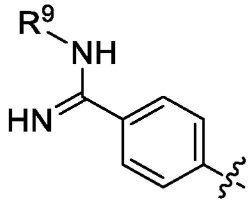
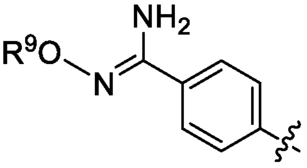
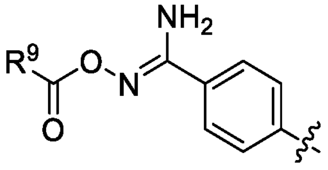
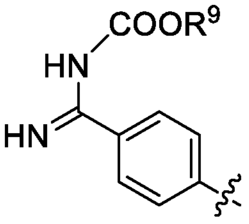


.

In some embodiments, R^1 has one of the following structures:

 ;  ;  ;

 or  .

In some embodiments, R^9 is C_{1-6} alkyl or C_{1-6} haloalkyl. In certain embodiments, R^9 is methyl. In some specific embodiments, R^9 is trifluoromethyl. In certain specific embodiments, R^1 is an unsubstituted phenyl.

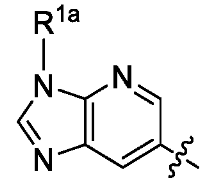
In some more specific embodiments, R^1 is a substituted or unsubstituted heteroaryl. In some embodiments, R^1 is a substituted or unsubstituted 5-10 membered heteroaryl. In certain embodiments, R^1 is a substituted or unsubstituted pyridinyl, a substituted or unsubstituted pyrrolopyridinyl, a substituted or unsubstituted imidazopyridinyl, a substituted or unsubstituted thienopyridinyl, a substituted or unsubstituted benzoimidazolyl, a substituted or unsubstituted isoindolinyl, or a substituted or unsubstituted benzothiazolyl.

In some more specific embodiments, R^1 is a heteroaryl substituted with one or more of R^{1a}, R^{1b}, R^{1c}, R^{1d}, or R^{1e} wherein R^{1a}, R^{1b}, R^{1c}, R^{1d}, and R^{1e} are each independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} deuterated alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, C_{1-6} haloalkyl, aminylalkyl, hydroxyalkyl, cyano, OR^9, SR^9, $C(O)R^9$, $C(O)NR^9R^{10}$, $C(O)OR^9$, $OC(O)R^9$, $OC(O)OR^9$, $OC(O)NR^9R^{10}$, NR^9R^{10}, $N(R^9)C(O)R^{10}$, $N(R^9)C(O)NR^{10}R^{11}$, $N(R^9)C(O)OR^{10}$, $C(=NR^9)NR^{10}R^{11}$, $C(=NOR^9)NR^{10}R^{11}$, $C(=NOC(O)R^9)NR^{10}R^{11}$, $C(=NR^9)N(R^{10})C(O)OR^{11}$, $N(R^9)C(=NR^{10})NR^{11}R^{12}$, $S(O)R^9$, $S(O)NR^9R^{10}$, $S(O)_2R^9$, $N(R^9)S(O)_2R^{10}$, $S(O)_2NR^9R^{10}$, oxo, substituted or unsubstituted C_{6-10} aryl, substituted or unsubstituted C_{6-10} arylalkyl, substituted or unsubstituted C_{6-10} aryloxy, substituted or unsubstituted C_{6-10} arylalkoxy, substituted or unsubstituted 5-10 membered heteroaryl, substituted or unsubstituted C_{3-10} cycloalkyl, and substituted or unsubstituted 4-10 membered heterocyclyl, wherein R^9,

R^{10}, R^{11}, and R^{12}, are, at each occurrence, independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, hydroxyl, C_{1-6} alkoxy, aryl, arylalkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, cycloalkyl, heterocyclyl, and heteroaryl.

In certain more specific embodiments, R^{1a}, R^{1b}, R^{1c}, R^{1d}, or R^{1e} is optionally substituted with one or more substituents selected from the group consisting of halo, CN, OR^{13}, SR^{13}, $C(O)R^{13}$, $C(O)NR^{13}R^{14}$, $C(O)OR^{13}$, $OC(O)R^{13}$, $OC(O)NR^{13}R^{14}$, $NR^{13}R^{14}$, $NR^{13}C(O)R^{14}$, $NR^{13}C(O)NR^{14}R^{15}$, $NR^{13}C(O)OR^{14}$, $C(=NR^{13})NR^{14}R^{15}$, $NR^{13}C(=NR^{14})NR^{15}R^{16}$, $S(O)R^{13}$, $S(O)NR^{13}R^{14}$, $S(O)_2R^{13}$, $NR^{13}S(O)_2R^{14}$, $S(O)_2NR^{13}R^{14}$ and oxo when R^{1a}, R^{1b}, R^{1c}, R^{1d}, or R^{1e} is a substituted C_{6-10} aryl, a substituted C_{6-10} arylalkyl, a substituted C_{6-10} aryloxy, a substituted C_{6-10} arylalkoxy, a substituted 5-10 membered heteroaryl, a substituted C_{3-10} cycloalkyl, and a substituted 4-10 membered heterocyclyl, wherein R^{13}, R^{14}, R^{15}, and R^{16} are, at each occurrence, independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, hydroxyl, C_{1-6} alkoxy, aryl, arylalkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, cycloalkyl, heterocyclyl, and heteroaryl.

In some embodiments, R^1 has one of the following structures:



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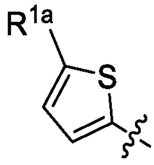

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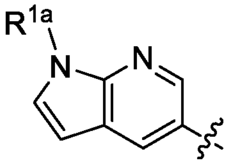

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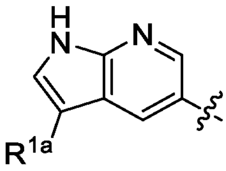

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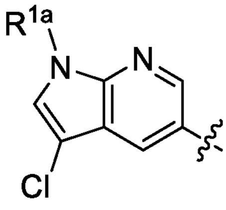

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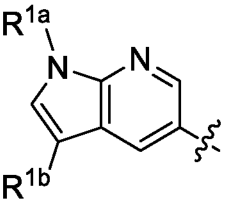

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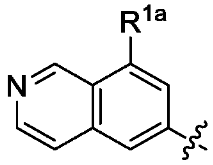

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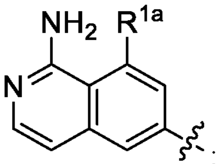

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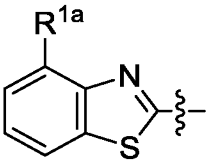

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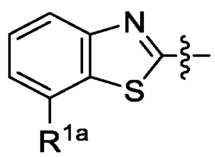

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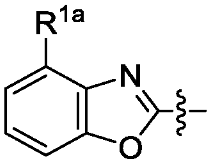

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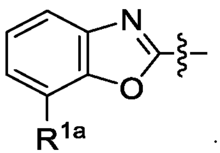

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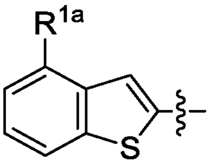

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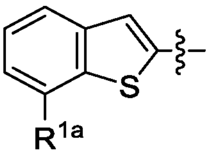

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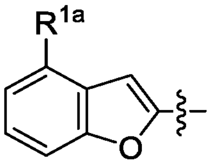

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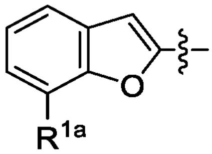
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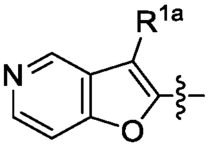
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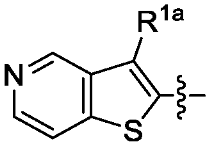
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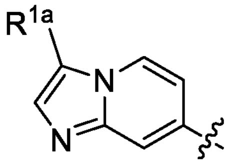
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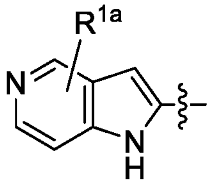
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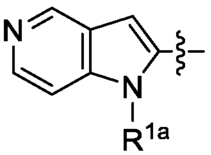
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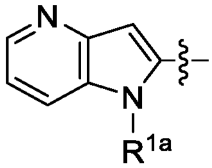
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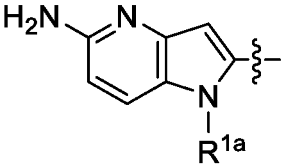
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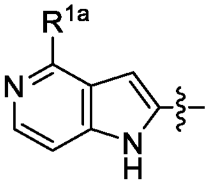
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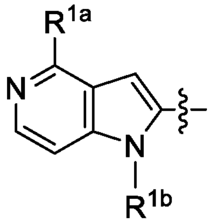
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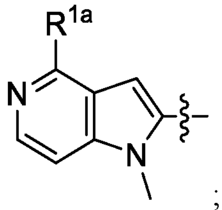
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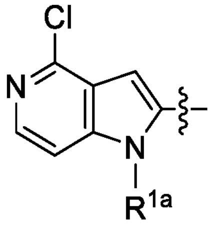
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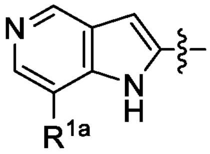
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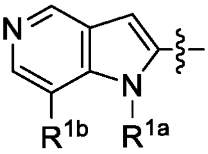
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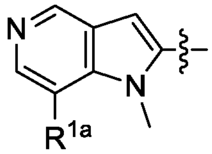
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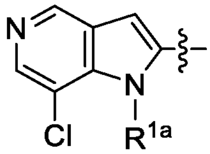
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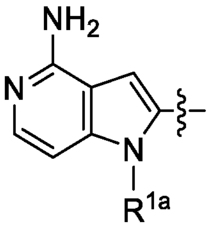
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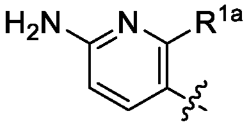
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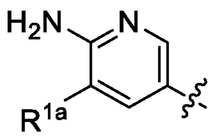
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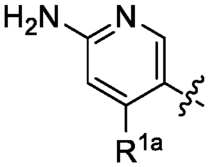
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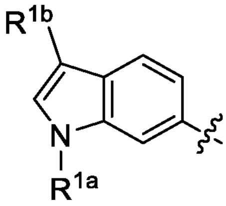
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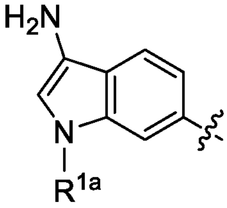
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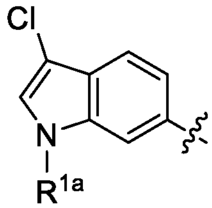
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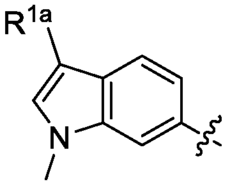
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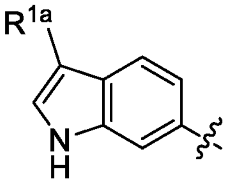
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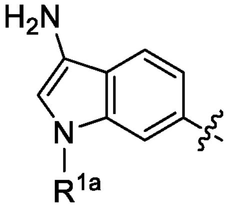
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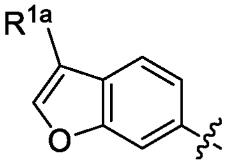
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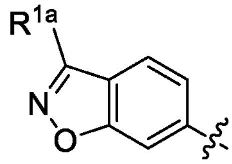
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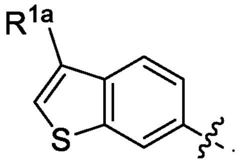
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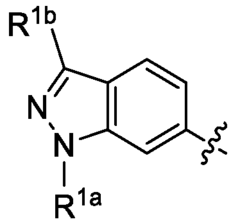
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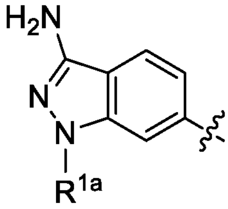
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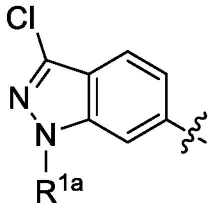
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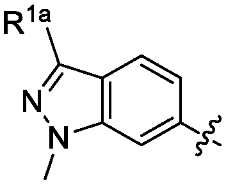
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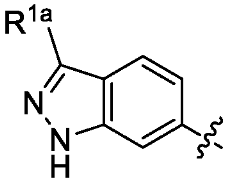
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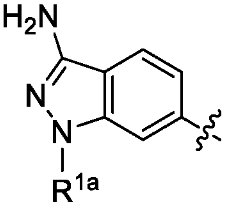
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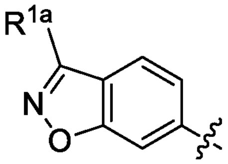
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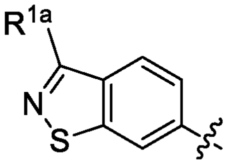
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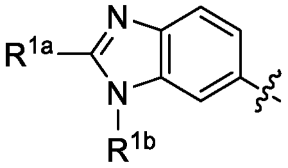
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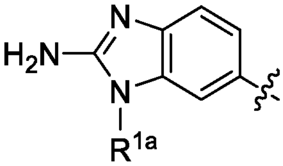
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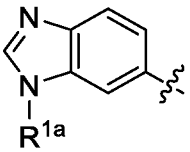
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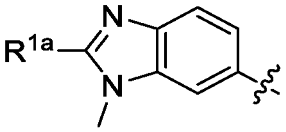
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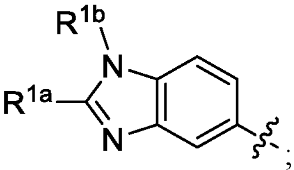
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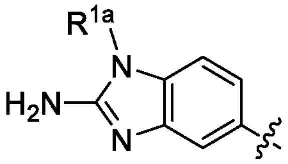
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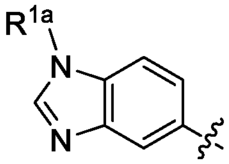
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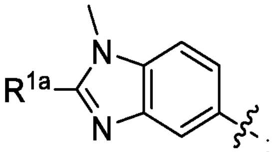
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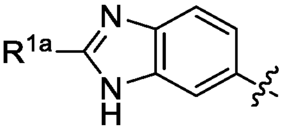
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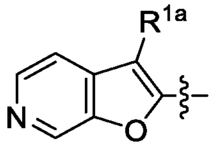
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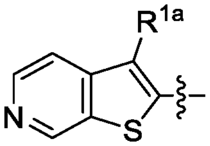
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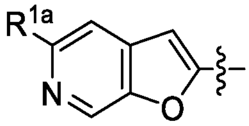
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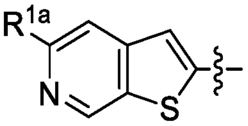
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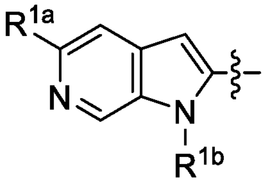
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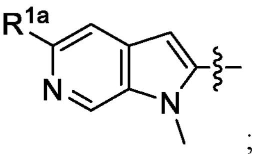
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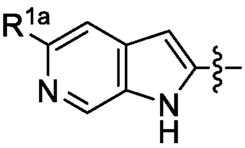
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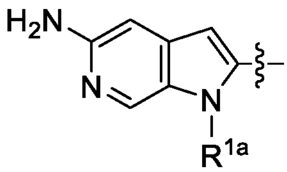
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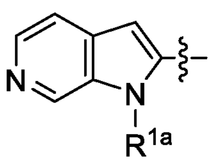
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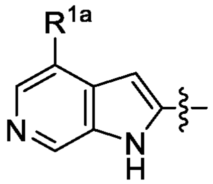
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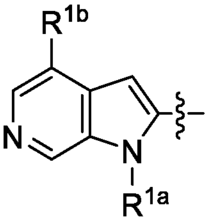
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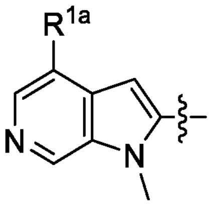
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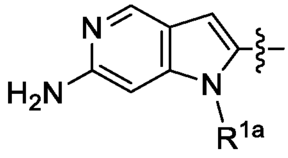
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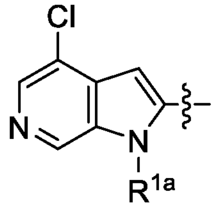
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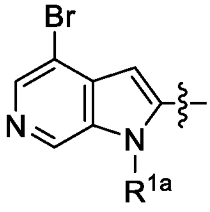
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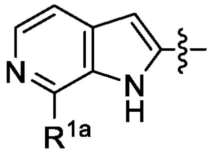
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N
H
R1a
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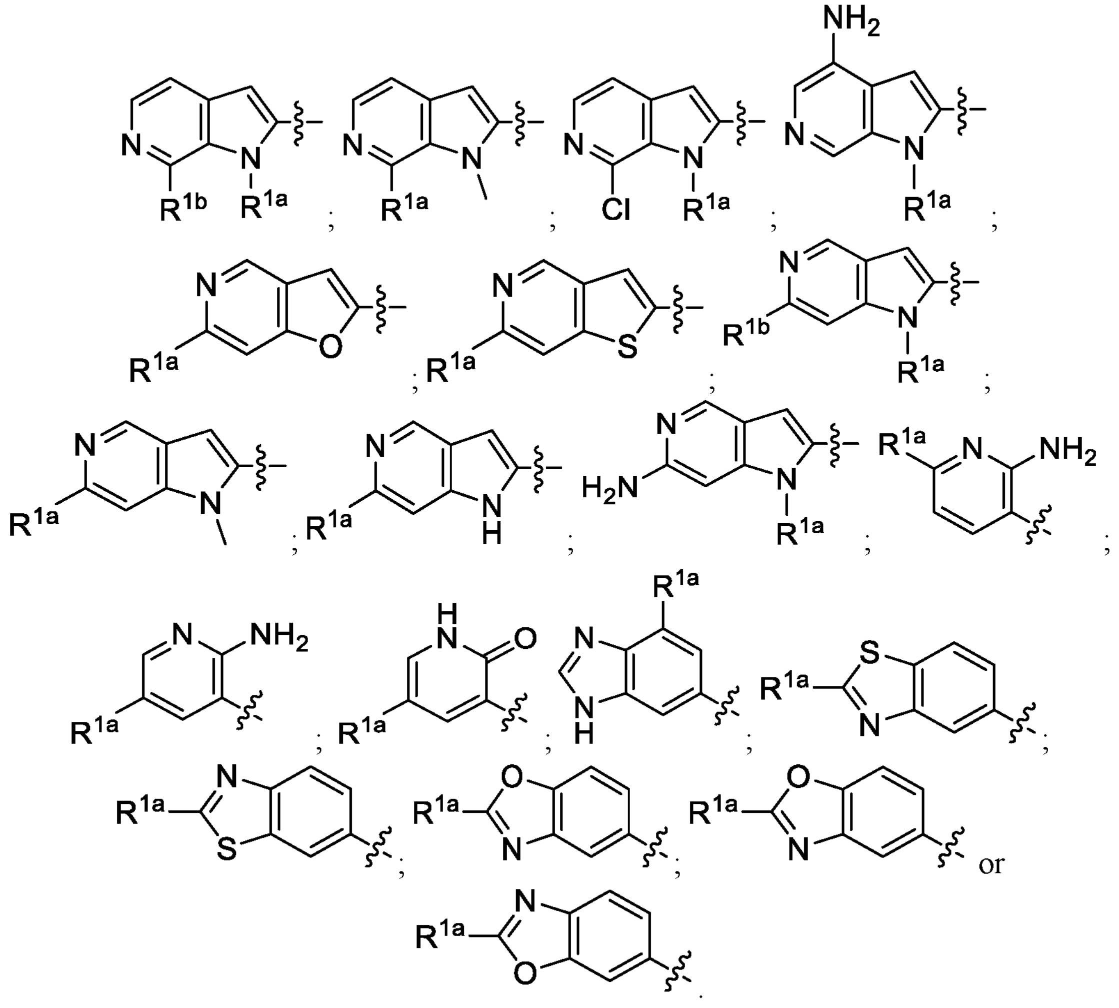
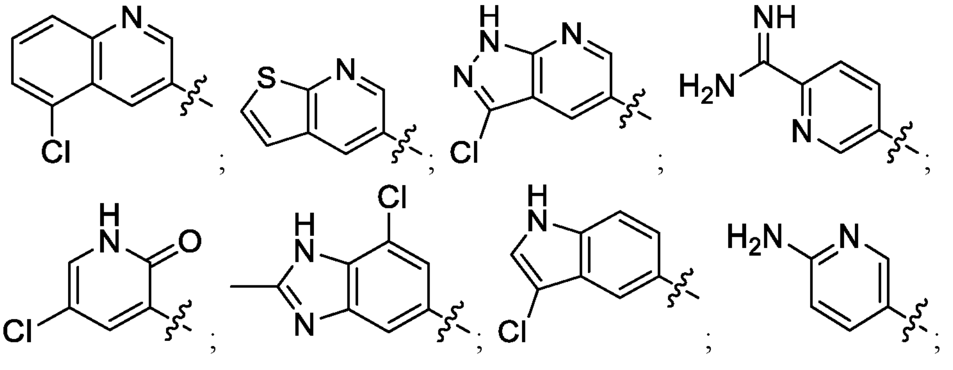
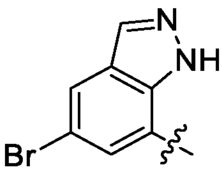


In some embodiments, R^{1a} or R^{1b} is independently C_{1-6} alkyl, C_{1-6} deuterated alkyl, amino, or halo. In certain embodiments, R^{1a} or R^{1b} is methyl or CD_3. In some specific embodiments, R^{1a} or R^{1b} is F, Cl, or Br. In certain specific embodiments, each R^{1a} or R^{1b} attached to nitrogen is C_{1-6} alkyl. In some more specific embodiments, R^{1a} or R^{1b} is methyl or ethyl.

In some embodiments, R^1 has one of the following structures:

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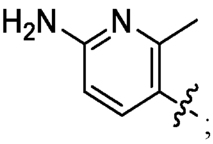
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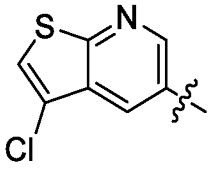
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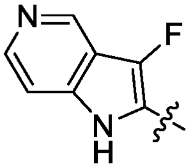
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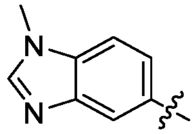
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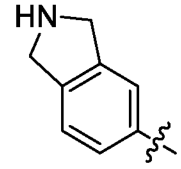
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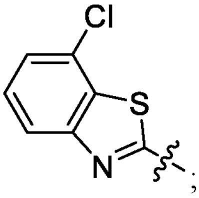
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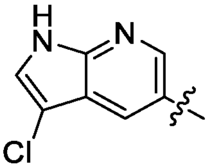
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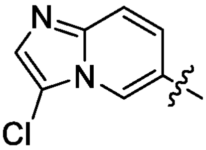
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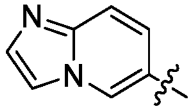
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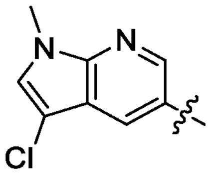
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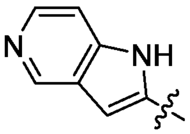
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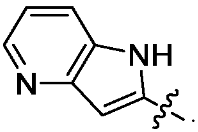
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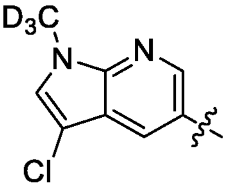
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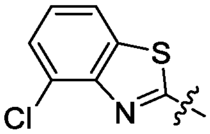
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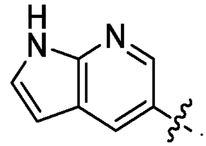
In certain embodiments, R^1 has one of the following structures: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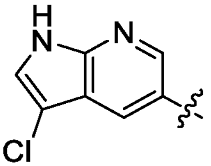
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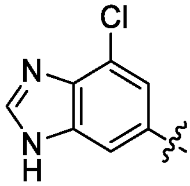
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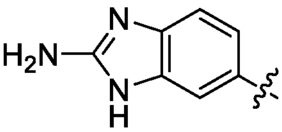
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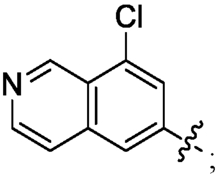
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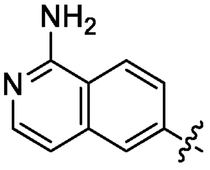
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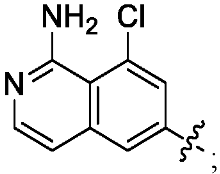
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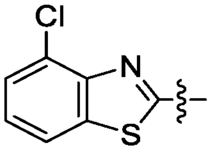
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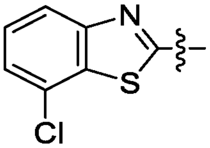
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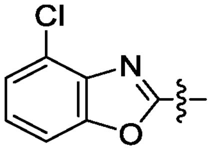
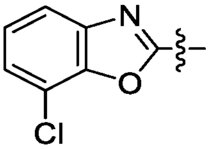
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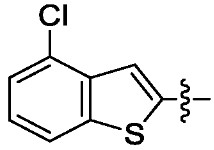
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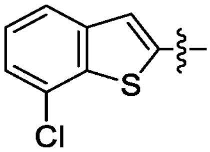
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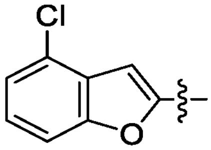
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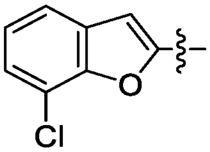
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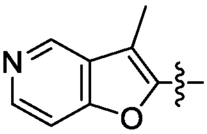
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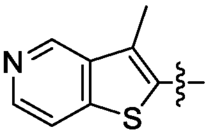
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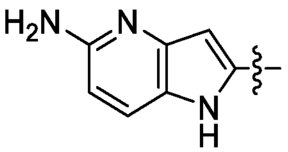
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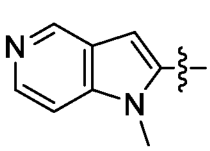
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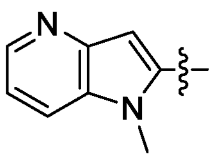
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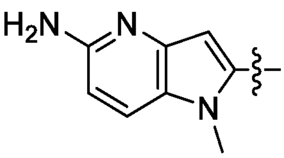
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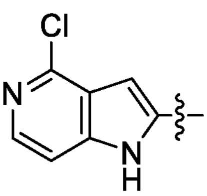
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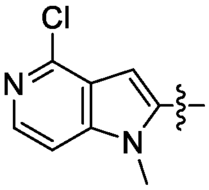
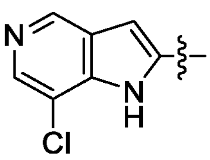
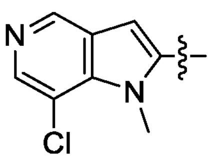
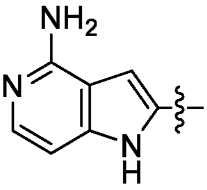
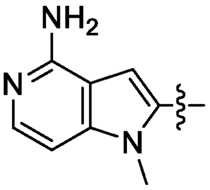
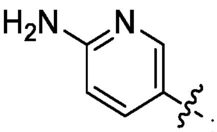
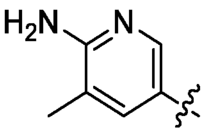
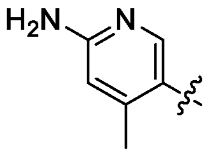
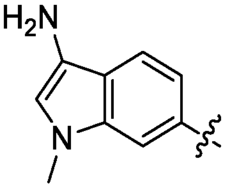
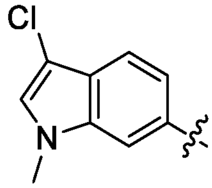
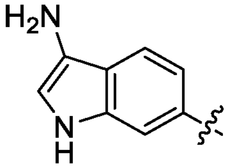
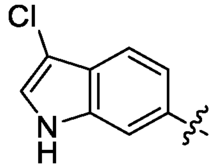
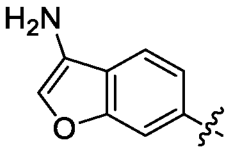
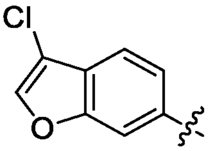
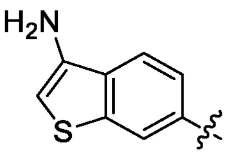
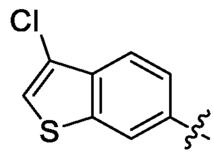
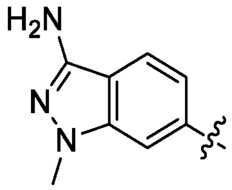
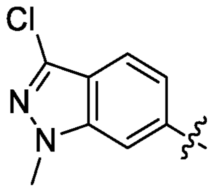
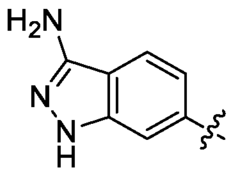
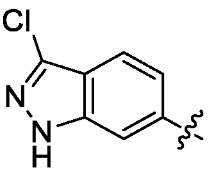
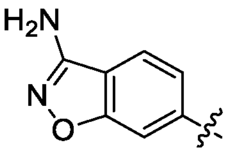
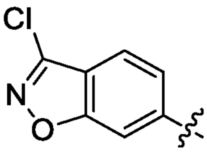
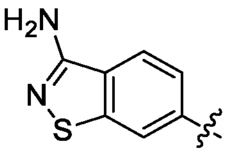
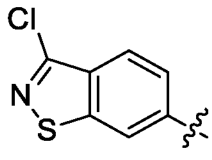
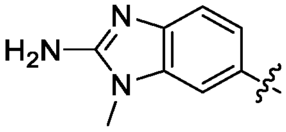
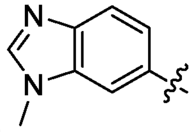
 ;;  ;  ;  ;  ;

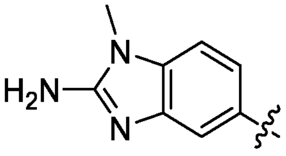
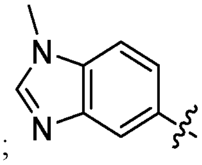
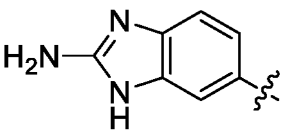
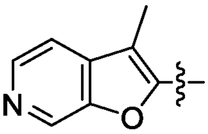
 ;  ;  ;  ;  ;

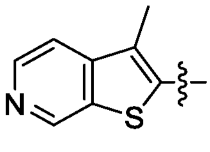
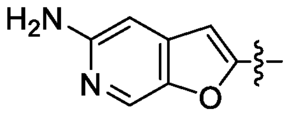
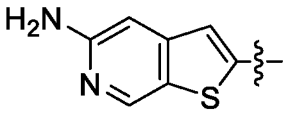
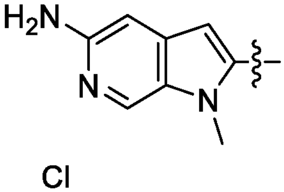
 ;  ;  ;  ;

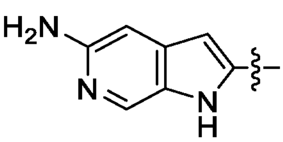
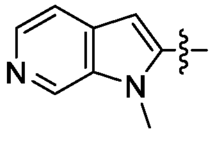
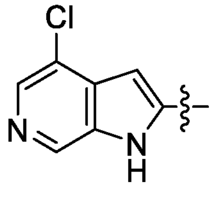
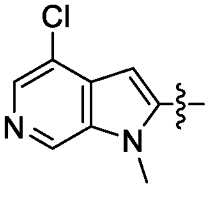
 ;  ;  ;  ;

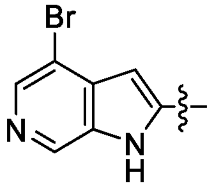
 ;  ;  ;  ;

 ;  ;  ;  ;

 ;  ;  ;  ;

 ;  ;  ;  ;

 ;  ;  ;  ;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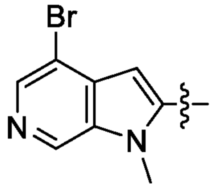
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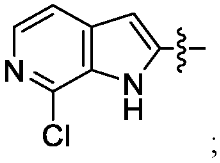
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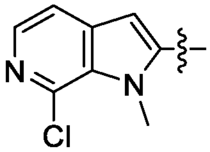
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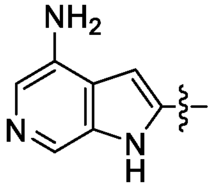
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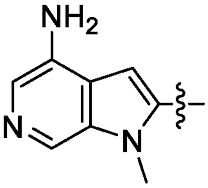
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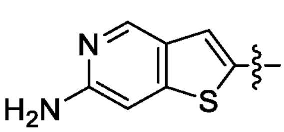
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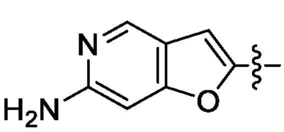
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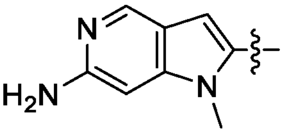
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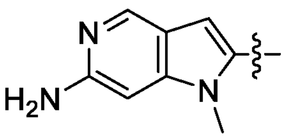
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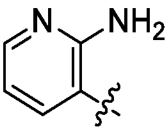
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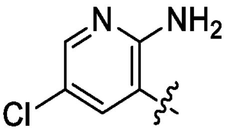
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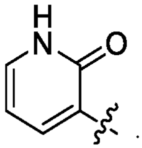
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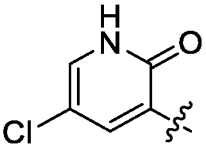
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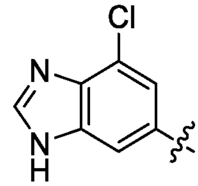
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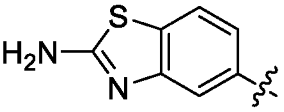
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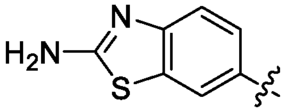
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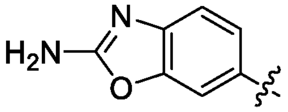
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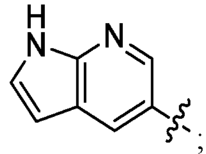
In some embodiments, R^1 has one of the following structures: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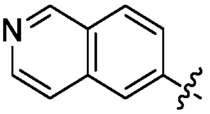
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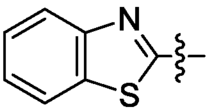
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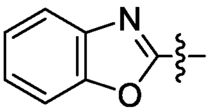
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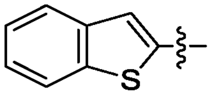
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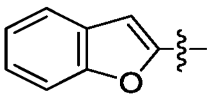
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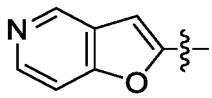
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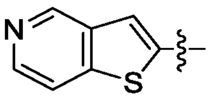
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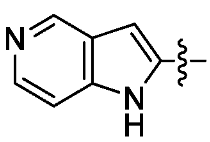
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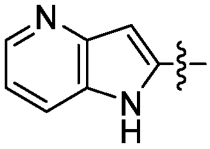
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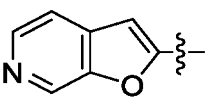
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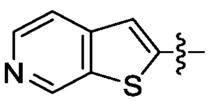
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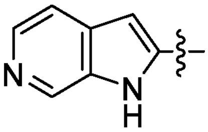
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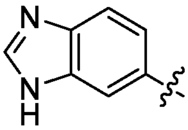
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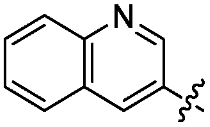
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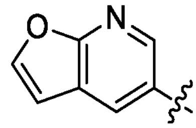
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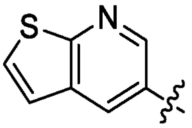
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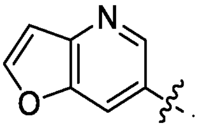
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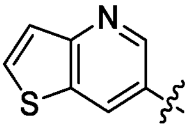
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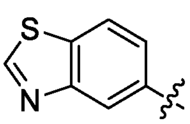
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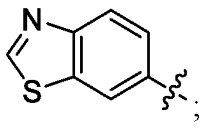
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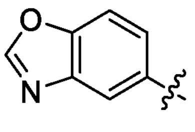
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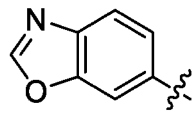
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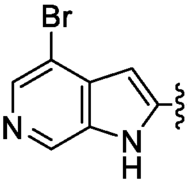
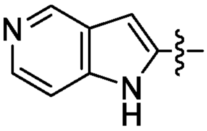
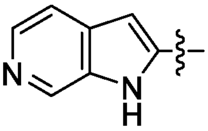
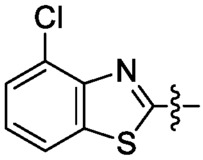
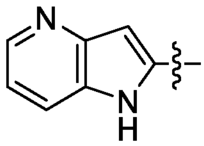
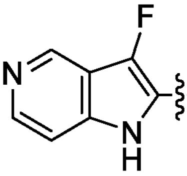
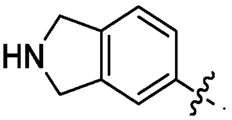
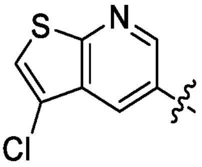
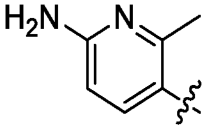
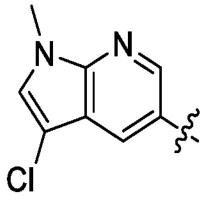
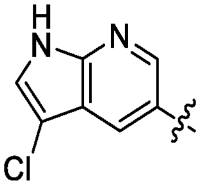
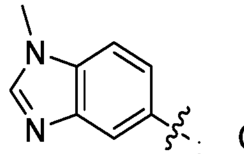
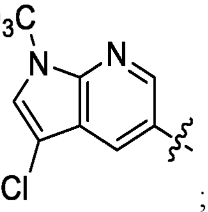
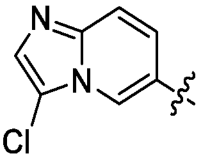
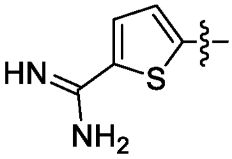
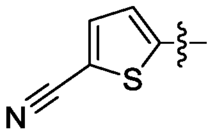
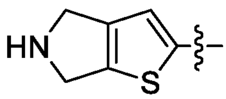
In some embodiments, R^1 has one of the following structures:

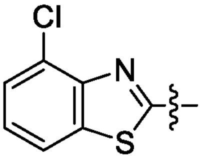
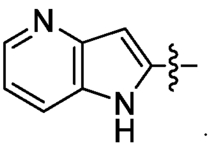
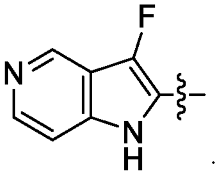
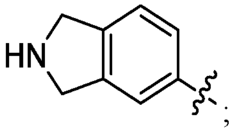
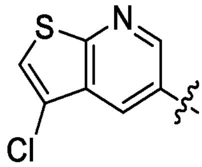
 ;  ;  ;  ;  ;

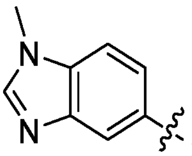
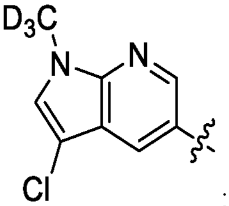
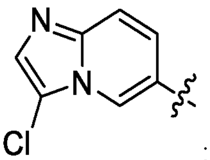
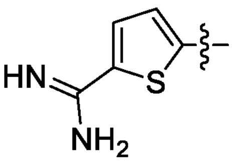
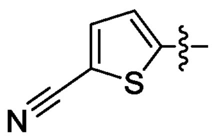
 ;  ;  ;  ;  ;

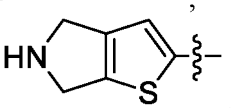
 ;  ;  ;  ;  ;

 or  .

In some embodiments, R^1 has one of the following structures:

 ;  ;  ;  ;  ;

 ;  ;  ;  ; 

or  .

In some embodiments, R^1 is a substituted or unsubstituted cycloalkyl. In certain embodiments, R^1 is a substituted or unsubstituted C_3-C_6 cycloalkyl. In some specific embodiments, R^1 is a substituted C_3-C_6 cycloalkyl.

In some more specific embodiments, R^1 is a C_3-C_6 cycloalkyl substituted with one or more of R^{1a}, R^{1b}, R^{1c}, R^{1d}, or R^{1e} wherein R^{1a}, R^{1b}, R^{1c}, R^{1d}, and R^{1e} are each independently selected from the group consisting of $C_{1\text{-}6}$ alkyl, $C_{2\text{-}6}$ alkenyl, $C_{2\text{-}6}$ alkynyl, $C_{1\text{-}6}$ haloalkyl, aminylalkyl, hydroxyalkyl, OR^9, SR^9, $C(O)R^9$, $C(O)NR^9R^{10}$, $C(O)OR^9$,

OC(O)R^9, OC(O)OR^9, OC(O)NR^9R^{10}, NR^9R^{10}, N(R^9)C(O)R^{10}, N(R^9)C(O)N$R^{10}R^{11}$, N(R^9)C(O)OR^{10}, C(=NR^9)N$R^{10}R^{11}$, C(=NOR^9)N$R^{10}R^{11}$, C(=NOC(O)R^9)N$R^{10}R^{11}$, C(=NR^9)N(R^{10})C(O)OR^{11}, N(R^9)C(=NR^{10})N$R^{11}R^{12}$, S(O)R^9, S(O)NR^9R^{10}, S(O)$_2R^9$, N(R^9)S(O)$_2R^{10}$, S(O)$_2$NR^9R^{10}, oxo, substituted or unsubstituted $C_{6\text{-}10}$ aryl, substituted or unsubstituted $C_{6\text{-}10}$ arylalkyl, substituted or unsubstituted $C_{6\text{-}10}$ aryloxy, substituted or unsubstituted $C_{6\text{-}10}$ arylalkoxy, substituted or unsubstituted 5-10 membered heteroaryl, substituted or unsubstituted $C_{3\text{-}10}$ cycloalkyl, and substituted or unsubstituted 4-10 membered heterocyclyl, wherein R^9, R^{10}, R^{11}, and R^{12}, are, at each occurrence, independently selected from the group consisting of hydrogen, $C_{1\text{-}6}$ alkyl, $C_{2\text{-}6}$ alkenyl, $C_{2\text{-}6}$ alkynyl, hydroxyl, $C_{1\text{-}6}$ alkoxy, aryl, arylalkyl, $C_{1\text{-}6}$ haloalkyl, $C_{1\text{-}6}$ haloalkoxy, $C_{1\text{-}6}$ hydroxyalkyl, cycloalkyl, heterocyclyl, and heteroaryl.

In certain more specific embodiments, R^{1a}, R^{1b}, R^{1c}, R^{1d}, or R^{1e} is optionally substituted with one or more substituents selected from the group consisting of halo, CN, OR^{13}, SR^{13}, C(O)R^{13}, C(O)N$R^{13}R^{14}$, C(O)OR^{13}, OC(O)R^{13}, OC(O)N$R^{13}R^{14}$, N$R^{13}R^{14}$, NR^{13}C(O)R^{14}, NR^{13}C(O)N$R^{14}R^{15}$, NR^{13}C(O)OR^{14}, C(=NR^{13})N$R^{14}R^{15}$, NR^{13}C(=NR^{14})N$R^{15}R^{16}$, S(O)R^{13}, S(O)N$R^{13}R^{14}$, S(O)$_2R^{13}$, NR^{13}S(O)$_2R^{14}$, S(O)$_2$N$R^{13}R^{14}$ and oxo when R^{1a}, R^{1b}, R^{1c}, R^{1d}, or R^{1e} is a substituted $C_{6\text{-}10}$ aryl, a substituted $C_{6\text{-}10}$ arylalkyl, a substituted $C_{6\text{-}10}$ aryloxy, a substituted $C_{6\text{-}10}$ arylalkoxy, a substituted 5-10 membered heteroaryl, a substituted $C_{3\text{-}10}$ cycloalkyl, and a substituted 4-10 membered heterocyclyl, wherein R^{13}, R^{14}, R^{15}, and R^{16} are, at each occurrence, independently selected from the group consisting of hydrogen, $C_{1\text{-}6}$ alkyl, $C_{2\text{-}6}$ alkenyl, $C_{2\text{-}6}$ alkynyl, hydroxyl, $C_{1\text{-}6}$ alkoxy, aryl, arylalkyl, $C_{1\text{-}6}$ haloalkyl, $C_{1\text{-}6}$ haloalkoxy, $C_{1\text{-}6}$ hydroxyalkyl, cycloalkyl, heterocyclyl, and heteroaryl.

In some embodiments, R^1 is an unsubstituted a C_3-C_6 cycloalkyl. In certain embodiments, R^1 is a substituted or unsubstituted heterocyclyl. In some specific embodiments, R^1 is a substituted or unsubstituted 4-10 membered heterocyclyl. In certain specific embodiments, R^1 is a substituted 4-10 membered heterocyclyl.

In some more specific embodiments, R^1 is a 4-10 membered heterocyclyl substituted with one or more of R^{1a}, R^{1b}, R^{1c}, R^{1d}, or R^{1e} wherein R^{1a}, R^{1b}, R^{1c}, R^{1d}, and R^{1e} are each independently selected from the group consisting of $C_{1\text{-}6}$ alkyl, $C_{2\text{-}6}$ alkenyl,

C_{2-6} alkynyl, halo, C_{1-6} haloalkyl, aminylalkyl, hydroxyalkyl, cyano, OR^9, SR^9, $C(O)R^9$, $C(O)NR^9R^{10}$, $C(O)OR^9$, $OC(O)R^9$, $OC(O)OR^9$, $OC(O)NR^9R^{10}$, NR^9R^{10}, $N(R^9)C(O)R^{10}$, $N(R^9)C(O)NR^{10}R^{11}$, $N(R^9)C(O)OR^{10}$, $C(=NR^9)NR^{10}R^{11}$, $C(=NOR^9)NR^{10}R^{11}$, $C(=NOC(O)R^9)NR^{10}R^{11}$, $C(=NR^9)N(R^{10})C(O)OR^{11}$, $N(R^9)C(=NR^{10})NR^{11}R^{12}$, $S(O)R^9$, $S(O)NR^9R^{10}$, $S(O)_2R^9$, $N(R^9)S(O)_2R^{10}$, $S(O)_2NR^9R^{10}$, oxo, substituted or unsubstituted C_{6-10} aryl, substituted or unsubstituted C_{6-10} arylalkyl, substituted or unsubstituted C_{6-10} aryloxy, substituted or unsubstituted C_{6-10} arylalkoxy, substituted or unsubstituted 5-10 membered heteroaryl, substituted or unsubstituted C_{3-10} cycloalkyl, and substituted or unsubstituted 4-10 membered heterocyclyl, wherein R^9, R^{10}, R^{11}, and R^{12}, are, at each occurrence, independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, hydroxyl, C_{1-6} alkoxy, aryl, arylalkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, cycloalkyl, heterocyclyl, and heteroaryl.

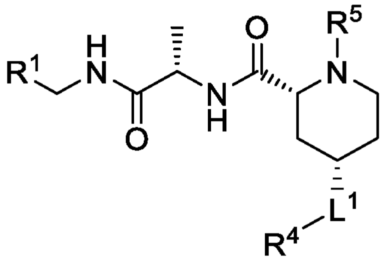
In certain more specific embodiments, R^{1a}, R^{1b}, R^{1c}, R^{1d}, or R^{1e} is optionally substituted with one or more substituents selected from the group consisting of OR^{13}, SR^{13}, $C(O)R^{13}$, $C(O)NR^{13}R^{14}$, $C(O)OR^{13}$, $OC(O)R^{13}$, $OC(O)NR^{13}R^{14}$, $NR^{13}R^{14}$, $NR^{13}C(O)R^{14}$, $NR^{13}C(O)NR^{14}R^{15}$, $NR^{13}C(O)OR^{14}$, $C(=NR^{13})NR^{14}R^{15}$, $NR^{13}C(=NR^{14})NR^{15}R^{16}$, $S(O)R^{13}$, $S(O)NR^{13}R^{14}$, $S(O)_2R^{13}$, $NR^{13}S(O)_2R^{14}$, $S(O)_2NR^{13}R^{14}$ and oxo when R^{1a}, R^{1b}, R^{1c}, R^{1d}, or R^{1e} is a substituted C_{6-10} aryl, a substituted C_{6-10} arylalkyl, a substituted C_{6-10} aryloxy, a substituted C_{6-10} arylalkoxy, a substituted 5-10 membered heteroaryl, a substituted C_{3-10} cycloalkyl, and a substituted 4-10 membered heterocyclyl, wherein R^{13}, R^{14}, R^{15}, and R^{16} are, at each occurrence, independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, hydroxyl, C_{1-6} alkoxy, aryl, arylalkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, cycloalkyl, heterocyclyl, and heteroaryl.

In some embodiments, R^1 is an unsubstituted 4-10 membered heterocyclyl. In certain embodiments, R^2 is hydrogen, C_1-C_6 alkyl, or R^2 and R^3, together with the carbon and nitrogen to which they are attached, respectively, form an optionally substituted 4-7 membered heterocyclyl.

In some specific embodiments, R^2 is C_1-C_6 alkyl. In certain specific embodiments, R^2 is $-CH_3$. In some more specific embodiments, R^2 is $-CH_2OH$.

In some embodiments, R^2 and R^3, together with the carbon and nitrogen to which they are attached, respectively, form an optionally substituted 4-7 membered heterocyclyl. In certain embodiments, R^2 and R^3, together with the carbon and nitrogen to which they are attached, respectively, form an optionally substituted 4, 5, or 6 membered heterocyclyl. In some specific embodiments, R^2 and R^3, together with the carbon and nitrogen to which they are attached, respectively, form an optionally substituted 4-membered heterocyclyl.

In some embodiments, the compound has one of the following Structures (IA1a), (IB1a), (IC1a), (ID1a), (IE1a), (IF1a), (IG1a), or (IH1a):



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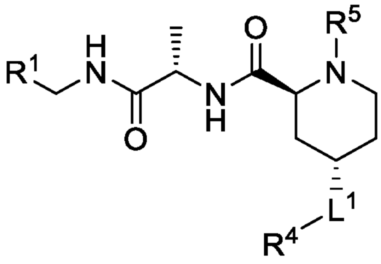
(IA1a)



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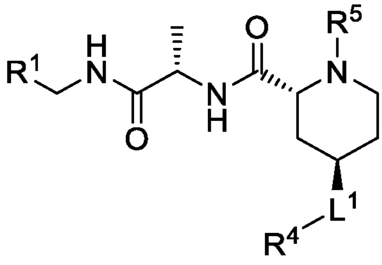
(IB1a)



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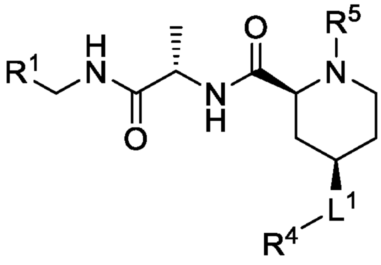
(IC1a)



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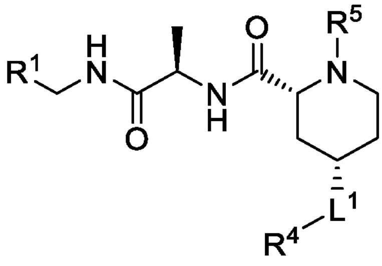
(ID1a)



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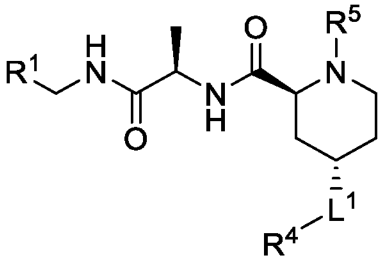
(IE1a)



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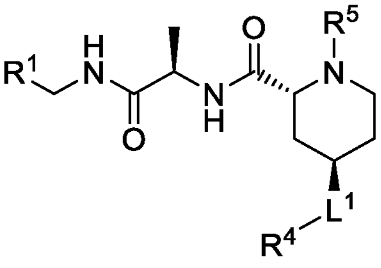
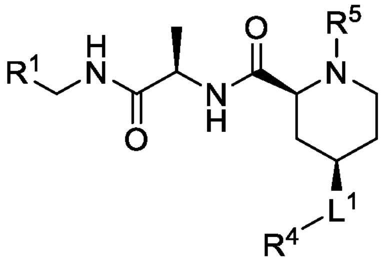
(IF1a)



or

(IG1a)



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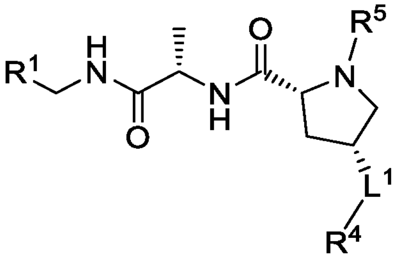
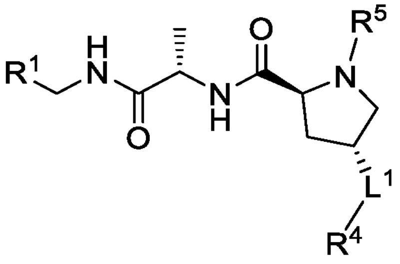
(IH1a)

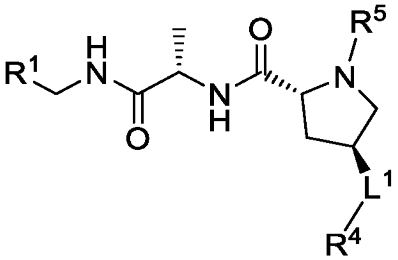
In certain embodiments, the compound has one of the following Structures (IA1b), (IB1b), (IC1b), (ID1b), (IE1b), (IF1b), (IG1b), or (IH1b):


;

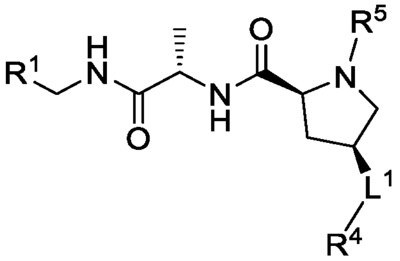
(IA1b)


;

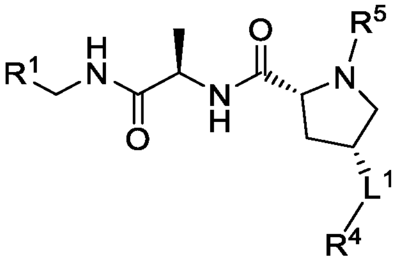
(IB1b)


;

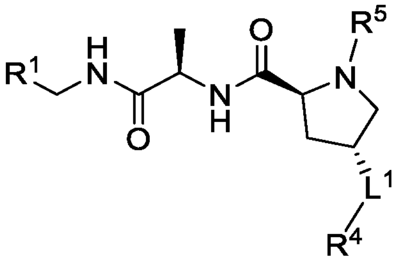
(IC1b)


;

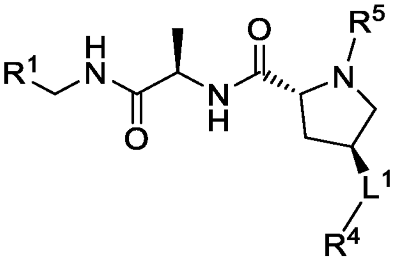
(ID1b)


;

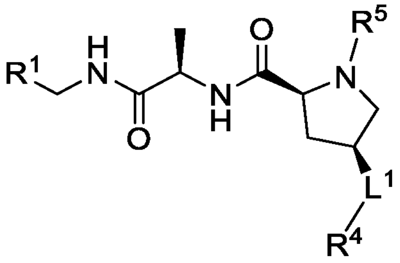
(IE1b)


;

(IF1b)

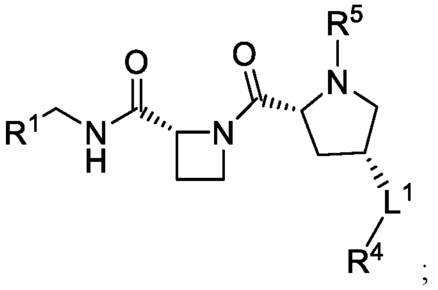

or

(IG1b)

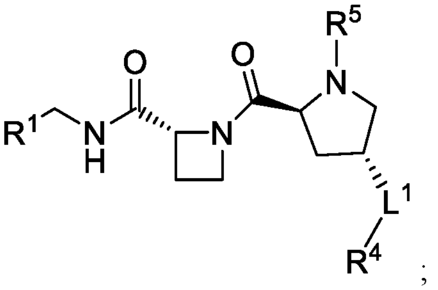

.

(IH1b)

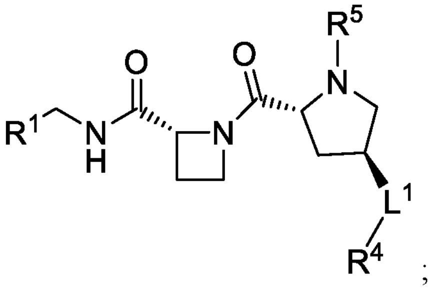
In some embodiments, the compound has one of the following Structures (IA2a), (IB2a), (IC2a), (ID2a), (IE2a), (IF2a), (IG2a), or (IH2a):



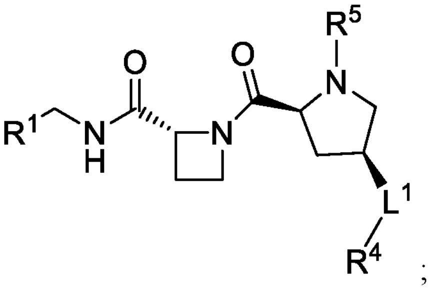
(IA2a)



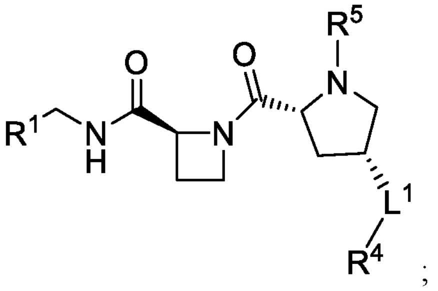
(IB2a)



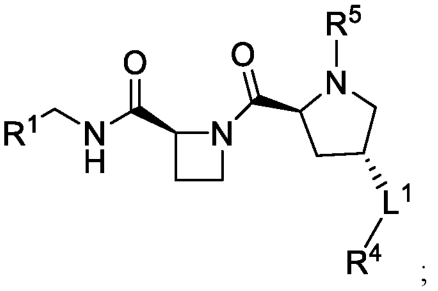
(IC2a)



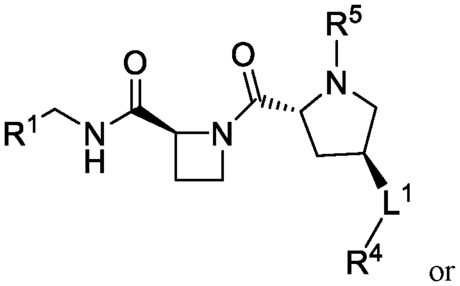
(ID2a)



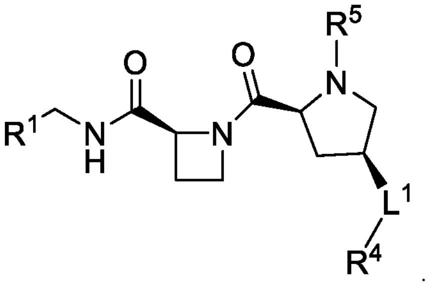
(IE2a)



(IF2a)

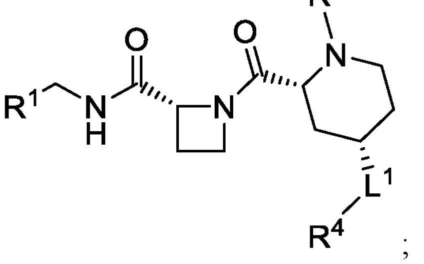


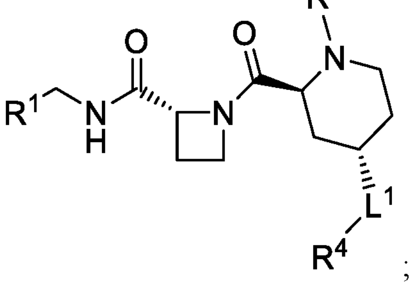
(IG2a)



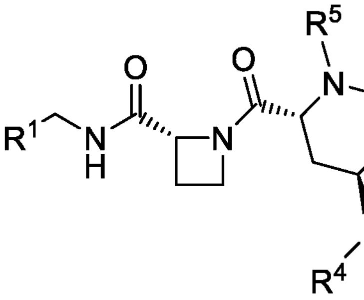
(IH2a)

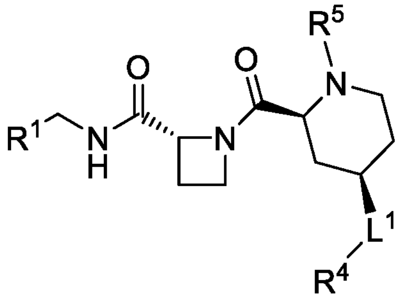
In certain specific embodiments, the compound has one of the following Structures (IA2b), (IB2b), (IC2b), (ID2b), (IE2b), (IF2b), (IG2b), or (IH2b):



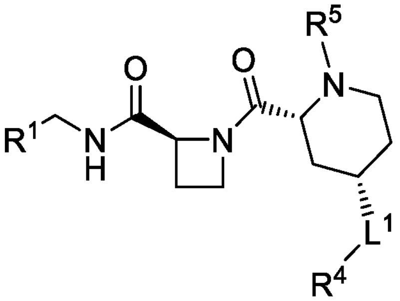


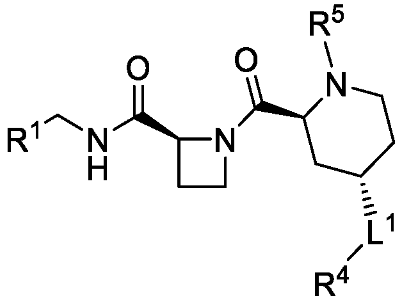
(IA2b) (IB2b)


;

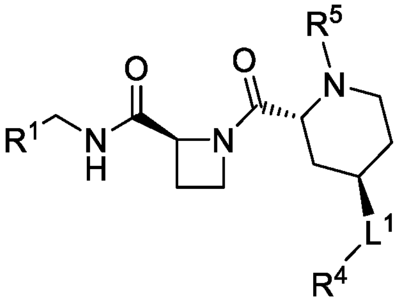

;

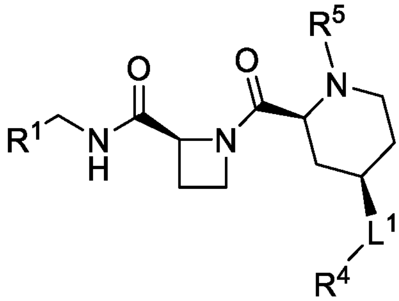
(IC2b) (ID2b)


;


;

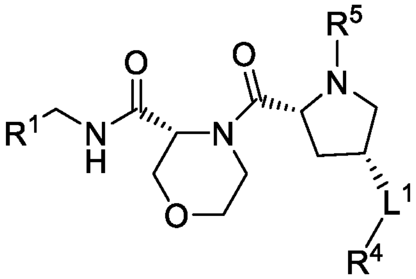
(IE2b) (IF2b)

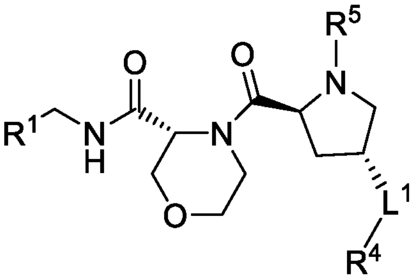

or


.

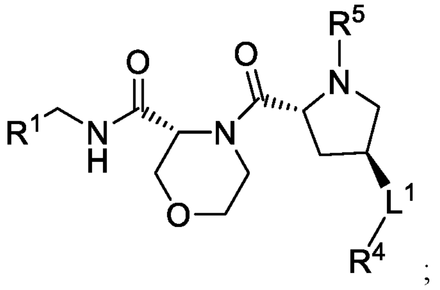
(IG2b) (IH2b)

In some embodiments, the compound has one of the following Structures (IA3a), (IB3a), (IC3a), (ID3a), (IE3a), (IF3a), (IG3a), or (IH3a):

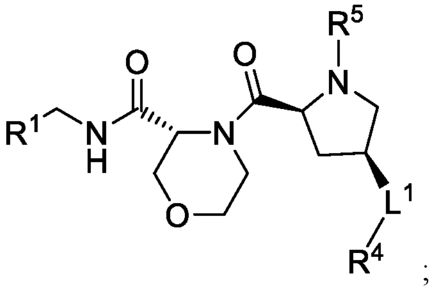

;


;

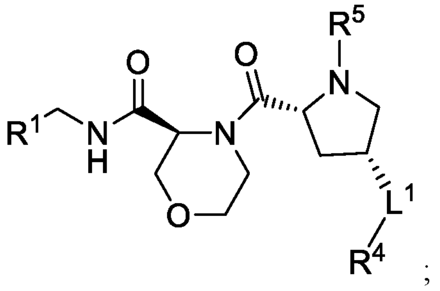
(IA3a) (IB3a)



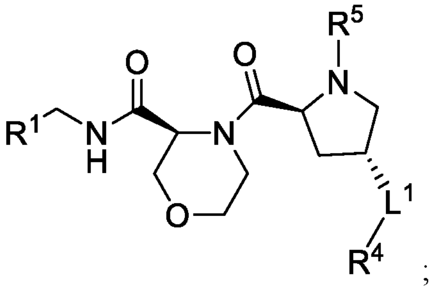
(IC3a)



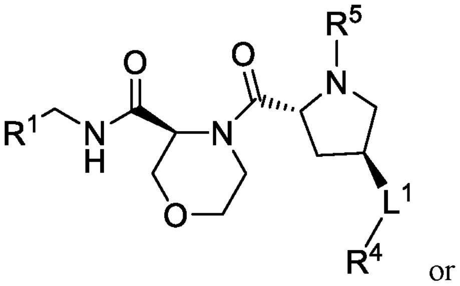
(ID3a)



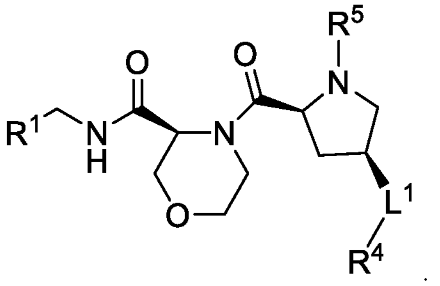
(IE3a)



(IF3a)

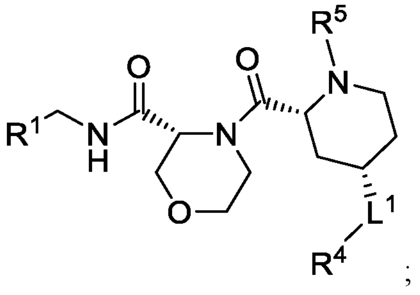


(IG3a)

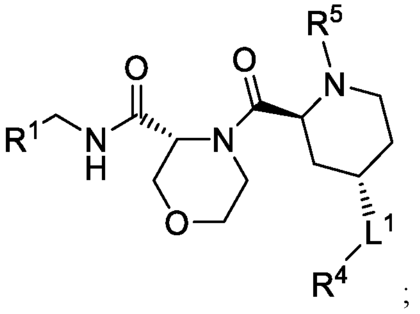


(IH3a)

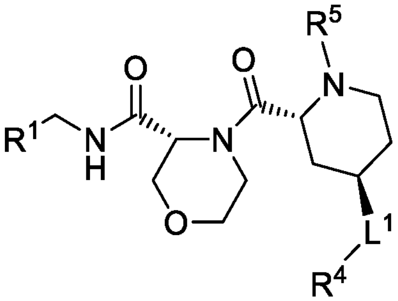
In certain embodiments, the compound has one of the following Structures (IA3b), (IB3b), (IC3b), (ID3b), (IE3b), (IF3b), (IG3b), or (IH3b):



(IA3b)

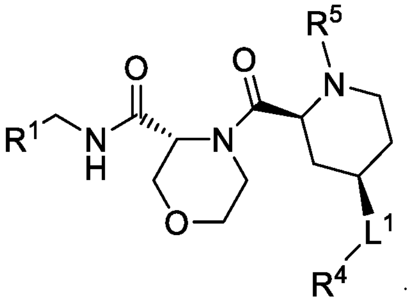


(IB3b)



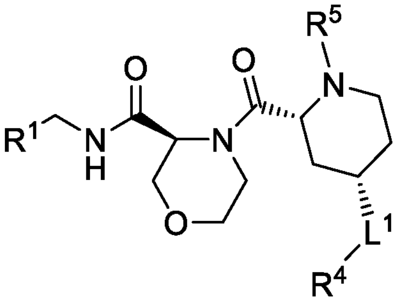
;

(IC3b)



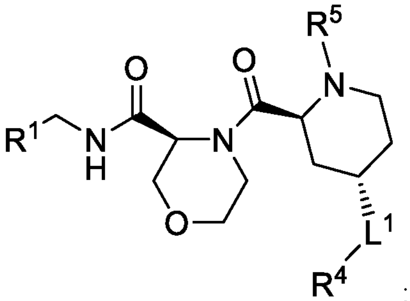
;

(ID3b)



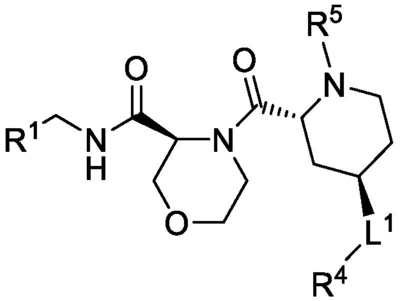
;

(IE3b)



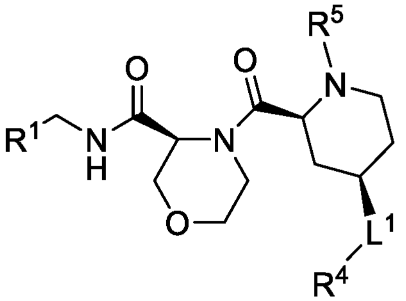
;

(IF3b)



or

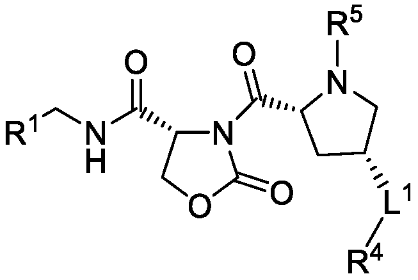
(IG3b)



.

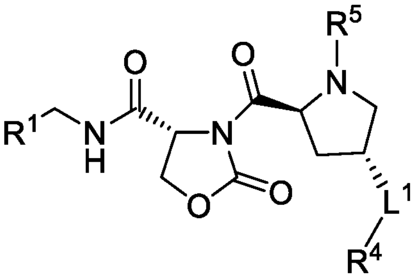
(IH3b)

In certain embodiments, the compound has one of the following Structures (IA4a), (IB4a), (IC4a), (ID4a), (IE4a), (IF4a), (IG4a), or (IH4a):



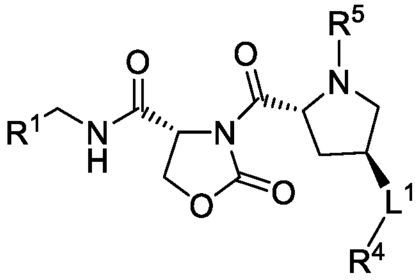
;

(IA4a)

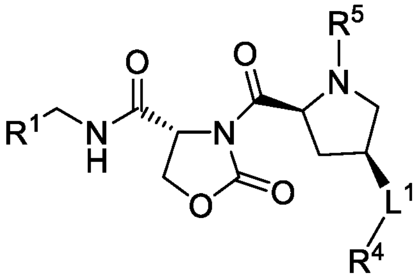


;

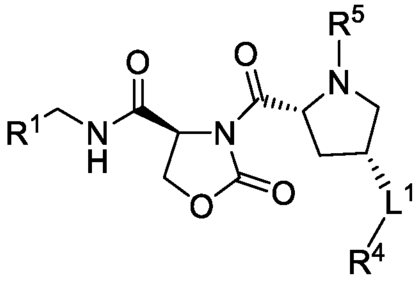
(IB4a)


;

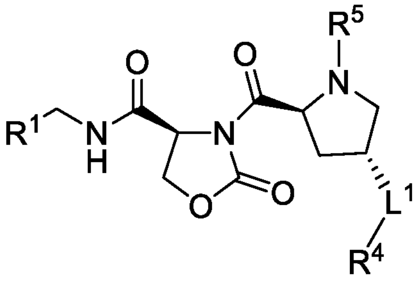
(IC4a)


;

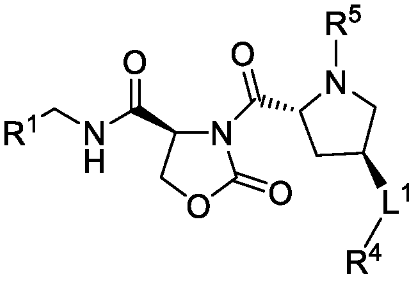
(ID4a)


;

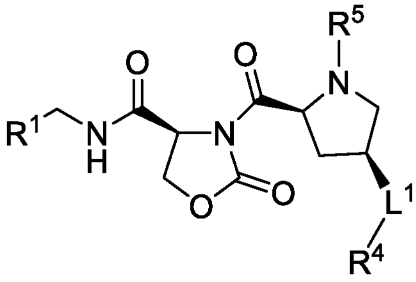
(IE4a)


;

(IF4a)

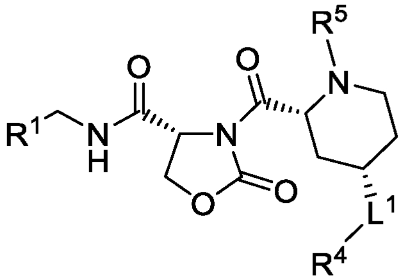

or

(IG4a)

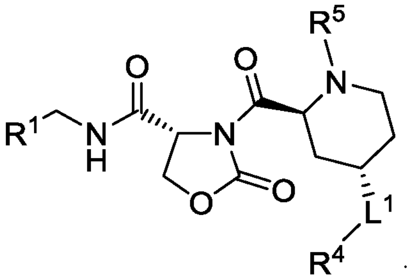

.

(IH4a)

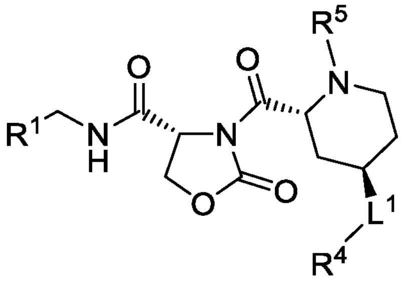
In some specific embodiments, the compound has one of the following Structures (IA4b), (IB4b), (IC4b), (ID4b), (IE4b), (IF4b), (IG4b), or (IH4b):

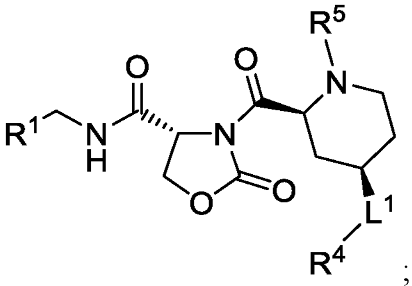

;

(IA4b)

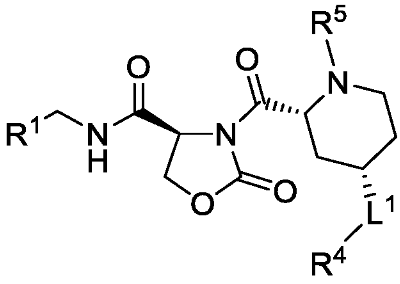

;

(IB4b)

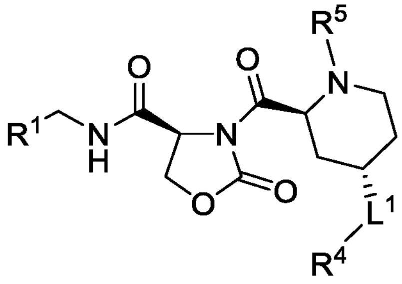

;


;

(IC4b) (ID4b)

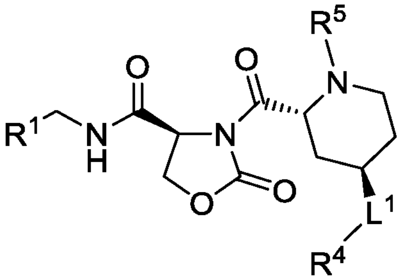


;

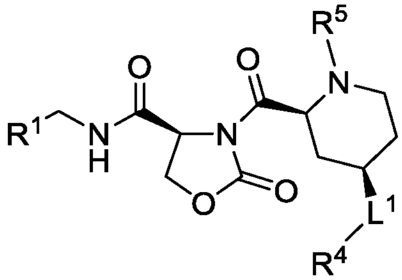


;

(IE4b) (IF4b)



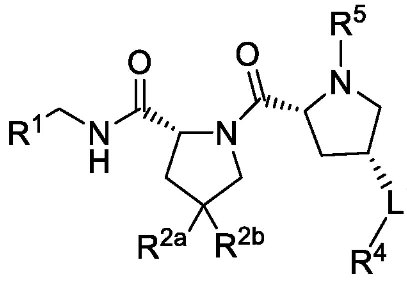
or



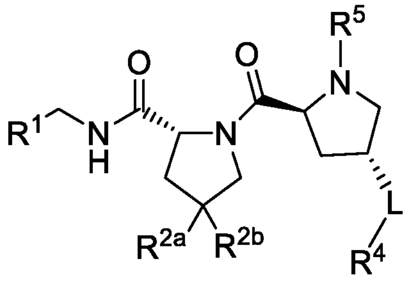
.

(IG4b) (IH4b)

In some more specific embodiments, the compound has one of the following Structures (IA5a), (IB5a), (IC5a), (ID5a), (IE5a), (IF5a), (IG5a), or (IH5a):

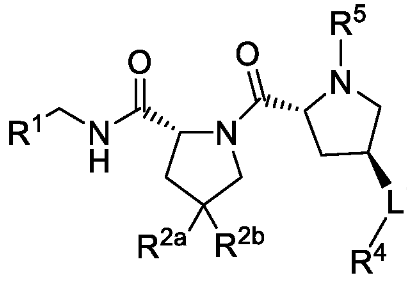


;

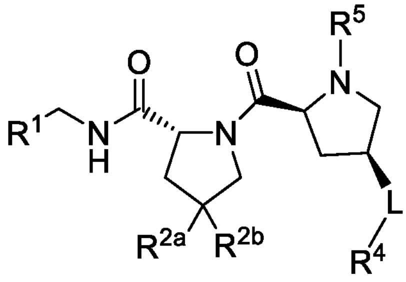


;

(IA5a) (IB5a)

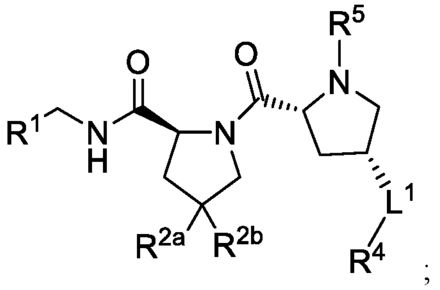


;

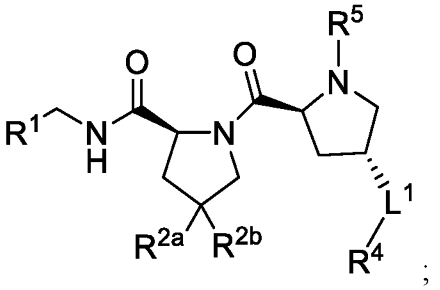


;

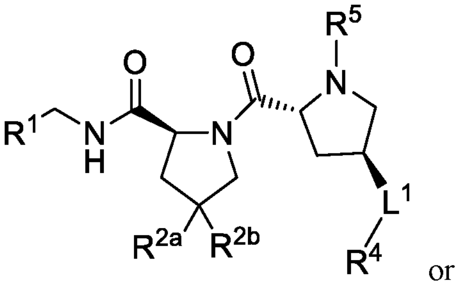
(IC5a) (ID5a)


;

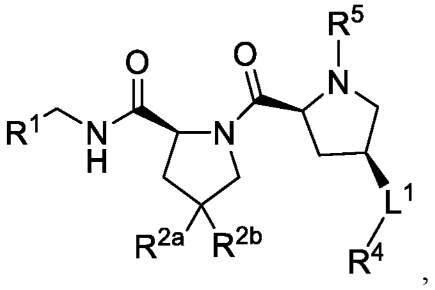
(IE5a)


;

(IF5a)


or

(IG5a)

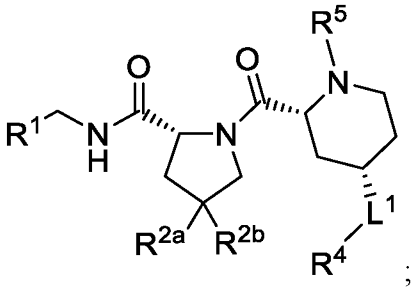

,

(IH5a)

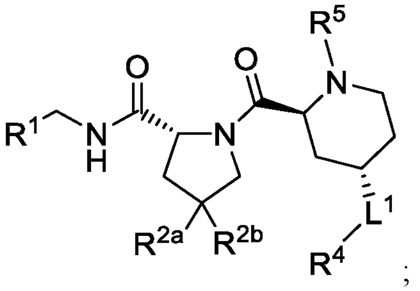
wherein:

R^{2a} and R^{2b} are each independently hydrogen or halo.

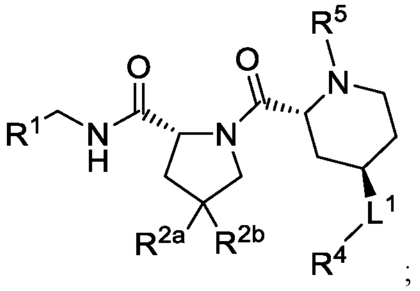
In certain more specific embodiments, the compound has one of the following Structures (IA5b), (IB5b), (IC5b), (ID5b), (IE5b), (IF5b), (IG5b), or (IH5b):


;

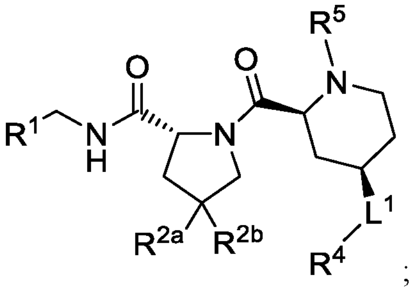
(IA5b)


;

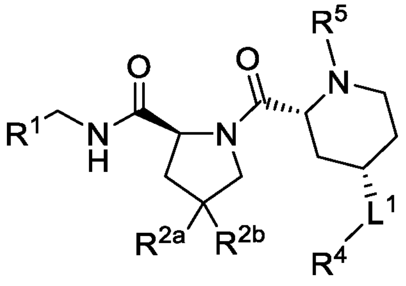
(IB5b)


;

(IC5b)


;

(ID5b)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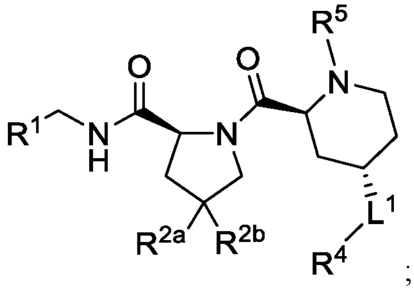
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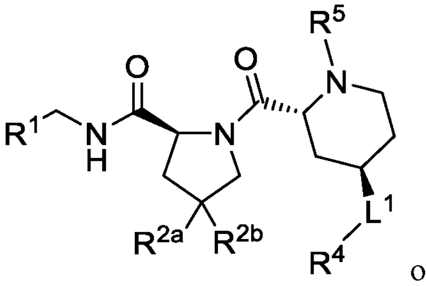
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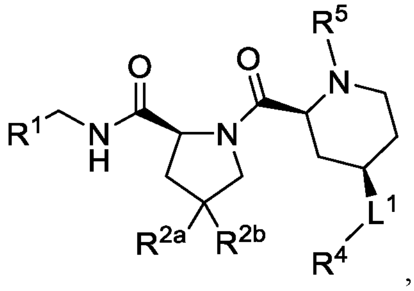
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(IH5b)

wherein:

R^{2a} and R^{2b} are each independently hydrogen or halo.

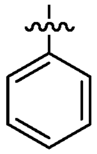
In some embodiments, R^{2a} and R^{2b} are both halo (e.g., F, Br, Cl, or I). In certain embodiments, R^{2a} and R^{2b} are both fluoro.

In some specific embodiments, R^4 is a substituted or unsubstituted aryl. In certain embodiments, R^4 is a substituted or unsubstituted C_6-C_{10} aryl. In some more specific embodiments, R^4 is a substituted or unsubstituted phenyl. In certain embodiments, R^4 is an unsubstituted phenyl.

In some specific embodiments, R^4 is phenyl substituted with one or more of R^{4a}, R^{4b}, R^{4c}, R^{4d}, or R^{4e} wherein R^{4a}, R^{4b}, R^{4c}, R^{4d}, and R^{4e} are each independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, C_{1-6} haloalkyl, aminylalkyl, hydroxyalkyl, cyano, nitro, OR^{17}, SR^{17}, $C(O)R^{17}$, $C(O)NR^{17}R^{18}$, $C(O)OR^{17}$, $OC(O)R^{17}$, $OC(O)OR^{17}$, $OC(O)NR^{17}R^{18}$, $NR^{17}R^{18}$, $N(R^{17})C(O)R^{18}$, $N(R^{17})C(O)NR^{18}R^{19}$, $N(R^{17})C(O)OR^{18}$, $C(=NR^{17})NR^{18}R^{19}$, $C(=NOR^{17})NR^{18}R^{19}$, $C(=NOC(O)R^{17})NR^{18}R^{19}$, $C(=NR^{17})N(R^{18})C(O)OR^{19}$, $N(R^{17})C(=NR^{18})NR^{19}R^{20}$, $S(O)R^{17}$, $S(O)NR^{17}R^{18}$, $S(O)_2R^{17}$, $N(R^{17})S(O)_2R^{18}$, $S(O)_2NR^{17}R^{18}$, oxo, substituted or unsubstituted C_{6-10} aryl, substituted or unsubstituted C_{6-10} arylalkyl, substituted or unsubstituted C_{6-10} aryloxy, substituted or unsubstituted C_{6-10} arylalkoxy, substituted or unsubstituted 5-10 membered heteroaryl, substituted or unsubstituted C_{3-10} cycloalkyl, and substituted or unsubstituted 4-10 membered heterocyclyl, wherein R^{17}, R^{18}, R^{19}, and R^{20}, are, at each occurrence, independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, hydroxyl, C_{1-6} alkoxy, aryl, arylalkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, cycloalkyl, heterocyclyl, and heteroaryl.

In some embodiments, R^{4a}, R^{4b}, R^{4c}, R^{4d}, or R^{4e} is optionally substituted with one or more substituents selected from the group consisting of OR^{21}, SR^{21}, $C(O)R^{21}$, $C(O)NR^{21}R^{22}$, $C(O)OR^{21}$, $OC(O)R^{21}$, $OC(O)NR^{21}R^{22}$, $NR^{21}R^{22}$, $NR^{21}C(O)R^{22}$, $NR^{21}C(O)NR^{22}R^{23}$, $NR^{21}C(O)OR^{22}$, $C(=NR^{21})NR^{22}R^{23}$, $NR^{21}C(=NR^{22})NR^{23}R^{24}$, $S(O)R^{21}$, $S(O)NR^{21}R^{22}$, $S(O)_2R^{21}$, $NR^{21}S(O)_2R^{22}$, $S(O)_2NR^{21}R^{22}$ and oxo when R^{4a}, R^{4b}, R^{4c}, R^{4d}, or R^{4e} is a substituted C_{6-10} aryl, a substituted C_{6-10} arylalkyl, a substituted C_{6-10} aryloxy, a substituted C_{6-10} arylalkoxy, a substituted 5-10 membered heteroaryl, a substituted C_{3-10} cycloalkyl, and a substituted 4-10 membered heterocyclyl, wherein R^{21}, R^{22}, R^{23}, and R^{24} are, at each occurrence, independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, hydroxyl, C_{1-6} alkoxy, aryl, arylalkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, cycloalkyl, heterocyclyl, and heteroaryl.

In some embodiments, R^4 has one of the following structures: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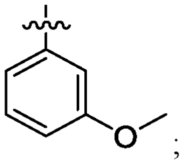

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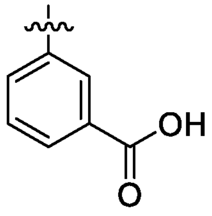

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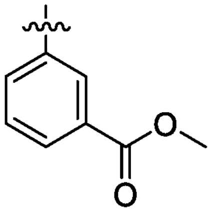

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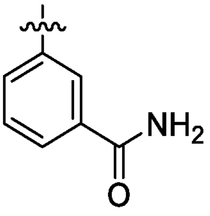

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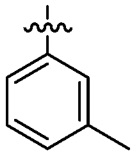
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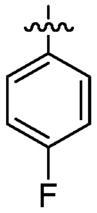

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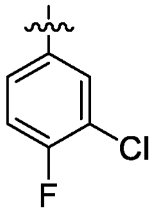

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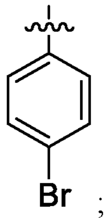

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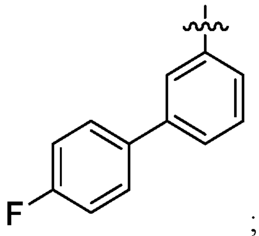

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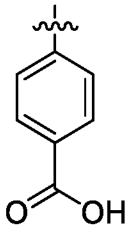

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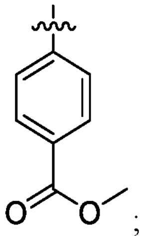

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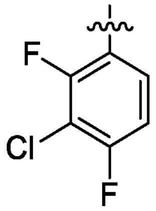
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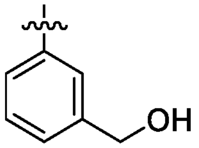
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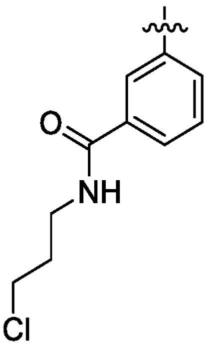
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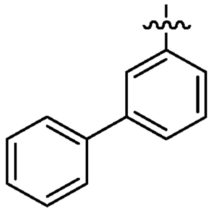
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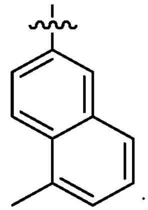
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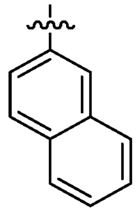
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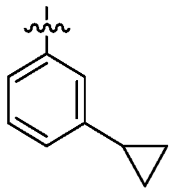
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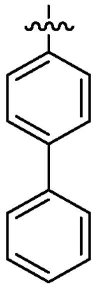
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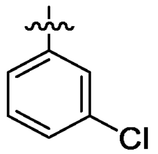
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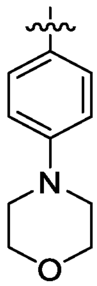
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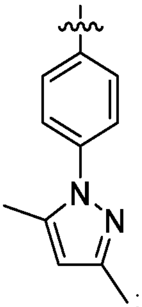
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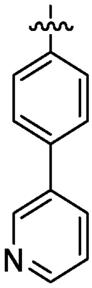
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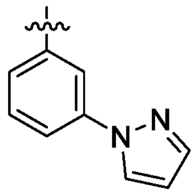
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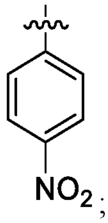
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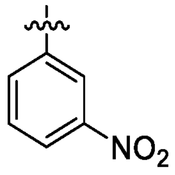
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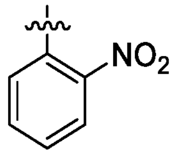
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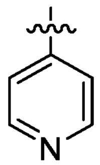
In some embodiments, R^4 is a substituted or unsubstituted heteroaryl. In certain embodiments, R^4 is a 4-10 membered heteroaryl. In some specific embodiments, R^4 is an unsubstituted 4-10 membered heteroaryl.

In some more specific embodiments, R^4 is a 4-10 membered heteroaryl substituted with one or more of R^{4a}, R^{4b}, R^{4c}, R^{4d}, or R^{4e} wherein R^{4a}, R^{4b}, R^{4c}, R^{4d}, and R^{4e} are each independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, C_{1-6} haloalkyl, aminylalkyl, hydroxyalkyl, cyano, nitro, OR^{17}, SR^{17}, $C(O)R^{17}$, $C(O)NR^{17}R^{18}$, $C(O)OR^{17}$, $OC(O)R^{17}$, $OC(O)OR^{17}$, $OC(O)NR^{17}R^{18}$, $NR^{17}R^{18}$, $N(R^{17})C(O)R^{18}$, $N(R^{17})C(O)NR^{18}R^{19}$, $N(R^{17})C(O)OR^{18}$, $C(=NR^{17})NR^{18}R^{19}$, $C(=NOR^{17})NR^{18}R^{19}$, $C(=NOC(O)R^{17})NR^{18}R^{19}$, $C(=NR^{17})N(R^{18})C(O)OR^{19}$, $N(R^{17})C(=NR^{18})NR^{19}R^{20}$, $S(O)R^{17}$, $S(O)NR^{17}R^{18}$, $S(O)_2R^{17}$, $N(R^{17})S(O)_2R^{18}$, $S(O)_2NR^{17}R^{18}$, oxo, substituted or unsubstituted C_{6-10} aryl, substituted or unsubstituted C_{6-10} arylalkyl, substituted or unsubstituted C_{6-10} aryloxy, substituted or unsubstituted C_{6-10} arylalkoxy, substituted or unsubstituted 5-10 membered heteroaryl, substituted or unsubstituted C_{3-10} cycloalkyl, and substituted or unsubstituted 4-10 membered heterocyclyl, wherein R^{17}, R^{18}, R^{19}, and R^{20}, are, at each occurrence, independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, hydroxyl, C_{1-6} alkoxy, aryl, arylalkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, cycloalkyl, heterocyclyl, and heteroaryl.

In certain more specific embodiments, R^{4a}, R^{4b}, R^{4c}, R^{4d}, or R^{4e} is optionally substituted with one or more substituents selected from the group consisting of halo, CN, OR^{21}, SR^{21}, $C(O)R^{21}$, $C(O)NR^{21}R^{22}$, $C(O)OR^{21}$, $OC(O)R^{21}$, $OC(O)NR^{21}R^{22}$, $NR^{21}R^{22}$, $NR^{21}C(O)R^{22}$, $NR^{21}C(O)NR^{22}R^{23}$, $NR^{21}C(O)OR^{22}$, $C(=NR^{21})NR^{22}R^{23}$, $NR^{21}C(=NR^{22})NR^{23}R^{24}$, $S(O)R^{21}$, $S(O)NR^{21}R^{22}$, $S(O)_2R^{21}$, $NR^{21}S(O)_2R^{22}$, $S(O)_2NR^{21}R^{22}$ and oxo when R^{4a}, R^{4b}, R^{4c}, R^{4d}, or R^{4e} is a substituted C_{6-10} aryl, a substituted C_{6-10} arylalkyl, a substituted C_{6-10} aryloxy, a substituted C_{6-10} arylalkoxy, a substituted 5-10 membered heteroaryl, a substituted C_{3-10} cycloalkyl, and a substituted 4-10 membered heterocyclyl, wherein R^{21}, R^{22}, R^{23}, and R^{24} are, at each occurrence, independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, hydroxyl, C_{1-6} alkoxy, aryl, arylalkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, cycloalkyl, heterocyclyl, and heteroaryl.

In some embodiments, R^4 has one of the following structures:



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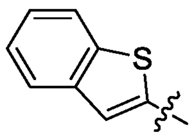

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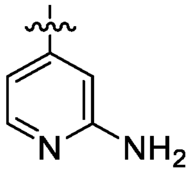

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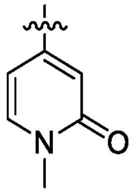

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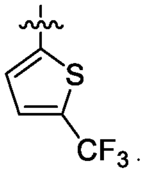

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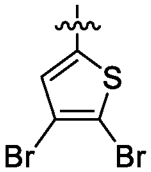

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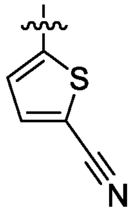

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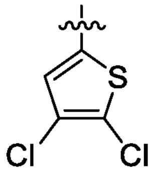

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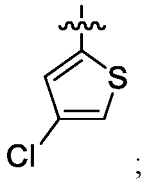

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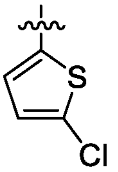

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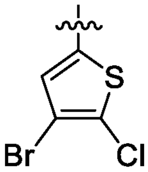

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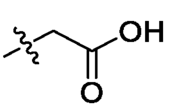
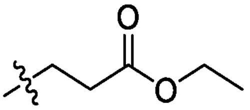
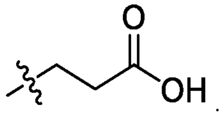
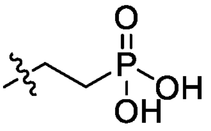
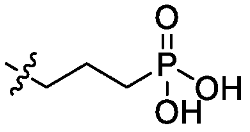
In some embodiments, R^5 is hydrogen. In certain embodiments, R^5 is alkyl, phosphonalkyl, $(CH_2)_mNR^6S(O)_2R^7$, or $(CH_2)_mC(=O)OR^6$.

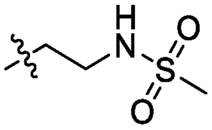
In some specific embodiments, R^5 is alkyl. In certain specific embodiments, R^5 is methyl. In more specific embodiments, R^5 is ethyl. In certain specific embodiments, R^5 is $(CH_2)_mC(=O)OR^6$. In some embodiments, R^5 has one of the following structures:

 ;  or .

In some embodiments, R^5 is phosphonalkyl. In more specific embodiments, R^5 has one of the following structures:

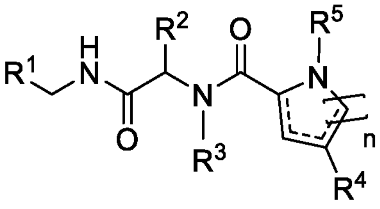
 or .

In some embodiments, R^5 is $(CH_2)_mNR^6S(O)_2R^7$. In more specific embodiments, R^5 has the following structure:

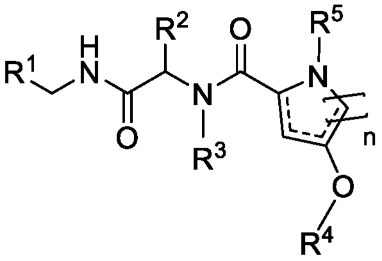
.

In certain embodiments, ═══ represents a single bond at each occurrence. In other embodiments, ═══ represents a double bond for at least one occurrence. In some more specific embodiments, ═══ represents a double bond at one occurrence. In certain more specific embodiments, ═══ represents a double bond at two occurrences.

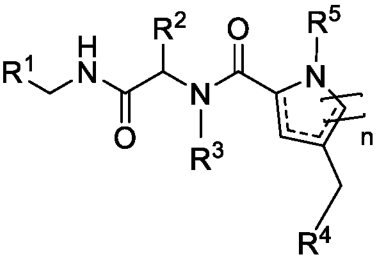
In some embodiments, L^1 is a direct bond. That is, in certain embodiments, the compound of Structure (I) has the following structure:

.

In some embodiments, L^1 is -O-. That is, in certain embodiments, the compound of Structure (I) has the following structure:

.

In some embodiments, L^1 is $-CH_2-$. That is, in certain embodiments, the compound of Structure (I) has the following structure:



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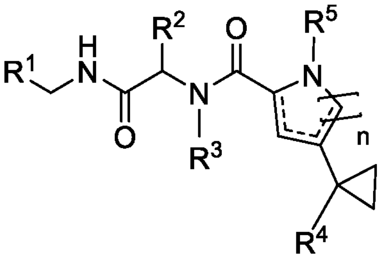
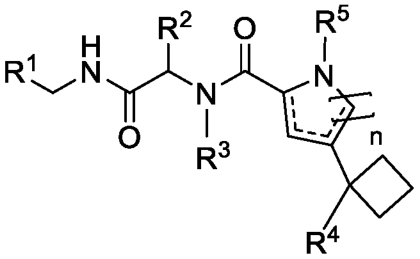
In some embodiments, L^1 is $-CR^{8a}R^{8b}-$ and R^{8a} and R^{8b} together with the carbon to which they are attached form an optionally substituted 3-6 membered cycloalkyl. In certain embodiments, R^{8a} and R^{8b}, together with the carbon to which they are attached form an optionally substituted 3, 4, or 5 membered cycloalkyl. In some specific embodiments, R^{8a} and R^{8b}, together with the carbon to which they are attached form an optionally substituted 3 membered cycloalkyl. In certain specific embodiments, the 3-membered cycloalkyl is unsubstituted.

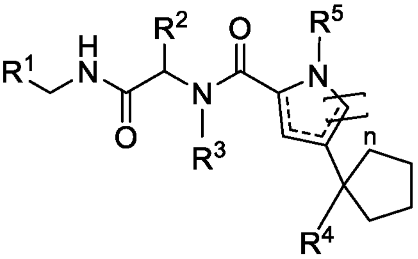
In some more specific embodiments, the compound of Structure (I) has one of the following structures:



;



or



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In some embodiments, R^{8c} is hydrogen, alkyl, haloalkyl, or a substituted or unsubstituted cycloalkyl.

In some embodiments, the compounds of Structure (I), and embodiments thereof, can be in the form of a salt such as a pharmaceutically acceptable salt.

The compounds of Structure (I), and embodiments thereof, are useful as inhibitors of MASP-2 and for therapeutic use. The compounds of Structure (I), and embodiments thereof, are useful in the treatment of MASP-2-associated diseases and disorders, and in the manufacture of medicaments for treating MASP-2-associated diseases and disorders. The present disclosure also provides methods of treating a MASP-2-associated disease and disorder comprising administering to a patient a therapeutically effective amount of a compound of Structure (I), or an embodiment thereof, optionally in the form of a salt.

In some embodiments the compound Structure (I) or an embodiment thereof is provided in the form of a pharmaceutical composition comprising the compound or a salt thereof, such as a pharmaceutically acceptable salt, and at least one pharmaceutically acceptable carrier or excipient.

In certain aspects, the compound is one or more selected from the compounds of Structure (I) set forth in the Examples, including the compounds listed in Table 1, (*e.g.*, compounds with selectivity for MASP-2 over thrombin). In certain aspects, one or more of the variables defining the compounds of Structure (I) is selected from the corresponding substituents in the compounds of Structure (I) in the Examples including the compounds listed in Table 1, preferably, those of the compounds with selectivity for MASP-2 over thrombin.

In certain aspects, the disclosure sets forth a stereochemically pure enantiomer or diastereomer (*e.g.*, an optically active compound with one or more stereocenter(s)). Unless specifically indicated otherwise, for any compound with one or more stereocenters is intended to include and to describe both the pure (+) and (-) enantiomers, any other diastereomers, mixtures that are enriched in an enantiomer or diastereomer (*e.g.*, 10%, 20%, 30%, 40%, 50%, 60%, 70% 75%, 80%, 85, 90%, or 95% enantiomeric or diastereomeric excess), and a racemic mixture of enantiomers or diastereomers.

Certain embodiments provide a pharmaceutically acceptable salt of the indicated chemical structure (*e.g.*, a hydrohalide, such as a hydrochloride or dihydrochloride). Examples of pharmaceutically acceptable salts are set forth in, *e.g.*, Burge, S. M. et al., J. Pharm. Sci 1977, 66, 1-19. They include chlorides, bromides, iodides, formates, acetates, propionates, oxalates, malonates, succinates, fumarates, maleates, tartrates, citrates, benzoates, phthalates, sulfonates, arylsulfonates, alkylsulfonates, salts of fatty acids, and the like. Salts can be prepared by a variety of methods known to the skilled artisan, including a precipitation with the conjugate acid or base (*e.g.*, treatment with gaseous HCl or an HCl solution).

In certain embodiments provide a prodrug. A prodrug is a compound that is converted to a biologically active form under physiological conditions, often by hydrolysis, oxidation, or reduction (*e.g.*, ester to acid form; carbamate to amino or hydroxy group; hydroxyamidine to amidine) Exemplary prodrugs are set forth in, *e.g.*, Tilley, J.W., "Prodrugs of Benzamide," *Prodrugs* 2007, 191-222; Peterlin-Masic et al. *Curr. Pharma. Design* 2006, 12, 73-91. Prodrugs for the amidine group include amidoximes, O-alkylamidoximes, acylamidines, carbamates, 1,2,4-oxadiazolin-4-ones, and the like.

In certain aspects, the compound is useful for selectively inhibiting MASP-2 over thrombin, the method comprising administering the compound as described herein. In certain aspects, the selectivity ratio of MASP-2:thrombin is at least 1.1:1, 1.25:1, 1.5:1, 1.75:1, 2:1, 3:1, 4:1, 5:1, 6:1, 7:1, 8:1, 9:1, 10:1, 11:1, 12:1, 13:1, 14:1, 15:1, 16:1, 17:1, 18:1, 19:1, 20:1, 21:1, 22:1, 23:1, 24:1, 25:1, or 30:1.

III. Synthesis

Compounds described herein, including salts thereof, can be prepared using known organic synthesis techniques and can be synthesized according to any of numerous possible synthetic routes, such as those illustrated in the Examples below.

The reactions for preparing compounds described herein can be carried out in suitable solvents which can be readily selected by one of skill in the art of organic synthesis. Suitable solvents can be substantially non-reactive with the starting materials (reactants), the intermediates or products at the temperatures at which the reactions are carried out, *e.g.*, temperatures which can range from the solvent's freezing temperature to the solvent's boiling temperature. A given reaction can be carried out in one solvent or a mixture of more than one solvent. Depending on the particular reaction step, suitable solvents for a particular reaction step can be selected by the skilled artisan.

Preparation of compounds of the disclosure can involve the protection and deprotection of various chemical groups. The need for protection and deprotection, and the selection of appropriate protecting groups, can be readily determined by one skilled in the art. The chemistry of protecting groups is described, *e.g.*, in Kocienski, Protecting Groups, (Thieme, 2007); Robertson, Protecting Group Chemistry, (Oxford University Press, 2000); Smith *et al.*, March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, 6th Ed. (Wiley, 2007); Petursion et al., "Protecting Groups in Carbohydrate Chemistry," *J. Chem. Educ.*, 1997, *74*(11), 1297; and Wuts *et al.*, Protective Groups in Organic Synthesis, 4th Ed., (Wiley, 2006).

Reactions can be monitored according to any suitable method known in the art. For example, product formation can be monitored by spectroscopic means, such as nuclear magnetic resonance spectroscopy (*e.g.*, ^{1}H or ^{13}C), infrared spectroscopy, spectrophotometry (*e.g.*, UV-visible), mass spectrometry, or by chromatographic methods such as high-performance liquid chromatography (HPLC) or thin layer chromatography (TLC).

The particular synthetic methods used in the Examples provide general guidance in connection with preparing the compounds of the disclosure. One skilled in the art would understand that the preparations can be modified or optimized using general knowledge of organic chemistry to prepare various compounds within the scope of the present disclosure.

Starting materials, reagents and intermediates whose synthesis is not described herein are either commercially available, known in the literature, or may be prepared by methods known to one skilled in the art.

It will be appreciated by one skilled in the art that the processes described are not the exclusive means by which compounds of the disclosure may be synthesized and that a broad repertoire of synthetic organic reactions is available to be potentially employed in synthesizing compounds of the disclosure. The person skilled in the art knows how to select and implement appropriate synthetic routes. Suitable synthetic methods of starting materials, intermediates and products may be identified by reference to the literature, including reference sources such as: *Advances in Heterocyclic*

Chemistry, Vols. 1-107 (Elsevier, 1963-2012); *Journal of Heterocyclic Chemistry*, Vols. 1-49 (Journal of Heterocyclic Chemistry, 1964-2012); Carreira, *et al.* (Ed.) *Science of Synthesis*, Vols. 1-48 (2001-2010) and Knowledge Updates KU2010/1-4; 2011/1-4; 2012/1-2 (Thieme, 2001-2012); Katritzky, *et al.* (Ed.) *Comprehensive Organic Functional Group Transformations*, (Pergamon Press, 1996); Katritzky *et al.* (Ed.); *Comprehensive Organic Functional Group Transformations II* (Elsevier, 2nd Edition, 2004); Katritzky *et al.* (Ed.), *Comprehensive Heterocyclic Chemistry* (Pergamon Press, 1984); Katritzky *et al.*, *Comprehensive Heterocyclic Chemistry II* (Pergamon Press, 1996); Smith *et al.*, *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 6th Ed. (Wiley, 2007); Trost *et al.* (Ed.), *Comprehensive Organic Synthesis* (Pergamon Press, 1991).

IV. Methods of Treatment

In another aspect, the present disclosure provides a method of treating a patient suffering from, or at risk for developing a MASP-2-associated disease or disorder such as a MASP-2-dependent complement-associated disease or disorder comprising administering a small molecule inhibitor of MASP-2.

The compound can be any small molecule inhibitor of MASP-2. In some embodiments, the compound can be a small molecule inhibitor of MASP-2 that binds to the serine protease domain of MASP-2. In some embodiments, the compound can be a small molecule inhibitor such as a synthetic small molecule inhibitor of MASP-2. In some embodiments, the compound can be a small molecule inhibitor of MASP-2 that binds to the catalytic, substrate-binding region of MASP-2. In some embodiments, the compound selectively inhibits MASP-2 relative to thrombin. For example, in some embodiments, the compound is a compound of Structure (I) as described in any of the foregoing embodiments.

As described in U.S. Patent No. 7,919,094; U.S. Patent No. 8,840,893; U.S. Patent No. 8,652,477; U.S. Patent No. 8,951,522, U.S. Patent No. 9,011,860, U.S. Patent No. 9,475,885, U.S. Patent No. 9,644,035, U.S. Patent Application Publication Nos. US 2013/0344073, US 2013/0266560, US 2015/0166675, US 2017/0137537, US

2017/0166660, US 2017/0189525,US 2017/0267781, US 2017/0283508, US 2017/0253667, US 2018/0105604, and PCT Publication Nos. WO 2018/045054, WO 2019/036460 and co-pending U.S. Patent Application Serial No. 62/688,611 (each of which is assigned to Omeros Corporation, the assignee of the instant application, each of which is hereby incorporated by reference), MASP-2-dependent complement activation has been implicated as contributing to the pathogenesis of numerous acute and chronic disease states. For example, as described in U.S. Patent No. 8,951,522, the primary function of the complement system, a part of the innate immune system, is to protect the host against infectious agents, however, inappropriate or over-activation of the complement system can lead to serious disease, such as thrombotic microangiopathies (TMAs, including aHUS, TTP and HUS) in which endothelial damage as well as fibrin and platelet-rich thrombi in the microvasculature lead to organ damage. The lectin pathway plays a dominant role in activating complement in settings of endothelial cell stress or injury and preventing the activation of MASP-2 and the lectin pathway halts the sequence of enzymatic reactions that lead to the formation of the membrane attack complex, platelet activation and leukocyte recruitment. As described in U.S. Patent No. 8,652,477, in addition to initiation of the lectin pathway, MASP-2 can also activate the coagulation system and is capable of cleaving prothrombin to thrombin.

Accordingly, in some embodiments, the method comprises administering to a patient suffering from or at risk for developing a MASP-2-dependent complement-associated disease or disorder an amount of a compound of the disclosure in an amount sufficient to inhibit MASP-2 dependent complement activation in the mammalian subject to thereby treat the disease or disorder. In some embodiments, the method can further comprise, prior to administering a compound of the disclosure to the patient, determining that the patient is afflicted with the lectin complement-associated disease or disorder.

In some embodiments, the MASP-2-dependent complement-associated disease or disorder is selected from the group consisting of a thrombotic microangiopathy (TMA), a renal condition, an inflammatory reaction resulting from tissue or organ transplantation, an ischemia reperfusion injury, a complication associated with diabetes, a cardiovascular disease or disorder, an inflammatory gastrointestinal disorder, a pulmonary disorder, an ophthalmic disease or disorder, disseminated intravascular coagulation, graft-versus-host disease, veno-occlusive disease, diffuse alveolar hemorrhage, or similar, as well as combinations thereof.

In some embodiments, the MASP-2-dependent complement-associated disease or disorder is a thrombotic microangiopathy (TMA) including thrombotic thrombocytopenic purpura (TTP), refractory TTP, Upshaw-Schulman Syndrome (USS), hemolytic uremic syndrome (HUS), atypical hemolytic syndrome (aHUS), non-Factor H-dependent atypical hemolytic syndrome, aHUS secondary to an infection, plasma therapy-resistant aHUS, a TMA secondary to cancer, a TMA secondary to chemotherapy, a TMA secondary to transplantation, or a TMA associated with hematopoietic stem cell transplant.

In some embodiments, the method comprises administering to a patient suffering from or at risk for developing graft-versus-host disease (GVHD), including acute GVHD, chronic GVHD or steroid-resistant GVHD an amount of a compound of the disclosure in an amount sufficient to inhibit MASP-2 dependent complement activation in the mammalian subject to thereby treat the disease or disorder. In some embodiments, the subject suffering from or at risk for developing GVHD has previously undergone, is undergoing, or will undergo a hematopoietic stem cell transplant.

In some embodiments, the method comprises administering to a patient suffering from, or at risk for developing diffuse alveolar hemorrhage (DAH) an amount of a compound of the disclosure in an amount sufficient to inhibit MASP-2 dependent complement activation in the mammalian subject to thereby treat the disease or disorder. In some embodiments, the subject suffering from, or at risk for developing DAH has previously undergone, is undergoing, or will undergo a hematopoietic stem cell transplant.

In some embodiments, the method comprises administering to a patient suffering from, or at risk for developing veno-occlusive disease (VOD) an amount of a compound of the disclosure in an amount sufficient to inhibit MASP-2 dependent complement activation in the mammalian subject to thereby treat the disease or disorder. In some embodiments, the subject suffering from, or at risk for developing VOD has previously undergone, is undergoing, or will undergo a hematopoietic stem cell transplant.

In some embodiments, the method comprises administering to a patient suffering from, or at risk for developing idiopathic pneumonia syndrome (IPS) an amount of a compound of the disclosure in an amount sufficient to inhibit MASP-2 dependent complement activation in the mammalian subject to thereby treat the disease or disorder. In some embodiments, the subject suffering from, or at risk for developing IPS has previously undergone, is undergoing, or will undergo a hematopoietic stem cell transplant.

In some embodiments, the method comprises administering to a patient suffering from, or at risk for developing capillary leak syndrome (CLS) an amount of a compound of the disclosure in an amount sufficient to inhibit MASP-2 dependent complement activation in the mammalian subject to thereby treat the disease or disorder. In some embodiments, the subject suffering from, or at risk for developing CLS has previously undergone, is undergoing, or will undergo a hematopoietic stem cell transplant.

In some embodiments, the method comprises administering to a patient suffering from, or at risk for developing engraftment syndrome (ES) an amount of a compound of the disclosure in an amount sufficient to inhibit MASP-2 dependent complement activation in the mammalian subject to thereby treat the disease or disorder. In some embodiments, the subject suffering from, or at risk for developing ES has previously undergone, is undergoing, or will undergo a hematopoietic stem cell transplant.

In some embodiments, the method comprises administering to a patient suffering from, or at risk for developing fluid overload (FO) an amount of a compound of the disclosure in an amount sufficient to inhibit MASP-2 dependent complement activation in the mammalian subject to thereby treat the disease or disorder. In some embodiments, the subject suffering from, or at risk for developing FO has previously undergone, is undergoing, or will undergo a hematopoietic stem cell transplant.

In some embodiments, the method comprises administering to a patient suffering from any of the above-referenced diseases or conditions an amount of a compound as disclosed in PCT Application No. PCT/US19/34225, which is hereby incorporated in its entirety.

In some embodiments, the MASP-2-dependent complement-associated disease or disorder is a renal condition including mesangioproliferative glomerulonephritis, membranous glomerulonephritis, membranoproliferative glomerulonephritis (mesangiocapillary glomerulonephritis), acute post infectious glomerulonephritis (poststreptococcal glomerulonephritis), C3 glomerulopathy, cryoglobulinemic glomerulonephritis, pauci-immune necrotizing crescentic glomerulonephritis, lupus nephritis, Henoch-Schonlein purpura nephritis, IgA nephropathy, and the like, as well as combinations thereof.

In some embodiments, the MASP-2-dependent complement-associated disease or disorder is renal fibrosis (*e.g.*, tubulointerstitial fibrosis) and/or proteinuria in a subject suffering from or at risk for developing chronic kidney disease, chronic renal failure, glomerular disease (*e.g.*, focal segmental glomerulosclerosis), an immune complex disorder (*e.g.*, IgA nephropathy, membranous nephropathy), lupus nephritis, nephrotic syndrome, diabetic nephropathy, tubulointerstitial damage and glomerulonepthritis (*e.g.*, C3 glomerulopathy), or a disease or condition associated with proteinuria, including, but not limited to, nephrotic syndrome, pre-eclampsia, eclampsia, toxic lesions of kidneys, amyloidosis, collagen vascular diseases (*e.g.*, systemic lupus erythematosus), dehydration, glomerular diseases (*e.g.*, membranous glomerulonephritis, focal segmental glomerulonephritis, C3 glomerulopathy, minimal change disease, lipoid nephrosis), strenuous exercise, stress, benign orthostatis (postural) proteinuria, focal segmental glomerulosclerosis, IgA nephropathy (*i.e.*, Berger' s disease), IgM nephropathy, membranoproliferative glomerulonephritis, membranous nephropathy, minimal change disease, sarcoidosis, Alport's syndrome, diabetes mellitus (diabetic nephropathy), drug-induced toxicity (*e.g.*, NSAIDS, nicotine, penicillamine, lithium carbonate, gold and other heavy metals, ACE inhibitors, antibiotics (*e.g.*, adriamycin), opiates (*e.g.*, heroin), or other nephrotoxins); Fabry's disease, infections (*e.g.*, HIV, syphilis, hepatitis A, B or C, poststreptococcal infection, urinary schistosomiasis); aminoaciduria, Fanconi syndrome, hypertensive nephrosclerosis, interstitial nephritis, sickle cell disease, hemoglobinuria, multiple myeloma, myoglobinuria, organ rejection (*e.g.*, kidney transplant rejection), ebola hemorrhagic fever, Nail patella syndrome, familial Mediterranean fever, HELLP syndrome, systemic lupus erythematosus, Wegener's granulomatosis, Rheumatoid arthritis, Glycogen storage disease type 1, Goodpasture's syndrome, Henoch-Schonlein purpura, urinary tract infection which has spread to the kidneys, Sjogren's syndrome and post-infections glomerulonepthritis.

In some embodiments, the MASP-2-dependent complement-associated disease or disorder is an inflammatory reaction resulting from tissue or solid organ transplantation, including allotransplantation or xenotransplantation of whole organs (*e.g.*, kidney, heart, liver, pancreas, lung, cornea, and the like) or tissue grafts (*e.g.*, valves, tendons, bone marrow, and the like).

In some embodiments, the MASP-2-dependent complement-associated disorder is an ischemia reperfusion injury (I/R), including myocardial I/R, gastrointestinal I/R, renal I/R, and I/R following an aortic aneurism repair, I/R associated with cardiopulmonary bypass, cerebral I/R, stroke, organ transplant or reattachment of severed or traumatized limbs or digits; revascularization to transplants and/or replants, and hemodynamic resuscitation following shock, surgical procedures, or similar, as well as combinations thereof.

In some embodiments, the MASP-2-dependent complement-associated disease or disorder is a complication associated with non-obese diabetes (Type-1 diabetes or Insulin-dependent diabetes mellitus) and/or complications associated with Type-1 or Type-2 (adult onset) diabetes including diabetic angiopathy, diabetic neuropathy, diabetic retinopathy, diabetic macular edema, and the like, as well as combinations thereof.

In some embodiments, the MASP-2-dependent complement-associated disease or disorder is a cardiovascular disease or disorder, including Henoch-Schonlein purpura nephritis, systemic lupus erythematosus-associated vasculitis, vasculitis associated with rheumatoid arthritis (also called malignant rheumatoid arthritis), immune complex vasculitis, and Takayasu's disease; dilated cardiomyopathy; diabetic angiopathy; Kawasaki's disease (arteritis); venous gas embolus (VGE); and inhibition of restenosis following stent placement, rotational atherectomy, percutaneous transluminal coronary angioplasty (PTCA), and the like as well as combinations thereof.

In some embodiments, the MASP-2-dependent complement-associated disease or disorder is an inflammatory gastrointestinal disorder, including pancreatitis, diverticulitis and bowel disorders including Crohn's disease, ulcerative colitis, irritable bowel syndrome, inflammatory bowel disease (IBD), or similar, as well as combinations thereof.

In some embodiments, the MASP-2-dependent complement-associated disease or disorder is a pulmonary disorder, including acute respiratory distress syndrome, transfusion-related acute lung injury, ischemia/reperfusion acute lung injury, chronic obstructive pulmonary disease, asthma, Wegener's granulomatosis, antiglomerular basement membrane disease (Goodpasture's disease), meconium aspiration syndrome, aspiration pneumonia, bronchiolitis obliterans syndrome, idiopathic pulmonary fibrosis, acute lung injury secondary to burn, non-cardiogenic pulmonary edema, transfusion-related respiratory depression, emphysema, and the like, as well as combinations thereof.

In some embodiments, the MASP-2-dependent complement-associated disease or disorder is an extracorporeal exposure-triggered inflammatory reaction and the method comprises treating a subject undergoing an extracorporeal circulation procedure. In some embodiments, the extracorporeal circulation procedure includes hemodialysis, plasmapheresis, leukopheresis, extracorporeal membrane oxygenation (ECMO), heparin-induced extracorporeal membrane oxygenation LDL precipitation (HELP), cardiopulmonary bypass (CPB), and the like.

In some embodiments, the MASP-2-dependent complement-associated disease or disorder is selected from inflammatory or non-inflammatory arthritides and other musculoskeletal disorders, *e.g.*, osteoarthritis, rheumatoid arthritis, juvenile rheumatoid arthritis, gout, neuropathic arthropathy, psoriatic arthritis, ankylosing spondylitis or other spondyloarthropathies and crystalline arthropathies, muscular dystrophy, systemic lupus erythematosus (SLE), or similar, as well as combinations thereof.

In some embodiments, the MASP-2-dependent complement-associated disease or disorder is a skin disorder; for example, psoriasis, autoimmune bullous dermatoses, eosinophilic spongiosis, bullous pemphigoid, epidermolysis bullosa acquisita, atopic dermatitis, herpes gestationis, and other skin disorders. In some embodiments, the MASP-2-dependent complement-associated disease or disorder is a thermal burn, chemical burn, or combinations thereof, including capillary leakage caused thereby.

In some embodiments, the MASP-2-dependent complement-associated disease or disorder is a peripheral nervous system (PNS) and/or central nervous system (CNS) disorder or injury including multiple sclerosis (MS), myasthenia gravis (MG), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), Guillain Barre syndrome, reperfusion following stroke, degenerative discs, cerebral trauma, Parkinson's disease (PD), Alzheimer's disease (AD), Miller-Fisher syndrome, cerebral trauma and/or hemorrhage, traumatic brain injury, demyelination, meningitis, or similar, as well as combinations thereof.

In some embodiments, the MASP-2-dependent complement-associated disease or disorder is sepsis or a condition resulting from sepsis including severe sepsis, septic shock, acute respiratory distress syndrome resulting from sepsis, hemolytic anemia, systemic inflammatory response syndrome, hemorrhagic shock, or the like, as well as combinations thereof.

In some embodiments, the MASP-2-dependent complement-associated disease or disorder is a urogenital disorder including painful bladder disease, sensory bladder disease, chronic abacterial cystitis and interstitial cystitis, male and female infertility, placental dysfunction and miscarriage, pre-eclampsia, or similar, as well as combinations thereof.

In some embodiments, the MASP-2-dependent complement-associated disease or disorder is an inflammatory reaction in a subject being treated with chemotherapeutics and/or radiation therapy, including for the treatment of cancerous conditions.

In some embodiments, the MASP-2-dependent complement-associated disease or disorder is an angiogenesis-dependent cancer, including a solid tumor(s), blood borne tumor(s), high-risk carcinoid tumors, tumor metastases, and the like, including combinations thereof.

In some embodiments, the MASP-2-dependent complement-associated disease or disorder is an angiogenesis-dependent benign tumor, including hemangiomas, acoustic neuromas, neurofibromas, trachomas, carcinoid tumors, pyogenic granulomas, or similar, as well as combinations thereof.

In some embodiments, the MASP-2-dependent complement-associated disease or disorder is an endocrine disorder including Hashimoto's thyroiditis, stress, anxiety, other potential hormonal disorders involving regulated release of prolactin, growth or insulin-like growth factor, adrenocorticotropin from the pituitary, or similar, as well as combinations thereof.

In some embodiments, the MASP-2-dependent complement-associated disease or disorder is an ophthalmic disease or disorder including age-related macular degeneration, glaucoma, endophthalmitis, and the like, as well as combinations thereof.

In some embodiments, the MASP-2-dependent complement-associated disease or disorder is an ocular angiogenic disease or condition including age-related macular degeneration, uveitis, ocular melanoma, corneal neovascularization, primary pterygium, HSV stromal keratitis, HSV-l-induced corneal lymphangiogenesis, proliferative diabetic retinopathy, diabetic macular edema, retinopathy of prematurity, retinal vein occlusion, corneal graft rejection, neovascular glaucoma, vitreous hemorrhage secondary to proliferative diabetic retinopathy, neuromyelitis optica, rubeosis, or similar, as well as combinations thereof.

In some embodiments, the MASP-2-dependent complement-associated disease or disorder is disseminated intravascular coagulation (DIC) or other complement mediated coagulation disorder, including DIC secondary to sepsis, severe trauma, including neurological trauma (*e.g.*, acute head injury; see Kumura et al, *Acta*

Neurochirurgica 55:23-28 (1987), infection (*e.g.*, bacterial, viral, fungal, parasitic), cancer, obstetrical complications, liver disease, severe toxic reaction (*e.g.*, snake bite, insect bite, transfusion reaction), shock, heat stroke, transplant rejection, vascular aneurysm, hepatic failure, cancer treatment by chemotherapy or radiation therapy, burn, or accidental radiation exposure.

In some embodiments, the MASP-2-dependent complement-associated disease or disorder is selected from the group consisting of acute radiation syndrome, dense deposit disease, Degos Disease, Catastrophic Antiphospholipid Syndrome (CAPS), Behcet's disease, cryoglobulinemia, paroxysmal nocturnal hemoglobinuria (PNH), cold agglutinin disease, and combinations thereof.

In some embodiments, the MASP-2-dependent complement-associated disease or disorder is selected from the group consisting of aHUS, HSCT-TMA, IgAN, Lupus Nepthritis (LN), and combinations thereof.

In some embodiments, the method comprises administering to a patient suffering from, or at risk for developing a disease, disorder or condition associated with fibrin-induced activation of the complement system and the associated activation of the coagulation and/or contact systems an amount of a compound according to any one of the foregoing embodiments (*e.g.*, a compound of Structure (I)) in an amount sufficient to inhibit MASP-2 dependent complement activation in the mammalian subject to thereby treat the disease or disorder. In some embodiments, the subject is suffering from, or at risk of developing, a disease, disorder or condition associated with complement-related inflammation, excessive coagulation or contact system activation initiated by fibrin or activated platelets. In some embodiments, the subject is suffering from a disease or disorder selected from the group consisting of arterial thrombosis, venous thrombosis, deep vein thrombosis, post-surgical thrombosis, restenosis following coronary artery bypass graft and/or an interventional cardiovascular procedure (*e.g.*, angioplasty or stent placement), atherosclerosis, plaque rupture, plaque instability, restenosis, hypotension, acute respiratory distress syndrome (ARDS), systemic inflammatory response syndrome (SIRS), disseminated intravascular coagulation (DIC), veno-occlusive disease (VOD), thrombotic microangiopathy, lupus nephritis, superficial thrombophlebitis, Factor V

Leiden mutation, ischemic/reperfusion injury, human immunodeficiency virus (HIV) infection, undergoing hormone-replacement therapy (HRT), Alzheimer's disease and/or suffering from a hypercoagulable state.

In some embodiments, the subject is suffering from, or at risk for developing an acquired hypercoagulable state due to at least one or more of the following: undergoing therapy with a drug selected from the group consisting of 5-FU, GM-CSF, cisplatin, heparin, COX-2 inhibitor, contrast media, corticosteroids and antipsychotics; venous stasis (immobilization, surgery, *etc.*), antiphospholipid syndrome, cancer (promyelocytic leukemia, lung, breast, prostate, pancreas, stomach and colon tumors), tissue injury due to trauma or surgery, presence of a catheter in a central vein, acquired deficiency of a protein involved in clot formation (*e.g.*, protein C), paroxysmal nocturnal hemoglobinuria (PNH), elevated levels of homocysteine, heart failure, presence of a mechanical valve, pulmonary hypertension with *in situ* thrombosis, atrial fibrillation, heparin-induced thrombocytopenia (HIT), heparin-induced thrombocytopenia and thrombosis (HITT), Kawasaki disease with *in situ* thrombus, Takayasu arteritis with *in situ* thrombus, thrombophilia of metastatic cancer, elevated Factor VIII levels, pregnancy, inflammatory bowel disease (IBD), or due to a genetic defect that causes or increases the risk of developing, a hypercoagulable state, such as a genetic defect selected from the group consisting of a Prothrombin 20210 gene mutation, an MTHFR mutation, a deficiency of protein C, a deficiency of protein S, a deficiency of protein A, a deficiency of protein Z, an antithrombin deficiency, and a genetic disorder producing thrombophilia.

In some embodiments, the subject is suffering from, or at risk for developing, a disease or disorder that is amenable to treatment with a kallikrein inhibitor. In some embodiments, the subject is suffering from, or at risk for developing a disease or disorder amenable to treatment with a kallikrein inhibitor is selected from the group consisting of hereditary angioedema, diabetic macular edema and bleeding during cardiopulmonary bypass. In some embodiments, the subject is suffering from, or at risk for developing, a disease or disorder that is amenable to treatment with a thrombin inhibitor, such as arterial thrombosis, venous thrombosis, pulmonary embolism, atrial fibrillation, heparin-induced thrombocytopenia, conversion from one anticoagulant to another, or off-label use for extracorporeal circuit patency of continuous renal replacement therapy (CRRT) in critically ill patients with HIT (maintenance).

In some embodiments, the subject has previously experienced, is currently suffering from, or is at risk for developing atrial fibrillation and the MASP-2 inhibitory compound (*e.g.*, a compound of Structure (I)) is administered in an amount sufficient to reduce the risk of stroke in said subject. In some embodiments, the subject is suffering from, or at risk for developing, a disease or disorder that is amenable to treatment with a factor XII inhibitor, such as deep vein thrombosis (both primary prophylaxis and extended therapy), pulmonary embolism, nonvalvular atrial fibrillation, prevention of recurrent ischemia after acute coronary syndrome in subjects with or without atrial fibrillation, end-stage renal disease, cerebral ischemia, angina, or to reduce or prevent clotting associated with medical devices (*e.g.*, valves, small caliber grafts, *etc.*) and/or extracorporeal circuits.

In some embodiments, the subject has previously experienced, is currently suffering from, or is at risk for developing nonvalvular atrial fibrillation and the MASP-2 inhibitory compound (*e.g.*, a compound of Structure (I)) is administered in an amount sufficient to reduce the risk of stroke and/or embolism in said subject. In some embodiments, the subject has an acquired disease or disorder that increases the propensity for thromboembolism, such as a disease or disorder selected from the group consisting of atherosclerosis, antiphospholipid antibodies, cancer (*e.g.*, promyelocytic leukemia, lung, breast, prostate, pancreatic, stomach and colon), hyperhomocysteinemia, infection, tissue injury, venous stasis (such as due to surgery, orthopedic or paralytic immobilization, heart failure, pregnancy, or obesity) and a subject taking oral contraceptives that contain estrogen.

In some embodiments, the subject is in need of anticoagulant therapy and the MASP-2 inhibitory compound (*e.g.*, a compound of Structure (I)) is used as a replacement for standard anticoagulant therapy (*e.g.*, Warfarin). In some embodiments, the subject has a condition that normally prohibits standard anticoagulant therapy, such as CNS amyloid angiopathy. In some embodiments of the method, the MASP-2 inhibitory compound is administered as a bridging agent perioperatively in a subject otherwise on standard anticoagulation therapy. In some embodiments, the subject has sickle cell disease which is a vaso-occlusive disorder involving activation of platelets.

Atypical hemolytic uremic syndrome (aHUS) is part of a group of conditions termed "Thrombotic microangiopathies." In the atypical form of HUS (aHUS), the disease is associated with defective complement regulation and can be either sporadic or familial. Familial cases of aHUS are associated with mutations in genes coding for complement activation or complement regulatory proteins, including complement factor H, factor I, factor B, membrane cofactor CD46 as well as complement factor H-related protein 1 (CFHR1) and complement factor H-related protein 3 (CFHR3). (Zipfel, P.F., et al., PloS Genetics 3(3):e41 (2007)). The unifying feature of this diverse array of genetic mutations associated with aHUS is a predisposition to enhanced complement activation on cellular or tissue surfaces. A subject is a risk for developing aHUS upon the onset of at least one or more symptoms indicative of aHUS (*e.g.*, the presence of anemia, thrombocytopenia and/or renal insufficiency) and/or the presence of thrombotic microangiopathy in a biopsy obtained from the subject. The determination of whether a subject is at risk for developing aHUS comprises determining whether the subject has a genetic predisposition to developing aHUS, which may be carried out by assessing genetic information (*e.g.* from a database containing the genotype of the subject), or performing at least one genetic screening test on the subject to determine the presence or absence of a genetic marker associated with aHUS (*i.e.*, determining the presence or absence of a genetic mutation associated with aHUS in the genes encoding complement factor H (CFH), factor I (CFI), factor B (CFB), membrane cofactor CD46, C3, complement factor H-related protein 1 (CFHR1), or THBD (encoding the anticoagulant protein thrombodulin) or complement factor H-related protein 3 (CFHR3), or complement factor H-related protein 4 (CFHR4)) either via genome sequencing or gene-specific analysis (*e.g.*, PCR analysis), and/or determining whether the subject has a family history of aHUS. Methods of genetic screening for the presence or absence of a genetic mutation associated with aHUS are well established, for example, see Noris M et al. "Atypical Hemolytic-Uremic Syndrome," 2007 Nov 16 [Updated 2011 Mar 10]. In:

Pagon RA, Bird TD, Dolan CR, et al., editors. GeneReviews™, Seattle (WA): University of Washington, Seattle.

Hematopoietic stem cell transplant-associated TMA (HSCT-TMA) is a life-threatening complication that is triggered by endothelial injury. The kidney is the most commonly affected organ, though HSCT-TMA can be a multi-system disease that also involves the lung, bowel, heart, and brain. The occurrence of even mild TMA is associated with long-term renal impairment. Development of post-allogeneic HSCT-associated TMA differs in frequency based on varying diagnostic criteria and conditioning and graft-versus-host disease prophylaxis regimens, with calcineurin inhibitors being the most frequent drugs implicated (Ho VT et al., Biol Blood Marrow Transplant, 1 1(8):571-5, 2005).

Immunoglobulin A nephropathy (IgAN) is an autoimmune kidney disease resulting in intrarenal inflammation and kidney injury. IgAN is the most common primary glomerular disease globally. With an annual incidence of approximately 2.5 per 100,000, it is estimated that 1 in 1400 persons in the U.S. will develop IgAN. As many as 40% of patients with IgAN will develop end-stage renal disease (ESRD). Patients typically present with microscopic hematuria with mild to moderate proteinuria and variable levels of renal insufficiency (Wyatt R.J., et al., NEnglJ Med 36S(25):2402-4, 2013). Clinical markers such as impaired kidney function, sustained hypertension, and heavy proteinuria (over 1 g per day) are associated with poor prognosis (Goto M et al., Nephrol Dial Transplant 24(10):3068-74, 2009; Berthoux F. et al., J Am Soc Nephrol 22(4):752-61, 2011). Proteinuria is the strongest prognostic factor independent of other risk factors in multiple large observational studies and prospective trials (Coppo R. et al., J Nephrol 18(5):503-12, 2005; Reich H. N., et al., J Am Soc Nephrol 18(12):3177-83, 2007). It is estimated that 15-20% of patients reach ESRD within 10 years of disease onset if left untreated (D'Amico G., Am J Kidney Dis 36(2):227-37, 2000). The diagnostic hallmark of IgAN is the predominance of IgA deposits, alone or with IgG, IgM, or both, in the glomerular mesangium.

A main complication of systemic lupus erythematosus (SLE) is nephritis, also known as lupus nephritis, which is classified as a secondary form of glomerulonephritis. Up to 60% of adults with SLE have some form of kidney involvement later in the course of the disease (Koda-Kimble et al., Koda-Kimble and Young's Applied Therapeutics: the clinical use of drugs, 10th Ed, Lippincott Williams & Wilkins: pages 792-9, 2012) with a prevalence of 20-70 per 100,000 people in the U.S. Lupus nephritis often presents in patients with other symptoms of active SLE, including fatigue, fever, rash, arthritis, serositis, or central nervous system disease (Pisetsky D.S. et al., Med Clin North Am 81(1): 113-28, 1997). Some patients have asymptomatic lupus nephritis; however, during regular follow-up, laboratory abnormalities such as elevated serum creatinine levels, low albumin levels, or urinary protein or sediment suggest active lupus nephritis.

V. Compositions, Dosage, and Administration

The compounds as described herein (*e.g.*, a compound of Structure (I)) can be administered in a manner compatible with the dosage formulation, and in such amount as will be effective or suitable for treatment. The quantity to be administered depends on a variety of factors including, *e.g.*, the age, body weight, physical activity, and diet of the individual, and the desired effect. In certain embodiments, the size of the dose may also be determined by the existence, nature, and extent of any adverse side effects that accompany the administration of the compound in a particular individual.

It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied by a physician and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, hereditary characteristics, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

In certain embodiments, the dose may take the form of solid, semi-solid, or liquid forms, preferably in unit dosage forms suitable for simple administration of precise dosages.

As used herein, the term "unit dosage form" refers to physically discrete units suitable as unitary dosages for humans and other mammals, each unit containing a predetermined quantity of an active agent calculated to produce the desired onset, tolerability, and/or efficacious effects, in association with a suitable pharmaceutical excipient (*e.g.,* an ampoule). In addition, more concentrated dosage forms may be prepared, from which the more dilute unit dosage forms may then be produced.

The compounds described herein (*e.g.*, a compound of Structure (I)) can be administered to a subject in need of treatment using methods known in the art, such as by oral administration or by injection. The injection can be, *e.g.*, subcutaneous, intravenous, intraperitoneal, or intramuscular. As described herein, parenteral formulations can be prepared in dosage unit form for ease of administration and uniformity of dosage. As used herein the term "unit dosage form" refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect.

The pharmaceutical compositions of the present application comprise a therapeutically effective amount of a compound of the present disclosure ((*e.g.*, a compound of Structure (I)) formulated together with one or more pharmaceutically acceptable carriers or excipient. As used herein, the term "pharmaceutically acceptable carrier" means a non-toxic, inert solid, semi-solid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. The pharmaceutical compositions of this application can be administered to humans and other animals orally, rectally, parenterally, intracistemally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), buccally, or as an oral or nasal spray.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

Injectable preparations include, for example, sterile injectable aqueous or oleaginous suspensions formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

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

Solid compositions of a similar type may also be employed as fillers in soft and hard filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

The active compounds can also be in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as sucrose, lactose, or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, *e.g.*, tableting lubricants and other tableting aids such a magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

Dosage forms for topical or transdermal administration of a compound as disclosed in the foregoing embodiments (*e.g.*, a compound of Structure (I)) include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants, or patches. For example, the active component may be ad-mixed under sterile conditions with a pharmaceutically acceptable carrier or excipient and any needed preservatives or buffers as may be required.

Transdermal patches have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

According to the methods of treatment of the present disclosure, disorders are treated or prevented in a subject, such as a human or other animal, by administering to the subject a therapeutically effective amount of a compound according to any one of the foregoing embodiments, in such amounts and for such time as is necessary to achieve the desired result. As is well understood in the medical arts a therapeutically effective amount of a compound will be at a reasonable benefit/risk ratio applicable to any medical treatment.

In general, compounds (*e.g.*, compounds of Structure (I)) will be administered in therapeutically effective amounts via any of the usual and acceptable modes known in the art, either singly or in combination with one or more other therapeutic agents. A therapeutically effective amount may vary widely depending on the severity of the disease, the age and relative health of the subject, the potency of the compound used and other factors.

In general, satisfactory results are indicated to be obtained systemically at daily dosages of from about 0.03 to 2.5 $^{mg}/_{kg}$ per body weight. An indicated daily dosage in the larger mammal, *e.g.*, humans, is in the range from about 0.5 mg to about 250 mg, about 5 mg to about 150 mg, about 5 mg to about 100 mg, about 10 mg to about 75 mg, about 10 mg to about 50 mg, such as 10, 20, 30, 40, or about 50 mg, conveniently administered, *e.g.*, in divided doses up to four times a day or in retard form. Suitable unit dosage forms for oral administration comprise from ca. 1 to 60 mg active ingredient.

In certain embodiments, a therapeutic amount or dose of the compound (*e.g.*, compounds of Structure (I)) may range from about 0.1 $^{mg}/_{kg}$ to about 500 $^{mg}/_{kg}$, alternatively from about 1 $^{mg}/_{kg}$ to about 50 $^{mg}/_{kg}$. In general, treatment regimens according to the present application comprise administration to a patient in need of such treatment from about 10 mg to about 1000 mg of the compound(s) per day in single or multiple doses. Therapeutic amounts or doses will also vary depending on route of administration, as well as the possibility of co-usage with other agents.

Upon improvement of a subject's condition, a maintenance dose of a compound, composition or combination of this application may be administered, if necessary. Subsequently, the dosage or frequency of administration, or both, may be reduced, as a function of the symptoms, to a level at which the improved condition is retained when the symptoms have been alleviated to the desired level, treatment should cease. The subject may, however, require intermittent treatment on a long-term basis upon any recurrence of disease symptoms.

It will be understood, however, that the total daily usage of the compounds (*e.g.*, compounds of Structure (I)) and compositions thereof will be decided by an attending physician within the scope of sound medical judgment. The specific inhibitory dose for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed; and like factors well known in the medical arts.

The application also provides for a pharmaceutical combination, *e.g.*, a kit, comprising:

a) a first agent which is a compound of the application as disclosed herein, in free form or in pharmaceutically acceptable salt form, and

b) at least one co-agent. The kit can comprise instructions for its administration.

Methods for preparing such dosage forms are known to those skilled in the art (see, *e.g.*, REMINGTON'S PHARMACEUTICAL SCIENCES, 18th ED., Mack Publishing Co., Easton, PA (1990)). The dosage forms typically include a conventional pharmaceutical carrier or excipient and may additionally include other medicinal agents, carriers, adjuvants, diluents, tissue permeation enhancers, solubilizers, and the like. Appropriate excipients can be tailored to the particular dosage form and route of administration by methods well known in the art (see, *e.g.*, REMINGTON'S PHARMACEUTICAL SCIENCES, 18th ED., Mack Publishing Co., Easton, PA (1990)).

The following abbreviations may be used herein and, unless otherwise noted, have the meanings indicated below:

ACN (acetonitrile); chrom. (chromatography); CH_2Cl_2 (dichloromethane); DIAD (Diisopropyl azodicarboxylate); *m- (*meta*);* Ms (methanesulfonyl); NCS (*N*-chlorosuccinimide); NIS (*N*-iodosuccinimide); NMR (nuclear magnetic resonance); obsd (observed); Phth (Phthalimide); TPP (triphenylphosphine); and Tr (trityl). Other abbreviations may also be used and have the meanings that would be understood by the person having skill in the art.

EXAMPLES

The following examples are provided by way of illustration only and not by way of limitation. Those of skill will readily recognize a variety of noncritical parameters which could be changed or modified to yield essentially similar results.

GENERAL METHODS

If not otherwise stated, chromatography refers to flash chromatography conducted on silica gel.

HPLC purification was performed by one of two methods. Method 1: on a Gilson preparative reverse phase HPLC system with the combination of UV/ELS detectors (254 nm and 280 nm) and ThermoFisher Hypersil GOLD Agilent (21.2 × 250 mm) 5 µm C_{18} column. Eluents were a mixture of water and acetonitrile (with 0.05 % trifluoroacetic acid). Flow rate was typically 20 $^{mL}/_{min}$ with a linear gradient of water in acetonitrile from 2-90% in 45 minutes. The injection volume was from 1 to 3 mL with maximum 20 mg per load. Method 2: on a Waters preparative reverse phase HPLC system with the combination of UV/MS detectors (254 nm and 280 nm) and XBridge Prep (19 × 50 mm) C_{18} 10µM OBD column. Eluents were a mixture of water and acetonitrile (with 0.05 % trifluoroacetic acid). Flow rate was typically 50 $^{mL}/_{min}$ with a linear gradient of water in acetonitrile from 5-95% in 8 minutes. The injection volume was from 0.2 to 1 mL with maximum 20 mg per load.

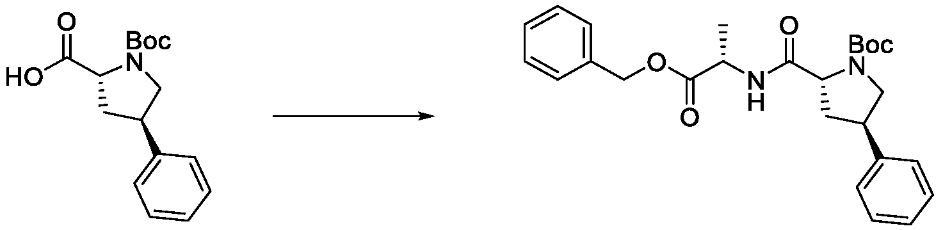
Abbreviations

µ	micro
°C	degrees Celsius
Ac	acetyl
anhyd	anhydrous
aq	aqueous
atm	atmosphere(s)
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bu	butyl
calcd	calculated
Cbz	benzyloxycarbonyl
CPME	cyclopentyl methyl ether
concd	concentrated
conc	concentration
DCC	*N, N'*-dicyclohexylcarbodiimide
DIEA	*N,N*-diisopropylethylamine
DMAP	4-(*N,N*-dimethylamino)pyridine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
EDC	*N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride
equiv	equivalent
ES	electrospray

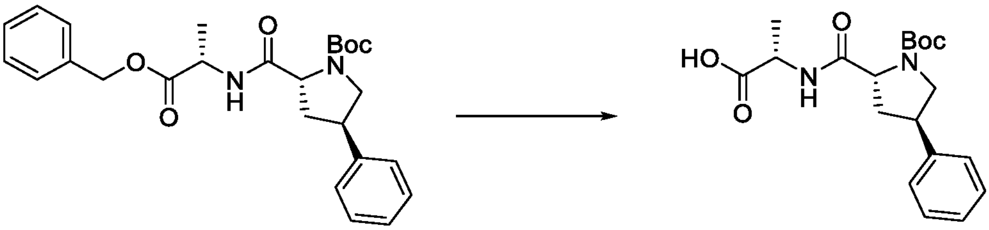
Et	ethyl
Et_2O	diethyl ether
g	gram(s)
h	hour(s)
HATU	*N*-[(Dimethylamino)-1*H*-1,2,3-triazolo-[4,5-*b*]pyridin-1-ylmethylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide
HBTU	*N,N,N',N'*-Tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate, *O*-(Benzotriazol-1-yl)-
HPLC	high-performance liquid chromatography/high-performance liquid chromatography
HOBt	1-hydroxybenzotriazole hydrate
*i*PrOH	*iso*-propanol
L	liter(s)
LiOH	lithium hydroxide
m	milli
M	molar
MeCN	acetonitrile
min	minute(s)
mL	milliliter
mol	mole; molecular (as in mol wt)
MS	mass spectrometry
MW	molecular weight
NBS	*N*-bromosuccinimide
NHS	*N*-hydroxysuccinimide
NMM	4-methylmorpholine
NMR	nuclear magnetic resonance
o	ortho
obsd	observed
p	para
Ph	phenyl
ppt	precipitate
Pr	propyl
psi	pounds per square inch
temp	temperature
TFA	trifluoroacetic acid
THF	tetrahydrofuran

EXAMPLE 1

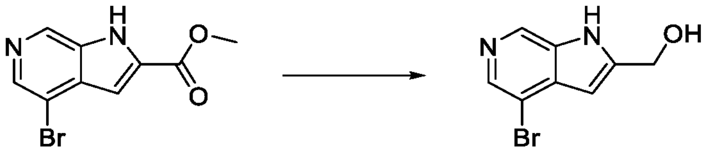
PREPARATION OF (2*R*,4*R*)-*N*-((*S*)-1-(((4-BROMO-1*H*-PYRROLO[2,3-C]PYRIDIN-2-YL)METHYL)AMINO)-1-OXOPROPAN-2-YL)-4-PHENYLPYRROLIDINE-2-CARBOXAMIDE DI-TRIFLUOROACETATE (COMPOUND I-1)



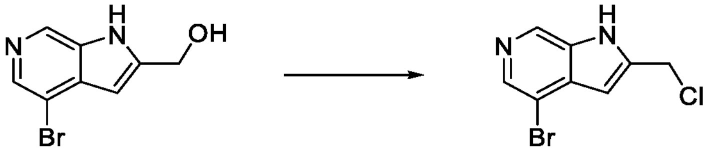
Step 1: To a solution of (2*R*,4*R*)-1-(*tert*-butoxycarbonyl)-4-phenylpyrrolidine-2-carboxylic acid (1.0 g, 3.43 mmol) in acetonitrile (70 mL, 0.05 M) was added HOBt (577 mg, 3.77 mmol), DIEA (2.39 mL, 13.7 mmol), and EDC (585 mg, 3.77 mmol). After stirring for 30 min at room temperature, benzyl *L*-alanine hydrochloride (814 mg, 3.77 mmol) was added and stirred for 16 h. The reaction mixture was concentrated and the residue was partitioned with ethyl acetate and 10% $KHSO_4$ solution. The organic layer was separated and washed with H_2O and sat. aq $NaHCO_3$. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum to give the crude *tert*-butyl (2*R*,4*R*)-2-(((*S*)-1-(benzyloxy)-1-oxopropan-2-yl)carbamoyl)-4-phenylpyrrolidine-1-carboxylate (1.33 g, 86% yield) which was used in the next step without further purification.



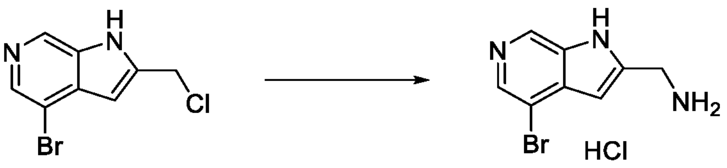
Step 2: A solution of the crude *tert*-butyl (2*R*,4*R*)-2-(((*S*)-1-(benzyloxy)-1-oxopropan-2-yl)carbamoyl)-4-phenylpyrrolidine-1-carboxylate (1.55 g, 3.42 mmol) in MeOH (50 mL, 0.07 M) was degassed with a stream of argon for 2 min. 10% Pd/C (70 mg) was added and a vacuum was pulled for 1 min. A balloon of H_2 was added and the reaction was monitored for the consumption of starting material for 1.5 h. The catalyst was removed by filtration and the solution was evaporated to give ((2*R*,4*R*)-1-(*tert*-butoxycarbonyl)-4-phenylpyrrolidine-2-carbonyl)-*L*-alanine (1.24 g, 100% yield).



Step 3: To a 0 °C solution of methyl 4-bromo-1*H*-pyrrolo[2,3-c]pyridine-2-carboxylate (1 g, 3.9 mmol) in THF (20 mL, 0.2 M) was added lithium aluminum hydride (1.0 M in THF, 6.3 mL, 6.3 mmol). After stirring for 1 h at the same temperature, the reaction was quenched by addition of H_2O and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by chromatography (0-100% ethyl acetate-hexanes) to give (4-bromo-1*H*-pyrrolo[2,3-c]pyridin-2-yl)methanol (412 mg, 46% yield).

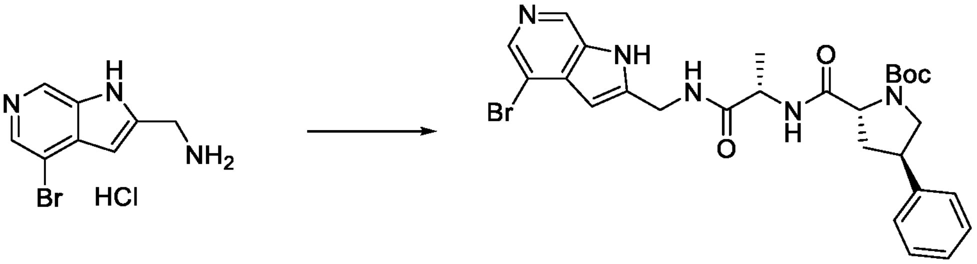


Step 4: To a solution of (4-bromo-1*H*-pyrrolo[2,3-c]pyridin-2-yl)methanol (206 mg, 0.91 mmol) in CH_2Cl_2 (1.5 mL, 0.6 M) was added HCl (4.0 M in dioxane, 2.2 mL). After stirring for 15 min at room temperature, the reaction mixture was evaporated to dryness. To this residue was added thionyl chloride (1 mL) at 0 °C. The mixture was heated to 80 °C and stirred for 2 min by which time the residue had turned to white solid, indicating completion. The residue was concentrated under vacuum to give the crude 4-bromo-2-(chloromethyl)-1*H*-pyrrolo[2,3-c]pyridine (256 mg, 100% yield) which was used in the next step without further purification.

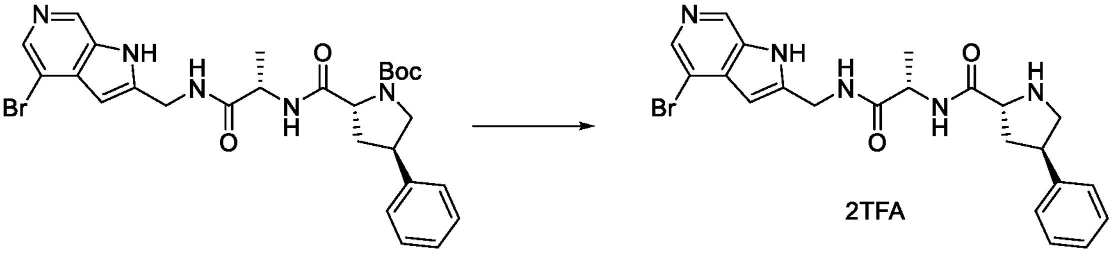


Step 5: Di-*tert*-butyl iminodicarboxylate (295 mg, 1.36 mmol) was dissolved in DMF (5 mL, 0.27 M) and sodium hydride (50 mg, 2.0 mmol) was added portion-wise. The reaction mixture was stirred for 30 min at which point 4-bromo-2-(chloromethyl)-1*H*-pyrrolo[2,3-c]pyridine (256 mg, 0.91 mol) dissolved in DMF was added dropwise. The reaction mixture was stirred at room temperature for 2 h at which point another 0.5 eq of sodium hydride was added. After stirring for 16 h at the same

temperature, the reaction was quenched by addition of H_2O and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The residue was dissolved in CH_2Cl_2 (5 mL) and HCl (4.0 M in dioxane, 10 mL) was added. After stirring for 22 h at room temperature, the reaction mixture was concentrated to give the crude (4-bromo-1*H*-pyrrolo[2,3-c]pyridin-2-yl)methanamine hydrochloride (233 mg, 100% yield) which was used in the next step without further purification.



Step 6: To a solution of (4-bromo-1*H*-pyrrolo[2,3-c]pyridin-2-yl)methanamine hydrochloride (233 mg, 0.78 mmol) in DMF (10 mL, 0.08 mmol) was added ((2*R*,4*R*)-1-(*tert*-butoxycarbonyl)-4-phenylpyrrolidine-2-carbonyl)-*L*-alanine (217 mg, 0.6 mmol). The resulting mixture was cooled to 0 °C. HBTU (296 mg, 0.78 mmol) and DIEA (0.42 mL, 2.4 mmol) were added to the above mixture. After stirring for 30 min at the same temperature, the reaction was warmed to room temperature. The reaction was stirred for 90 min then concentrated under vacuum. The residue was dissolved in ethyl acetate-CH_2Cl_2 then washed with 10% $KHSO_4$, H_2O, sat. aq $NaHCO_3$, and brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by chromatography (0-100% [5% 7 N NH_3 in MeOH/CH_2Cl_2]-CH_2Cl_2) to give *tert*-butyl (2*R*,4*R*)-2-(((*S*)-1-(((4-bromo-1*H*-pyrrolo[2,3-c]pyridin-2-yl)methyl)amino)-1-oxopropan-2-yl)carbamoyl)-4-phenylpyrrolidine-1-carboxylate (22 mg, 5% yield).

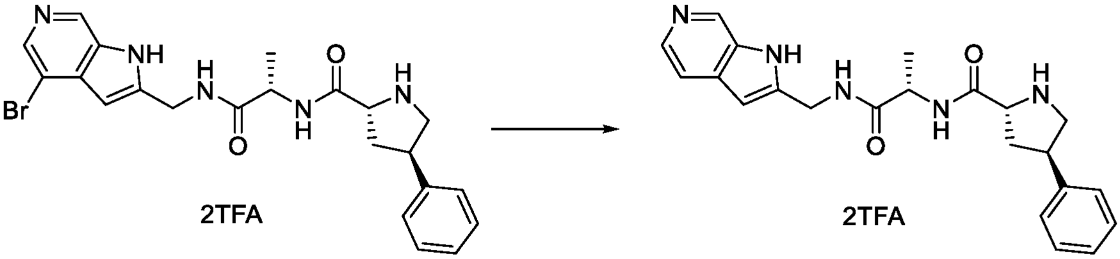


Step 7: To a 0 °C solution of *tert*-butyl (2*R*,4*R*)-2-(((*S*)-1-(((4-bromo-1*H*-pyrrolo[2,3-c]pyridin-2-yl)methyl)amino)-1-oxopropan-2-yl)carbamoyl)-4-phenylpyrrolidine-1-carboxylate (22 mg, 0.04 mmol) in CH_2Cl_2 (0.5 mL, 0.08 M) was added 20% TFA in CH_2Cl_2 (0.5 mL). After stirring for 2 h at room temperature, the reaction mixture was concentrated. The crude material was purified using reverse-phase HPLC to give (2*R*,4*R*)-*N*-((*S*)-1-(((4-bromo-1*H*-pyrrolo[2,3-c]pyridin-2-yl)methyl)amino)-1-oxopropan-2-yl)-4-phenylpyrrolidine-2-carboxamide di-trifluoroacetate (1.5 mg, 25% yield).

EXAMPLE 2

PREPARATION OF (2*R*,4*R*)-*N*-((*S*)-1-(((1*H*-PYRROLO[2,3-C]PYRIDIN-2-YL)METHYL)AMINO)-1-OXOPROPAN-2-YL)-4-PHENYLPYRROLIDINE-2-CARBOXAMIDE DI-TRIFLUOROACETATE

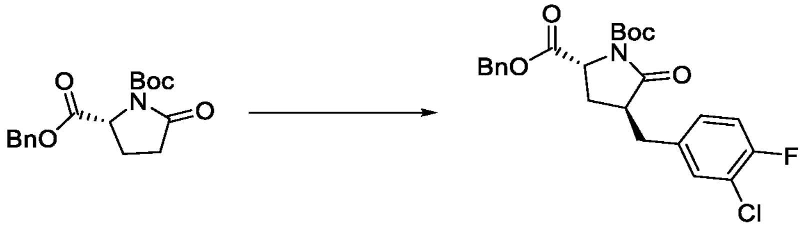
(COMPOUND I-3)



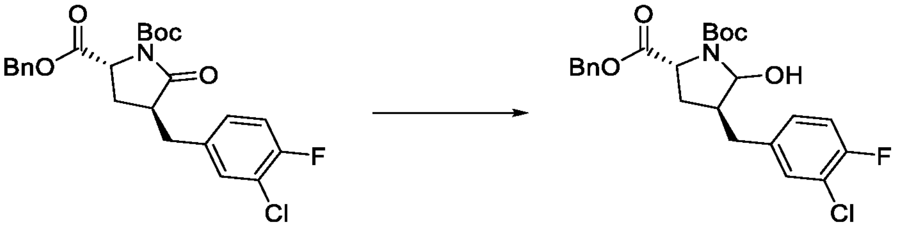
Step 1: A solution of (2*R*,4*R*)-*N*-((*S*)-1-(((4-bromo-1*H*-pyrrolo[2,3-c]pyridin-2-yl)methyl)amino)-1-oxopropan-2-yl)-4-phenylpyrrolidine-2-carboxamide trifluoroacetate (2 mg, 0.004 mmol, prepared according to the procedures for Compound I-1, steps 1-7) was degassed with a stream of argon for 2 min. 10% Pd/C (1.2 mg) was added and a vacuum was pulled for 1 min. A balloon of H_2 was added and the reaction was monitored for the consumption of starting material for 4 h. The catalyst was removed by filtration and the solution was evaporated to give (2*R*,4*R*)-*N*-((*S*)-1-(((1*H*-pyrrolo[2,3-c]pyridin-2-yl)methyl)amino)-1-oxopropan-2-yl)-4-phenylpyrrolidine-2-carboxamide di-trifluoroacetate (2.0 mg, 100% yield).

EXAMPLE 3

PREPARATION OF (2*R*,4*S*)-*N*-((*S*)-1-(((1*H*-PYRROLO[3,2-C]PYRIDIN-2-YL)METHYL)AMINO)-1-OXOPROPAN-2-YL)-4-(3-CHLORO-4-FLUOROBENZYL)PYRROLIDINE-2-CARBOXAMIDE DI-TRIFLUOROACETATE (COMPOUND I-2)

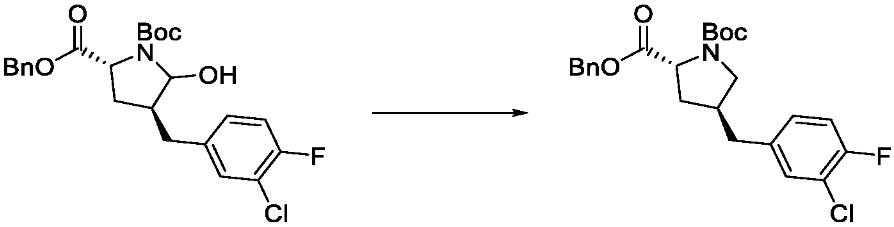


Step 1: To a −78 °C solution of 2-benzyl 1-(*tert*-butyl) (*R*)-5-oxopyrrolidine-1,2-dicarboxylate (600 mg, 1.88 mmol) in THF (12.5 mL) was slowly added lithium bis(trimethylsilyl)amide (1.0 M in THF, 2.06 mL, 2.06 mmol) under Ar. After stirring for 1 h at the same temperature, 4-(bromomethyl)-2-chloro-1-fluorobenzene (505 mg, 2.26 mmol) in 1 mL THF was added and the stirring continued for an additional 2 h. The reaction mixture was quenched by addition of sat. aq NH_4Cl solution and extracted with diethyl ether. The combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by chromatography (ethyl acetate-hexanes) gave 2-benzyl 1-(*tert*-butyl) (2*R*,4*S*)-4-(3-chloro-4-fluorobenzyl)-5-oxopyrrolidine-1,2-dicarboxylate (450 mg, 62% yield).

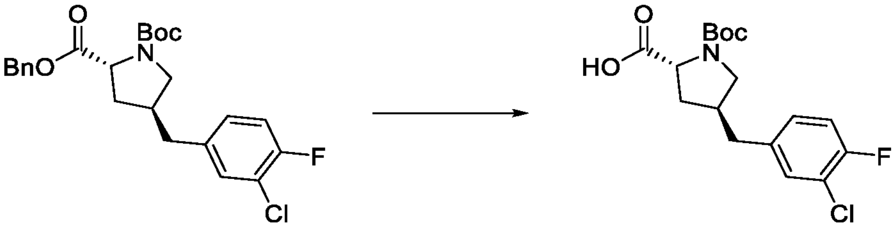


Step 2: To a −78 °C solution of 2-benzyl 1-(*tert*-butyl) (2*R*,4*S*)-4-(3-chloro-4-fluorobenzyl)-5-oxopyrrolidine-1,2-dicarboxylate (450 mg, 0.97 mmol) in THF (5 mL, 0.2 M) was added lithium triethylborohydride solution (1.0 M in THF, 1.07 mL, 1.07 mmol) under Ar. After stirring for 30 min at the same temperature, the reaction mixture was quenched with sat. aq $NaHCO_3$ solution (3 mL) and warmed to 0 °C. 30% H_2O_2 (about 10 drops) was added and the reaction mixture was stirred for 30 min at the same temperature. The organic volatiles were removed under vacuum and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried over

anhydrous Na_2SO_4, filtered, concentrated to give 2-benzyl 1-(*tert*-butyl) (2*R*,4*S*)-4-(3-chloro-4-fluorobenzyl)-5-hydroxypyrrolidine-1,2-dicarboxylate (350 mg) which was used in the next step without further purification.

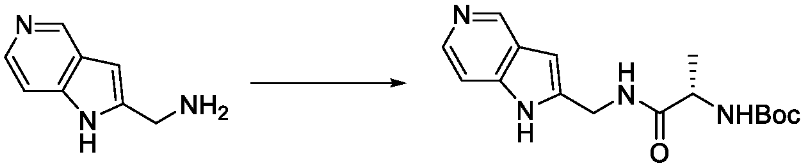


Step 3: To a −78 °C solution of 2-benzyl 1-(*tert*-butyl) (2*R*,4*S*)-4-(3-chloro-4-fluorobenzyl)-5-hydroxypyrrolidine-1,2-dicarboxylate (350 mg, 0.75 mmol) in CH_2Cl_2 (5 mL, 0.15 M), were added triethylsilane (0.25 mL, 1.56 mmol) and boron trifluoride diethyl etherate (0.19 mL, 1.56 mmol) under Ar. After stirring 30 min at the same temperature, additional triethylsilane (0.25 mL, 1.56 mmol) and boron trifluoride diethyl etherate (0.19 mL, 1.56 mmol) were added. After stirring for 2 h at the same temperature, the reaction mixture was quenched by addition of sat. aq $NaHCO_3$ solution (5 mL) and extracted with CH_2Cl_2. The combined extracts were dried over anhydrous Na_2SO_4, filtered, concentrated under vacuum. The residue was purified by chromatography (ethyl acetate-hexanes) to give 2-benzyl 1-(*tert*-butyl) (2*R*,4*S*)-4-(3-chloro-4-fluorobenzyl)pyrrolidine-1,2-dicarboxylate (220 mg, 51% yield for two steps).

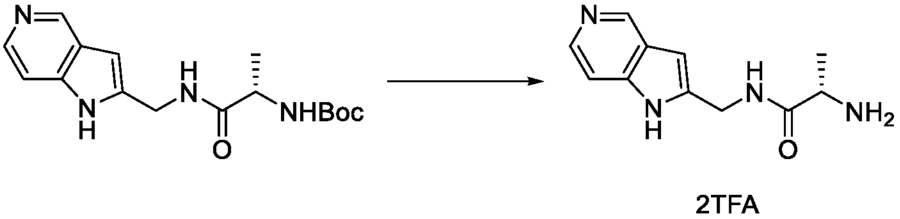


Step 4: A solution of 2-benzyl 1-(*tert*-butyl) (2*R*,4*S*)-4-(3-chloro-4-fluorobenzyl)pyrrolidine-1,2-dicarboxylate (220 mg, 0.49 mmol) in THF (12 mL), MeOH (6 mL), and water (6 mL) was added lithium hydroxide (176 mg, 7.4 mmol). After stirring for 4 h at room temperature, 6 mL of 1 N HCl was added to the reaction mixture and organic volatiles were removed under vacuum. The aqueous layer was extracted with ethyl acetate. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum to give (2*R*,4*S*)-1-(*tert*-butoxycarbonyl)-4-(3-chloro-4-

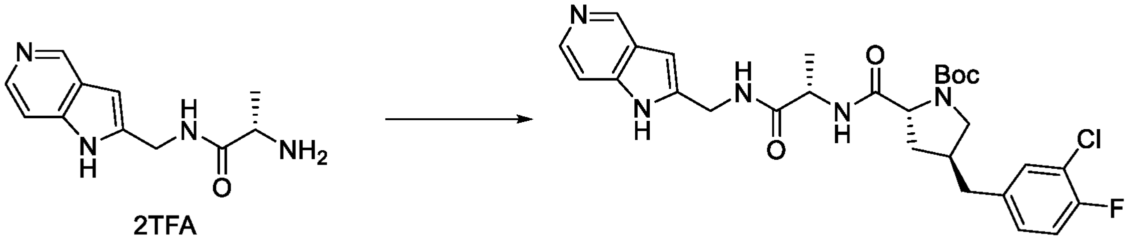
fluorobenzyl)pyrrolidine-2-carboxylic acid (158 mg, 90% yield) which was used in the next step without further purification..



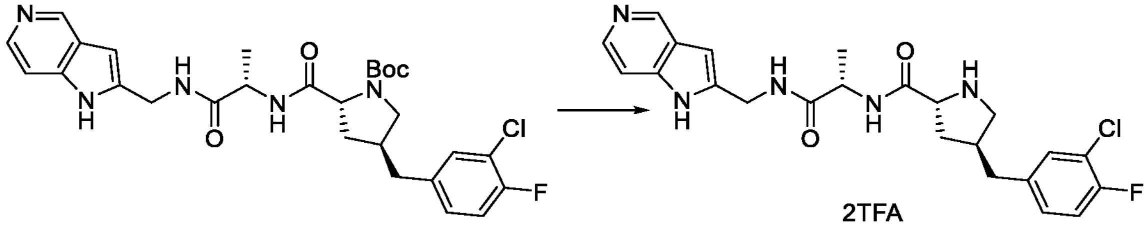
Step 5: *tert*-Butyl (*S*)-(1-(((1*H*-pyrrolo[3,2-c]pyridin-2-yl)methyl)amino)-1-oxopropan-2-yl)carbamate (683 mg, 63% yield) was synthesized from (1*H*-pyrrolo[3,2-c]pyridin-2-yl)methanamine (500 mg, 3.4 mmol) and (*tert*-butoxycarbonyl)-*L*-alanine (495 mg, 2.6 mmol) according to the procedure for compound Compound I-1, step 6.



Step 6: Deprotection of *tert*-Butyl (*S*)-(1-(((1*H*-pyrrolo[3,2-c]pyridin-2-yl)methyl)amino)-1-oxopropan-2-yl)carbamate (683 mg, 2.15 mmol) was conducted according to the procedure for Compound I-1, step 7.



Step 7: *tert*-Butyl (2*R*,4*S*)-2-(((*S*)-1-(((1*H*-pyrrolo[3,2-c]pyridin-2-yl)methyl)amino)-1-oxopropan-2-yl)carbamoyl)-4-(3-chloro-4-fluorobenzyl)pyrrolidine-1-carboxylate (27 mg, 69% yield) was synthesized from *tert*-butyl (*S*)-(1-(((1*H*-pyrrolo[3,2-c]pyridin-2-yl)methyl)amino)-1-oxopropan-2-yl)carbamate di-trifluoroacetate (37 mg, 0.08 mmol) and (2*R*,4*S*)-1-(*tert*-butoxycarbonyl)-4-(3-chloro-4-fluorobenzyl)pyrrolidine-2-carboxylic acid (25 mg, 0.07 mmol) according to the procedure for Compound I-1, step 6.

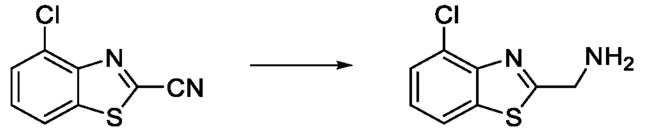


Step 8: Deprotection of *tert*-Butyl (2*R*,4*S*)-2-(((*S*)-1-(((1*H*-pyrrolo[3,2-c]pyridin-2-yl)methyl)amino)-1-oxopropan-2-yl)carbamoyl)-4-(3-chloro-4-fluorobenzyl)pyrrolidine-1-carboxylate (27 mg, 0.05 mmol) was conducted according to the procedure for Compound I-1, step 7.

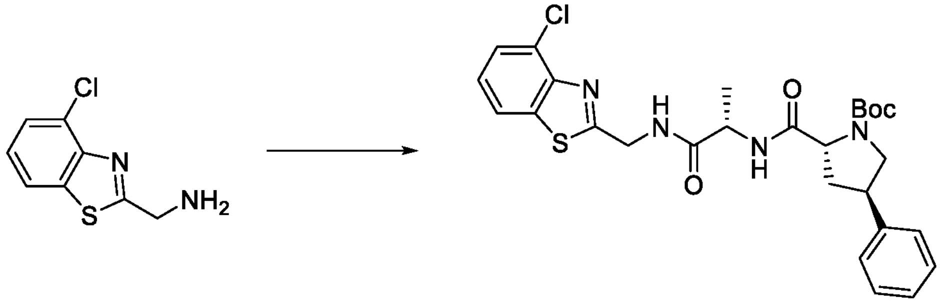
EXAMPLE 4

PREPARATION OF (2*R*,4*R*)-*N*-((*S*)-1-(((4-CHLOROBENZO[D]THIAZOL-2-YL)METHYL)AMINO)-1-OXOPROPAN-2-YL)-4-PHENYLPYRROLIDINE-2-CARBOXAMIDE TRIFLUOROACETATE

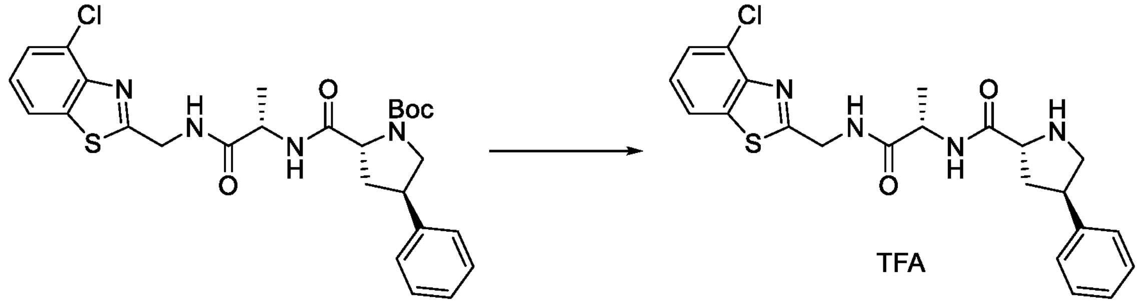
(COMPOUND I-4)



Step 1: A solution of 4-chlorobenzo[d]thiazole-2-carbonitrile (70 mg, 0.36 mmol) in MeOH (1.5 mL) and 7 N NH_3 in MeOH (7 mL) was degassed with a stream of argon 2 times. Raney nickel (100 mg) was added and a vacuum was pulled for 1 min. A balloon of H_2 was added and the reaction mixture was stirred for 16 h at room temperature. Upon completion, the reaction mixture was degassed with a stream of argon 2 times. The catalyst was removed by diatomaceous earth filtration and the solution was concentrated. The residue was taken up in 5% H_2O in MeOH, filtered (0.2 μm syringe filter), and the filtrate was concentrated under vacuum to give 3-(aminomethyl)-5-chloropyridin-2-amine (55 mg, 77% yield).



Step 2: *tert*-Butyl (2*R*,4*R*)-2-(((*S*)-1-(((4-chlorobenzo[d]thiazol-2-yl)methyl)amino)-1-oxopropan-2-yl)carbamoyl)-4-phenylpyrrolidine-1-carboxylate (34 mg, 29%) was synthesized from 3-(aminomethyl)-5-chloropyridin-2-amine (55 mg, 0.28 mmol) and ((2*R*,4*R*)-1-(*tert*-butoxycarbonyl)-4-phenylpyrrolidine-2-carbonyl)-*L*-alanine (77 mg, 0.21 mmol) prepared according to the procedure for Compound I-1, step 2) according to the procedure for Compound I-1, step 6.



Step 3: Deprotection of *tert*-Butyl (2*R*,4*R*)-2-(((*S*)-1-(((4-chlorobenzo[d]thiazol-2-yl)methyl)amino)-1-oxopropan-2-yl)carbamoyl)-4-phenylpyrrolidine-1-carboxylate (34 mg, 0.06 mmol) was conducted according to the procedure for Compound I-1, step 7.

EXAMPLE 5

PREPARATION OF (2*R*,4*S*)-*N*-((*S*)-1-(((1*H*-PYRROLO[3,2-C]PYRIDIN-2-YL)METHYL)AMINO)-1-OXOPROPAN-2-YL)-4-(3-CHLOROBENZYL)PYRROLIDINE-2-CARBOXAMIDE DI-TRIFLUOROACETATE (COMPOUND I-5)

(2*R*,4*S*)-*N*-((*S*)-1-(((1*H*-Pyrrolo[3,2-c]pyridin-2-yl)methyl)amino)-1-oxopropan-2-yl)-4-(3-chlorobenzyl)pyrrolidine-2-carboxamide di-trifluoroacetate was synthesized according to the procedures for Compound I-2.

EXAMPLE 6

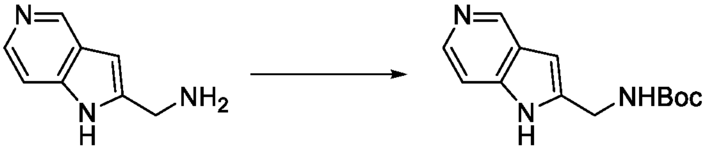
PREPARATION OF (2*R*,4*R*)-*N*-((*S*)-1-(((1*H*-PYRROLO[3,2-B]PYRIDIN-2-YL)METHYL)AMINO)-1-OXOPROPAN-2-YL)-4-PHENYLPYRROLIDINE-2-CARBOXAMIDE DI-TRIFLUOROACETATE

(COMPOUND I-6)

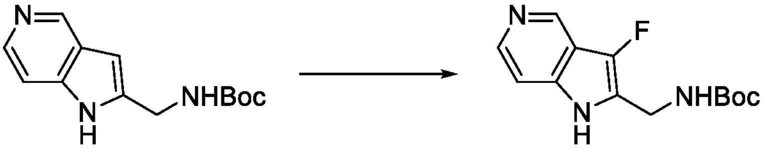
(2*R*,4*R*)-*N*-((*S*)-1-(((1*H*-Pyrrolo[3,2-b]pyridin-2-yl)methyl)amino)-1-oxopropan-2-yl)-4-phenylpyrrolidine-2-carboxamide di-trifluoroacetate was synthesized according to the procedures for Compound I-1 starting from commercially available (1*H*-pyrrolo[3,2-b]pyridin-2-yl)methanamine.

EXAMPLE 7

PREPARATION OF (2*R*,4*R*)-*N*-((*S*)-1-(((3-FLUORO-1*H*-PYRROLO[3,2-C]PYRIDIN-2-YL)METHYL)AMINO)-1-OXOPROPAN-2-YL)-4-PHENYLPYRROLIDINE-2-CARBOXAMIDE DI-TRIFLUOROACETATE (COMPOUND I-7)

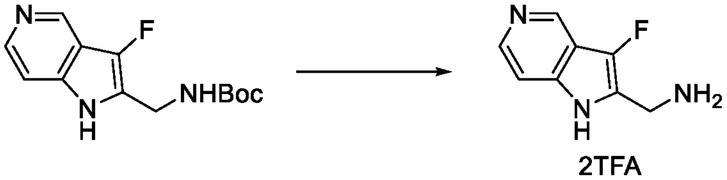


Step 1: To a solution of (1*H*-pyrrolo[3,2-c]pyridin-2-yl)methanamine (200 mg, 1.36 mmol) in acetonitrile (15 mL, 0.09 M) were added Et_3N (0.57 mL, 4.08 mmol), Boc_2O (593 mg, 2.72 mmol), and DMAP (166 mg, 1.36 mmol). After stirring for 16 h at room temperature, the reaction mixture was concentrated and the residue was partitioned with ethyl acetate and H_2O. The organic layer was separated, washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by chromatography (0-100% ethyl acetate-hexanes) to give *tert*-butyl ((1*H*-pyrrolo[3,2-c]pyridin-2-yl)methyl)carbamate (69 mg, 21% yield).

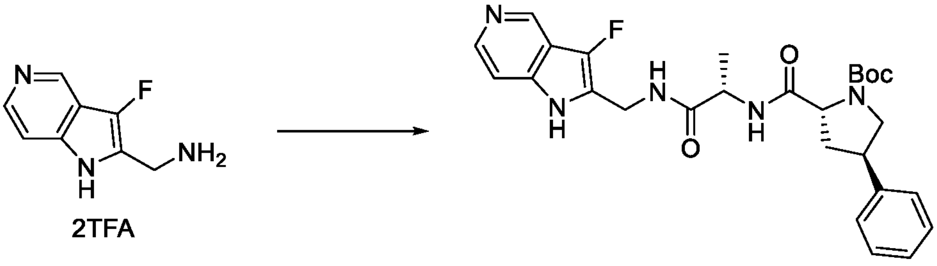


Step 2: To a solution of *tert*-butyl ((1*H*-pyrrolo[3,2-c]pyridin-2-yl)methyl)carbamate (69 mg, 0.28 mmol) in acetonitrile (4 mL) and acetic acid (0.4 mL) was added Selectfluor™ (148 mg, 0.42 mmol). After stirring for 1 h at 50 °C under N_2,

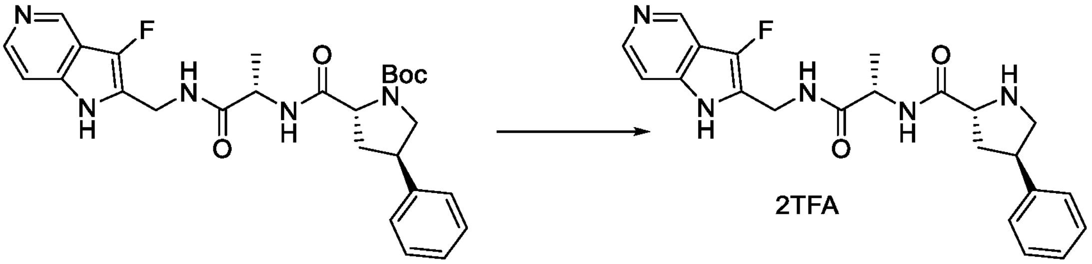
the reaction was quenched by addition of H_2O and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by chromatography (0-100% ethyl acetate-hexanes) to give *tert*-butyl ((3-fluoro-1*H*-pyrrolo[3,2-c]pyridin-2-yl)methyl)carbamate (14 mg, 19% yield).



<u>Step 3</u>: Deprotection of *tert*-butyl ((3-fluoro-1*H*-pyrrolo[3,2-c]pyridin-2-yl)methyl)carbamate (14 mg, 0.05 mmol) was conducted according to the procedure for Compound I-1, step 7.



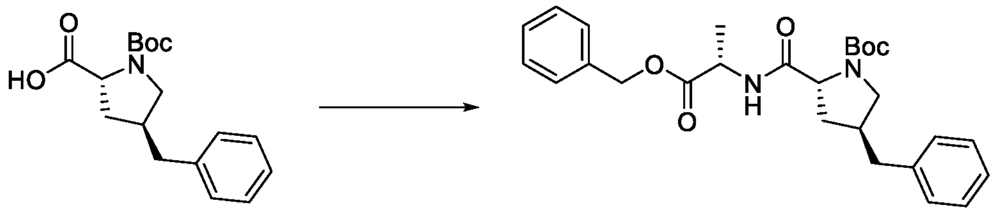
<u>Step 4</u>: *tert*-Butyl (2*R*,4*R*)-2-(((*S*)-1-(((3-fluoro-1*H*-pyrrolo[3,2-c]pyridin-2-yl)methyl)amino)-1-oxopropan-2-yl)carbamoyl)-4-phenylpyrrolidine-1-carboxylate was synthesized from (3-fluoro-1*H*-pyrrolo[3,2-c]pyridin-2-yl)methanamine di-trifluoroacetate (26 mg, 0.07 mmol) and ((2*R*,4*R*)-1-(*tert*-butoxycarbonyl)-4-phenylpyrrolidine-2-carbonyl)-*L*-alanine (19 mg, 0.05 mmol, prepared according to the procedures for Compound I-1, steps 1-2) according to the procedure for Compound I-1, step 6.



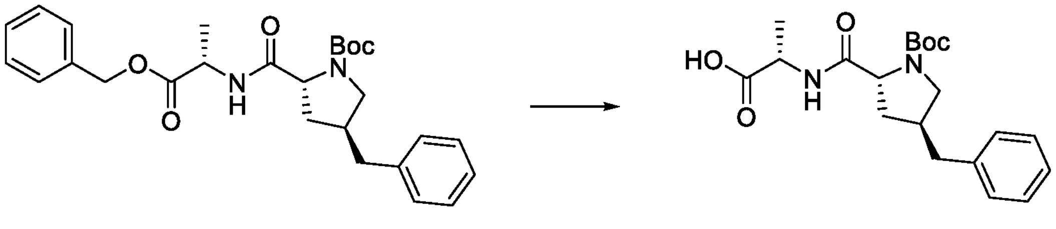
<u>Step 5</u>: Deprotection of *tert*-butyl ((3-fluoro-1*H*-pyrrolo[3,2-c]pyridin-2-yl)methyl)carbamate (14 mg, 0.05 mmol) was conducted according to the procedure for Compound I-1, step 7.

EXAMPLE 8

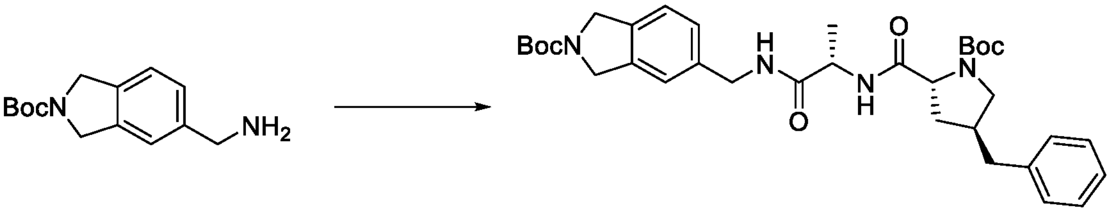
PREPARATION OF (2*R*,4*S*)-4-BENZYL-*N*-((*S*)-1-((ISOINDOLIN-5-YLMETHYL)AMINO)-1-OXOPROPAN-2-YL)PYRROLIDINE-2-CARBOXAMIDE DI-TRIFLUOROACETATE (COMPOUND I-9)



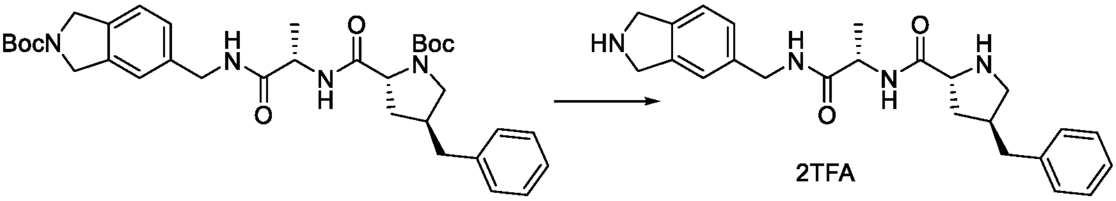
<u>Step 1</u>: To a solution of (2*R*,4*S*)-4-benzyl-1-(tert-butoxycarbonyl)pyrrolidine-2-carboxylic acid (500 mg, 1.64 mmol, prepared according to the procedures for Compound I-2, steps 1-4) in acetonitrile (10 mL, 0.16 M) was added HOBt (326 mg, 2.13 mmol), DIEA (1.14 mL, 6.55 mmol), and EDC (391 mg, 2.05 mmol). After stirring for 30 min at room temperature, benzyl *L*-alanine hydrochloride (423 mg, 1.97 mmol) was added and stirred for 16 h. The reaction mixture was concentrated and the residue was partitioned with ethyl acetate and 10% $KHSO_4$ solution. The organic layer was separated and washed with H_2O and sat. aq $NaHCO_3$. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by chromatography (0-100% ethyl acetate-hexanes) to give *tert*-butyl (2*R*,4*S*)-4-benzyl-2-(((*S*)-1-(benzyloxy)-1-oxopropan-2-yl)carbamoyl)pyrrolidine-1-carboxylate (272 mg, 36% yield).



<u>Step 2</u>: A solution of the crude *tert*-butyl (2*R*,4*S*)-4-benzyl-2-(((*S*)-1-(benzyloxy)-1-oxopropan-2-yl)carbamoyl)pyrrolidine-1-carboxylate (272 mg, 0.58 mmol) was degassed with a stream of argon for 2 min. 10% Pd/C (13 mg) was added and a vacuum was pulled for 1 min. A balloon of H_2 was added and the reaction was monitored for the consumption of starting material for 1.5 h. The catalyst was removed by filtration and the solution was evaporated to give ((2*R*,4*S*)-4-benzyl-1-(*tert*-butoxycarbonyl)pyrrolidine-2-carbonyl)-*L*-alanine (227 mg, 100% yield).



Step 3: *tert*-Butyl 5-((((*S*)-2-((2*R*,4*S*)-4-benzyl-1-(*tert*-butoxycarbonyl)pyrrolidine-2-carboxamido)propanamido)methyl)isoindoline-2-carboxylate (42 mg, 58% yield) was synthesized from *tert*-butyl 5-(aminomethyl)isoindoline-2-carboxylate (39 mg, 0.16 mmol) according to the procedure for Compound I-1, step 6.



Step 4: Deprotection of *tert*-butyl 5-((((*S*)-2-((2*R*,4*S*)-4-benzyl-1-(*tert*-butoxycarbonyl)pyrrolidine-2-carboxamido)propanamido)methyl)isoindoline-2-carboxylate di-trifluoroacetate (45 mg, 0.12 mmol) was conducted according to the procedure for Compound I-1, step 7.

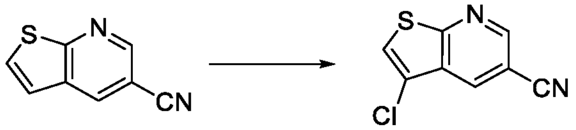
EXAMPLE 9

PREPARATION OF (2*R*,4*S*)-4-BENZYL-*N*-((*S*)-1-(((4-FLUORO-1*H*-PYRROLO[3,2-C]PYRIDIN-2-YL)METHYL)AMINO)-1-OXOPROPAN-2-YL)PYRROLIDINE-2-CARBOXAMIDE DI-TRIFLUOROACETATE (COMPOUND I-10)

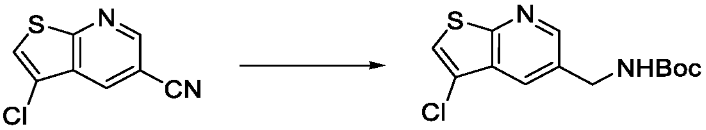
(2*R*,4*S*)-4-Benzyl-*N*-((*S*)-1-(((4-fluoro-1*H*-pyrrolo[3,2-c]pyridin-2-yl)methyl)amino)-1-oxopropan-2-yl)pyrrolidine-2-carboxamide di-trifluoroacetate was synthesized according to the procedures for Compound I-7 and Compound I-9, steps 1-2.

EXAMPLE 10

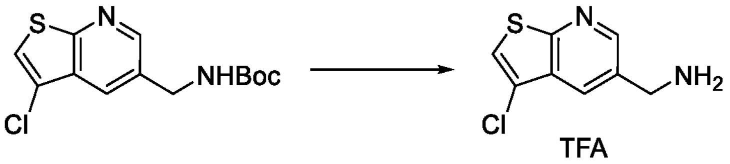
PREPARATION OF (2*R*,4*S*)-4-BENZYL-*N*-((*S*)-1-(((3-CHLOROTHIENO[2,3-B]PYRIDIN-5-YL)METHYL)AMINO)-1-OXOPROPAN-2-YL)PYRROLIDINE-2-CARBOXAMIDE TRIFLUOROACETATE (COMPOUND I-11)



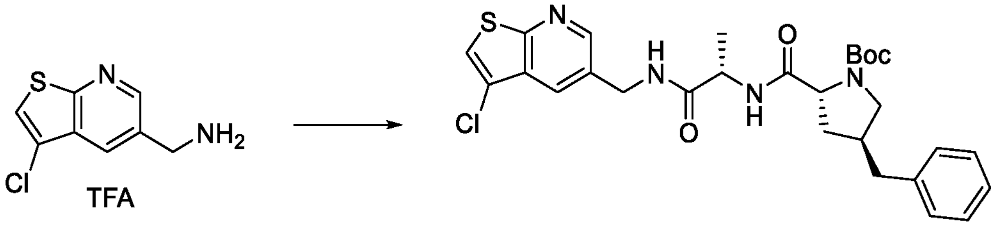
Step 1: To a solution of thieno[2,3-b]pyridine-5-carbonitrile (500 mg, 3.12 mmol) in acetic acid (10 mL, 0.006 M) was added *N*-chlorosuccinimide (417 mg, 3.12 mmol). After stirring for 20 h at reflux, the reaction mixture was cooled to room temperature and diluted with ethyl acetate. The mixture was washed with H_2O, sat. aq $NaHCO_3$, and brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by chromatography (50-100% ethyl acetate-hexanes) to give 3-chlorothieno[2,3-b]pyridine-5-carbonitrile (152 mg, 25% yield)



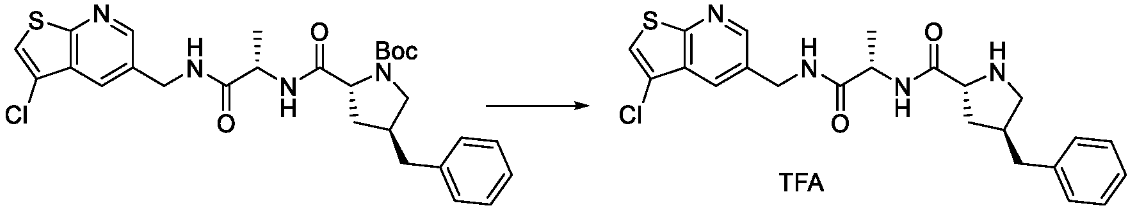
Step 2: To a 0 °C solution of 3-chlorothieno[2,3-b]pyridine-5-carbonitrile (40 mg, 0.21 mmol) in MeOH (5 mL, 0.04 M) was added $NiCl_2$ (50 mg, 0.21 mmol) and di-*tert*-butyl dicarbonate (90 mg, 0.41 mmol). To the above mixture was added $NaBH_4$ (100 mg, 2.87 mmol) portion-wise and the reaction mixture was stirred for 5 days at room temperature. Upon completion, the reaction mixture was concentrated, and the residue was dissolved in $CHCl_3$. The mixture was washed with H_2O, sat. aq $NaHCO_3$, and brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by chromatography (50-100% ethyl acetate-hexanes) to give *tert*-butyl ((3-chlorothieno[2,3-b]pyridin-5-yl)methyl)carbamate (11 mg, 17% yield).



Step 3: Deprotection of *tert*-butyl ((3-chlorothieno[2,3-b]pyridin-5-yl)methyl)carbamate (11 mg, 0.04 mmol) was conducted according to the procedure for Compound I-1, step 7.



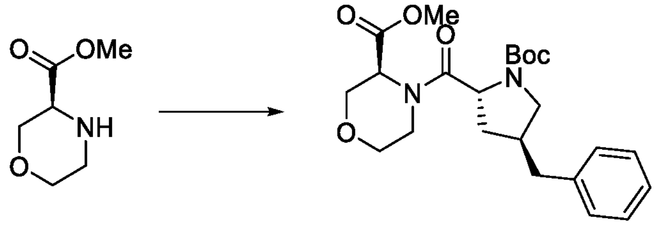
Step 4: *tert*-Butyl (2*R*,4*S*)-4-benzyl-2-(((*S*)-1-(((3-chlorothieno[2,3-b]pyridin-5-yl)methyl)amino)-1-oxopropan-2-yl)carbamoyl)pyrrolidine-1-carboxylate (17 mg, 80%) was synthesized from (3-chlorothieno[2,3-b]pyridin-5-yl)methanamine trifluoroacetate (12 mg, 0.04 mmol) and ((2*R*,4*S*)-4-benzyl-1-(*tert*-butoxycarbonyl)pyrrolidine-2-carbonyl)-*L*-alanine (11 mg, 0.03 mmol) according to the procedure for Compound I-1, step 6.



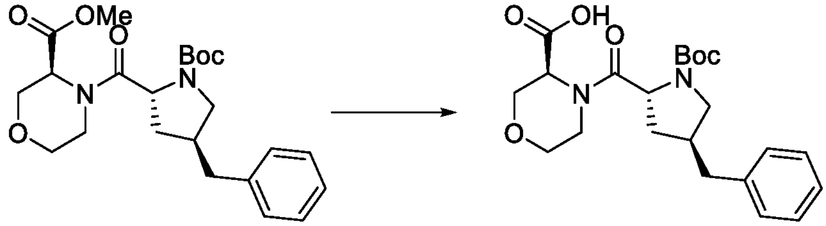
Step 5: Deprotection of *tert*-butyl (2*R*,4*S*)-4-benzyl-2-(((*S*)-1-(((3-chlorothieno[2,3-b]pyridin-5-yl)methyl)amino)-1-oxopropan-2-yl)carbamoyl)pyrrolidine-1-carboxylate (17 mg, 0.03 mmol) was conducted according to the procedure for Compound I-1, step 7.

EXAMPLE 11

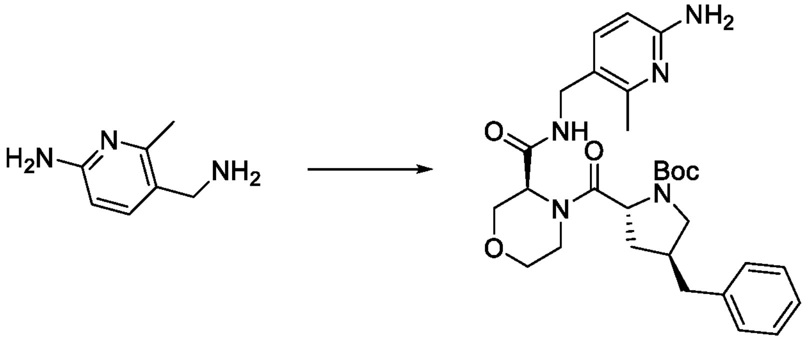
PREPARATION OF (*S*)-*N*-((6-AMINO-2-METHYLPYRIDIN-3-YL)METHYL)-4-((2*R*,4*S*)-4-BENZYLPYRROLIDINE-2-CARBONYL)MORPHOLINE-3-CARBOXAMIDE DI-TRIFLUOROACETATE (COMPOUND I-12)



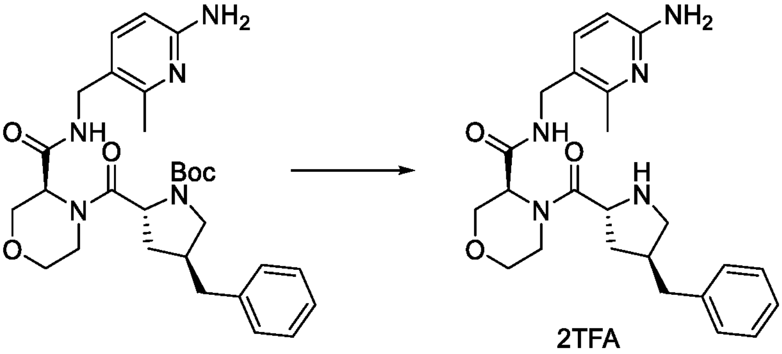
Step 1: Methyl (*S*)-4-((2*R*,4*S*)-4-benzyl-1-(*tert*-butoxycarbonyl)pyrrolidine-2-carbonyl)morpholine-3-carboxylate (68 mg, 58% yield) was synthesized from methyl (S)-morpholine-3-carboxylate according to the procedure for Compound I-9, step 1.



Step 2: To a solution of methyl (*S*)-4-((2*R*,4*S*)-4-benzyl-1-(*tert*-butoxycarbonyl)pyrrolidine-2-carbonyl)morpholine-3-carboxylate (68 mg, 0.16 mmol) in THF (1.5 mL) and H_2O (1.5 mL) was added lithium hydroxide (8 mg, 0.32 mmol). After stirring for 4 h at room temperature, the reaction mixture was concentrated to remove THF. To the above mixture was added 10% $KHSO_4$ solution, extracted with ethyl acetate, dried over anhydrous Na_2SO_4, and concentrated under vacuum to give the crude (*S*)-4-((2*R*,4*S*)-4-benzyl-1-(*tert*-butoxycarbonyl)pyrrolidine-2-carbonyl)morpholine-3-carboxylic acid (66 mg, 100% yield) which was used in the next step without further purification.



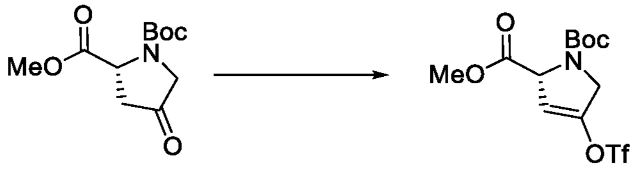
Step 3: *tert*-Butyl (2*R*,4*S*)-2-((*S*)-3-(((6-amino-2-methylpyridin-3-yl)methyl)carbamoyl)morpholine-4-carbonyl)-4-benzylpyrrolidine-1-carboxylate (47 mg, 56% yield for 2 steps) was synthesized from 5-(aminomethyl)-6-methylpyridin-2-amine (28 mg, 0.2 mmol) and ((2*R*,4*S*)-4-benzyl-1-(*tert*-butoxycarbonyl)pyrrolidine-2-carbonyl)-*L*-alanine (66 mg, 0.16 mmol) according to the procedure for Compound I-1, step 6.



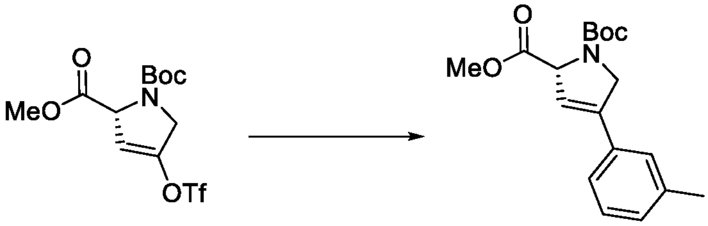
Step 4: Deprotection of *tert*-butyl (2*R*,4*S*)-2-((*S*)-3-(((6-amino-2-methylpyridin-3-yl)methyl)carbamoyl)morpholine-4-carbonyl)-4-benzylpyrrolidine-1-carboxylate (47 mg, 0.09 mmol) was conducted according to the procedure for Compound I-1, step 7.

EXAMPLE 12

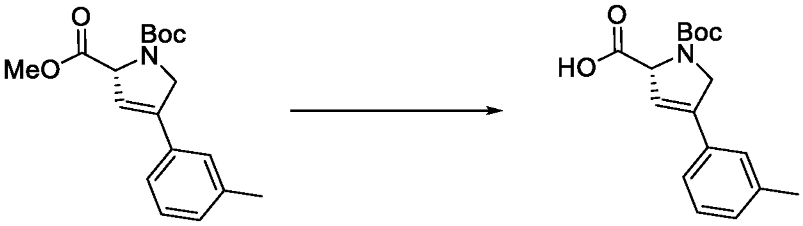
PREPARATION OF (2*R*,4*R*)-*N*-((*S*)-1-((4-CARBAMIMIDOYLBENZYL)AMINO)-1-OXOPROPAN-2-YL)-4-(*M*-TOLYL)PYRROLIDINE-2-CARBOXAMIDE (COMPOUND I-13)



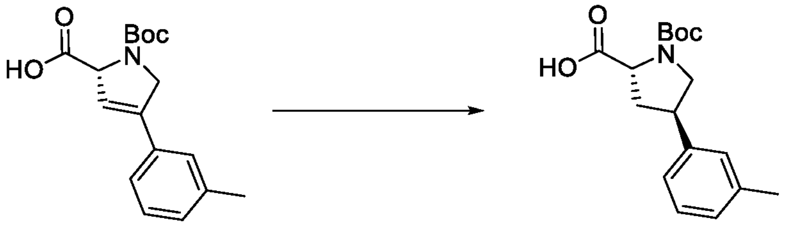
Step 1: To a −78 °C solution of 1-(*tert*-butyl) 2-methyl (*R*)-4-oxopyrrolidine-1,2-dicarboxylate (1.50 g, 6.16 mmol) in THF (15 mL, 0.4 mmol) was slowly added lithium bis(trimethylsilyl)amide (1.0 M in THF, 7.40 mL, 7.40 mmol) under Ar. After stirring for 1 h at the same temperature, Comin's reagent (2.99 g, 7.40 mmol) in THF (5 mL) was added and the stirring continued for an additional 1 h. After stirring for 18 h at −20 °C, the reaction was quenched by addition of 20 mL water and extracted with diethyl ether. The combined extracts were washed with 2 N NaOH solution, dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by chromatography (0-100% ethyl acetate-hexanes) to give 1-(*tert*-butyl) 2-methyl (*R*)-4-(((trifluoromethyl)sulfonyl)oxy)-2,5-dihydro-1*H*-pyrrole-1,2-dicarboxylate (1.85 g, 80% yield).



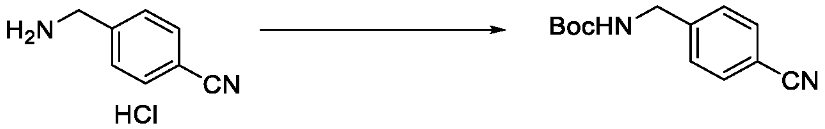
Step 2: To a solution of 1-(*tert*-butyl) 2-methyl (*R*)-4-(((trifluoromethyl)sulfonyl)oxy)-2,5-dihydro-1*H*-pyrrole-1,2-dicarboxylate (400 mg, 1.06 mmol) in dioxane (7 mL, 0.15 mmol) was added $Pd(PPh_3)_4$ (123 mg, 0.11 mmol) and *m*-tolyl boronic acid (215 mg, 1.17 mmol) followed by K_2CO_3 (442 mg, 3.20 mmol) as an aqueous solution (in 1.5 mL water). The mixture was heated to 80 °C and stirred for 30 min by which time the solution had turned from orange to dark black, indicating completion. The reaction mixture was cooled to room temperature and concentrated under vacuum. The residue was diluted with H_2O and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by chromatography (0-100% ethyl acetate-hexanes) to give 1-(*tert*-butyl) 2-methyl (*R*)-4-(*m*-tolyl)-2,5-dihydro-1*H*-pyrrole-1,2-dicarboxylate (330 mg, 86% yield) as a colorless solid.



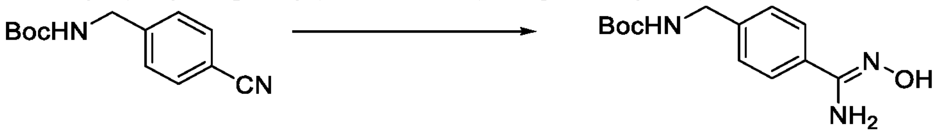
Step 3: To a solution of 1-(*tert*-butyl) 2-methyl (*R*)-4-(*m*-tolyl)-2,5-dihydro-1*H*-pyrrole-1,2-dicarboxylate (317 mg, 1 mmol) in THF (24 mL), MeOH (12 mL), and water (12 mL) was added lithium hydroxide (360 mg, 15 mmol). After stirring for 4 h at room temperature, 12 mL of 1 N HCl was added to the reaction mixture and organic volatiles were removed under vacuum. The aqueous layer was extracted with ethyl acetate. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum to give (*R*)-1-(*tert*-butoxycarbonyl)-4-(*m*-tolyl)-2,5-dihydro-1*H*-pyrrole-2-carboxylic acid (288 mg crude, 95% yield) which was used in the next step without further purification.



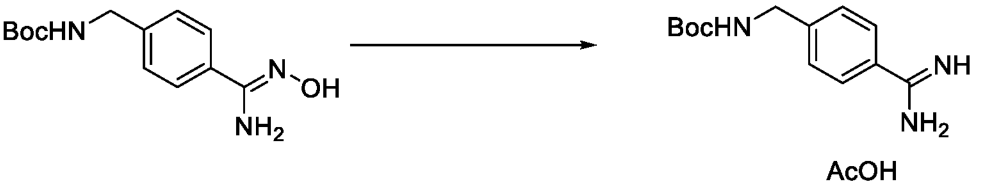
Step 4: To a solution of (*R*)-1-(*tert*-butoxycarbonyl)-4-(*m*-tolyl)-2,5-dihydro-1*H*-pyrrole-2-carboxylic acid (134 mg, 0.44 mmol) in THF (6 mL) and MeOH (6 mL) was added Et_3N (0.06 mL, 0.44 mmol) and chlorotris(triphenylphosphine)rhodium (40 mg, 0.04 mmol) were dissolved in anhydrous THF (15 mL), MeOH (15 mL), and Et_3N (0.13 mL, 0.95 mmol). The mixture was bubbled with argon for 5 minutes and a balloon of H_2 was added and the reaction was monitored for the consumption of starting material for 3 days. The volatiles were evaporated, the residue was diluted with sat. aq $NaHCO_3$ and the pH adjusted to approximately 10 with 1 N NaOH. The mixture was washed with ethyl acetate and the organic layer was washed with sat. aq $NaHCO_3$ and the combined aqueous layers were brought to pH 3-4 using 1 M HCl. The aqueous layer was subsequently back-extracted with ethyl acetate and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum to give (2*R*,4*R*)-1-(*tert*-butoxycarbonyl)-4-(*m*-tolyl)pyrrolidine-2-carboxylic acid (80 mg, 60% yield).



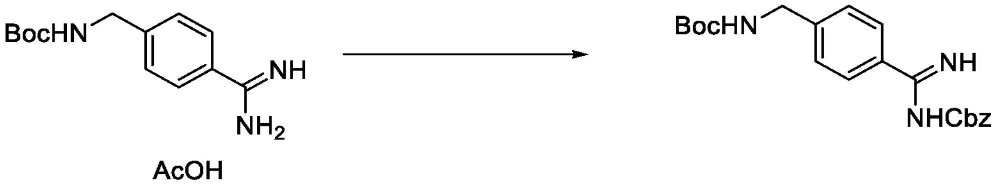
Step 5: A mixture of 4-(aminomethyl)benzonitrile hydrochloride (20.1 g, 119.2 mmol) in acetonitrile (100 mL, 1.19 M) was set under N_2, treated with DIEA (23 mL), and $(Boc)_2O$ (27.5 g, 126 mmol) at room temperature. The reaction was stirred at room temperature overnight. Volatiles was evaporated under reduced pressure. The residue was diluted with ethyl acetate, washed with 10% $KHSO_4$ 2 times, washed with brine, dried over Na_2SO_4, vacuum filtered, and evaporated under reduced pressure to afford *tert*-butyl (4-cyanophenyl)carbamate (27.2g, 98% yield).



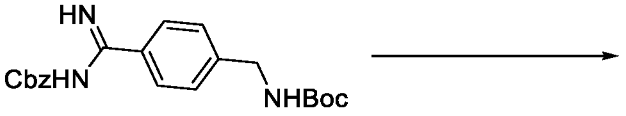
Step 6: A mixture of *tert*-butyl (4-cyanophenyl)carbamate (27.2 g, 117.0 mmol) and hydroxylamine hydrochloride (32.5 g, 468.0 mmol) in MeOH (300 mL, 0.39 M) was set under N_2 and treated with DIEA (82.0 mL, 471.0 mmol). The reaction was heated at 90 °C for 4 h. Volatiles was removed under reduced pressure. The crude product was mixed with water (200 mL). White solid was formed, collected by filtration, washed with water 2 times, and dried to afford *tert*-butyl (*Z*)-(4-(N'-hydroxycarbamimidoyl)benzyl)carbamate (26 g, 84% yield).



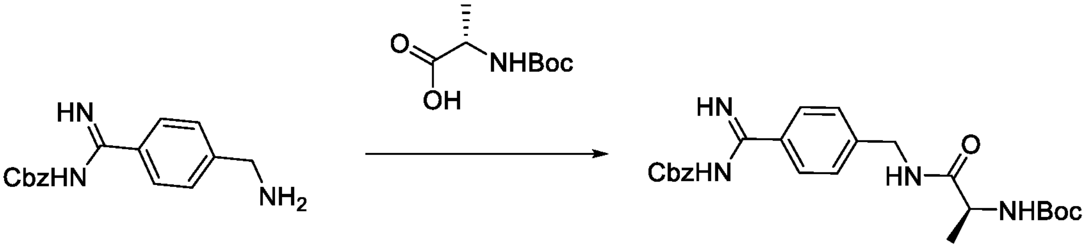
Step 7: A solution of *tert*-butyl (*Z*)-(4-(N'-hydroxycarbamimidoyl)benzyl)carbamate (25.9 g, 97.6 mmol) and acetic anhydride (14.0 mL, 148.0 mmol) in acetic acid (220.0 mL, 0.44 M) was degassed with argon for 3 min. 10% Pd/C (1.45 g) was added. After air was removed and back filled with N_2 5 times, H_2 was introduced from a balloon. The reaction was stirred overnight, filtered through a pad of Celite, and washed with MeOH (50.0 mL) 2 times. Volatiles was evaporated under reduced pressure. The residue was mixed with ether (200 mL) and filtered. The white solid was collected, washed with ether (50 mL) 2 times, and dried to afford *tert*-butyl (4-carbamimidoylbenzyl)carbamate acetate (24.5 g, 81% yield).



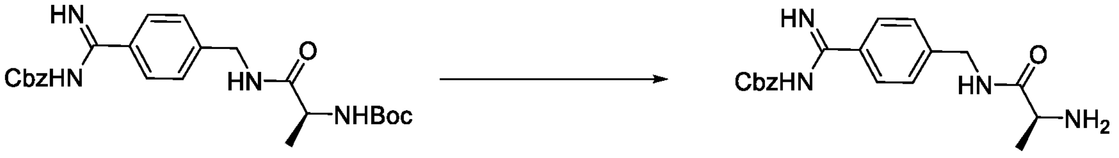
Step 8: A mixture of *tert*-butyl (4-carbamimidoylbenzyl)carbamate acetate (24.5 g, 79.2 mmol) and sat. $NaHCO_3$ solution in THF (220 mL) was treated with CbzCl (12.3 mL, 87.2 mmol) at room temperature. The reaction was stirred overnight and diluted with ethyl acetate. The organic layer was collected, washed with brine, dried over Na_2SO_4, vacuum filtered, and evaporated under reduced pressure. The crude product was dissolved in CH_2Cl_2 and adsorbed onto silica gel. Purification by chromatography (0-100% ethyl acetate-DCM) afforded *tert*-butyl (4-(*N*-((benzyloxy)carbonyl)carbamimidoyl)benzyl)carbamate (18.1 g, 60% yield).



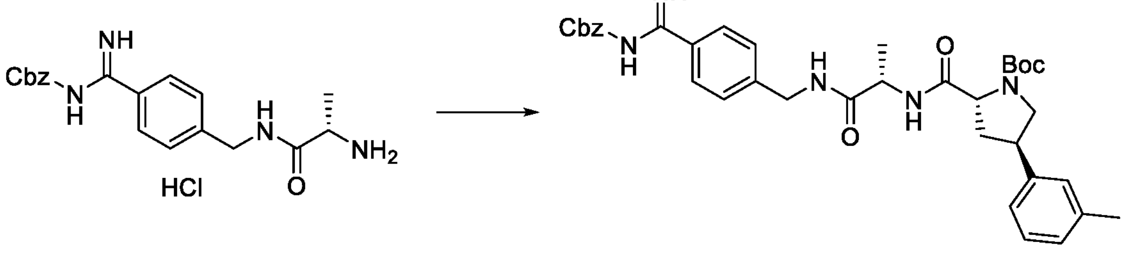
Step 9: To a solution of *tert*-butyl (4-(*N*-((benzyloxy)carbonyl)carbamimidoyl)benzyl)carbamate (4.6 g, 12.0 mmol) in MeOH (20 mL, 0.6 M) was set under N_2 and treated with a solution of HCl in MeOH (30 mL, ca. 10 M) at 0 °C. The reaction was stirred at room temperature overnight. Volatiles were evaporated under reduced pressure to afford the crude benzyl ((4-(aminomethyl)phenyl)(imino)methyl)carbamate hydrochloride. The crude product was dissolved in CH_2Cl_2 and adsorbed onto silica gel. Purification by chromatography (0-10% 7N NH_3 in MeOH-DCM) afforded benzyl ((4-(aminomethyl)phenyl)(imino)methyl)carbamate (2.71 g, 80% yield).



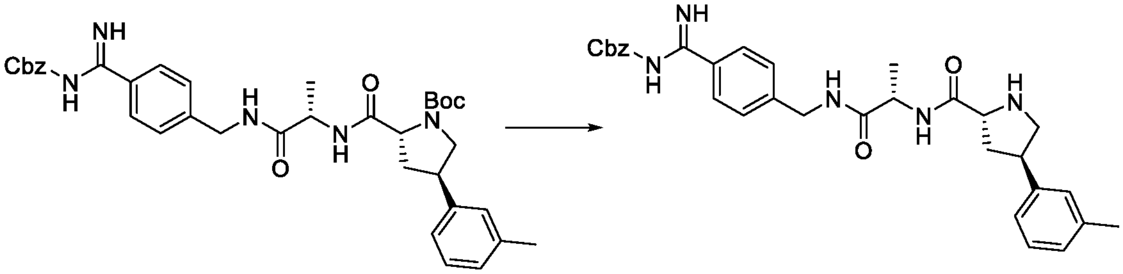
Step 10: Benzyl (*S*)-((4-((2-((*tert*-butoxycarbonyl)amino)propanamido)methyl)phenyl) (imino)methyl)carbamate was synthesized according to the procedure for Compound I-17, step 3.



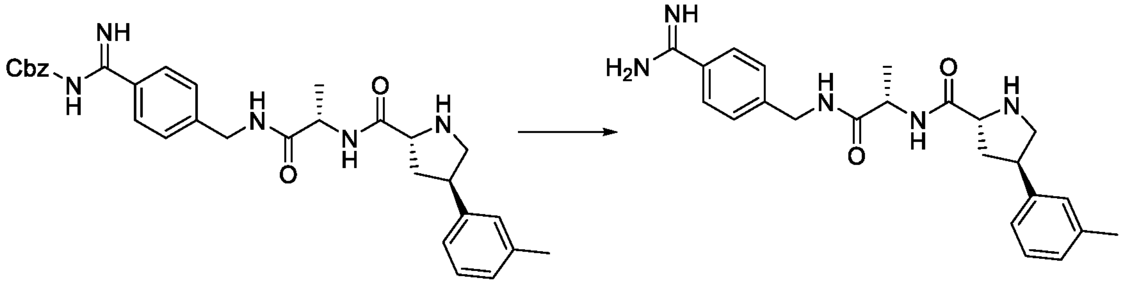
Step 11: Benzyl (*S*)-((4-((2-aminopropanamido)methyl)phenyl)(imino)methyl)carbamate was synthesized according to the procedure for Compound I-17, step 4.



Step 12: *tert*-Butyl (2*R*,4*R*)-2-(((*S*)-1-((4-(*N*-((benzyloxy)carbonyl)carbamimidoyl) benzyl)amino)-1-oxopropan-2-yl)carbamoyl)-4-(*m*-tolyl)pyrrolidine-1-carboxylate (69 mg, 41% yield) and its unknown diastereomer (35 mg, 21% yield) were synthesized from benzyl (*S*)-((4-((2-aminopropanamido)methyl)phenyl)(imino)methyl)carbamate hydrochloride (133 mg, 0.34 mmol) and (2*R*,4*R*)-1-(*tert*-butoxycarbonyl)-4-(*m*-tolyl)pyrrolidine-2-carboxylic acid (80 mg, 0.26 mmol) according to the procedure for Compound I-1, step 6.



Step 13: Deprotection of *tert*-butyl (2*R*,4*R*)-2-(((*S*)-1-((4-(*N*-((benzyloxy)carbonyl)carbamimidoyl)benzyl)amino)-1-oxopropan-2-yl)carbamoyl)-4-(*m*-tolyl)pyrrolidine-1-carboxylate(69 mg, 0.11 mmol) was conducted according to the procedure for Compound I-1, step 7 except that the crude material was purified by chromatography (0-100% [5% 7 N NH_3 in $MeOH/CH_2Cl_2$]-CH_2Cl_2) to give benzyl (imino(4-(((*S*)-2-((2*R*,4*R*)-4-(*m*-tolyl)pyrrolidine-2-carboxamido)propanamido)methyl)phenyl)methyl)carbamate.



Step 14: Deprotection of benzyl (imino(4-(((*S*)-2-((2*R*,4*R*)-4-(*m*-tolyl)pyrrolidine-2-carboxamido)propanamido)methyl)phenyl)methyl)carbamate (63 mg, 0.12 mmol) was conducted according to the procedure for Compound I-1, step 2.

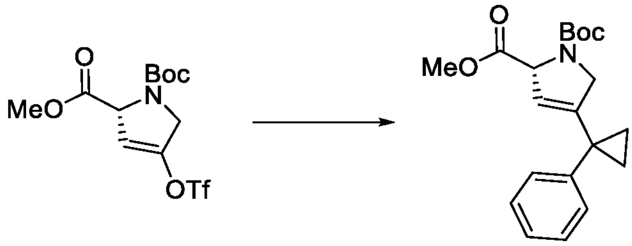
EXAMPLE 13

PREPARATION OF *N*-(1-((4-CARBAMIMIDOYLBENZYL)AMINO)-1-OXOPROPAN-2-YL)-4-(*M*-TOLYL)PYRROLIDINE-2-CARBOXAMIDE (COMPOUND I-14)

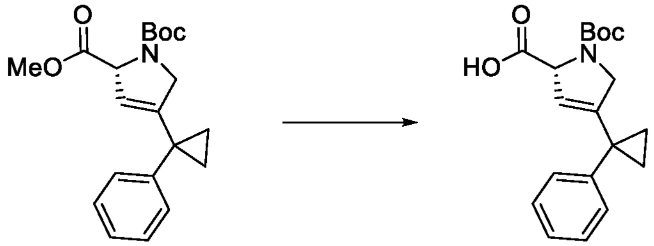
N-(1-((4-Carbamimidoylbenzyl)amino)-1-oxopropan-2-yl)-4-(*m*-tolyl)pyrrolidine-2-carboxamide was synthesized from the diastereomer of *tert*-butyl (2*R*,4*R*)-2-(((*S*)-1-((4-(*N*-((benzyloxy)carbonyl)carbamimidoyl) benzyl)amino)-1-oxopropan-2-yl)carbamoyl)-4-(*m*-tolyl)pyrrolidine-1-carboxylate (prepared in the step 12 of the procedures for Compound I-13) according to the procedures for Compound I-13.

EXAMPLE 14

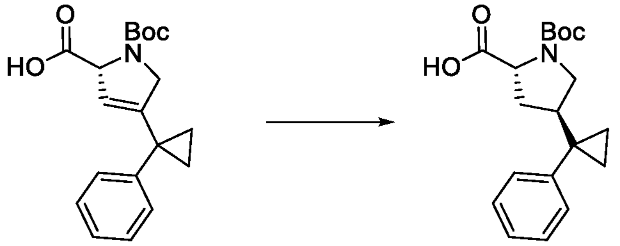
PREPARATION OF (2*R*,4*R*)-*N*-((*S*)-1-(((1*H*-PYRROLO[3,2-C]PYRIDIN-2-YL)METHYL)AMINO)-1-OXOPROPAN-2-YL)-4-(1-PHENYLCYCLOPROPYL)PYRROLIDINE-2-CARBOXAMIDE DI-TRIFLUOROACETATE (COMPOUND I-8)



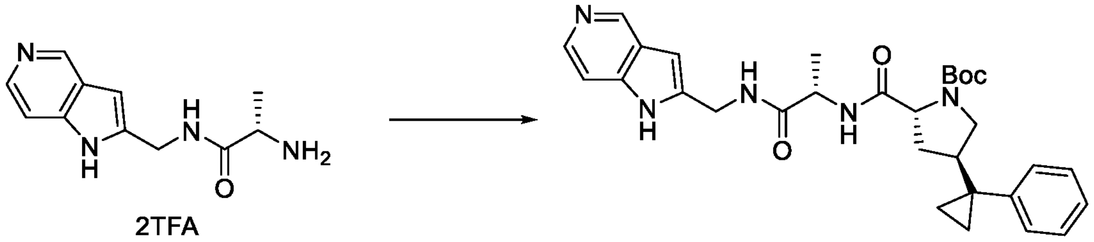
<u>Step 1</u>: To a solution of 1-(*tert*-butyl) 2-methyl (*R*)-4-(((trifluoromethyl)sulfonyl)oxy)-2,5-dihydro-1*H*-pyrrole-1,2-dicarboxylate (400 mg, 1.06 mmol, prepared according to the procedure for Compound I-13, step 1) in toluene (20 mL) and water (2 mL) was added potassium trifluoro(1-phenylcyclopropyl)boranuide (216 mg, 1 mmol), cataCXium® A Pd G3 (30 mg, 0.05 mmol), and Cs_2CO_3 (652 mg, 2 mmol). The resulting mixture was degassed by bubbling N_2 through the solution for 10 min. After stirring for 2 h at 95 °C, the reaction mixture was cooled to room temperature and the catalyst was removed by diatomaceous earth filtration and the solution was concentrated. The residue was purified by chromatography (0-100% ethyl acetate-hexanes) to give 1-(*tert*-butyl) 2-methyl (*R*)-4-(1-phenylcyclopropyl)-2,5-dihydro-1*H*-pyrrole-1,2-dicarboxylate (250 mg, 73% yield) as a colorless solid.



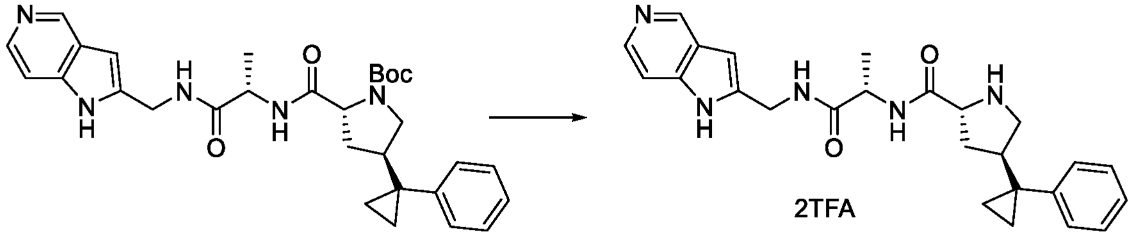
Step 2: (*R*)-1-(*tert*-Butoxycarbonyl)-4-(1-phenylcyclopropyl)-2,5-dihydro-1*H*-pyrrole-2-carboxylic acid (240 mg, 99% yield) was synthesized from 1-(*tert*-butyl) 2-methyl (*R*)-4-(1-phenylcyclopropyl)-2,5-dihydro-1*H*-pyrrole-1,2-dicarboxylate (250 mg, 0.73 mmol) according to the procedure for Compound I-13, step 3.



Step 3: (2*R*,4*R*)-1-(*tert*-Butoxycarbonyl)-4-(1-phenylcyclopropyl)pyrrolidine-2-carboxylic acid (150 mg, 62% yield) was synthesized from (*R*)-1-(*tert*-butoxycarbonyl)-4-(1-phenylcyclopropyl)-2,5-dihydro-1*H*-pyrrole-2-carboxylic acid (240 mg, 0.73 mmol) according to the procedure for Compound I-13, step 4.



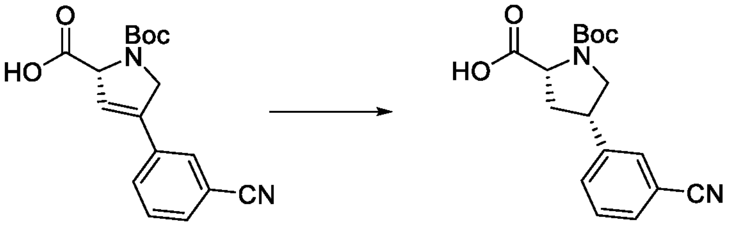
Step 4: *tert*-Butyl (2*R*,4*R*)-2-(((*S*)-1-(((1*H*-pyrrolo[3,2-c]pyridin-2-yl)methyl)amino)-1-oxopropan-2-yl)carbamoyl)-4-(1-phenylcyclopropyl)pyrrolidine-1-carboxylate (39 mg, 61% yield) was synthesized from *tert*-butyl (*S*)-(1-(((1*H*-pyrrolo[3,2-c]pyridin-2-yl)methyl)amino)-1-oxopropan-2-yl)carbamate di-trifluoroacetate (67 mg, 0.14 mmol) and (2*R*,4*R*)-1-(*tert*-butoxycarbonyl)-4-(1-phenylcyclopropyl)pyrrolidine-2-carboxylic acid (40 mg, 0.12 mmol) according to the procedure for Compound I-1, step 1 except that the crude material was purified by chromatography (0-100% [5% 7 N NH_3 in $MeOH/CH_2Cl_2$]-CH_2Cl_2).



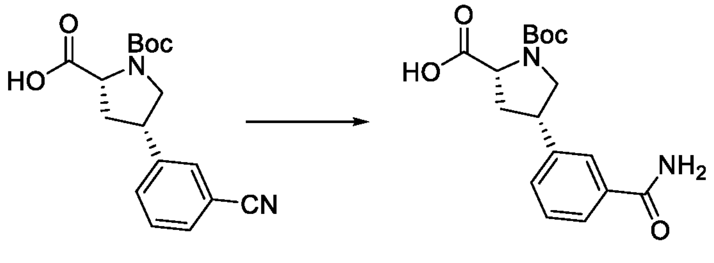
Step 5: Deprotection of *tert*-Butyl (2*R*,4*R*)-2-(((*S*)-1-(((1*H*-pyrrolo[3,2-c]pyridin-2-yl)methyl)amino)-1-oxopropan-2-yl)carbamoyl)-4-(1-phenylcyclopropyl)pyrrolidine-1-carboxylate (39 mg, 0.07 mmol) was conducted according to the procedure for Compound I-1, step 7.

EXAMPLE 15

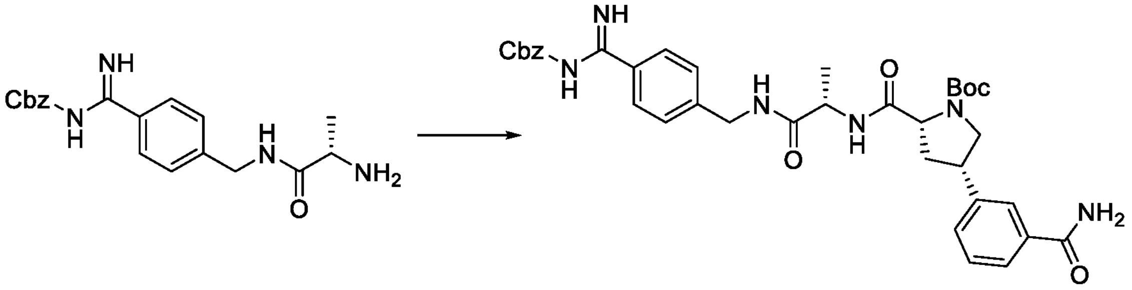
PREPARATION OF (2*R*,4*S*)-*N*-((*S*)-1-((4-CARBAMIMIDOYLBENZYL)AMINO)-1-OXOPROPAN-2-YL)-4-(3-CARBAMOYLPHENYL)PYRROLIDINE-2-CARBOXAMIDE DI-TRIFLUOROACETATE (COMPOUND I-15)



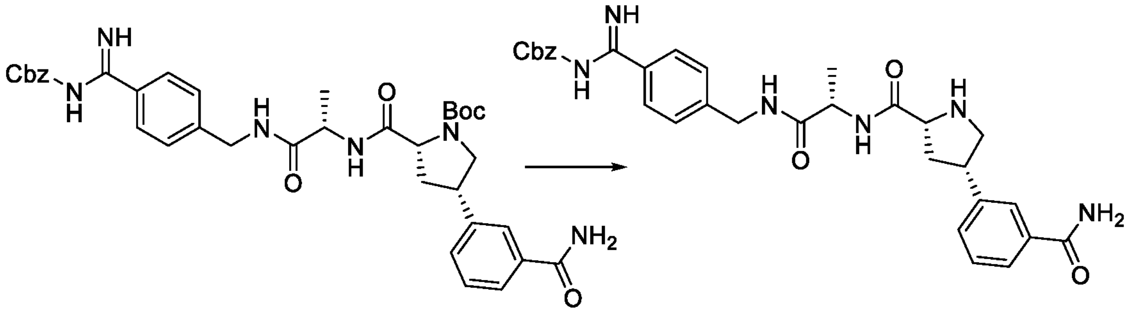
Step 1: A solution of the crude (*R*)-1-(*tert*-butoxycarbonyl)-4-(3-cyanophenyl)-2,5-dihydro-1*H*-pyrrole-2-carboxylic acid (148 mg, 0.47 mmol, prepared according to the procedures for Compound I-13, steps 1-3) in MeOH (10 mL, 0.05 M) was degassed with a stream of Ar for 2 min. 10% Pd/C (10 mg) was added and a vacuum was pulled for 1 min. A balloon of H_2 was added and the reaction was monitored for the consumption of starting material for 16 h. The catalyst was removed by filtration and the solution was evaporated to give (2*R*,4*S*)-1-(*tert*-butoxycarbonyl)-4-(3-cyanophenyl)pyrrolidine-2-carboxylic acid (1.24 g, 100% yield).



Step 2: To a 0 °C solution of (2*R*,4*S*)-1-(*tert*-butoxycarbonyl)-4-(3-cyanophenyl)pyrrolidine-2-carboxylic acid (75 mg, 0.24 mmol) in methanol, was added 30% H_2O_2 (0.08 mL, 0.7 mmol) and 1 N NaOH (0.23 mL). After stirring for 4 h at room temperature, the reaction was quenched by addition of sat. aq Na_2CO_3 at 0 °C. The mixture was washed with ethyl acetate and the organic layer was washed with sat. aq $NaHCO_3$ and the combined aqueous layers were brought to pH 3-4 using 10% $KHSO_4$. The aqueous layer was subsequently back-extracted with ethyl acetate and CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by chromatography (0-100% [5% 7 N NH_3 in MeOH/CH_2Cl_2]-CH_2Cl_2) to give (2*R*,4*S*)-1-(*tert*-butoxycarbonyl)-4-(3-carbamoylphenyl)pyrrolidine-2-carboxylic acid (25 mg, 0.08 mmol).

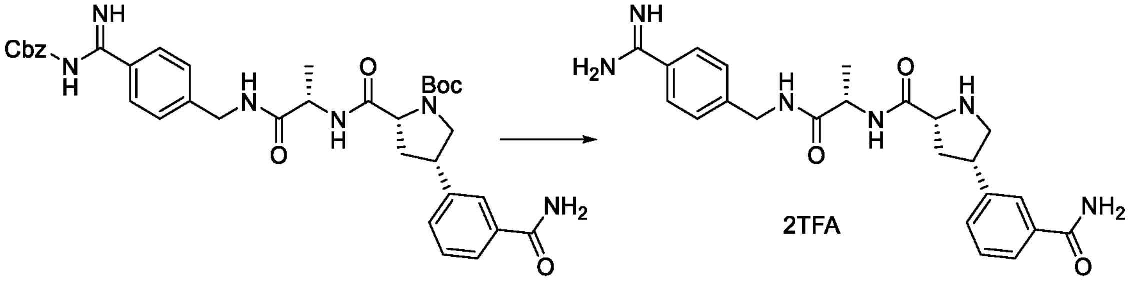


Step 3: *tert*-Butyl (2*R*,4*S*)-2-(((*S*)-1-((4-(*N*-((benzyloxy)carbonyl)carbamimidoyl)benzyl)amino)-1-oxopropan-2-yl)carbamoyl)-4-(3-carbamoylphenyl)pyrrolidine-1-carboxylate (38 mg, 78% yield) was synthesized from benzyl (*S*)-((4-((2-aminopropanamido)methyl)phenyl)(imino) methyl)carbamate (35 mg, 0.1 mmol, prepared according to the procedures for Compound I-13, steps 5-11) and (2*R*,4*S*)-1-(*tert*-butoxycarbonyl)-4-(3-carbamoylphenyl)pyrrolidine-2-carboxylic acid (25 mg, 0.08 mmol) according to the procedure for Compound I-13, step 12.



Step 4: Deprotection of *tert*-butyl (2*R*,4*S*)-2-(((*S*)-1-((4-(*N*-((benzyloxy)carbonyl)carbamimidoyl)benzyl)amino)-1-oxopropan-2-yl)carbamoyl)-4-

(3-carbamoylphenyl)pyrrolidine-1-carboxylate (38 mg, 0.06 mmol) was conducted according to the procedure for Compound I-13, step 13.



Step 5: Deprotection of *tert*-butyl (2*R*,4*S*)-2-(((*S*)-1-((4-(*N*-((benzyloxy)carbonyl) carbamimidoyl)benzyl)amino)-1-oxopropan-2-yl)carbamoyl)-4-(3-carbamoylphenyl)pyrrolidine-1-carboxylate (8 mg, 0.01 mmol) was conducted according to the procedure for Compound I-13, step 14 except that the crude material was purified using reverse-phase HPLC.

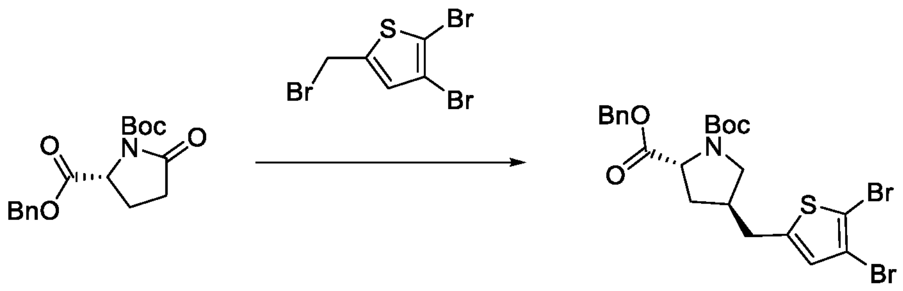
EXAMPLE 16

PREPARATION OF (2*R*,4*R*)-*N*-((*S*)-1-((4-CARBAMIMIDOYLBENZYL)AMINO)-1-OXOPROPAN-2-YL)-4-(3-METHOXYPHENYL)PYRROLIDINE-2-CARBOXAMIDE DIHYDROCHLORIDE (COMPOUND I-16)

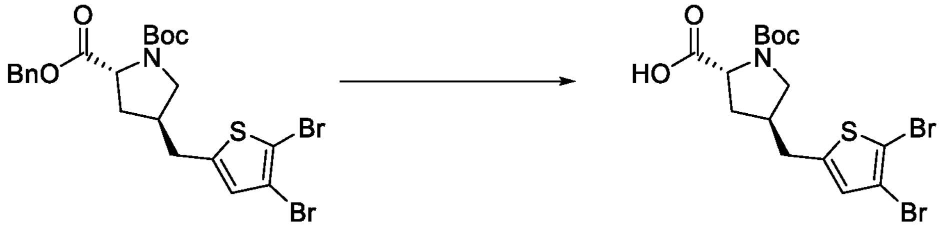
(2*R*,4*R*)-*N*-((*S*)-1-((4-Carbamimidoylbenzyl)amino)-1-oxopropan-2-yl)-4-(3-methoxyphenyl)pyrrolidine-2-carboxamide dihydrochloride was synthesized according to the procedures for Compound I-13 except that the final compound was converted to the hydrochloride salt.

EXAMPLE 17

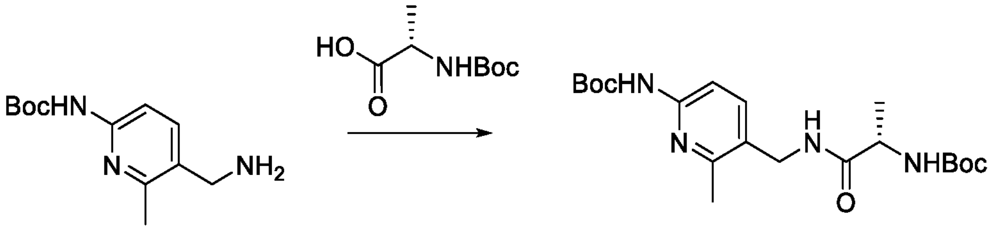
Preparation of (2*R*,4*R*)-*N*-((*S*)-1-(((6-amino-2-methylpyridin-3-yl)methyl)amino)-1-oxopropan-2-yl)-4-((4,5-dibromothiophen-2-yl)methyl)pyrrolidine-2-carboxamide di- trifluoroacetate (Compound I-17)



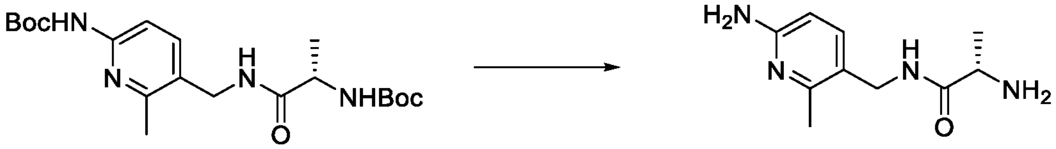
Step 1: 2-Benzyl 1-(*tert*-butyl) (2*R*,4*R*)-4-((4,5-dibromothiophen-2-yl)methyl)pyrrolidine-1,2-dicarboxylate di-trifluoroacetate was synthesized according to the procedures for Compound I-2, steps 1-3.



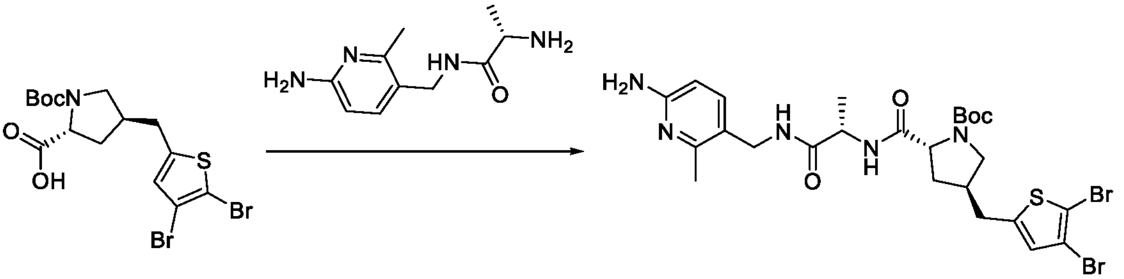
Step 2: To a solution of 2-benzyl 1-(*tert*-butyl) (2*R*,4*R*)-4-((4,5-dibromothiophen-2-yl)methyl)pyrrolidine-1,2-dicarboxylate (87.6 mg, 0.157 mmol) in THF (3.6 mL), MeOH (1.8 mL), and water (1.8 mL) was added lithium hydroxide (56.7 mg, 2.37 mmol). The reaction was stirred at room temp for 16 h, diluted with water, and washed with ethyl acetate. The aqueous layer was collected, acidified with 1 M $KHSO_4$ solution to pH about 3, and extracted 3 times with ethyl acetate. The organic layers were combined, washed with brine, dried over Na_2SO_4, vacuum filtered, and evaporated under reduced pressure to afford the crude (2*R*,4*R*)-1-(*tert*-butoxycarbonyl)-4-((4,5-dibromothiophen-2-yl)methyl)pyrrolidine-2-carboxylic acid.



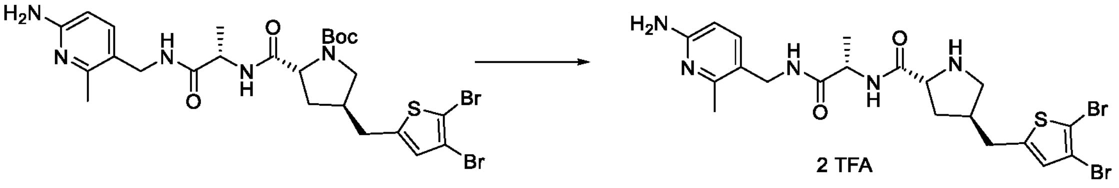
Step 3: To a solution of (*tert*-butoxycarbonyl)-L-alanine (3.4 g, 18.0 mmol) in DCM (300 mL) was added NHS (2.3 g, 20.0 mmol) and DCC (4.0 g, 19.4 mmol). After purging with N_2, the reaction was stirred at room temp for 45 min and *tert*-butyl (5-(aminomethyl)-6-methylpyridin-2-yl)carbamate (4.7 g, 19.8 mmol) was added. The reaction was stirred at room temp for 16 h and evaporated under reduced pressure to dryness. The crude product was dissolved in CH_2Cl_2 and adsorbed onto silica gel. Purification by chromatography (0-10% MeOH-CH_2Cl_2) afforded *tert*-butyl (*S*)-(1-(((6-((*tert*-butoxycarbonyl)amino)-2-methylpyridin-3-yl)methyl)amino)-1-oxopropan-2-yl)carbamate (6.4 g, 87 %).



Step 4: To a solution of *tert*-butyl (*S*)-(1-(((6-((*tert*-butoxycarbonyl)amino)-2-methylpyridin-3-yl)methyl)amino)-1-oxopropan-2-yl)carbamate (6.4 g, 15.7 mmol) in MeOH (30 mL) was added a solution of HCl in MeOH (ca. 10 M) at 0 °C. The reaction was stirred at room temp for 16 h and evaporated under reduced pressure to dryness. The crude product was dissolved in CH_2Cl_2 and adsorbed onto silica gel. Purification by chromatography (0-10% 7 N NH_3 in MeOH-CH_2Cl_2) afforded (*S*)-2-amino-*N*-((6-amino-2-methylpyridin-3-yl)methyl)propenamide (3.0 g, 92% yield).



Step 5: *tert*-Butyl (2*R*,4*R*)-2-(((*S*)-1-(((6-amino-2-methylpyridin-3-yl)methyl)amino)-1-oxopropan-2-yl)carbamoyl)-4-((4,5-dibromothiophen-2-yl)methyl)pyrrolidine-1-carboxylate was synthesized according to the procedure for Compound I-17, step 3.



Step 6: Deprotection of (2*R*,4*R*)-*N*-((*S*)-1-(((6-amino-2-methylpyridin-3-yl)methyl)amino)-1-oxopropan-2-yl)-4-((4,5-dibromothiophen-2-yl)methyl)pyrrolidine-2-carboxamide was synthesized according to the procedure for Compound I-1, step 7.

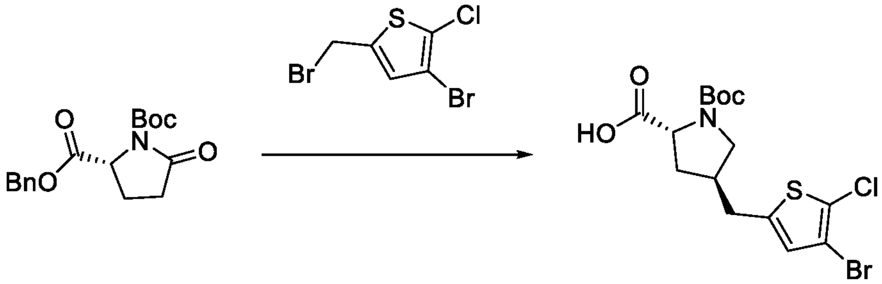
EXAMPLE 18

PREPARATION OF (2*R*,4*R*)-*N*-((*S*)-1-(((6-AMINO-2-METHYLPYRIDIN-3-YL)METHYL)AMINO)-1-OXOPROPAN-2-YL)-4-((4,5-DICHLOROTHIOPHEN-2-YL)METHYL)PYRROLIDINE-2-CARBOXAMIDE DI- TRIFLUOROACETATE (COMPOUND I-18)

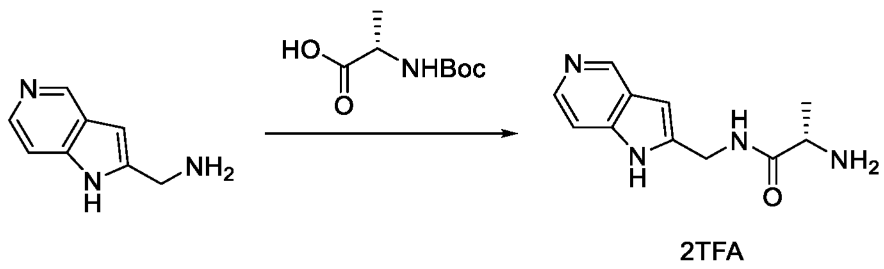
(2*R*,4*R*)-*N*-((*S*)-1-(((6-Amino-2-methylpyridin-3-yl)methyl)amino)-1-oxopropan-2-yl)-4-((4,5-dichlorothiophen-2-yl)methyl)pyrrolidine-2-carboxamide di-trifluoroacetate was synthesized according to the procedures for Compound I-17, steps 1-6.

EXAMPLE 19

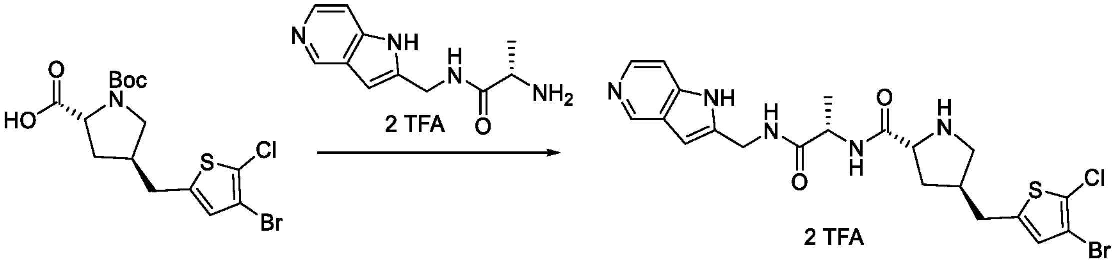
PREPARATION OF (2*R*,4*R*)-*N*-((*S*)-1-(((1*H*-PYRROLO[3,2-C]PYRIDIN-2-YL)METHYL)AMINO)-1-OXOPROPAN-2-YL)-4-((4-BROMO-5-CHLOROTHIOPHEN-2-YL)METHYL)PYRROLIDINE-2-CARBOXAMIDE DI- TRIFLUOROACETATE (COMPOUND I-21)



Step 1: (2*R*,4*R*)-4-((4-Bromo-5-chlorothiophen-2-yl)methyl)-1-(*tert*-butoxycarbonyl)pyrrolidine-2-carboxylic acid was synthesized according to the procedures for Compound I-17, steps 1-2.



Step 2: (*S*)-*N*-((1*H*-Pyrrolo[3,2-c]pyridin-2-yl)methyl)-2-aminopropanamide di-trifluoroacetate was synthesized according to the procedures for Compound I-2, steps 5-6.



Step 3: (2*R*,4*R*)-*N*-((*S*)-1-(((1*H*-Pyrrolo[3,2-c]pyridin-2-yl)methyl)amino)-1-oxopropan-2-yl)-4-((4-bromo-5-chlorothiophen-2-yl)methyl)pyrrolidine-2-carboxamide carboxamide di- trifluoroacetate was synthesized according to the procedures for Compound I-1, steps 6-7 except that the final product was purified using reverse-phase HPLC.

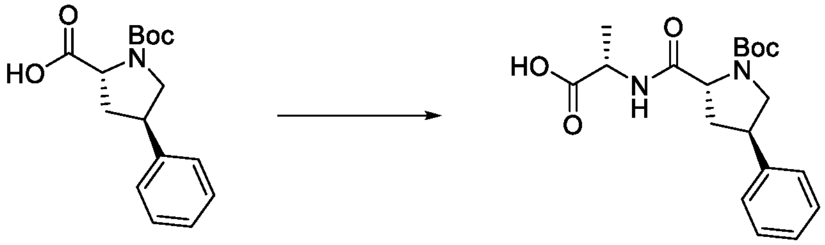
EXAMPLE 20

PREPARATION OF (2*R*,4*R*)-*N*-((*S*)-1-(((1*H*-PYRROLO[3,2-C]PYRIDIN-2-YL)METHYL)AMINO)-1-OXOPROPAN-2-YL)-4-((4,5-DICHLOROTHIOPHEN-2-YL)METHYL)PYRROLIDINE-2-CARBOXAMIDE DI- TRIFLUOROACETATE (COMPOUND I-22)

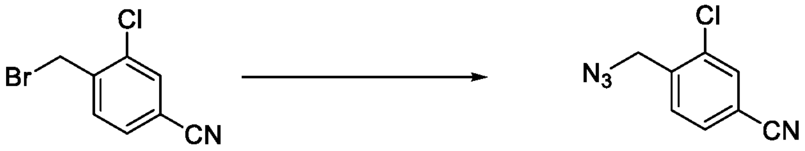
(2*R*,4*R*)-*N*-((*S*)-1-(((1*H*-Pyrrolo[3,2-c]pyridin-2-yl)methyl)amino)-1-oxopropan-2-yl)-4-((4,5-dichlorothiophen-2-yl)methyl)pyrrolidine-2-carboxamide di-trifluoroacetate was synthesized according to the procedures for Compound I-21, steps 1-3.

EXAMPLE 21

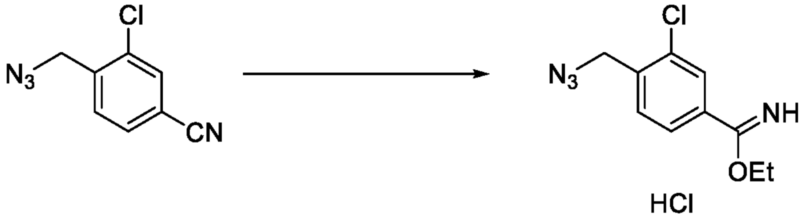
PREPARATION OF (2*R*,4*R*)-*N*-((*S*)-1-((4-CARBAMIMIDOYL-2-CHLOROBENZYL)AMINO)-1-OXOPROPAN-2-YL)-4-PHENYLPYRROLIDINE-2-CARBOXAMIDE DI-TRIFLUOROACETATE (COMPOUND I-24)



Step 1: ((2*R*,4*R*)-1-(*tert*-Butoxycarbonyl)-4-phenylpyrrolidine-2-carbonyl)-*L*-alanine was synthesized according to the procedures for Compound I-1, steps 1-2.

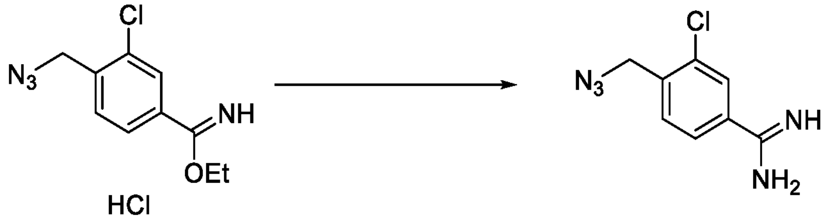


Step 2: To a solution of 4-(bromomethyl)-3-chlorobenzonitrile (4.08 g, 17.7 mmol) in DMF (28 mL) was added NaN_3 (2.3 g, 35.4 mmol). The reaction was set under N_2, stirred at room temperature overnight, and quenched with water. The mixture was extracted with ethyl acetate 3 times. The organic layers were combined, washed with water 3 times, washed with brine, dried over Na_2SO_4, vacuum filtered, and evaporated under reduced pressure. The crude product was dissolved in CH_2Cl_2 and adsorbed onto silica gel. Purification by chromatography (0-40% ethyl acetate-hexanes) afforded 4-(azidomethyl)-3-chlorobenzonitrile (3.61 g, 93% yield).

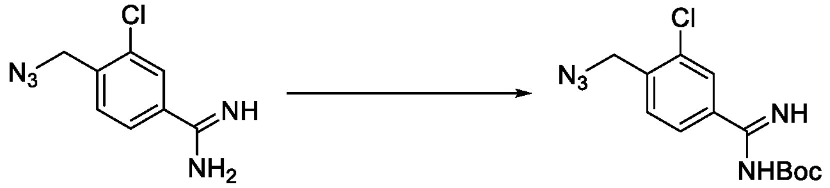


Step 3: A solution of 4-(azidomethyl)-3-chlorobenzonitrile (3.88 g, 20.2 mmol) in EtOH (100 mL) was set under Ar and bubbled with HCl gas at 0 °C for 45 min. The reaction was warmed to room temperature and stirred for 5.5 h. Volatiles was

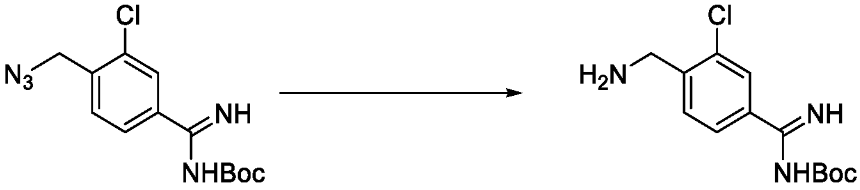
removed under reduced pressure to afford the crude ethyl 4-(azidomethyl)-3-chlorobenzimidate hydrochloride, which was used in the next step.



Step 4: A mixture of the crude ethyl 4-(azidomethyl)-3-chlorobenzimidate hydrochloride in EtOH (75 mL) was set under argon and bubble with NH_3 gas at 0 °C for 10 min. The solution was warmed to room temperature and stirred overnight. Volatiles were removed under reduced pressure to afford the crude 4-(azidomethyl)-3-chlorobenzimidamide, which was used in the next step.

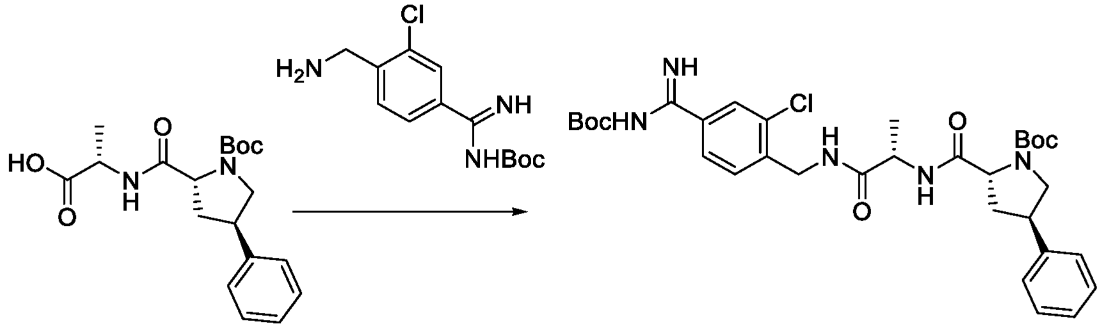


Step 5: To a solution of crude 4-(azidomethyl)-3-chlorobenzimidamide in THF (50 mL) and acetonitrile (25 mL) was added DIEA (7.5 mL, 43.1 mmol) and Boc_2O (4.7 g, 21.5 mmol). The reaction was set under N_2 and stirred at room temperature overnight and concentrated. The residue was dissolved in ethyl acetate. The organic layer was washed with 10% $KHSO_4$ 2 times, washed with brine, dried over Na_2SO_4, vacuum filtered, and evaporated under reduced pressure. The crude product was dissolved in CH_2Cl_2 and adsorbed onto silica gel. Purification by chromatography (0-100% ethyl acetate-hexanes) afforded *tert*-butyl ((4-(azidomethyl)-3-chlorophenyl)(imino)methyl)carbamate (5.5 g, 88% yield over 3 steps).

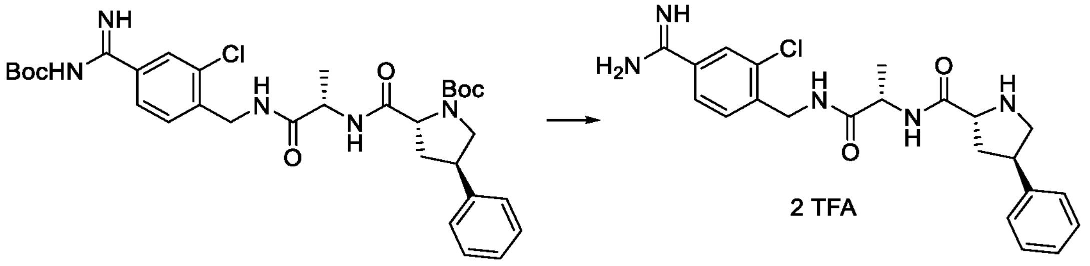


Step 6: To a solution of *tert*-butyl ((4-(azidomethyl)-3-chlorophenyl)(imino)methyl)carbamate (534 mg, 1.72 mmol) in THF (6 mL) and water (0.69 mL) was added PPh_3 (676 mg, 2.58 mmol). The reaction was stirred at room temperature overnight, quenched with 1 M $KHSO_4$ (40 mL), and washed with water 3

times. The ethereal layers were discarded. The pH of the aqueous layer was adjusted to 12 by adding 5 M NaOH solution. The basic aqueous layer was extracted with ethyl acetate 3 times. The organic layers were combined, washed with brine, dried over Na_2SO_4, vacuum filtered, and evaporated under reduced pressure. The crude product was dissolved in CH_2Cl_2 and adsorbed onto silica gel. Purification by chromatography (0-10% 7 N NH_3 in MeOH-CH_2Cl_2) afforded *tert*-butyl ((4-(aminomethyl)-3-chlorophenyl)(imino)methyl)carbamate (309 mg, 63% yield).



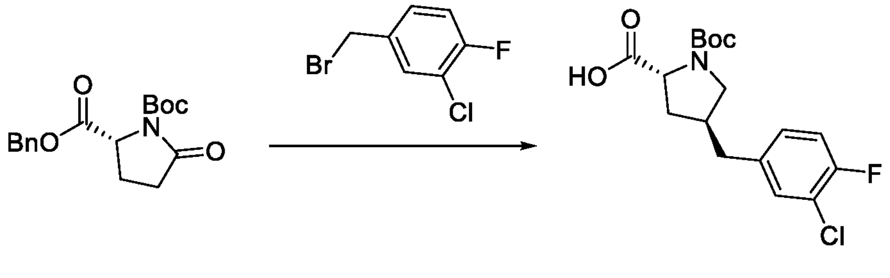
Step 7: *tert*-Butyl (2*R*,4*R*)-2-(((*S*)-1-((4-(*N*-(*tert*-butoxycarbonyl)carbamimidoyl)-2-chlorobenzyl)amino)-1-oxopropan-2-yl)carbamoyl)-4-phenylpyrrolidine-1-carboxylate was synthesized according to the procedure for Compound I-17, step 3.



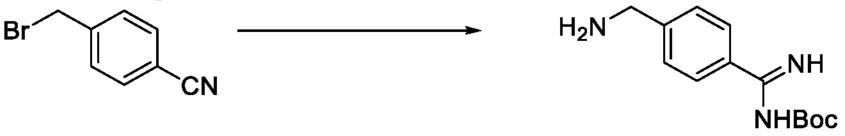
Step 8: To a solution of *tert*-butyl (2*R*,4*R*)-2-(((*S*)-1-((4-(*N*-(*tert*-butoxycarbonyl)carbamimidoyl)-2-chlorobenzyl)amino)-1-oxopropan-2-yl)carbamoyl)-4-phenylpyrrolidine-1-carboxylate (29.2 mg, 0.0442 mmol) in DCM (1 mL) was added TES (50 μL) at room temperature. The reaction was set under N_2 and cooled to 0 °C. TFA (0.5 mL) was added and the reaction was warmed to room temperature and stirred overnight. Volatiles were evaporated under reduced pressure. The residue was purified by reverse phase HPLC to afford (2*R*,4*R*)-*N*-((*S*)-1-((4-carbamimidoyl-2-chlorobenzyl)amino)-1-oxopropan-2-yl)-4-phenylpyrrolidine-2-carboxamide di-trifluoroacetate (11 mg, 37% yield).

EXAMPLE 22

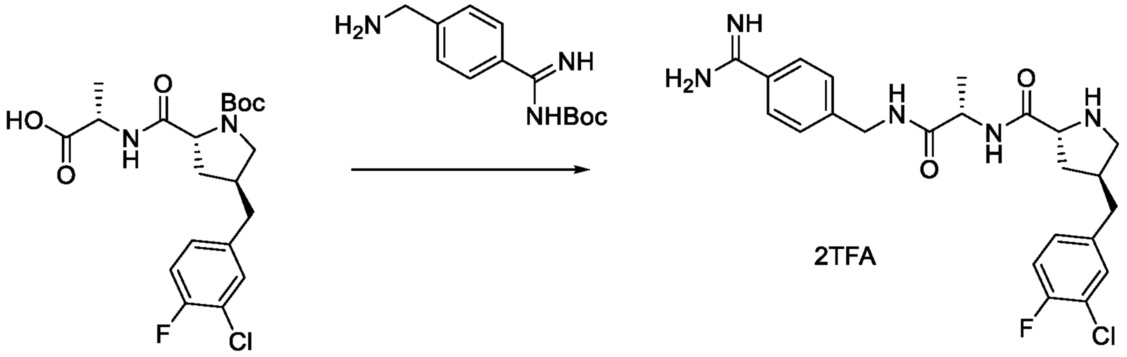
PREPARATION OF (2*R*,4*S*)-*N*-((*S*)-1-((4-CARBAMIMIDOYLBENZYL)AMINO)-1-OXOPROPAN-2-YL)-4-(3-CHLORO-4-FLUOROBENZYL)PYRROLIDINE-2-CARBOXAMIDE DI-TRIFLUOROACETATE (COMPOUND I-23)



Step 1: (2*R*,4*S*)-1-(*tert*-Butoxycarbonyl)-4-(3-chloro-4-fluorobenzyl)pyrrolidine-2-carboxylic acid was synthesized according to the procedures for Compound I-17, steps 1-2.



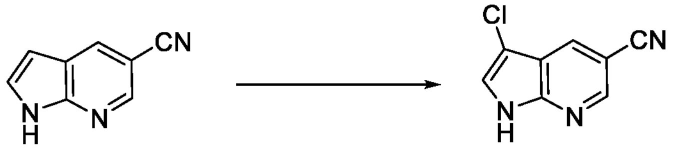
Step 2: *tert*-Butyl ((4-(aminomethyl)phenyl)(imino)methyl)carbamate was synthesized according to the procedures for Compound I-24, steps 2-6.



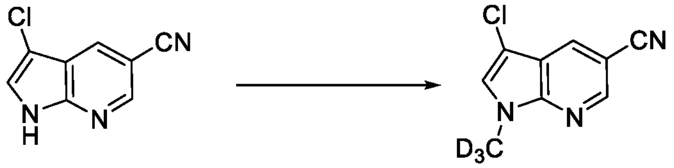
Step 3: (2*R*,4*S*)-*N*-((*S*)-1-((4-Carbamimidoylbenzyl)amino)-1-oxopropan-2-yl)-4-(3-chloro-4-fluorobenzyl)pyrrolidine-2-carboxamide was synthesized according to the procedures for Compound I-24, steps 7-8.

EXAMPLE 23

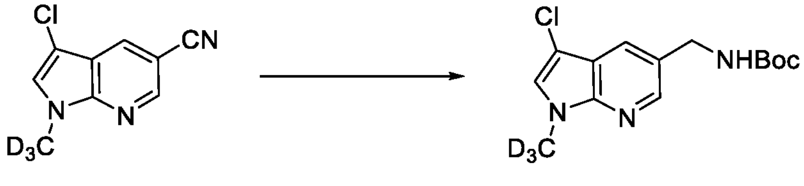
PREPARATION OF (2*R*,4*S*)-4-BENZYL-*N*-((*S*)-1-(((3-CHLORO-1-(METHYL-D3)-1*H*-PYRROLO[2,3-B]PYRIDIN-5-YL)METHYL)AMINO)-1-OXOPROPAN-2-YL)PYRROLIDINE-2-CARBOXAMIDE HYDROCHLORIDE (COMPOUND I-45)



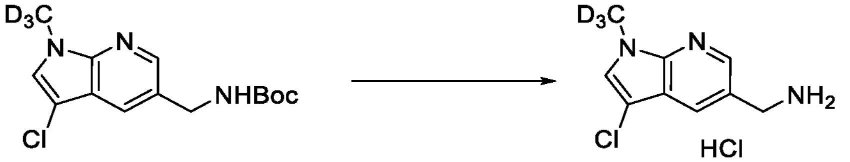
Step 1: To a solution of 1*H*-pyrrolo[2,3-*b*]pyridine-5-carbonitrile (1.04 g, 7.24 mmol) in anhydrous DMF (14 mL) under argon was added NCS (1.06 g, 6.9 mmol). The mixture was heated at 55 °C for 2.5 h, cooled to room temperature, then diluted with H_2O until the final volume was ~90 mL. The mixture was cooled and the solid was isolated by filtration, rinsed with H_2O and dried in a vac oven (at room temperature) to give 3-chloro-1*H*-pyrrolo[2,3-*b*]pyridine-5-carbonitrile (1.2 g, 93% yield).



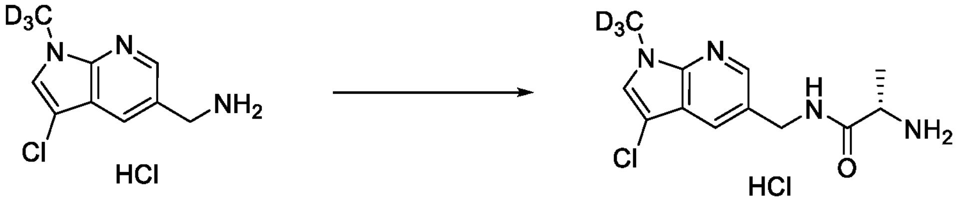
Step 2: A solution of 3-chloro-1*H*-pyrrolo[2,3-*b*]pyridine-5-carbonitrile (215 mg, 1.21 mmol) in dry DMF (7 mL) was added to an ice-cold suspension of NaH (60% in oil; 538 mg, 13.4 mmol) in dry DMF (2 mL) under Ar. After stirring for 30 min at room temperature, the mixture was cooled over an ice bath and iodomethane-d3 (0.22 ml, 3.5 mmol) was added over 5 min. The mixture was slowly warmed to room temperature, stirred 3 h, then cooled over an ice bath. The reaction was quenched with H_2O then ethyl acetate was added. The layers were separated. The aq layer was extracted with ethyl acetate and the combined organics were washed with brine, dried (Na_2SO_4) and concentrated under vacuum. Purification by chromatography (10-35% ethyl acetate-hexanes) gave 3-chloro-1-methyl-1*H*-pyrrolo[2,3-*b*]pyridine-5-carbonitrile (226 mg, 97% yield).



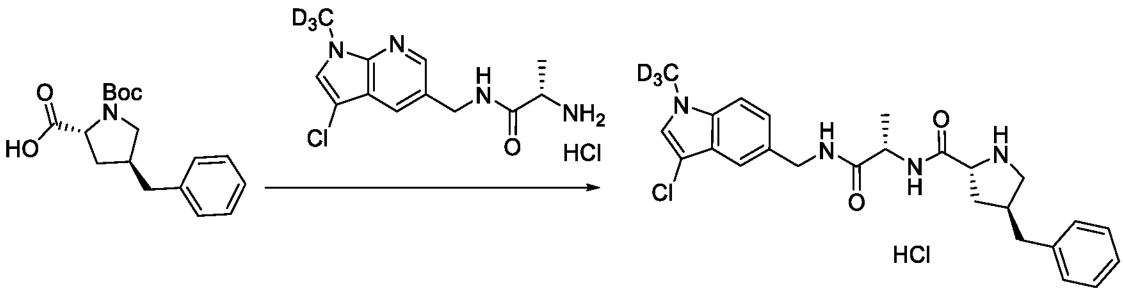
Step 3: To a suspension of 3-chloro-1*H*-pyrrolo[2,3-*b*]pyridine-5-carbonitrile (0.50 g, 2.8 mmol) in MeOH (75 mL) was added di-*tert*-butyl di-carbonate (1.29 g, 5.9 mmol) and $CoCl_2·6H_2O$ (0.36 g, 1.5 mmol). $NaBH_4$ (0.37 g, 9.8 mmol) was added in 4 aliquots over 20 min. The mixture was stirred for 2 h then additional $NaBH_4$ (0.21 g, 5.6 mmol) was added and stirred overnight. The reaction was acidified with 0.5 M $KHSO_4$ until the pH was neutral. Volatiles were removed under vacuum then the aqueous mixture was extracted with 10% MeOH-CH_2Cl_2 twice. The aqueous layer was re-adjusted to neutral pH and extracted with 10% MeOH-CH_2Cl_2. The combined organics were concentrated under vacuum to remove all volatiles and H_2O. Purification by chromatography (two runs: with 0-5% MeOH-CH_2Cl_2 then 0-25% acetone-CH_2Cl_2) gave *tert*-butyl ((3-chloro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)methyl)carbamate (307 mg, 39% yield).



Step 4: To a suspension of *tert*-butyl ((3-chloro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)methyl)carbamate (305 mg, 1.08 mmol) in MeOH (6 mL) was added 3 M HCl-cyclopentyl methyl ether (CPME; 9 mL). The resulting solution was stirred for 2.5 h then additional 3 M HCl-CPME (5 mL) was added. After stirring for 45 min, the solution was concentrated under vacuum. The residue was dissolved in methanol and concentrated under vacuum. The solid was suspended in MeOH-Et_2O and the solid was collected by filtration and air dried to give (3-chloro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)methanamine hydrochloride (285 mg, quant.).



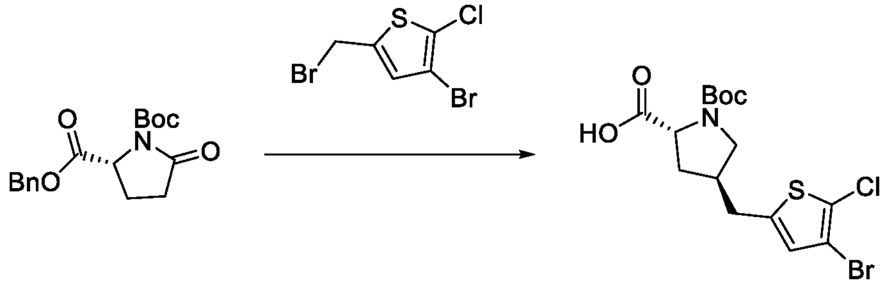
Step 5: (*S*)-2-Amino-*N*-((3-chloro-1-(methyl-d_3)-1*H*-pyrrolo[2,3-b]pyridin-5-yl)methyl)propenamide hydrochloride was synthesized according to the procedures for Compound I-44 steps 4-5.



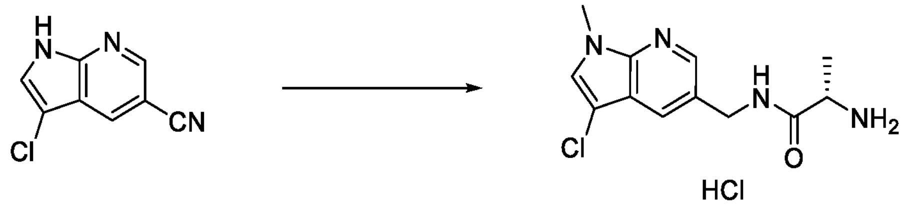
Step 6: (2*R*,4*S*)-4-Benzyl-*N*-((*S*)-1-(((3-chloro-1-(methyl-d3)-1*H*-pyrrolo[2,3-b]pyridin-5-yl)methyl)amino)-1-oxopropan-2-yl)pyrrolidine-2-carboxamide hydrochloride was synthesized according to the procedures for Compound I-44 steps 6-7.

EXAMPLE 24

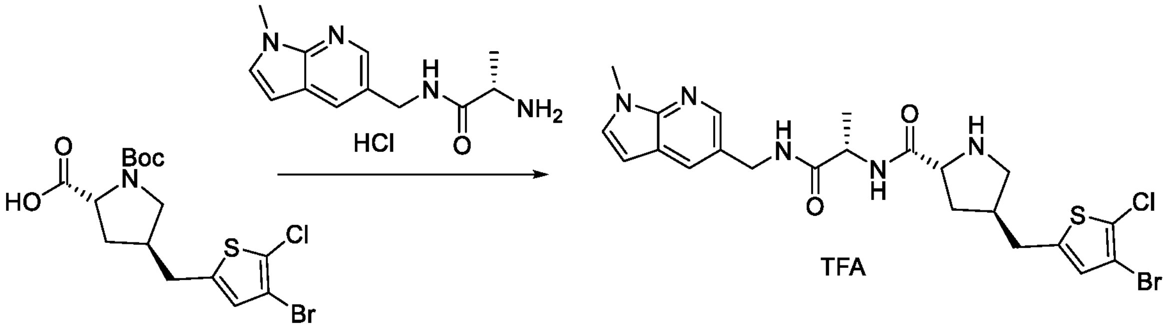
PREPARATION OF (2*R*,4*R*)-4-((4-BROMO-5-CHLOROTHIOPHEN-2-YL)METHYL)-*N*-((*S*)-1-(((3-CHLORO-1-METHYL-1*H*-PYRROLO[2,3-B]PYRIDIN-5-YL)METHYL)AMINO)-1-OXOPROPAN-2-YL)PYRROLIDINE-2-CARBOXAMIDE TRIFLUOROACETATE (COMPOUND I-19)



Step 1: (2*R*,4*R*)-4-((4-Bromo-5-chlorothiophen-2-yl)methyl)-1-(*tert*-butoxycarbonyl)pyrrolidine-2-carboxylic acid was synthesized according to the procedures for Compound I-17, steps 1-2.



Step 2: (*S*)-2-Amino-*N*-((3-chloro-1-methyl-1*H*-pyrrolo[2,3-b]pyridin-5-yl)methyl)propenamide was synthesized according to the procedures for Compound I-45, steps 1-4.



Step 3: (2*R*,4*R*)-4-((4-Bromo-5-chlorothiophen-2-yl)methyl)-*N*-((*S*)-1-(((1-methyl-1*H*-pyrrolo[2,3-b]pyridin-5-yl)methyl)amino)-1-oxopropan-2-yl)pyrrolidine-2-carboxamide trifluoroacetate was synthesized according to the procedures for Compound I-1, steps 6-7 except that the final product was purified using reverse-phase HPLC.

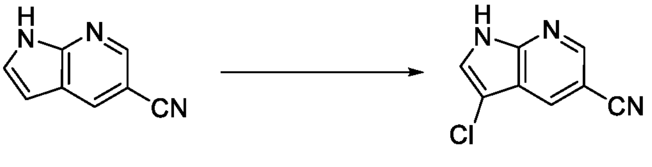
EXAMPLE 25

PREPARATION OF (2*R*,4*R*)-4-((4,5-DICHLOROTHIOPHEN-2-YL)METHYL)-*N*-((*S*)-1-(((1-METHYL-1*H*-PYRROLO[2,3-B]PYRIDIN-5-YL)METHYL)AMINO)-1-OXOPROPAN-2-YL)PYRROLIDINE-2-CARBOXAMIDE TRIFLUOROACETATE (COMPOUND I-20)

(2*R*,4*R*)-4-((4,5-Dichlorothiophen-2-yl)methyl)-*N*-((*S*)-1-(((1-methyl-1*H*-pyrrolo[2,3-b]pyridin-5-yl)methyl)amino)-1-oxopropan-2-yl)pyrrolidine-2-carboxamide trifluoroacetate was synthesized according to the procedures for Compound I-19, steps 1-3.

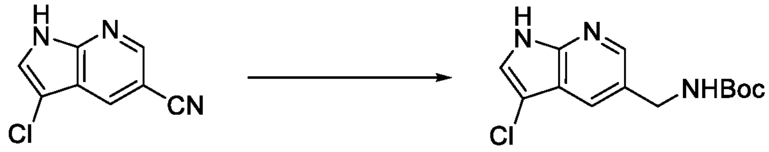
EXAMPLE 26

PREPARATION OF (2*R*,4*S*)-*N*-((*S*)-1-(((3-CHLORO-1*H*-PYRROLO[2,3-B]PYRIDIN-5-YL)METHYL)AMINO)-1-OXOPROPAN-2-YL)-4-(3-CHLORO-4-FLUOROBENZYL)PYRROLIDINE-2-CARBOXAMIDE TRIFLUOROACETATE (COMPOUND I-25)

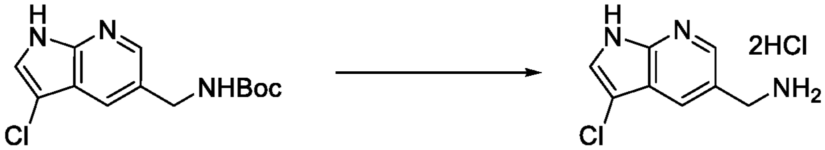


Step 1: To a solution of 1*H*-pyrrolo[2,3-*b*]pyridine-5-carbonitrile (1.04 g, 7.24 mmol) in anhydrous DMF (14 mL) under argon was added N-chlorosuccinimide (1.06 g, 6.9 mmol). The mixture was heated at 55 °C for 2.5 h, cooled to room

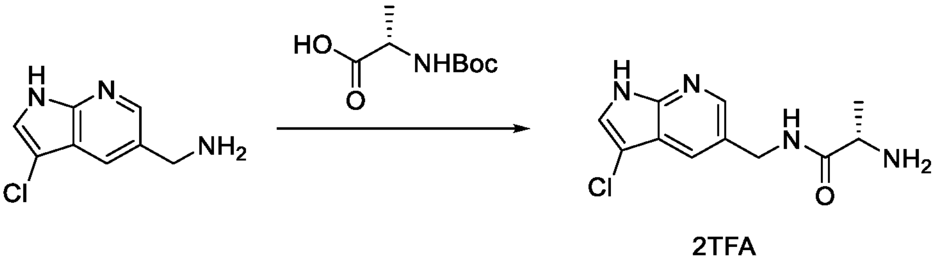
temperature, then diluted with H_2O until the final volume was ~90 mL. The mixture was cooled and the solid was isolated by filtration, rinsed with H_2O and dried in a vac oven (at room temperature) to give 3-chloro-1*H*-pyrrolo[2,3-*b*]pyridine-5-carbonitrile (1.2 g, 93% yield).



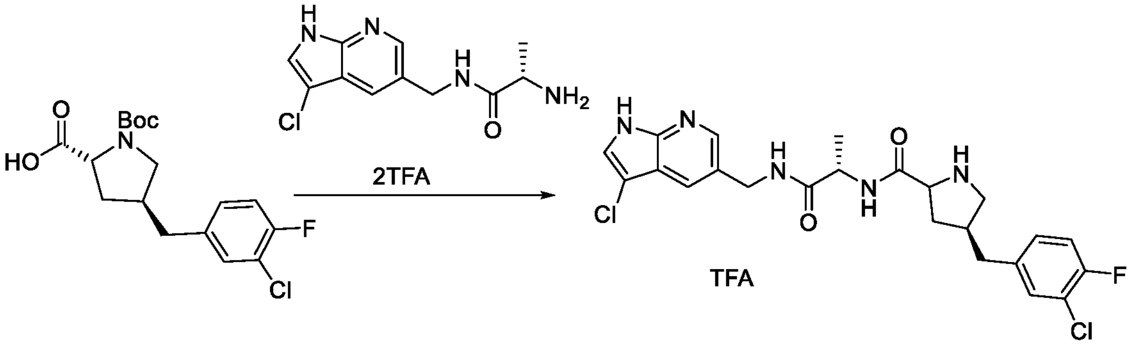
Step 2: To a suspension of 3-chloro-1*H*-pyrrolo[2,3-*b*]pyridine-5-carbonitrile (0.50 g, 2.8 mmol) in MeOH (75 mL) was added di-*tert*-butyl di-carbonate (1.29 g, 5.9 mmol) and $CoCl_2 \cdot 6H_2O$ (0.36 g, 1.5 mmol). $NaBH_4$ (0.37 g, 9.8 mmol) was added in 4 aliquots over 20 min. The mixture was stirred for 2 h then additional $NaBH_4$ (0.21 g, 5.6 mmol) was added and stirred overnight. The reaction was acidified with 0.5 M $KHSO_4$ until the pH was neutral. Volatiles were removed under reduced pressure then the aqueous mixture was extracted with 10% MeOH-CH_2Cl_2 twice. The aqueous layer was re-adjusted to neutral pH and extracted with 10% MeOH-CH_2Cl_2. The combined organics were concentrated under reduced pressure to remove all volatiles and H_2O. Purification by chromatography (two runs: with 0-5% MeOH-CH_2Cl_2 then 0-25% acetone-CH_2Cl_2) gave *tert*-butyl ((3-chloro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)methyl)carbamate (307 mg, 39% yield).



Step 3: To a suspension of *tert*-butyl ((3-chloro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)methyl)carbamate (305 mg, 1.08 mmol) in MeOH (6 mL) was added 3 M HCl-CPME (9 mL). The resulting solution was stirred for 2.5 h then additional 3 M HCl-CPME (5 mL) was added. After stirring for 45 min, the solution was conc under reduced pressure. The residue was dissolved in MeOH and concentrated under reduced pressure. The solid was suspended in MeOH-Et_2O and the solid was collected by filtration and air dried to give (3-chloro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)methanamine dihydrochloride (285 mg, quant. yield).



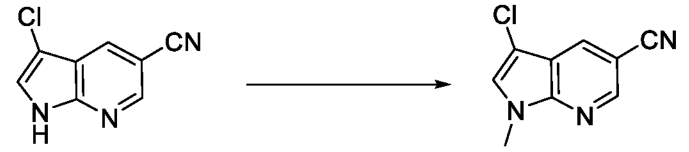
Step 4: (*S*)-2-amino-*N*-((3-chloro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)methyl)propenamide di-trifluoroacetate was synthesized according to the procedures for Compound I-2, steps 5-6



Step 5: (4*S*)-*N*-((*S*)-1-(((3-chloro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)methyl)amino)-1-oxopropan-2-yl)-4-(3-chloro-4-fluorobenzyl)pyrrolidine-2-carboxamide trifluoroacetate was synthesized according to the procedures for Compound I-1, steps 6-7.

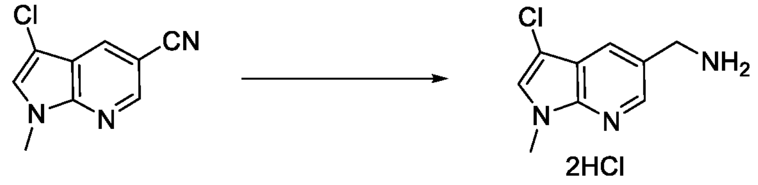
EXAMPLE 27

PREPARATION OF (2*R*,4*S*)-*N*-((*S*)-1-(((3-CHLORO-1-METHYL-1*H*-PYRROLO[2,3-B]PYRIDIN-5-YL)METHYL)AMINO)-1-OXOPROPAN-2-YL)-4-(3-CHLORO-4-FLUOROBENZYL)-1-ETHYLPYRROLIDINE-2-CARBOXAMIDE (COMPOUND I-26)

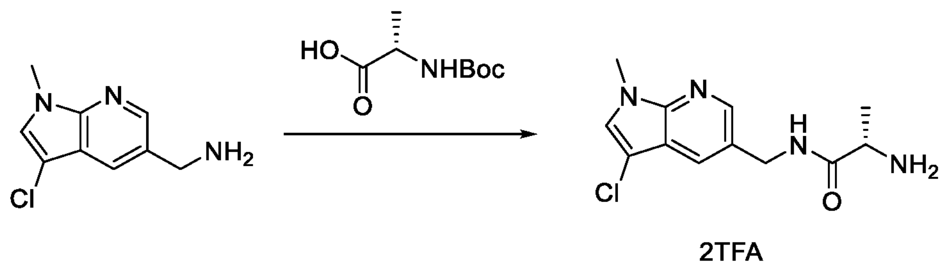


Step 1: A solution of 3-chloro-1*H*-pyrrolo[2,3-*b*]pyridine-5-carbonitrile (215 mg, 1.21 mmol, prepared according to the procedures for Compound I-61) in anhydrous DMF (7 mL) was added to an ice-cold suspension of NaH (60% in oil, 538 mg, 13.4 mmol) in anhydrous DMF (2 mL) under Ar. After stirring for 30 min at room temperature, the mixture was cooled over an ice bath and iodomethane (0.22 µl, 3.5

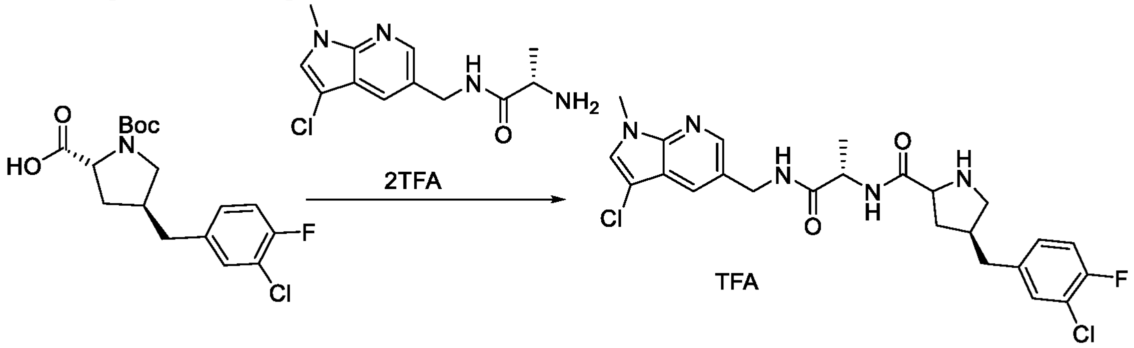
mmol) was added over 5 min. The mixture was slowly warmed to room temperature, stirred for 3 h, then cooled over an ice bath. The reaction was quenched with H_2O then ethyl acetate was added. The layers were separated. The aqueous layer was extracted with ethyl acetate and the combined organics were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by chromatography (10-35% ethyl acetate-hexanes) gave 3-chloro-1-methyl-1*H*-pyrrolo[2,3-*b*]pyridine-5-carbonitrile (226 mg, 97% yield).



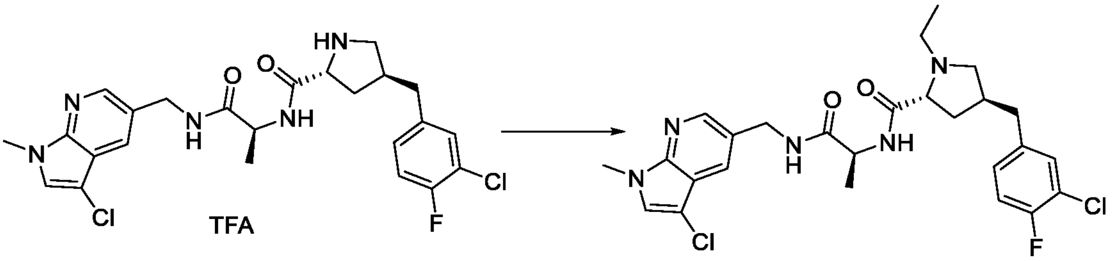
Steps 2-3: 3-Chloro-1-methyl-1*H*-pyrrolo[2,3-*b*]pyridine-5-carbonitrile was reduced using the two-step procedure described for Compound I-25, step 2-3 to give (3-chloro-1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)methanamine dihydrochloride (75 mg, 54% for two steps).



Step 4: (*S*)-2-amino-*N*-((3-chloro-1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)methyl)propenamide di-trifluoroacetate was synthesized according to the procedures for Compound I-2, steps 5-6.



Step 5: (4*S*)-*N*-((*S*)-1-(((3-chloro-1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)methyl)amino)-1-oxopropan-2-yl)-4-(3-chloro-4-fluorobenzyl)pyrrolidine-2-carboxamide trifluoroacetate was synthesized according to the procedures for Compound I-1, steps 6-7.



Step 6: To a stirred solution of (2*R*,4*S*)-*N*-((*S*)-1-(((3-chloro-1-methyl-1*H*-pyrrolo[2,3-b]pyridin-5-yl)methyl)amino)-1-oxopropan-2-yl)-4-(3-chloro-4-fluorobenzyl)pyrrolidine-2-carboxamide trifluoroacetate (35 mg, 0.048 mmol) in DCM (1 mL) and Et_3N (0.1 mL) was added ethyl bromide (0.017 ml, 0.24 mmol) under Argon atmosphere. After stirring for 18 h at room temperature, the reaction mixture was concentrated and purified on an amine-column using 100% ethyl acetate as the mobile phase to yield (2*R*,4*S*)-*N*-((*S*)-1-(((3-chloro-1-methyl-1*H*-pyrrolo[2,3-b]pyridin-5-yl)methyl)amino)-1-oxopropan-2-yl)-4-(3-chloro-4-fluorobenzyl)-1-ethylpyrrolidine-2-carboxamide (12 mg, 47%).

EXAMPLE 28

PREPARATION OF (2*R*,4*S*)-*N*-((*S*)-1-(((3-CHLORO-1*H*-PYRROLO[2,3-B]PYRIDIN-5-YL)METHYL)AMINO)-1-OXOPROPAN-2-YL)-4-(3-CHLORO-4-FLUOROBENZYL)-1-ETHYLPYRROLIDINE-2-CARBOXAMIDE (COMPOUND I-27)

(2*R*,4*S*)-*N*-((*S*)-1-(((3-Chloro-1*H*-pyrrolo[2,3-b]pyridin-5-yl)methyl)amino)-1-oxopropan-2-yl)-4-(3-chloro-4-fluorobenzyl)-1-ethylpyrrolidine-2-carboxamide was synthesized according to the procedures for Compound I-26.

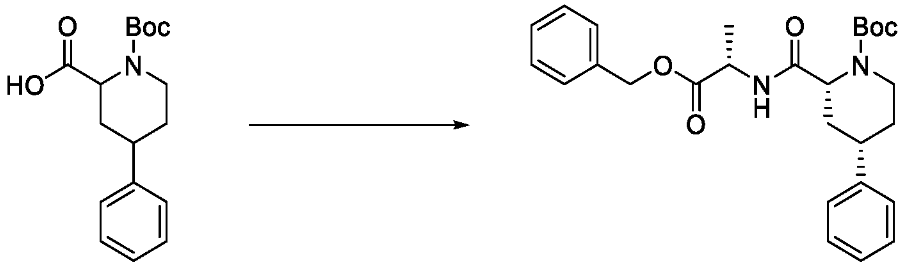
EXAMPLE 29

PREPARATION OF (2*R*,4*S*)-4-BENZYL-*N*-((*S*)-1-(((1-METHYL-1*H*-BENZO[D]IMIDAZOL-5-YL)METHYL)AMINO)-1-OXOPROPAN-2-YL)PYRROLIDINE-2-CARBOXAMIDE TRIFLUOROACETATE (COMPOUND I-30)

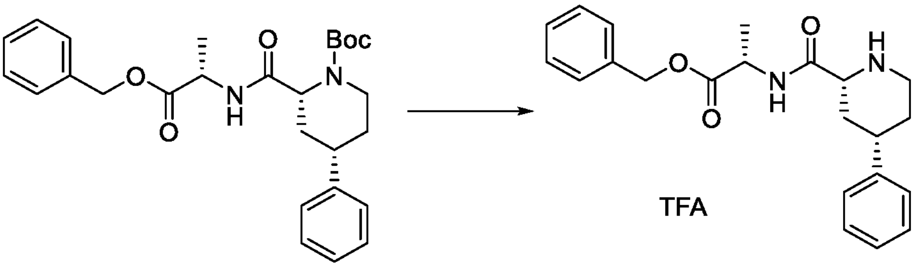
(2*R*,4*S*)-4-Benzyl-*N*-((*S*)-1-(((1-methyl-1*H*-benzo[d]imidazol-5-yl)methyl)amino)-1-oxopropan-2-yl)pyrrolidine-2-carboxamide trifluoroacetate was synthesized according to the procedures for Compound I-10 using commercially available (1-methyl-1*H*-benzo[*d*]imidazol-5-yl)methanamine.

EXAMPLE 30

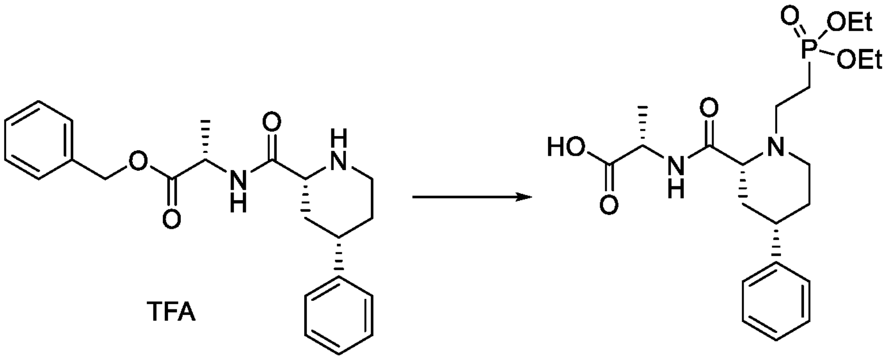
PREPARATION OF (2-((2*R*,4*S*)-2-(((*S*)-1-(((1*H*-PYRROLO[3,2-C]PYRIDIN-2-YL)METHYL)AMINO)-1-OXOPROPAN-2-YL)CARBAMOYL)-4-PHENYLPIPERIDIN-1-YL)ETHYL)PHOSPHONIC ACID DI-TRIFLUOROACETATE (COMPOUND I-39)



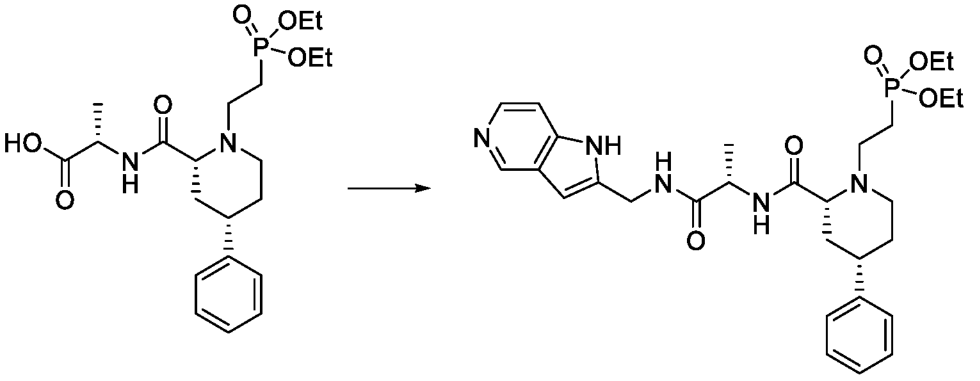
Step 1: To a solution of *(2R,4S)*-1-(*tert*-butoxycarbonyl)-4-phenylpiperidine-2-carboxylic acid (4.5 g, 14.7 mmol) in DMF (35 mL, 0.42 M) was added HOBt (2.2 g, 16.2 mmol), DIEA (3 mL), and EDC (3.1 g, 16.2 mmol). After stirring for 30 min at room temperature, benzyl *L*-alanine hydrochloride (3.5 g, 16.2 mmol) was added and stirred for 16 h. The reaction mixture was concentrated under vacuum and the residue was partitioned with ethyl acetate and 10% $KHSO_4$ solution. The organic layer was separated and washed with H_2O and sat. aq $NaHCO_3$. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by chromatography (0-20% ethyl acetate-hexanes; the 3rd UV-active material eluting from the column) to give *tert*-butyl *(2R,4S)*-2-((*(S)*-1-(benzyloxy)-1-oxopropan-2-yl)carbamoyl)-4-phenylpiperidine-1-carboxylate (2.59 g, 34% yield).



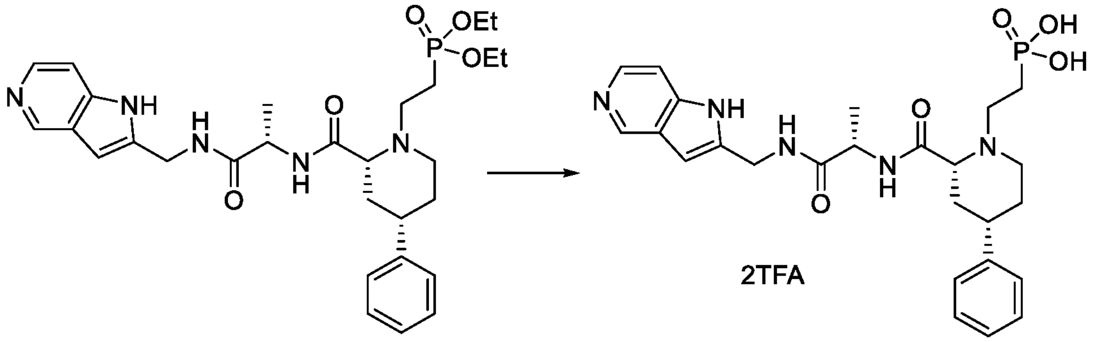
Step 2: To a stirred solution of *tert*-butyl *(2R,4S)*-2-((*(S)*-1-(benzyloxy)-1-oxopropan-2-yl)carbamoyl)-4-phenylpiperidine-1-carboxylate (200 mg, 0.43 mmol) in DCM (2 mL) was added TFA (1 mL) and stirred at room temperature for 1 h. The reaction was concentrated under vacuum to yield benzyl ((2*R*,4*S*)-4-phenylpiperidine-2-carbonyl)-*L*-alaninate trifluoroacetate (201 mg, 100% yield)



Step 3: To (2*R*,4*S*)-4-phenylpiperidine-2-carbonyl)-*L*-alaninate trifluoroacetate (70 mg, 0.15 mmol) dissolved in DMF (2 mL) was added K_2CO_3 (100 mg, 0.72 mmol) and stirred for 30 min. To the above mixture, diethyl (2-bromoethyl)phosphonate (0.2 mL) was added and stirred at 50 °C for 2 h. The reaction was monitored by LCMS. The crude reaction mixture was quenched with water and extracted with ethyl acetate (2 × 20 mL). The crude product was dissolved in MeOH and charged with 10% Pd/C (7 mg) under argon. The reaction was stirred under H_2 atmosphere for 1 h. The crude reaction mixture was filtered over Celite washed with methanol and concentrated under vacuum to yield ((2*R*,4*S*)-1-(2-(diethoxyphosphoryl)ethyl)-4-phenylpiperidine-2-carbonyl)-*L*-alanine. The crude material was used in the next reaction without further purification.



Step 4: To a stirred solution of (2*R*,4*S*)-1-(2-(diethoxyphosphoryl)ethyl)-4-phenylpiperidine-2-carbonyl)-*L*-alanine (50 mg, 0.11 mmol) in DCM (5 mL) was added NHS (13 mg, 0.11 mmol) with stirring at room temperature until dissolved. DCC (23 mg, 0.11 mmol) was added and stirred for 1 h then 1*H*-pyrrolo[3,2-c]pyridin-2-yl)methanamine (32 mg, 0.22 mmol) was added with sonication and stirred overnight at room temperature. The solution was filtered and evaporated to dryness. Flash chromatography on an amine column gave diethyl (2-((2*R*,4*S*)-2-(((*S*)-1-(((1*H*-pyrrolo[3,2-c]pyridin-2-yl)methyl)amino)-1-oxopropan-2-yl)carbamoyl)-4-phenylpiperidin-1-yl)ethyl)phosphonate (70 mg, 82% yield over two steps) as a white solid.

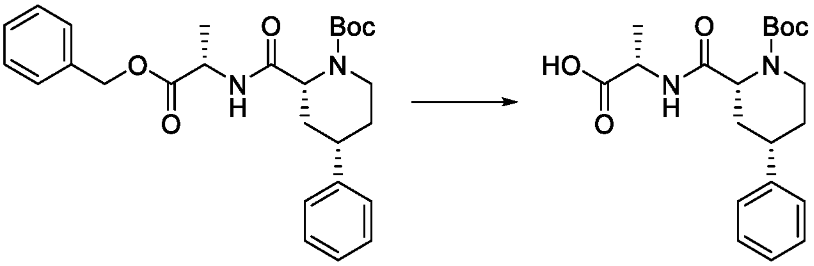


Step 5: To a stirred solution diethyl (2-((2*R*,4*S*)-2-(((*S*)-1-(((1*H*-pyrrolo[3,2-c]pyridin-2-yl)methyl)amino)-1-oxopropan-2-yl)carbamoyl)-4-phenylpiperidin-1-yl)ethyl)phosphonate (70 mg, 0.12 mmol) in DCM was added TMSBr (1 mL) and stirred at 40 °C for 3 h. The reaction was monitored by TLC then slowly quenched with MeOH (2 mL) at 0 °C. The solvent was evaporated under vacuum and resuspended in MeOH and was purified by HPLC to yield (2-((2*R*,4*S*)-2-(((*S*)-1-(((1*H*-

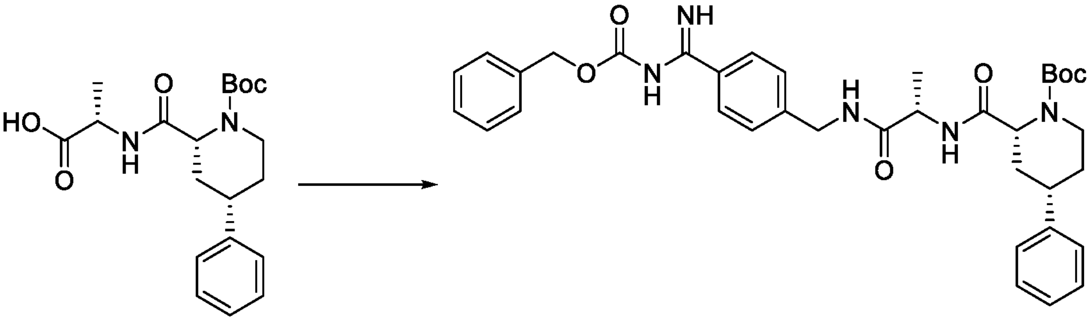
pyrrolo[3,2-c]pyridin-2-yl)methyl)amino)-1-oxopropan-2-yl)carbamoyl)-4-phenylpiperidin-1-yl)ethyl)phosphonic acid di-trifluoroacetate (71 mg, 80% yield) as a white solid.

EXAMPLE 31

PREPARATION OF ETHYL 3-((2*R*,4*S*)-2-(((*S*)-1-((4-CARBAMIMIDOYLBENZYL)AMINO)-1-OXOPROPAN-2-YL)CARBAMOYL)-4-PHENYLPIPERIDIN-1-YL)PROPANOATE (COMPOUND I-31)

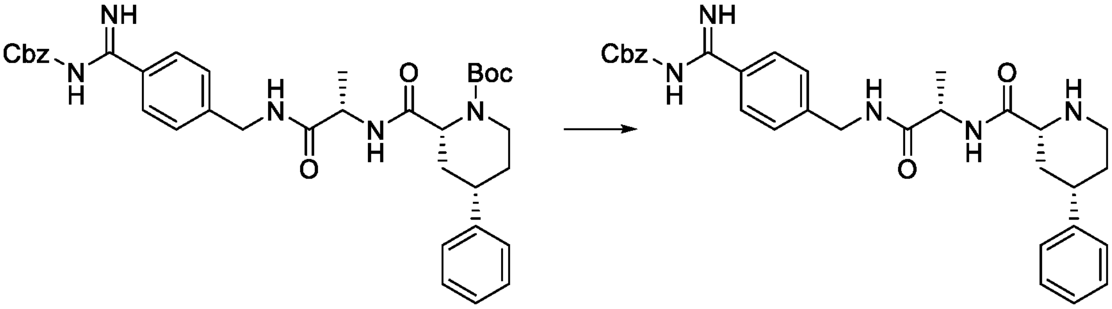


Step 1: A solution of *tert*-butyl *(2R,4S)*-2-((*(S)*-1-(benzyloxy)-1-oxopropan-2-yl)carbamoyl)-4-phenylpiperidine-1-carboxylate (2.59 g, 5.54 mmol) (prepared according to the procedure for Compound I-39, step 1) was degassed with a stream of argon for 2 min. 10% Pd/C (130 mg) was added and a vacuum was pulled for 1 min. A balloon of H_2 was added and the reaction was monitored for the consumption of starting material for 1.5 h. The catalyst was removed by filtration and the solution was evaporated to give (*(2R,4S)*-1-(*tert*-butoxycarbonyl)-4-phenylpiperidine-2-carbonyl)-*L*-alanine (1.8 g, 86%).

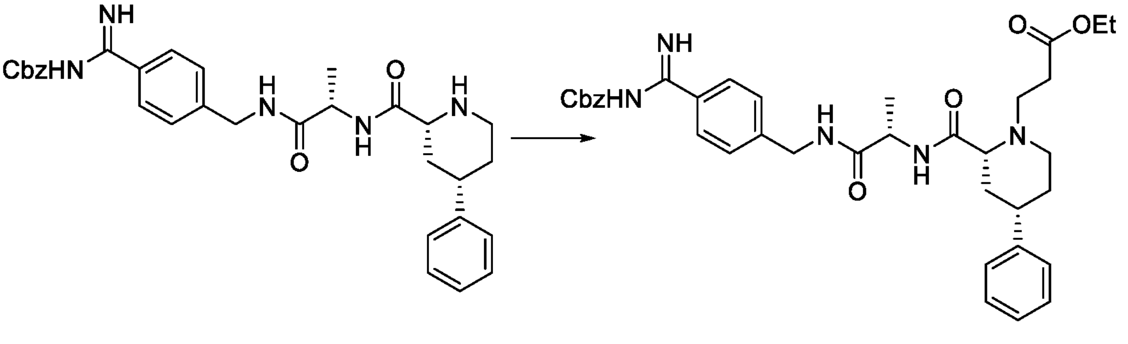


Step 2: To a stirred solution of *tert*-Butyl *(2R,4S)*-2-((*(S)*-1-((4-(*N*-((benzyloxy)carbonyl)carbamimidoyl)benzyl)amino)-1-oxopropan-2-yl)carbamoyl)-4-phenylpiperidine-1-carboxylate (200 mg, 0.53 mmol) in DCM was added DCC (109 mg,

0.53 mmol), NHS (61 mg, 0.53 mmol) and stirred at room temperature for 30 min. Benzyl ((4-(aminomethyl)phenyl)(imino)methyl)carbamate hydrochloride (170 mg, 0.53 mmol) was suspended in sat. $NaHCO_3$ and added to the reaction mixture and stirred at room temperature for 30 min. The reaction mixture was diluted with water and extracted with DCM (3 × 20 mL). The crude product was purified using flash chromatography (100 % ethyl acetate) to yield *tert*-butyl (2*R*,4*S*)-2-(((*S*)-1-((4-(*N*-((benzyloxy)carbonyl)carbamimidoyl)benzyl)amino)-1-oxopropan-2-yl)carbamoyl)-4-phenylpiperidine-1-carboxylate (180 mg, 53% yield) as a white solid.

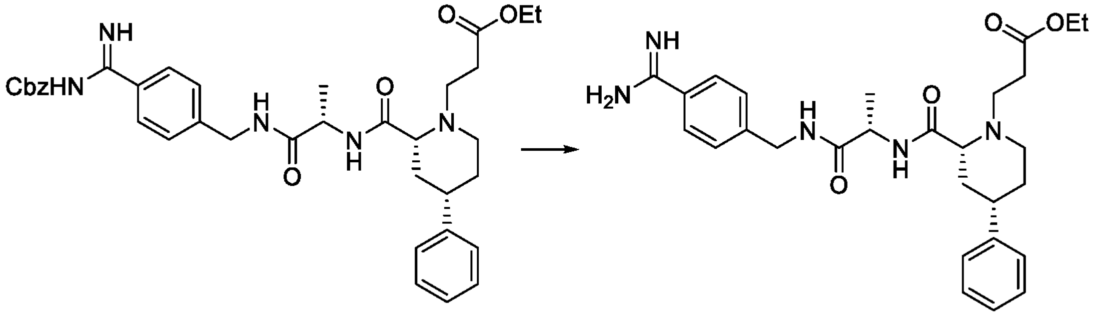


Step 3: To a stirred solution of (2*R*,4*S*)-2-(((*S*)-1-((4-(*N*-((benzyloxy)carbonyl)carbamimidoyl)benzyl)amino)-1-oxopropan-2-yl)carbamoyl)-4-phenylpiperidine-1-carboxylate (180 mg, 0.28 mmol) in DCM (5 mL) was added TFA (0.5 mL) and stirred at room temperature for 30 min. The solution was concentrated and used in the next reaction without further purification.



Step 4: To a stirred solution of benzyl (imino(4-(((*S*)-2-((2*R*,4*S*)-4-phenylpiperidine-2-carboxamido)propanamido)methyl)phenyl)methyl)carbamate trifluoroacetate (100 mg, 0.14 mmol) in DCM (2 mL) and Et_3N (0.8 mL) was added ethyl-3-bromopropionate (0.2 ml) under argon atmosphere. After stirring for 24 h at room temperature, the reaction mixture was concentrated and purified on the amine column to

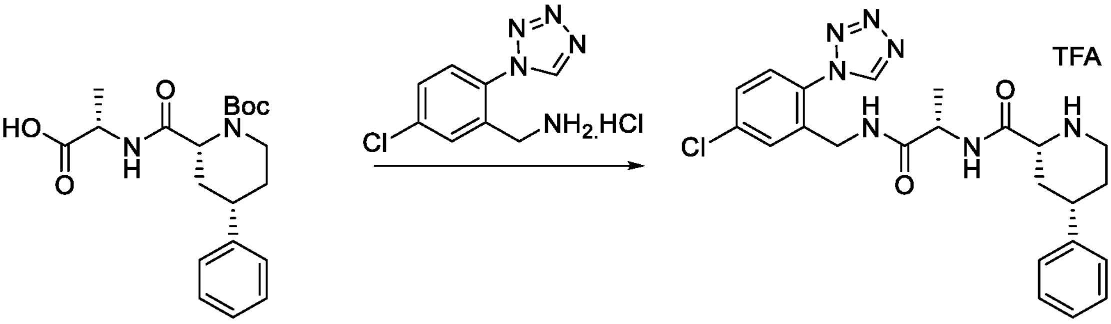
yield ethyl 3-((2*R*,4*S*)-2-(((*S*)-1-((4-(*N*-((benzyloxy)carbonyl)carbamimidoyl)benzyl)amino)-1-oxopropan-2-yl)carbamoyl)-4-phenylpiperidin-1-yl)propanoate (70 mg, 78% yield) as a white solid.



Step 5: To a stirred solution of ethyl 3-((2*R*,4*S*)-2-(((*S*)-1-((4-(*N*-((benzyloxy)carbonyl)carbamimidoyl)benzyl)amino)-1-oxopropan-2-yl)carbamoyl)-4-phenylpiperidin-1-yl)propanoate (55 mg, 0.085 mmol) in MeOH (15 mL) was added 10% Pd/C (15 mg) and stirred under H_2 for 2 h. The reaction was monitored by LCMS. The reaction mixture was filtered through Celite and washed with MeOH. The organic residues were concentrated to yield ethyl 3-((2*R*,4*S*)-2-(((*S*)-1-((4-carbamimidoylbenzyl)amino)-1-oxopropan-2-yl)carbamoyl)-4-phenylpiperidin-1-yl)propanoate (43 mg, 100%) as a white solid.

EXAMPLE 32

PREPARATION OF ETHYL 3-((2*R*,4*S*)-2-(((*S*)-1-((5-CHLORO-2-(1*H*-TETRAZOL-1-YL)BENZYL)AMINO)-1-OXOPROPAN-2-YL)CARBAMOYL)-4-PHENYLPIPERIDIN-1-YL)PROPANOATE (COMPOUND I-28)



Step 1: (2*R*,4*S*)-*N*-((*S*)-1-((5-chloro-2-(1*H*-tetrazol-1-yl)benzyl)amino)-1-oxopropan-2-yl)-4-phenylpiperidine-2-carboxamide was synthesized according to the

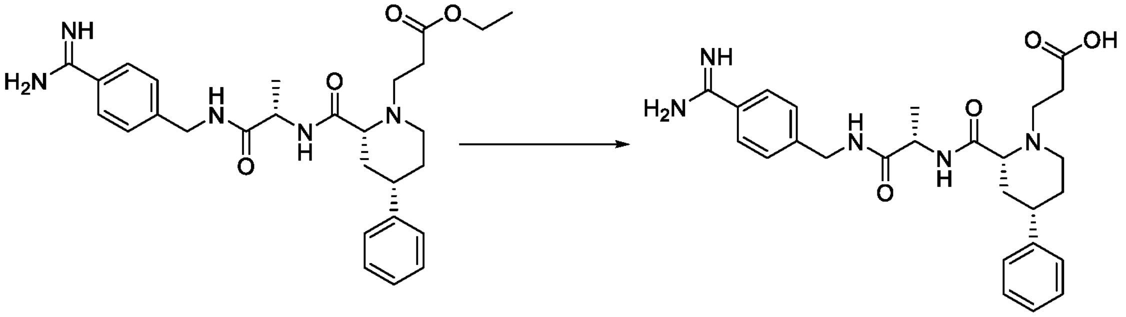
procedure described to synthesize Compound I-31, step 2 using commercially available (5-chloro-2-(1*H*-tetrazol-1-yl)phenyl)methanamine hydrochloride and *tert*-Butyl *(2R,4S)*-2-(((*S*)-1-((4-(*N*-((benzyloxy)carbonyl)carbamimidoyl)benzyl)amino)-1-oxopropan-2-yl)carbamoyl)-4-phenylpiperidine-1-carboxylate (synthesized according to the procedure for Compound I-31, step 1).

<u>Step 2:</u> Ethyl 3-((2*R*,4*S*)-2-(((*S*)-1-((5-chloro-2-(1*H*-tetrazol-1-yl)benzyl)amino)-1-oxopropan-2-yl)carbamoyl)-4-phenylpiperidin-1-yl)propanoate was synthesized according to the procedures for Compound I-31.

EXAMPLE 33

PREPARATION OF 3-((2*R*,4*S*)-2-(((*S*)-1-((4-CARBAMIMIDOYLBENZYL)AMINO)-1-OXOPROPAN-2-YL)CARBAMOYL)-4-PHENYLPIPERIDIN-1-YL)PROPANOIC ACID DI-TRIFLUOROACETATE

(COMPOUND I-32)



To a stirred solution of ethyl 3-((2*R*,4*S*)-2-(((*S*)-1-((4-carbamimidoylbenzyl)amino)-1-oxopropan-2-yl)carbamoyl)-4-phenylpiperidin-1-yl)propanoate (20 mg, 0.04 mmol, prepared according to the procedures for Compound I-31) in THF (2 mL) was added LiOH (15 mg) dissolved in 2 ml of water at room temperature and stirred at room temperature for 18 h. The reaction mixture was acidified with TFA and purified by HPLC to yield 3-((2*R*,4*S*)-2-(((*S*)-1-((4-carbamimidoylbenzyl)amino)-1-oxopropan-2-yl)carbamoyl)-4-phenylpiperidin-1-yl)propanoic acid di-trifluoroacetate (15 mg, 53% yield) as a white solid.

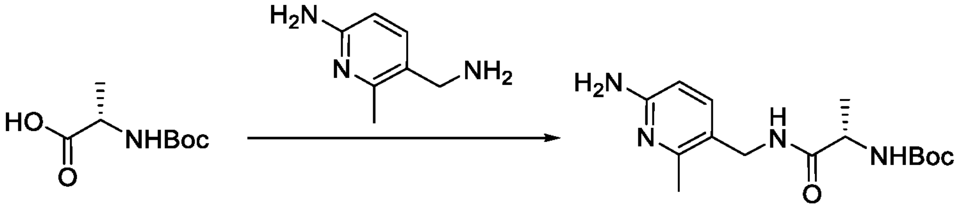
EXAMPLE 34

PREPARATION OF 3-((2*R*,4*S*)-2-(((*S*)-1-((5-CHLORO-2-(1*H*-TETRAZOL-1-YL)BENZYL)AMINO)-1-OXOPROPAN-2-YL)CARBAMOYL)-4-PHENYLPIPERIDIN-1-YL)PROPANOIC ACID TRIFLUOROACETATE (COMPOUND I-29)

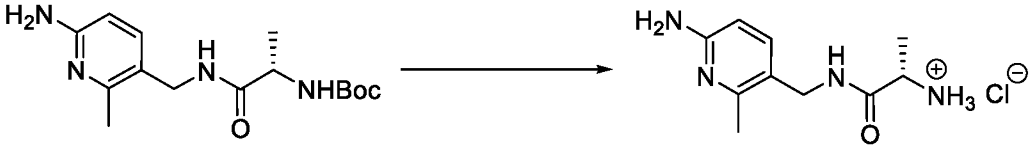
3-((2*R*,4*S*)-2-(((*S*)-1-((5-Chloro-2-(1*H*-tetrazol-1-yl)benzyl)amino)-1-oxopropan-2-yl)carbamoyl)-4-phenylpiperidin-1-yl)propanoic acid trifluoroacetate was synthesized from Compound I-56 using the procedure to synthesize Compound I-32.

EXAMPLE 35

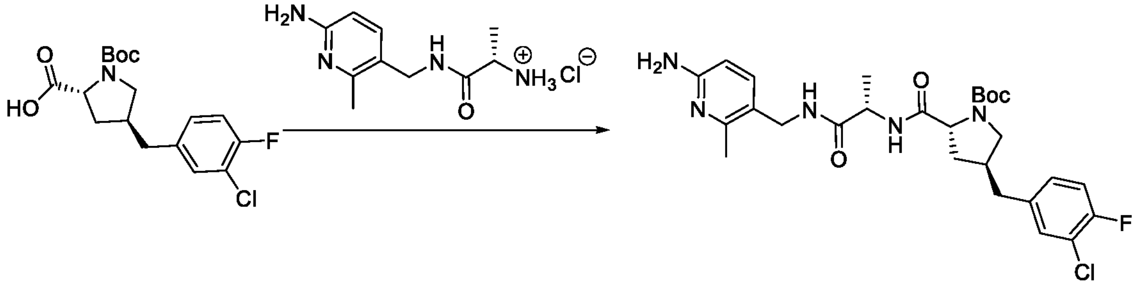
PREPARATION OF 2-((2*R*,4*S*)-2-(((*S*)-1-(((6-AMINO-2-METHYLPYRIDIN-3-YL)METHYL)AMINO)-1-OXOPROPAN-2-YL)CARBAMOYL)-4-(3-CHLORO-4-FLUOROBENZYL)PYRROLIDIN-1-YL)ACETIC ACID DI-TRIFLUOROACETATE (COMPOUND I-33)



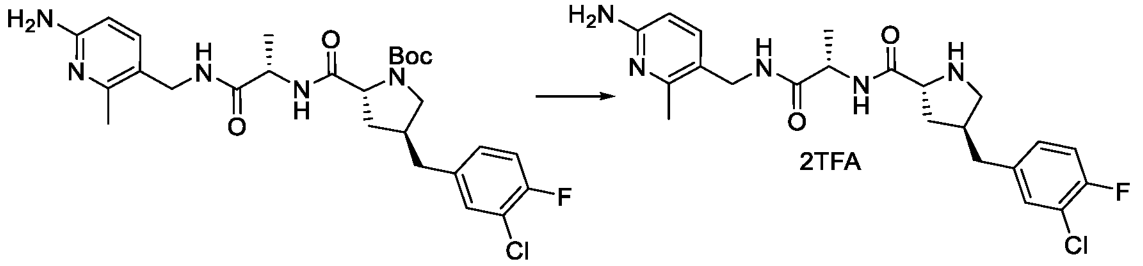
Step 1: To a stirred solution of (*tert*-butoxycarbonyl)-*L*-alanine (1.96 g, 10.38 mmol) in CH_2Cl_2 (55 mL) was added NHS (1.25 g, 10.89 mmol) at room temperature. To the above reaction mixture, DCC (2.25 g 10.9 mmol) was added and the reaction mixture was stirred for 1 h. 5-(aminomethyl)-6-methylpyridin-2-amine was added to the reaction mixture and sonicated for 5 min. The 5-(aminomethyl)-6-methylpyridin-2-amine was completely dissolved and stirred for 1 h at room temperature. The crude reaction mixture was filtered and concentrated under reduced pressure. The crude reaction mixture was purified by chromatography ($MeOH/CH_2Cl_2$) to afford *tert*-butyl (*S*)-(1-(((6-amino-2-methylpyridin-3-yl)methyl)amino)-1-oxopropan-2-yl)carbamate (2.35 g, 70% yield) as a white solid.



Step 2: To a *tert*-butyl (*S*)-(1-(((6-amino-2-methylpyridin-3-yl)methyl)amino)-1-oxopropan-2-yl)carbamate (2.35 g, 7.62 mmol) was added a solution of MeOH-HCl (2 M, 19 mL) with stirring at room temperature. After stirring for 1 h, the solution was evaporated to dryness and MeOH (50 mL) was added and evaporated to dryness to remove residual HCl gas to give (*S*)-2-amino-*N*-((6-amino-2-methylpyridin-3-yl)methyl)propanamide hydrochloride (1.60 g, 90% yield) as a off white solid (hygroscopic).



Step 3: *tert*-Butyl (2*R*,4*S*)-2-(((*S*)-1-(((6-amino-2-methylpyridin-3-yl)methyl)amino)-1-oxopropan-2-yl)carbamoyl)-4-(3-chloro-4-fluorobenzyl)pyrrolidine-1-carboxylate was synthesized from (2*R*,4*S*)-1-(*tert*-butoxycarbonyl)-4-(3-chloro-4-fluorobenzyl)pyrrolidine-2-carboxylic acid (Compound I-2, steps 1-4) according to the procedure for Compound I-17, step3.



Step 4: (2*R*,4*S*)-*N*-((*S*)-1-(((6-amino-2-methylpyridin-3-yl)methyl)amino)-1-oxopropan-2-yl)-4-(3-chloro-4-fluorobenzyl)pyrrolidine-2-carboxamide di-trifluoroacetate was synthesized according to the procedure for Compound I-1, step 7.

Step 5: Synthesis of 2-((2*R*,4*S*)-2-(((*S*)-1-(((6-amino-2-methylpyridin-3-yl)methyl)amino)-1-oxopropan-2-yl)carbamoyl)-4-(3-chloro-4-fluorobenzyl)pyrrolidin-1-yl)acetic acid di-trifluoroacetate was followed according to the procedures for Compound I-32.

EXAMPLE 36

PREPARATION OF 2-((2*R*,4*S*)-2-(((*S*)-1-((4-CARBAMIMIDOYLBENZYL)AMINO)-1-OXOPROPAN-2-YL)CARBAMOYL)-4-PHENYLPIPERIDIN-1-YL)ACETIC ACID DI-TRIFLUOROACETATE

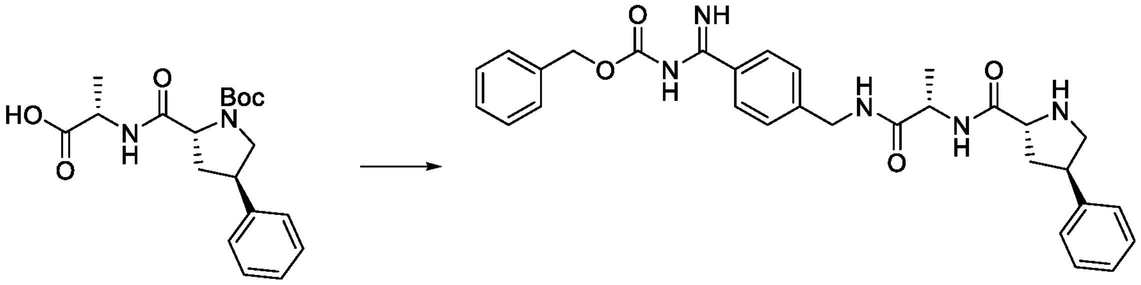
(COMPOUND I-34)

Synthesis of 2-((2*R*,4*S*)-2-(((*S*)-1-((4-carbamimidoylbenzyl)amino)-1-oxopropan-2-yl)carbamoyl)-4-phenylpiperidin-1-yl)acetic acid di-trifluoroacetate was followed according to the procedures for Compound I-32.

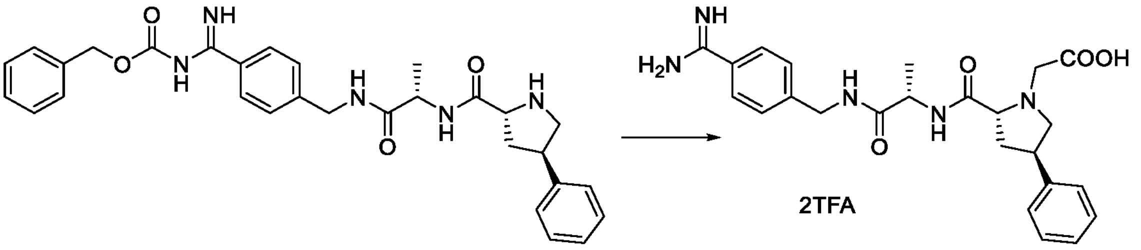
EXAMPLE 37

PREPARATION OF 2-((2*R*,4R)-2-(((S)-1-((4-CARBAMIMIDOYLBENZYL)AMINO)-1-OXOPROPAN-2-YL)CARBAMOYL)-4-PHENYLPYRROLIDIN-1-YL)ACETIC ACID DI-TRIFLUOROACETATE

(COMPOUND I-35)



<u>Step 1</u>: Benzyl (imino(4-(((*S*)-2-((2*R*,4*R*)-4-phenylpyrrolidine-2-carboxamido)propanamido)methyl)phenyl)methyl)carbamate trifluoroacetate was synthesized from ((2*R*,4*R*)-1-(*tert*-butoxycarbonyl)-4-phenylpyrrolidine-2-carbonyl)-*L*-alanine (100 mg, 0.27 mmol, prepared according to the procedures for Compound I-1, steps 1-2) according to the procedures for the synthesis of Compound I-31, steps 2-3.



<u>Step 2</u>: Synthesis of 2-((2*R*,4*R*)-2-(((*S*)-1-((4-carbamimidoylbenzyl)amino)-1-oxopropan-2-yl)carbamoyl)-4-phenylpyrrolidin-1-yl)acetic acid di-trifluoroacetate was conducted according to the procedures for Compound I-31, step 4 and Compound I-32.

EXAMPLE 38

PREPARATION OF 3-((2*R*,4*S*)-2-(((*S*)-1-((4-CARBAMIMIDOYLBENZYL)AMINO)-1-OXOPROPAN-2-YL)CARBAMOYL)-4-(3-CHLORO-4-FLUOROBENZYL)PYRROLIDIN-1-YL)PROPANOIC ACID DI-TRIFLUOROACETATE (COMPOUND I-36)

Synthesis of 3-((2*R*,4*S*)-2-(((*S*)-1-((4-carbamimidoylbenzyl)amino)-1-oxopropan-2-yl)carbamoyl)-4-(3-chloro-4-fluorobenzyl)pyrrolidin-1-yl)propanoic acid di-trifluoroacetate was conducted according to the procedures for Compound I-32 starting from benzyl ((4-(((*S*)-2-((2*R*,4*S*)-4-(3-chloro-4-fluorobenzyl)pyrrolidine-2-carboxamido)propanamido)methyl)phenyl)(imino)methyl)carbamate, as described for Compound I-23.

EXAMPLE 39

PREPARATION OF 3-((2*R*,4*S*)-2-(((*S*)-1-((4-CARBAMIMIDOYLBENZYL)AMINO)-1-OXOPROPAN-2-YL)CARBAMOYL)-4-(4-FLUOROBENZYL)PYRROLIDIN-1-YL)PROPANOIC ACID DI-TRIFLUOROACETATE (COMPOUND I-37)

Synthesis of 3-((2*R*,4*S*)-2-(((*S*)-1-((4-carbamimidoylbenzyl)amino)-1-oxopropan-2-yl)carbamoyl)-4-(4-fluorobenzyl)pyrrolidin-1-yl)propanoic acid di-trifluoroacetate was conducted according to the procedures for Compound I-36, starting with benzyl ((4-(((*S*)-2-((2*R*,4*S*)-4-(3-chloro-4-fluorobenzyl)pyrrolidine-2-carboxamido)propanamido)methyl)phenyl)(imino)methyl)carbamate.

EXAMPLE 40

PREPARATION OF (2-((2*R*,4*S*)-2-(((*S*)-1-((4-CARBAMIMIDOYLBENZYL)AMINO)-1-OXOPROPAN-2-YL)CARBAMOYL)-4-PHENYLPIPERIDIN-1-YL)ETHYL)PHOSPHONIC ACID DI-TRIFLUOROACETATE (COMPOUND I-38)

Synthesis of (2-((2*R*,4*S*)-2-(((*S*)-1-((4-carbamimidoylbenzyl)amino)-1-oxopropan-2-yl)carbamoyl)-4-phenylpiperidin-1-yl)ethyl)phosphonic acid di-trifluoroacetate was conducted according to the procedures for Compound I-32 except that final deprotection step was performed using procedure for the Compound I-39, step 5.

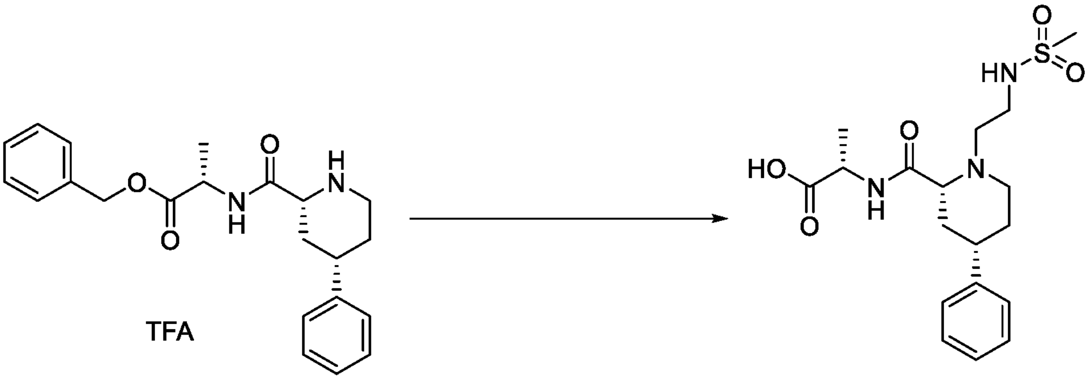
EXAMPLE 41

PREPARATION OF (3-((2*R*,4*S*)-2-(((*S*)-1-((5-CHLORO-2-(1*H*-TETRAZOL-1-YL)BENZYL)AMINO)-1-OXOPROPAN-2-YL)CARBAMOYL)-4-PHENYLPIPERIDIN-1-YL)PROPYL)PHOSPHONIC ACID DI-TRIFLUOROACETATE (COMPOUND I-40)

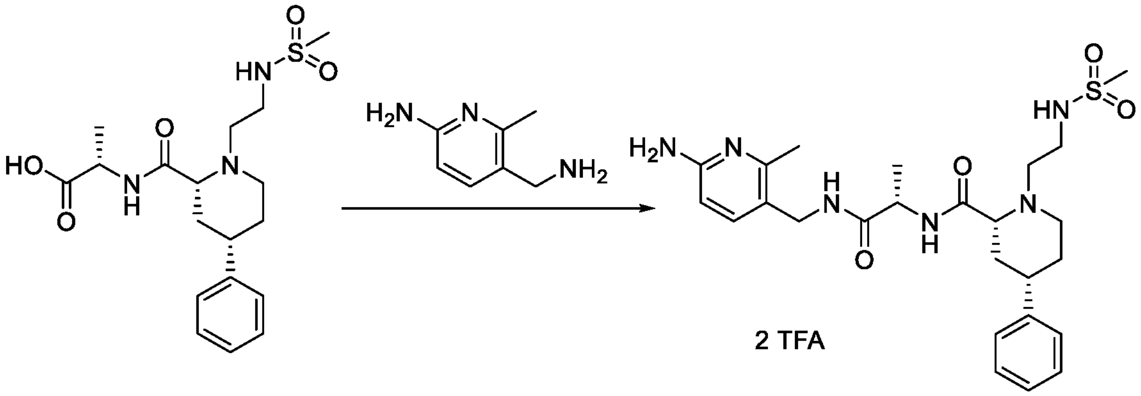
Synthesis of (3-((2*R*,4*S*)-2-(((*S*)-1-((5-chloro-2-(1*H*-tetrazol-1-yl)benzyl)amino)-1-oxopropan-2-yl)carbamoyl)-4-phenylpiperidin-1-yl)propyl)phosphonic acid trifluoroacetate was conducted according to the procedures for Compound I-32, starting with (2*R*,4*S*)-N-((*S*)-1-((5-chloro-2-(1H-tetrazol-1-yl)benzyl)amino)-1-oxopropan-2-yl)-4-phenylpiperidine-2-carboxamide. The final deprotection step was performed using the procedure for Compound I-39, step 5.

EXAMPLE 42

PREPARATION OF (2*R*,4*S*)-*N*-((*S*)-1-(((6-AMINO-2-METHYLPYRIDIN-3-YL)METHYL)AMINO)-1-OXOPROPAN-2-YL)-1-(2-(METHYLSULFONAMIDO)ETHYL)-4-PHENYLPIPERIDINE-2-CARBOXAMIDE DI-TRIFLUOROACETATE (COMPOUND I-41)



Step 1: To a solution of (2*R*,4*S*)-4-phenylpiperidine-2-carbonyl)-*L*-alaninate trifluoroacetate (154 mg, 0.32 mmol, prepared according to the procedures for Compound I-39, steps 1-2) in DMF (2 mL) was added K_2CO_3 (200 mg, 1.44 mmol). After stirring for 30 min at room temperature, *N*-(2-bromoethyl)methanesulfonamide (130 mg, 0.64 mmol) was added and stirred for 2 h at 70 °C. The reaction was monitored by LCMS. The crude reaction mixture was quenched with water and extracted with ethyl acetate (2 × 20 mL) and concentrated under reduced pressure. The crude material was used in the next reaction without further purification.



Step 2: To a stirred solution ((2*R*,4*S*)-1-(2-(methylsulfonamido)ethyl)-4-phenylpiperidine-2-carbonyl)-*L*-alanine (75 mg, 0.19 mmol) in DCM (15 mL) was added NHS (22 mg, 0.19 mmol) with stirring at room temperature until dissolved. DCC (42 mg, 0.19 mmol) was added and stirred for 1 h then 5-(aminomethyl)-6-methylpyridin-2-amine (26 mg, 0.19 mmol) was added with sonication and stirred overnight at room temperature.

The solution was filtered and evaporated to dryness. Purification by reverse phase HPLC chromatography afforded (2*R*,4*S*)-*N*-((*S*)-1-(((6-amino-2-methylpyridin-3-yl)methyl)amino)-1-oxopropan-2-yl)-1-(2-(methylsulfonamido)ethyl)-4-phenylpiperidine-2-carboxamide di-trifluoroacetate (30 mg, 18% yield over two steps) as a white solid.

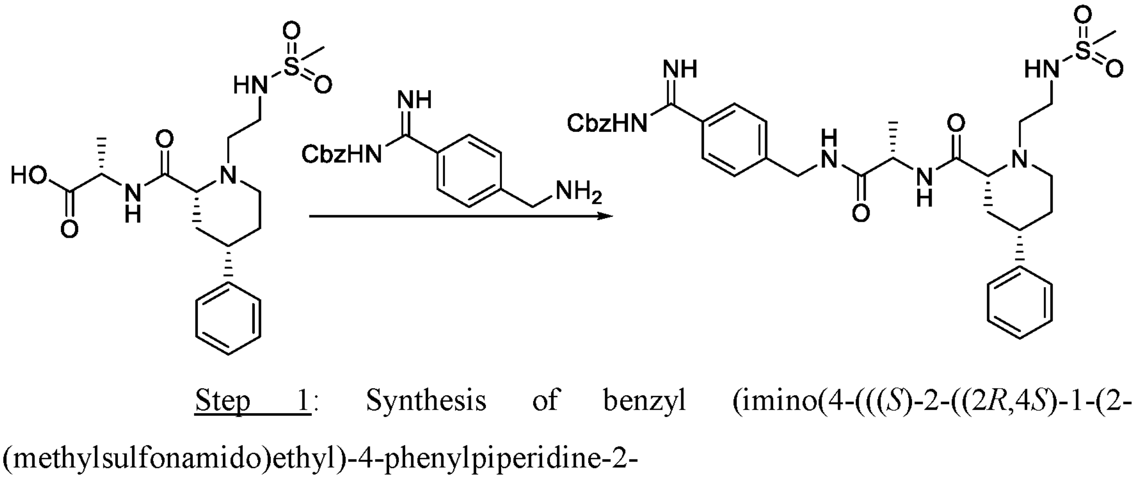
EXAMPLE 43

PREPARATION OF (2*R*,4*S*)-*N*-((*S*)-1-(((1*H*-PYRROLO[3,2-C]PYRIDIN-2-YL)METHYL)AMINO)-1-OXOPROPAN-2-YL)-1-(2-(METHYLSULFONAMIDO)ETHYL)-4-PHENYLPIPERIDINE-2-CARBOXAMIDE DI-TRIFLUOROACETATE (COMPOUND I-42)

Synthesis of (2*R*,4*S*)-*N*-((*S*)-1-(((1*H*-pyrrolo[3,2-c]pyridin-2-yl)methyl)amino)-1-oxopropan-2-yl)-1-(2-(methylsulfonamido)ethyl)-4-phenylpiperidine-2-carboxamide trifluoroacetate was followed according to the procedures for Compound I-41 except that commercially available (1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)methanamine was used in the step 2.

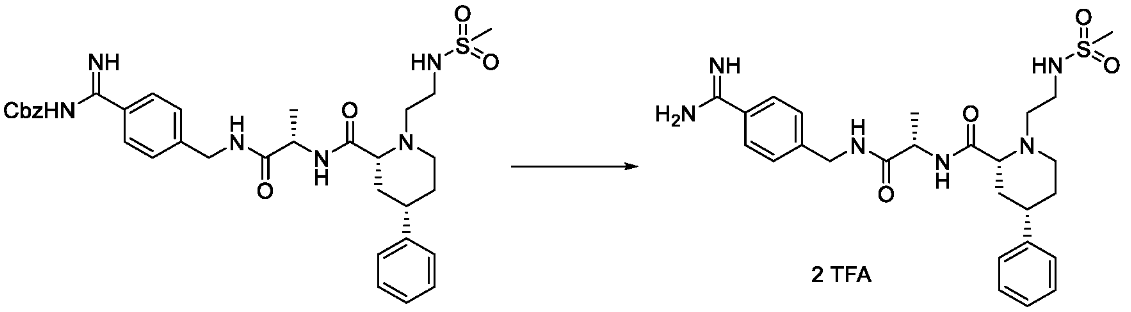
EXAMPLE 44

PREPARATION OF (2*R*,4*S*)-*N*-((*S*)-1-((4-CARBAMIMIDOYLBENZYL)AMINO)-1-OXOPROPAN-2-YL)-1-(2-(METHYLSULFONAMIDO)ETHYL)-4-PHENYLPIPERIDINE-2-CARBOXAMIDE DI-TRIFLUOROACETATE (COMPOUND I-43)



<u>Step 1</u>: Synthesis of benzyl (imino(4-(((*S*)-2-((2*R*,4*S*)-1-(2-(methylsulfonamido)ethyl)-4-phenylpiperidine-2-carboxamido)propanamido)methyl)phenyl)methyl)carbamate was followed according to the procedure for Compound I-41, step 2 using benzyl ((4-

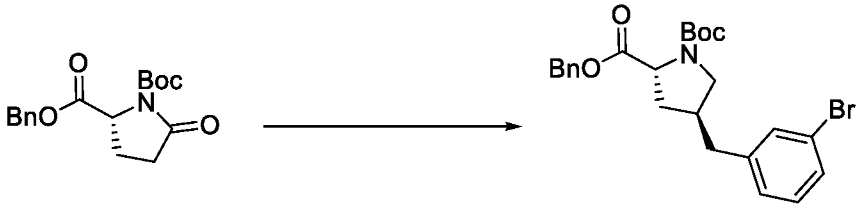
(aminomethyl)phenyl)(imino)methyl)carbamate (synthesized according to procedures for Compound I-13, steps 5-9).



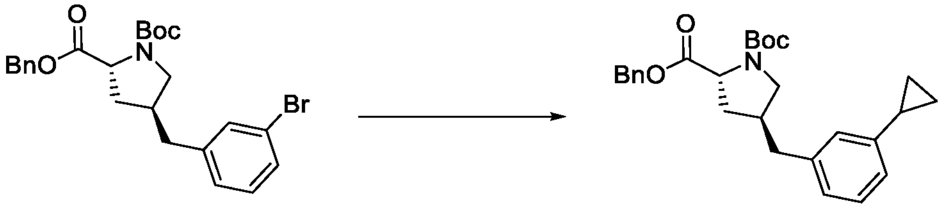
Step 2: Synthesis of (2*R*,4*S*)-*N*-((*S*)-1-((4-carbamimidoylbenzyl)amino)-1-oxopropan-2-yl)-1-(2-(methylsulfonamido)ethyl)-4-phenylpiperidine-2-carboxamide was conducted according to the procedure for Compound I-31, step 5 except that the final compound was purified on the reverse phase HPLC system.

EXAMPLE 45

PREPARATION OF (2*R*,4*S*)-*N*-((*S*)-1-(((6-AMINO-2-METHYLPYRIDIN-3-YL)METHYL)AMINO)-1-OXOPROPAN-2-YL)-4-(3-CYCLOPROPYLBENZYL)PYRROLIDINE-2-CARBOXAMIDE DI-TRIFLUOROACETATE (COMPOUND I-44)

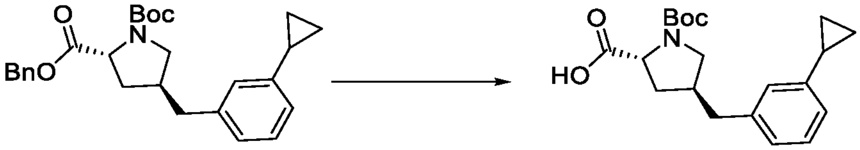


Step 1: 2-Benzyl 1-(*tert*-butyl) (2*R*,4*S*)-4-(3-bromobenzyl)pyrrolidine-1,2-dicarboxylate was synthesized according to the procedures for Compound I-2, steps 1-3.

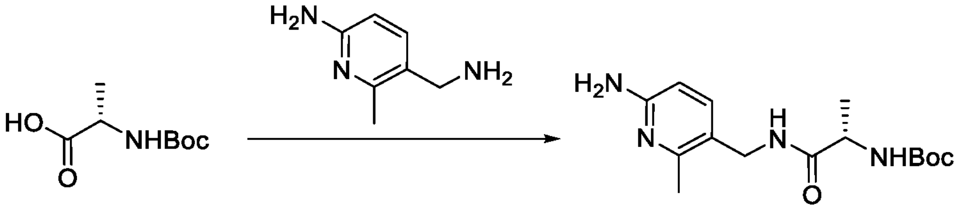


Step 2: In a 10 mL round bottom flask equipped with a stir bar and septum was added 2-benzyl 1-(*tert*-butyl) (2*R*,4*S*)-4-(3-bromobenzyl)pyrrolidine-1,2-

dicarboxylate (150 mg, 0.31 mmol), cyclopropyl boronic acid (82 mg, 0.95 mmol), Pd(dppf)Cl_2 (12 mg, 0.015 mmol), potassium phosphate tribasic (202 mg, 0.95 mmol), and 1,4-dioxane (1 mL). The resulting mixture was degassed by bubbling N_2 through the solution for 10 min. The reaction was then heated to 90 °C for 12 h. Upon cooling to rt, the reaction mixture was filtered through diatomaceous earth, eluted with ethyl acetate, concentrated and purified by chromatography using ethyl acetate-hexanes to afford 2-benzyl 1-(*tert*-butyl) (2*R*,4*S*)-4-(3-cyclopropylbenzyl)pyrrolidine-1,2-dicarboxylate (60 mg, 43% yield) as a colorless sticky liquid.

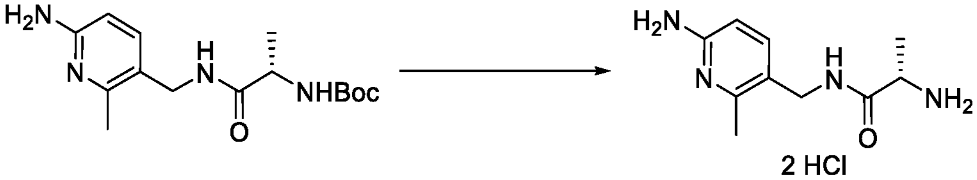


Step 3: A solution of 2-benzyl 1-(*tert*-butyl) (2*R*,4*S*)-4-(3-cyclopropylbenzyl)pyrrolidine-1,2-dicarboxylate (60 mg, 0.14 mmol) in MeOH (2 mL) was bubbled with Ar gas for 5 minutes. 10% Pd/C (6 mg) was added to the reaction mixture and the reaction was stirred under 1 atm of H_2 for 2 h. The reaction mixture was filtered (0.2 µm syringe filter) and the filtrate was concentrated under vacuum to give (2*R*,4*S*)-1-(*tert*-butoxycarbonyl)-4-(3-cyclopropylbenzyl)pyrrolidine-2-carboxylic acid (40 mg, 85% yield).

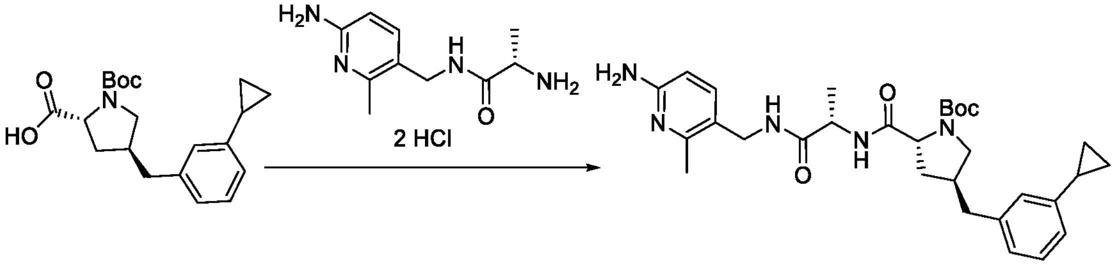


Step 4: To a solution of (*tert*-butoxycarbonyl)-*L*-alanine (1.96 g, 10.38 mmol) in CH_2Cl_2 (55 mL) was added NHS (1.25 g, 10.89 mmol) at room temperature. To the reaction mixture, DCC (2.25 g, 10.9 mmol) was added and the reaction mixture stirred for 1 h. 5-(Aminomethyl)-6-methylpyridin-2-amine (1.42 g, 10.38 mmol) was added to the reaction mixture and sonicated for 5 min. The 5-(aminomethyl)-6-methylpyridin-2-amine was completely dissolved and stirred for 1 h at room temperature. The crude reaction mixture was filtered and concentrated under reduced pressure. The residue was purified by chromatography using MeOH-CH_2Cl_2 to afford *tert*-butyl (*S*)-(1-

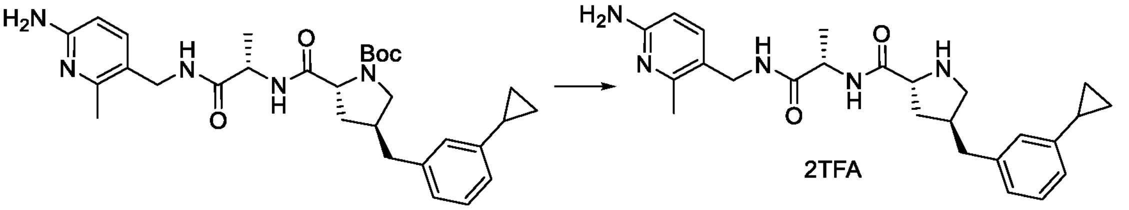
(((6-amino-2-methylpyridin-3-yl)methyl)amino)-1-oxopropan-2-yl)carbamate (2.35 g, 70% yield) as a white solid.



Step 5: To *tert*-butyl (*S*)-(1-(((6-amino-2-methylpyridin-3-yl)methyl)amino)-1-oxopropan-2-yl)carbamate (2.35 g, 7.62 mmol) was added a solution of MeOH-HCl (19 mL, 2 M) with stirring at room temperature while monitoring for the consumption of starting material (about 1 h). The solution was evaporated to dryness and MeOH (50 mL) was added and evaporated to dryness to remove residual HCl gas to give (*S*)-2-amino-*N*-((6-amino-2-methylpyridin-3-yl)methyl)propanamide dihydrochloride (1.60 g, 76% yield) as a off white solid (hygroscopic).



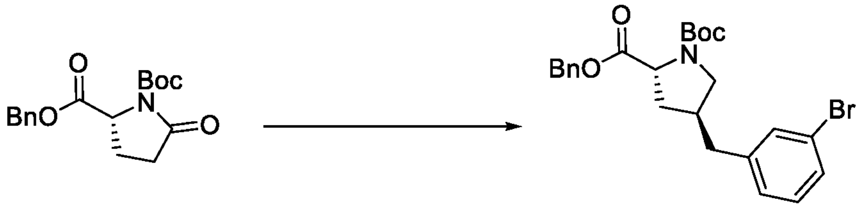
Step 6: To a solution of (2*R*,4*S*)-1-(*tert*-butoxycarbonyl)-4-(3-cyclopropylbenzyl)pyrrolidine-2-carboxylic acid (40 mg, 0.11 mmol) in anhydrous DMF (1 mL) was added HOBt (16 mg, 0.11 mmol), DIEA (0.07 mL, 0.42 mmol) and EDC (22 mg, 0.11 mmol) at rt. After stirring for 30 min at the same temperature, (*S*)-2-amino-*N*-((6-amino-2-methylpyridin-3-yl)methyl)propanamide dihydrochloride (26 mg, 0.12 mmol) was added to the reaction mixture and stirred overnight. The solution was evaporated to dryness and the residue was partitioned with ethyl acetate (10 mL) and 10% $KHSO_4$ (5 mL). The organic layer was separated and washed with sat. $NaHCO_3$ solution (10 ml), dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by chromatography using MeOH-CH_2Cl_2 to afford *tert*-butyl (2*R*,4*S*)-2-(((*S*)-1-(((6-amino-2-methylpyridin-3-yl)methyl)amino)-1-oxopropan-2-yl)carbamoyl)-4-(3-cyclopropylbenzyl)pyrrolidine-1-carboxylate (49 mg, 80% yield) as a white solid.



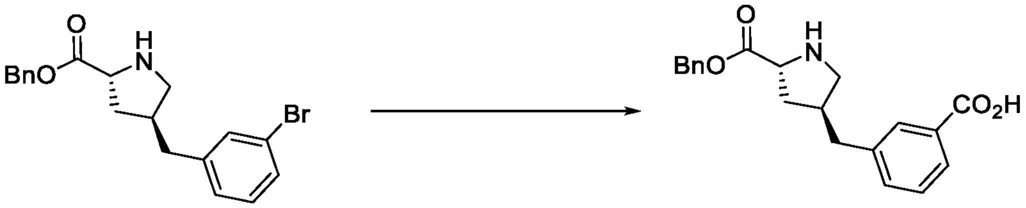
Step 7: To *tert*-butyl (2*R*,4*S*)-2-(((*S*)-1-(((6-amino-2-methylpyridin-3-yl)methyl)amino)-1-oxopropan-2-yl)carbamoyl)-4-(3-cyclopropylbenzyl)pyrrolidine-1-carboxylate (49 mg, 0.09 mmol) was added a solution of MeOH-HCl (2.0 mL, 3 M) with stirring at room temperature while monitoring for the consumption of starting material (about 1 h). The solution was evaporated to dryness and the residue was purified using reverse-phase HPLC to afford (2*R*,4*S*)-*N*-((*S*)-1-(((6-amino-2-methylpyridin-3-yl)methyl)amino)-1-oxopropan-2-yl)-4-(3-cyclopropylbenzyl)pyrrolidine-2-carboxamide di-trifluoroacetate (22.2 mg, 67% yield) as a white solid.

EXAMPLE 46

PREPARATION OF METHYL 3-(((3*S*,5*R*)-5-(((*S*)-1-(((6-AMINO-2-METHYLPYRIDIN-3-YL)METHYL)AMINO)-1-OXOPROPAN-2-YL)CARBAMOYL)PYRROLIDIN-3-YL)METHYL)BENZOATE DIHYDROCHLORIDE (COMPOUND I-47)

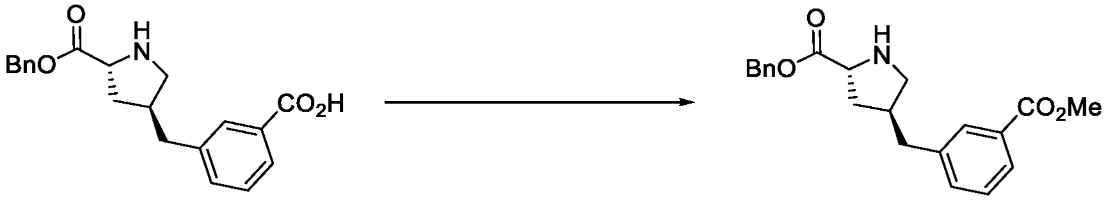


Step 1: 2-Benzyl 1-(*tert*-butyl) (2*R*,4*S*)-4-(3-bromobenzyl)pyrrolidine-1,2-dicarboxylate was synthesized according to the procedures for Compound I-2 steps 1-3.

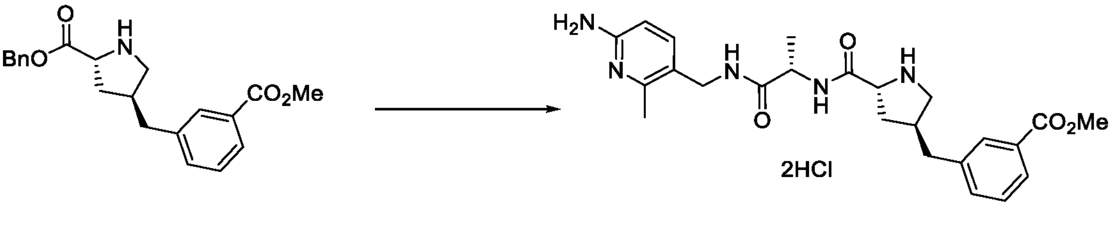


Step 2: A 25 mL vial equipped with a stir bar was charged with $(CO_2H{\cdot}H_2O)_2$ (80 mg, 0.63 mmol), $Pd(OAc)_2$ (1 mg, 0.0042), xantphos (2.5 mg, 0.0042), benzyl (2*R*,4*S*)-4-(3-bromobenzyl)pyrrolidine-2-carboxylate (200 mg, 0.42 mmol), Ac_2O

(60 µL, 0.633 mmol), DIEA (0.11 mL, 0.63 mmol), and DMF (2.0 mL) in air. The tube was quickly sealed with a Teflon® high pressure valve, frozen in liquid nitrogen, evacuated and backfilled with N_2 (5 times). After stirring for 6 h at 100 °C, the reaction mixture was cooled down to room temperature. The reaction mixture was diluted with ethyl acetate (10 mL), acidified with 2 M HCl (5 mL, once), and washed with brine (5 mL, twice). The organic phase was dried over anhydrous Na_2SO_4 and concentrated under vacuum to afford 3-(((3*S*,5*R*)-5-((benzyloxy)carbonyl)pyrrolidin-3-yl)methyl)benzoic acid (45 mg, 25% yield) that was directly used in the next step without further purification.



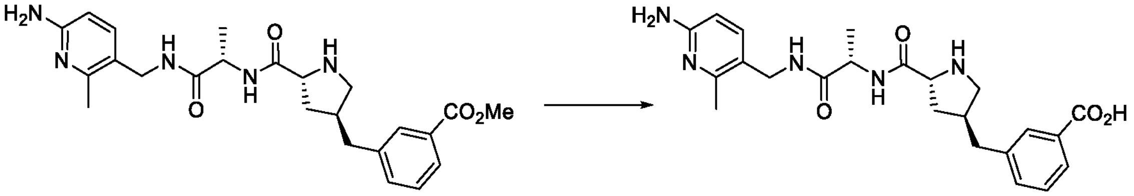
Step 3: To a solution of 3-(((3*S*,5*R*)-5-((benzyloxy)carbonyl)pyrrolidin-3-yl)methyl)benzoic acid (45 mg, 0.10 mmol) and potassium carbonate (27.6 mg, 0.20 mmol) in DMF (1 mL) at 0 °C was added methyl iodide (12 µL, 0.20 mmol). The reaction mixture was stirred at room temperature for 4 h and the solvents were removed under reduced pressure. The residue was purified by chromatography (ethyl acetate-hexanes) to afford benzyl (2*R*,4*S*)-4-(3-(methoxycarbonyl)benzyl)pyrrolidine-2-carboxylate (50 mg, 99%).



Step 4: Methyl 3-(((3*S*,5*R*)-5-(((*S*)-1-(((6-amino-2-methylpyridin-3-yl)methyl)amino)-1-oxopropan-2-yl)carbamoyl)pyrrolidin-3-yl)methyl)benzoate dihydrochloride was synthesized according to the procedures for Compound I-44 steps 3-7, except that the final product was submitted without further purification.

EXAMPLE 47

PREPARATION OF 3-(((3*S*,5*R*)-5-(((*S*)-1-(((6-AMINO-2-METHYLPYRIDIN-3-YL)METHYL)AMINO)-1-OXOPROPAN-2-YL)CARBAMOYL)PYRROLIDIN-3-YL)METHYL)BENZOIC ACID DI-TRIFLUOROACETATE (COMPOUND I-48)



Step 1: To a solution of methyl 3-(((3*S*,5*R*)-5-(((*S*)-1-(((6-amino-2-methylpyridin-3-yl)methyl)amino)-1-oxopropan-2-yl)carbamoyl)pyrrolidin-3-yl)methyl)benzoate (23 mg, 0.057 mmol) in THF (1 mL) and water (0.5 mL) was added LiOH (12 mg, 0.507 mmol) at room temperature. After stirring overnight at the same temperature, TFA was added to the reaction mixture to adjust the pH to ~3-4. The solution was evaporated to dryness and the resulting crude reaction mixture was purified using reverse-phase HPLC to afford 3-(((3*S*,5*R*)-5-(((*S*)-1-(((6-amino-2-methylpyridin-3-yl)methyl)amino)-1-oxopropan-2-yl)carbamoyl)pyrrolidin-3-yl)methyl)benzoic acid di-trifluoroacetate (13.3 mg, 56% yield) as a white solid.

EXAMPLE 48

PREPARATION OF METHYL 4-(((3*S*,5*R*)-5-(((*S*)-1-(((6-AMINO-2-METHYLPYRIDIN-3-YL)METHYL)AMINO)-1-OXOPROPAN-2-YL)CARBAMOYL)PYRROLIDIN-3-YL)METHYL)BENZOATE DIHYDROCHLORIDE (COMPOUND I-50)

Methyl 4-(((3*S*,5*R*)-5-(((*S*)-1-(((6-amino-2-methylpyridin-3-yl)methyl)amino)-1-oxopropan-2-yl)carbamoyl)pyrrolidin-3-yl)methyl)benzoate dihydrochloride was synthesized according to the procedures for Compound I-47.

EXAMPLE 49

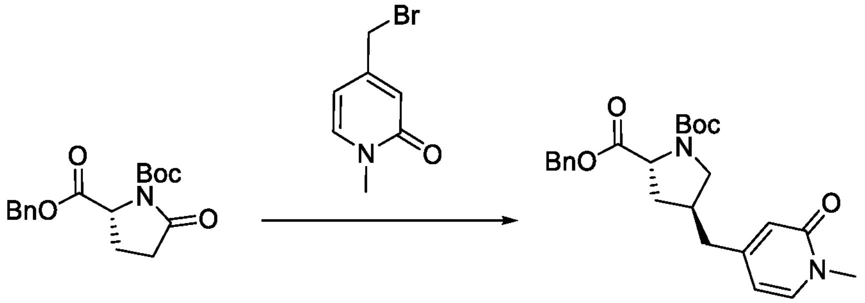
PREPARATION OF 4-(((3*S*,5*R*)-5-(((*S*)-1-(((6-AMINO-2-METHYLPYRIDIN-3-YL)METHYL)AMINO)-1-OXOPROPAN-2-YL)CARBAMOYL)PYRROLIDIN-3-YL)METHYL)BENZOIC ACID DI-TRIFLUOROACETATE (COMPOUND I-51)

4-(((3*S*,5*R*)-5-(((*S*)-1-(((6-Amino-2-methylpyridin-3-yl)methyl)amino)-1-oxopropan-2-yl)carbamoyl)pyrrolidin-3-yl)methyl)benzoic acid di-trifluoroacetate was synthesized according to the procedures for Compound I-48.

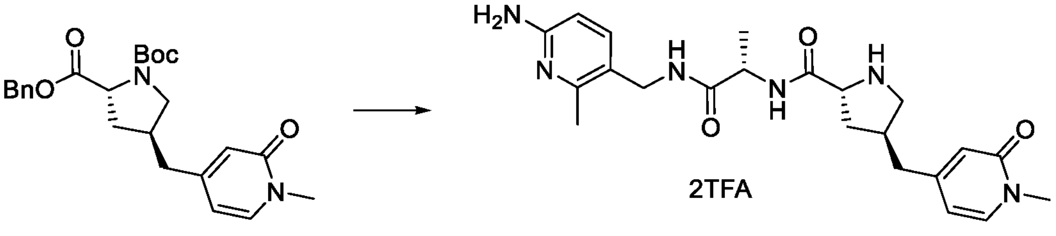
EXAMPLE 50

PREPARATION OF (2*R*,4*S*)-*N*-((*S*)-1-(((6-AMINO-2-METHYLPYRIDIN-3-YL)METHYL)AMINO)-1-OXOPROPAN-2-YL)-4-((1-METHYL-2-OXO-1,2-DIHYDROPYRIDIN-4-YL)METHYL)PYRROLIDINE-2-CARBOXAMIDE DI-TRIFLUOROACETATE (COMPOUND I-53)

Step 1: To a solution of 4-(hydroxymethyl)-1-methylpyridin-2(1*H*)-one (700 mg, 5.02 mmol) in DMF (20 mL) was added PBr_3 (0.33 mL, 3.51 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 3 h. Water (100 mL) was added to the reaction mixture and extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were thoroughly dried using Na_2SO_4, filtered, and concentrated to afford 4-(bromomethyl)-1-methylpyridin-2(1*H*)-one (707 mg crude, 3.51 mmol) that was directly used in the next step without further purification.



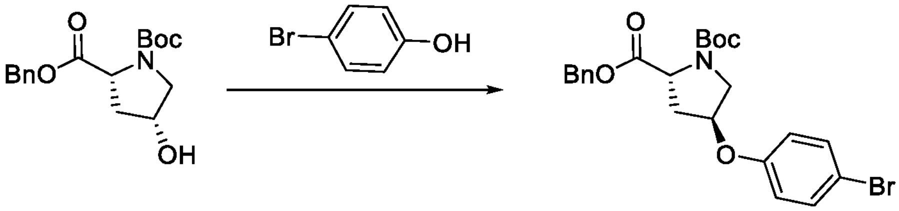
Step 2: 2-Benzyl 1-(*tert*-butyl) (2*R*,4*S*)-4-((1-methyl-2-oxo-1,2-dihydropyridin-4-yl)methyl)pyrrolidine-1,2-dicarboxylate was synthesized according to the procedures for Compound I-2 steps 1-3.



Step 3: (2*R*,4*S*)-*N*-((*S*)-1-(((6-Amino-2-methylpyridin-3-yl)methyl)amino)-1-oxopropan-2-yl)-4-((1-methyl-2-oxo-1,2-dihydropyridin-4-yl)methyl)pyrrolidine-2-carboxamide di-trifluoroacetate was synthesized according to the procedures for Compound I-44 steps 3-7.

EXAMPLE 51

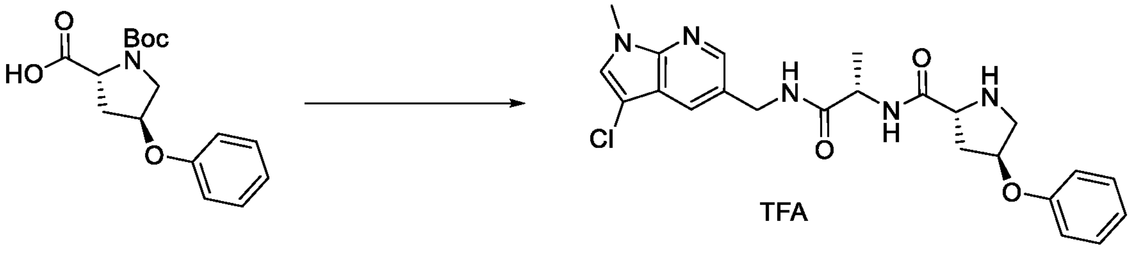
PREPARATION OF (2*R*,4*S*)-*N*-((*S*)-1-(((3-CHLORO-1-METHYL-1*H*-PYRROLO[2,3-B]PYRIDIN-5-YL)METHYL)AMINO)-1-OXOPROPAN-2-YL)-4-PHENOXYPYRROLIDINE-2-CARBOXAMIDE TRIFLUOROACETATE (COMPOUND I-46)



Step 1: To a solution of 2-benzyl 1-(*tert*-butyl) (2*R*,4*R*)-4-hydroxypyrrolidine-1,2-dicarboxylate (410 mg, 1.27 mmol), 4-bromophenol (242 mg, 1.39 mmol) and TPP (367 mg, 1.39 mmol) in THF (6.35 mL) was added DIAD (0.27 mL, 1.39 mmol). After stirring overnight at room temperature, the reaction mixture was concentrated under vacuum, the residue was purified by chromatography using ethyl acetate-hexanes to afford 2-benzyl 1-(*tert*-butyl) (2*R*,4*S*)-4-(4-bromophenoxy)pyrrolidine-1,2-dicarboxylate (533 mg, 88% yield) as a colorless solid.

Step 2: (2*R*,4*S*)-1-(*tert*-Butoxycarbonyl)-4-phenoxypyrrolidine-2-carboxylic acid was synthesized from 2-benzyl 1-(*tert*-butyl) (2*R*,4*S*)-4-(4-

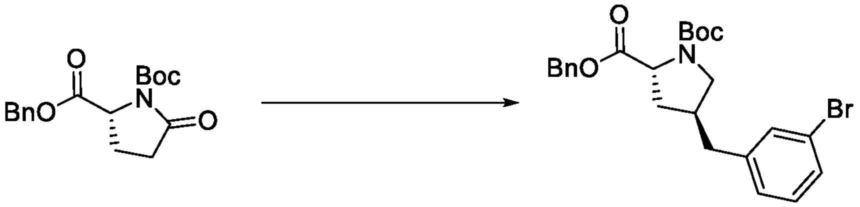
bromophenoxy)pyrrolidine-1,2-dicarboxylate according to the procedure for Compound I-44, step 3.



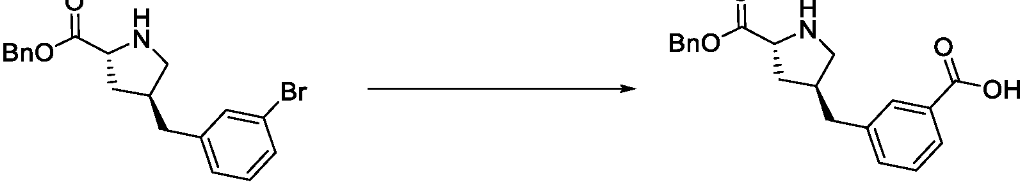
Step 3: (2*R*,4*S*)-*N*-((*S*)-1-(((3-Chloro-1-methyl-1*H*-pyrrolo[2,3-b]pyridin-5-yl)methyl)amino)-1-oxopropan-2-yl)-4-phenoxypyrrolidine-2-carboxamide trifluoroacetate was synthesized from (2*R*,4*S*)-1-(*tert*-butoxycarbonyl)-4-phenoxypyrrolidine-2-carboxylic acid according to the procedures for Compound I-44, steps 6-7.

EXAMPLE 52

PREPARATION OF (2*R*,4*S*)-*N*-((*S*)-1-(((6-AMINO-2-METHYLPYRIDIN-3-YL)METHYL)AMINO)-1-OXOPROPAN-2-YL)-4-(3-((3-CHLOROPROPYL)CARBAMOYL)BENZYL)PYRROLIDINE-2-CARBOXAMIDE DI-TRIFLUOROACETATE (COMPOUND I-49)

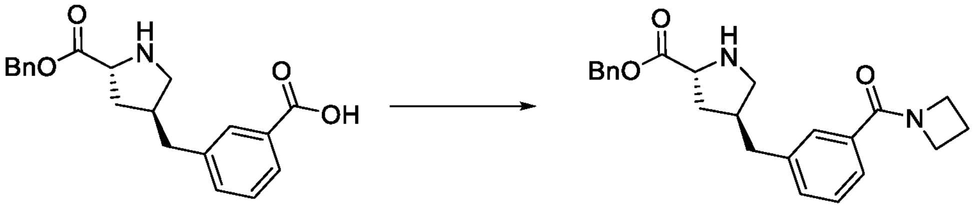


Step 1: 2-Benzyl 1-(*tert*-butyl) (2*R*,4*S*)-4-(3-bromobenzyl)pyrrolidine-1,2-dicarboxylate was synthesized according to the procedures for Compound I-2, steps 1-3.

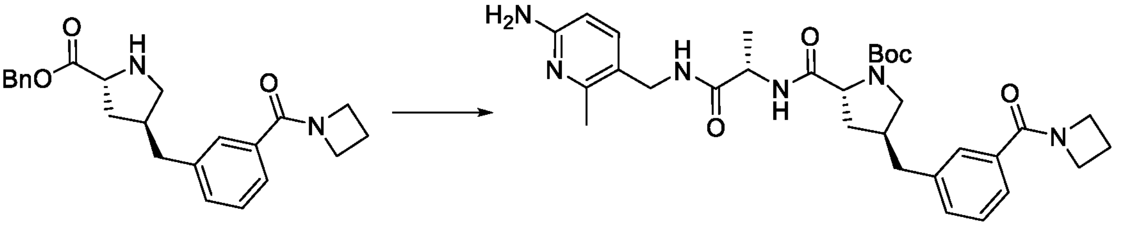


Step 2: A 25 mL vial equipped with a stir bar was charged with $(CO_2H \cdot H_2O)_2$ (80 mg, 0.63 mmol), $Pd(OAc)_2$ (1 mg, 0.0042), xantphos (2.5 mg, 0.0042), benzyl (2*R*,4*S*)-4-(3-bromobenzyl)pyrrolidine-2-carboxylate (200 mg, 0.42 mmol), Ac_2O

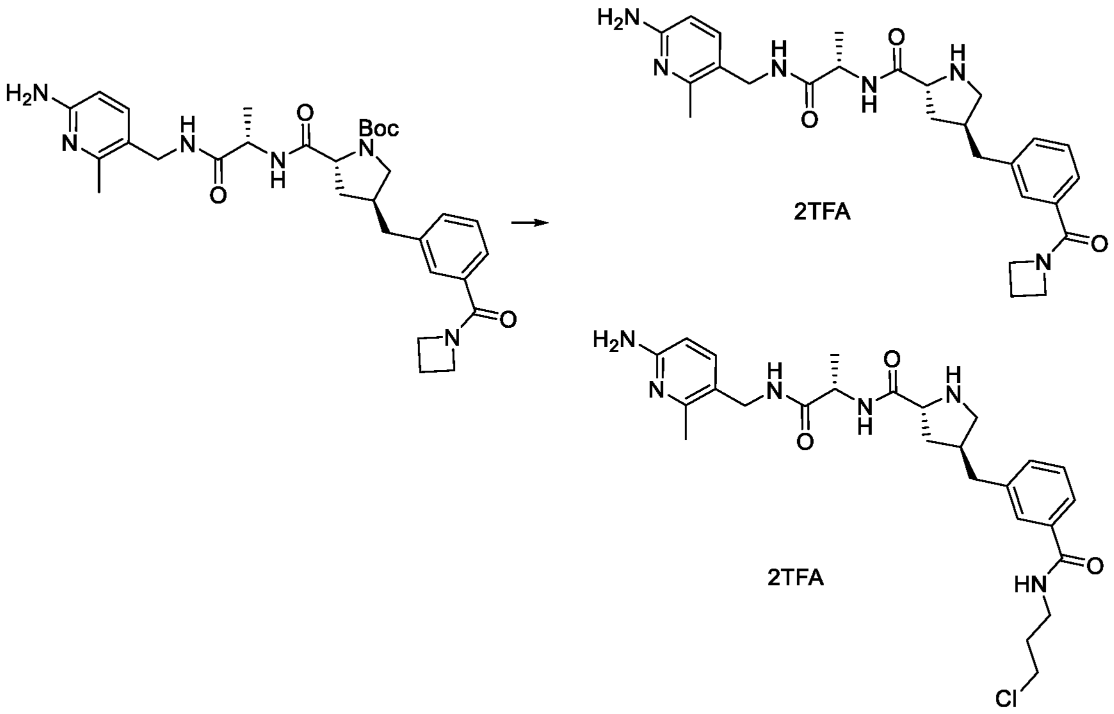
(60 µL, 0.633 mmol), DIEA (0.11 mL, 0.63 mmol), and DMF (2.0 mL) in air. The tube was quickly sealed with a Teflon® high pressure valve, frozen in liquid nitrogen, evacuated and backfilled with N_2 (5 times). After stirring for 6 h at 100 °C, the reaction mixture was cooled down to room temperature. The reaction mixture was diluted with ethyl acetate (10 mL), acidified with 2 M HCl (5 mL, once), and washed with brine (5 mL, twice). The organic phase was dried over anhydrous Na_2SO_4 and concentrated under vacuum to afford 3-(((3*S*,5*R*)-5-((benzyloxy)carbonyl)pyrrolidin-3-yl)methyl)benzoic acid (45 mg, 25% yield) that was directly used in the next step without further purification.



Step 3: To a solution of 3-(((3*S*,5*R*)-5-((benzyloxy)carbonyl)pyrrolidin-3-yl)methyl)benzoic acid (45 mg, 0.10 mmol) and triethylamine (0.10 mL, 0.70 mmol) in CH_2Cl_2 (1 mL) at 0 °C was added oxalyl chloride (0.34 µL, 0.40 mmol), azetidine (30 mg, 0.5 mmol) followed by DMF (2 drops) under Ar. After stirring overnight at room temperature, the solvents were removed under reduced pressure. The residue was purified by chromatography (ethyl acetate -hexanes) to afford benzyl (2*R*,4*S*)-4-(3-(azetidine-1-carbonyl)benzyl)pyrrolidine-2-carboxylate (31 mg, 61% yield).



Step 4: *tert*-Butyl (2*R*,4*S*)-2-(((*S*)-1-(((6-amino-2-methylpyridin-3-yl)methyl)amino)-1-oxopropan-2-yl)carbamoyl)-4-(3-(azetidine-1-carbonyl)benzyl)pyrrolidine-1-carboxylate was synthesized according to the procedures for Compound I-44, steps 3-6.

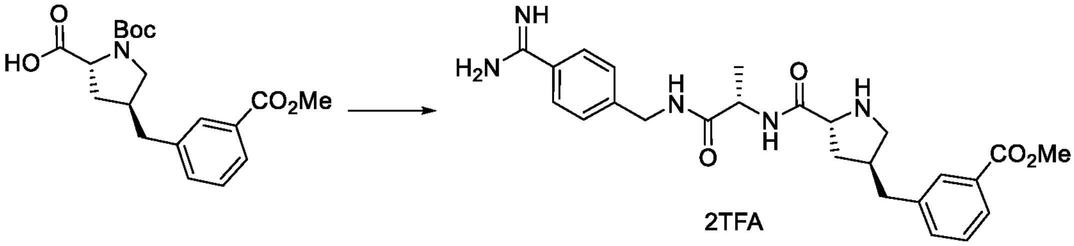


Step 5: To *tert*-butyl (2*R*,4*S*)-2-(((*S*)-1-(((6-amino-2-methylpyridin-3-yl)methyl)amino)-1-oxopropan-2-yl)carbamoyl)-4-(3-(azetidine-1-carbonyl)benzyl)pyrrolidine-1-carboxylate (70 mg, 0.12 mmol) was added a solution of IPA-HCl (3.0 mL, 6 M) with stirring at room temperature while monitoring for the consumption of starting material (2 h). Crude LCMS showed two products. The solution was evaporated to dryness and the resulting crude reaction mixture was purified using reverse-phase HPLC to separate both the compounds. (2*R*,4*S*)-*N*-((*S*)-1-(((6-amino-2-methylpyridin-3-yl)methyl)amino)-1-oxopropan-2-yl)-4-(3-((3-chloropropyl)carbamoyl)benzyl)pyrrolidine-2-carboxamide di-trifluoroacetate salt (10 mg, 16% yield) was eluted first from the HPLC as a white solid. (2*R*,4*S*)-*N*-((*S*)-1-(((6-amino-2-methylpyridin-3-yl)methyl)amino)-1-oxopropan-2-yl)-4-(3-(azetidine-1-carbonyl)benzyl)pyrrolidine-2-carboxamide di-trifluoroacetate (9.3 mg, 17% yield) was eluted as a second fraction from the HPLC as a white solid.

EXAMPLE 53

PREPARATION OF METHYL 3-(((3*S*,5*R*)-5-(((*S*)-1-((4-CARBAMIMIDOYLBENZYL)AMINO)-1-OXOPROPAN-2-YL)CARBAMOYL)PYRROLIDIN-3-YL)METHYL)BENZOATE DI-TRIFLUOROACETATE (COMPOUND I-54)

Step 1: (2*R*,4*S*)-1-(*tert*-Butoxycarbonyl)-4-(3-(methoxycarbonyl)benzyl)pyrrolidine-2-carboxylic acid was synthesized according to the procedure for Compound I-44, step 3.

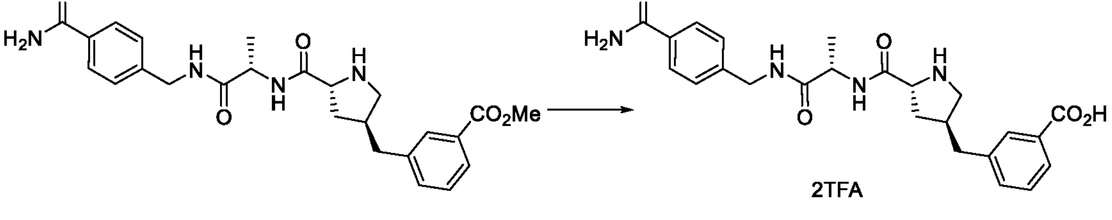


Step 2: Methyl 3-(((3*S*,5*R*)-5-(((*S*)-1-((4-carbamimidoylbenzyl)amino)-1-oxopropan-2-yl)carbamoyl)pyrrolidin-3-yl)methyl)benzoate di-trifluoroacetate was synthesized according to the procedures for Compound I-13, steps 5-14.

EXAMPLE 54

PREPARATION OF 3-(((3*S*,5*R*)-5-(((*S*)-1-((4-CARBAMIMIDOYLBENZYL)AMINO)-1-OXOPROPAN-2-YL)CARBAMOYL)PYRROLIDIN-3-YL)METHYL)BENZOIC ACID DI-TRIFLUOROACETATE

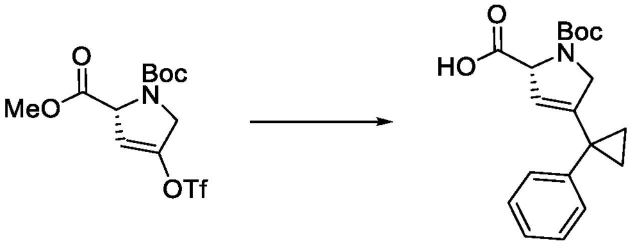
(COMPOUND I-55)



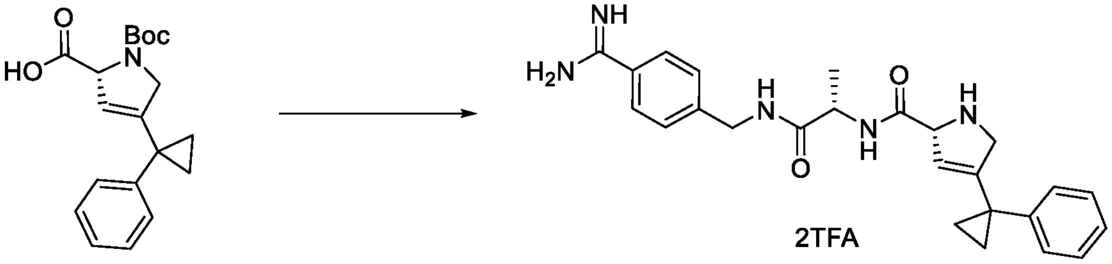
Step 1: 3-(((3*S*,5*R*)-5-(((*S*)-1-((4-Carbamimidoylbenzyl)amino)-1-oxopropan-2-yl)carbamoyl)pyrrolidin-3-yl)methyl)benzoic acid di-trifluoroacetate was synthesized according to the procedure for Compound I-48, step 2.

EXAMPLE 55

PREPARATION OF (*R*)-*N*-((*S*)-1-((4-CARBAMIMIDOYLBENZYL)AMINO)-1-OXOPROPAN-2-YL)-4-(1-PHENYLCYCLOPROPYL)-2,5-DIHYDRO-1*H*-PYRROLE-2-CARBOXAMIDE DI-TRIFLUOROACETATE (COMPOUND I-52)



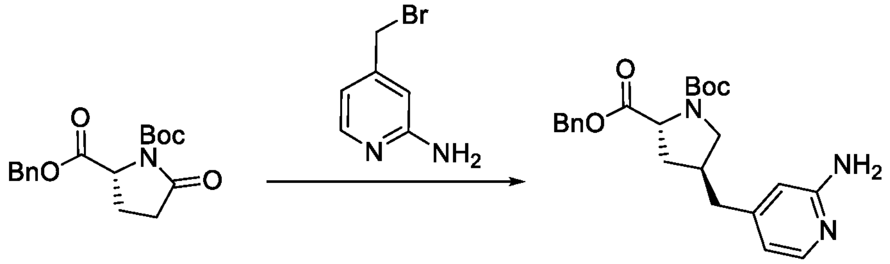
Step 1: (*R*)-1-(*tert*-butoxycarbonyl)-4-(1-phenylcyclopropyl)-2,5-dihydro-1*H*-pyrrole-2-carboxylic acid was synthesized according to the procedures for Compound I-76, steps 1-2.



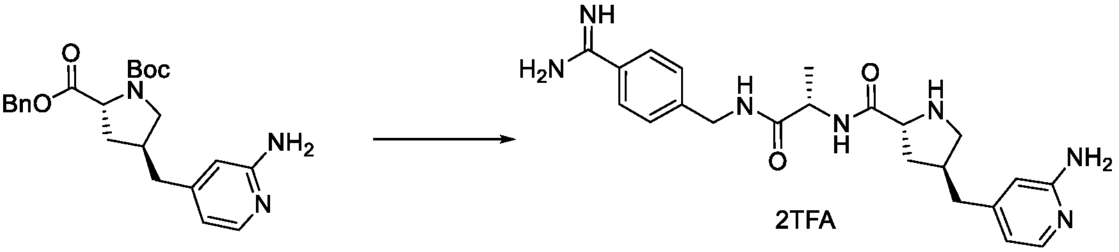
Step 2: (*R*)-*N*-((*S*)-1-((4-Carbamimidoylbenzyl)amino)-1-oxopropan-2-yl)-4-(1-phenylcyclopropyl)-2,5-dihydro-1*H*-pyrrole-2-carboxamide di-trifluoroacetate was synthesized according to the procedures for Compound I-13, steps 5-14 except that the reaction was stirred for 30 min in the step 14.

EXAMPLE 56

PREPARATION OF (2*R*,4*S*)-4-((2-AMINOPYRIDIN-4-YL)METHYL)-*N*-((*S*)-1-((4-CARBAMIMIDOYLBENZYL)AMINO)-1-OXOPROPAN-2-YL)PYRROLIDINE-2-CARBOXAMIDE DI-TRIFLUOROACETATE (COMPOUND I-56)



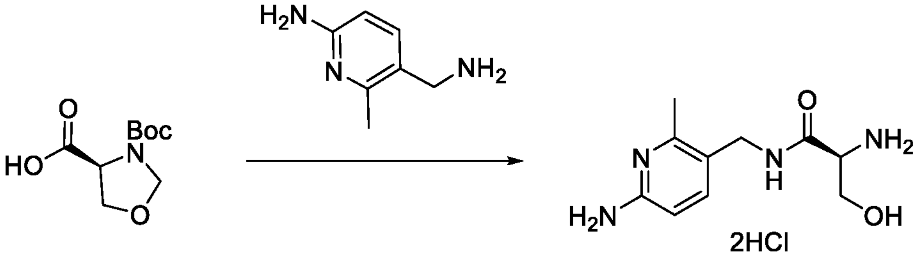
<u>Step 1</u>: 2-Benzyl 1-(*tert*-butyl) (2*R*,4*S*)-4-((2-aminopyridin-4-yl)methyl)pyrrolidine-1,2-dicarboxylate was synthesized according to the procedures for Compound I-44, steps 1-3.



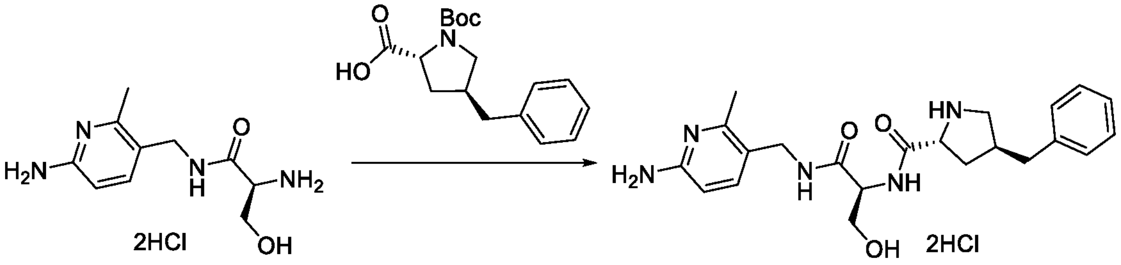
<u>Step 2</u>: (2*R*,4*S*)-4-((2-Aminopyridin-4-yl)methyl)-*N*-((*S*)-1-((4-carbamimidoylbenzyl)amino)-1-oxopropan-2-yl)pyrrolidine-2-carboxamide di-trifluoroacetate was synthesized according to the procedures for Compound I-54, steps 2-3.

EXAMPLE 57

PREPARATION OF (2*R*,4*S*)-*N*-((*S*)-1-(((6-AMINO-2-METHYLPYRIDIN-3-YL)METHYL)AMINO)-3-HYDROXY-1-OXOPROPAN-2-YL)-4-BENZYLPYRROLIDINE-2-CARBOXAMIDE DIHYDROCHLORIDE (COMPOUND I-57)



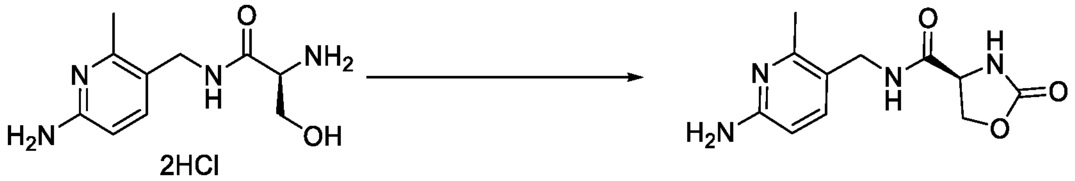
Steps 1-2: (*S*)-2-amino-*N*-((6-amino-2-methylpyridin-3-yl)methyl)-3-hydroxypropanamide dihydrochloride was prepared as a white, crystalline solid (1.09 g, 86% yield over two steps) according to steps 4-5 of the procedures for Compound I-44 using the appropriate starting materials.



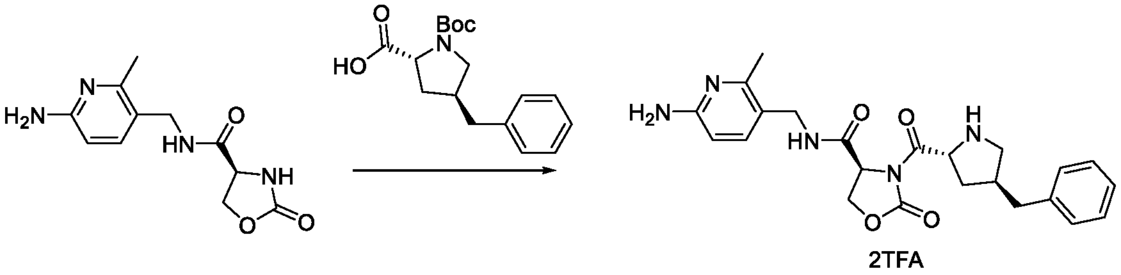
Steps 3-4: The title compound was prepared as a white solid (40.4 mg, 66% yield over two steps) according to the procedures for Compound I-44, steps 6-7 using the appropriate starting materials except with no purification after final step.

EXAMPLE 58

PREPARATION OF (*S*)-*N*-((6-AMINO-2-METHYLPYRIDIN-3-YL)METHYL)-3-((2*R*,4*S*)-4-BENZYLPYRROLIDINE-2-CARBONYL)-2-OXOOXAZOLIDINE-4-CARBOXAMIDE DI-TRIFLUOROACETATE (COMPOUND I-58)



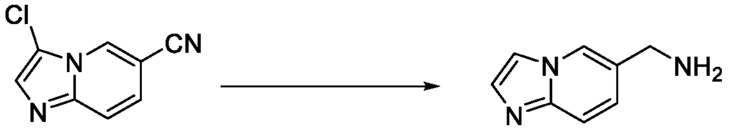
Step 1: A 100 mL round bottom flask was charged with (*S*)-2-amino-*N*-((6-amino-2-methylpyridin-3-yl)methyl)-3-hydroxypropanamide dihydrochloride (480 mg, 1.6 mmol), DIEA (1.27 mL, 73 mmol) and DCM (10 mL), then cooled to 0 °C. Triphosgene (297 mg, 1.0 mmol) was added to the stirring mixture, then the reaction warmed slowly to room temperature overnight. The reaction mixture was then quenched with H_2O, diluted with DCM and separated. The organics were dried over $MgSO_4$, concentrated under vacuum and purified by chromatography (0-100% [5% 7 N NH_3 in $MeOH/CH_2Cl_2$]-CH_2Cl_2) to afford (*S*)-*N*-((6-amino-2-methylpyridin-3-yl)methyl)-2-oxooxazolidine-4-carboxamide as a white solid (40 mg, 16% yield).



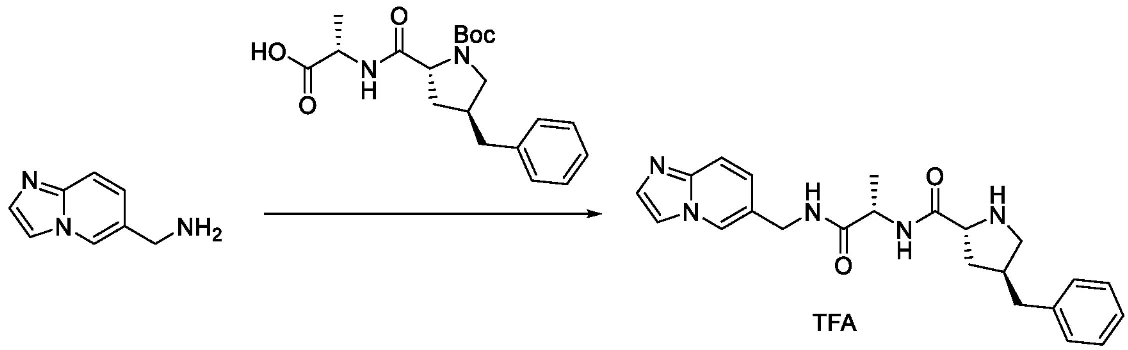
Steps 2-3: The title compound was prepared as a white solid (40.4 mg, 66% yield over two steps) according to the procedure for Compound I-44, step 4 and the procedure for Compound I-39, step 2 using the appropriate starting materials.

EXAMPLE 59

PREPARATION OF (2*R*,4*S*)-4-BENZYL-*N*-((*S*)-1-((IMIDAZO[1,2-A]PYRIDIN-6-YLMETHYL)AMINO)-1-OXOPROPAN-2-YL)PYRROLIDINE-2-CARBOXAMIDE TRIFLUOROACETATE (COMPOUND I-59)



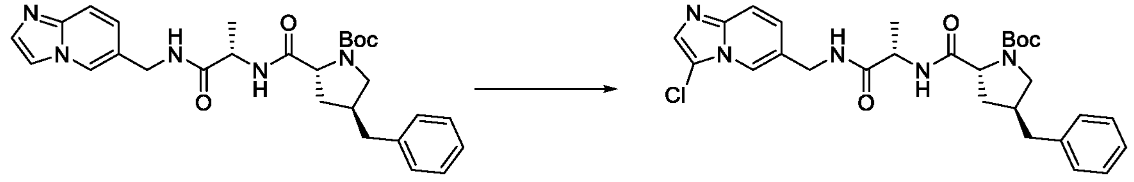
Step 1: Imidazo[1,2-a]pyridin-6-ylmethanamine was prepared as a pale green solid (82 mg, quant.) according to step 1 of the procedure for Compound I-4 using the appropriate starting materials.



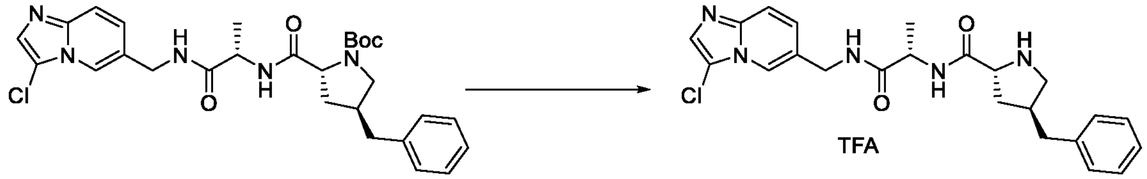
Steps 2-3: The title compound was prepared as a yellow, granular solid (3.2 mg, 31% yield) according to steps 4-5 of the procedure for Compound I-44 using the appropriate starting materials except for purification by prep-HPLC (ACN/H_2O + TFA).

EXAMPLE 60

PREPARATION OF (2*R*,4*S*)-4-BENZYL-*N*-((*S*)-1-(((3-CHLOROIMIDAZO[1,2-A]PYRIDIN-6-YL)METHYL)AMINO)-1-OXOPROPAN-2-YL)PYRROLIDINE-2-CARBOXAMIDE TRIFLUOROACETATE (COMPOUND I-60)



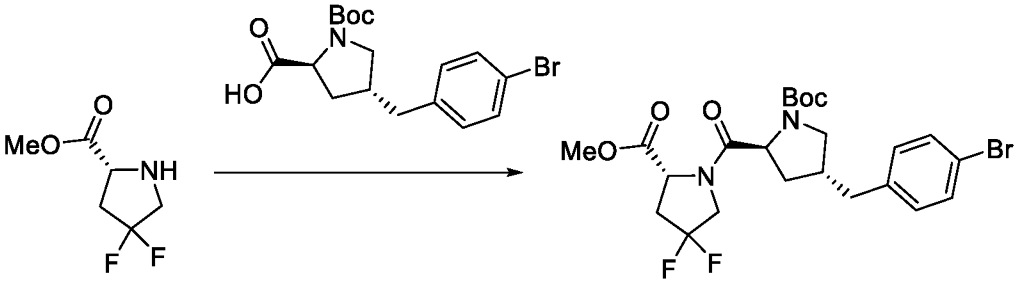
Step 1: *tert*-Butyl (2*R*,4*S*)-4-benzyl-2-(((*S*)-1-((imidazo[1,2-a]pyridin-6-ylmethyl)amino)-1-oxopropan-2-yl)carbamoyl)pyrrolidine-1-carboxylate (28 mg, 0.055 mmol, prepared according to the procedure for Compound I-59) was dissolved in $CHCl_3$ (1 mL) and treated with NCS (8.1 mg, 0.06 mmol) at room temperature. The resulting mixture was stirred for 16 h, then concentrated and purified by chromatography (ethyl acetate/hexanes) to afford *tert*-butyl (2*R*,4*S*)-4-benzyl-2-(((*S*)-1-(((3-chloroimidazo[1,2-a]pyridin-6-yl)methyl)amino)-1-oxopropan-2-yl)carbamoyl)pyrrolidine-1-carboxylate as a white solid (16 mg, 74% yield).



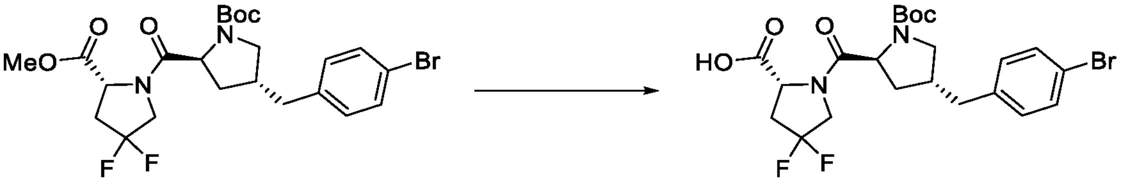
Step 2: The title compound was prepared as a white, granular solid (7 mg, 42% yield) according to the procedure for Compound I-44, step 5 using the appropriate starting materials.

EXAMPLE 61

PREPARATION OF (*R*)-*N*-((6-AMINO-2-METHYLPYRIDIN-3-YL)METHYL)-1-((2*S*,4*R*)-4-(4-BROMOBENZYL)PYRROLIDINE-2-CARBONYL)-4,4-DIFLUOROPYRROLIDINE-2-CARBOXAMIDE DIHYDROCHLORIDE (COMPOUND I-61)

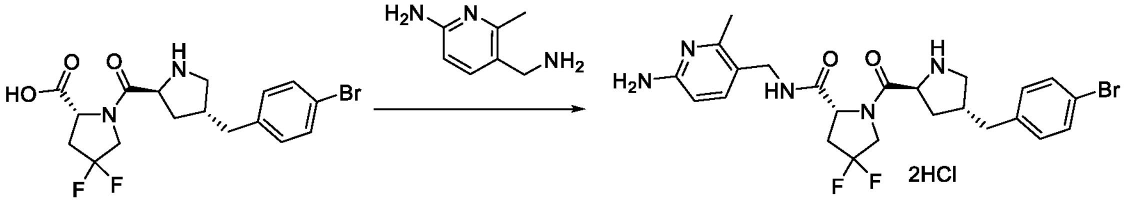


Step 1: To a stirring solution of (2*S*,4*R*)-4-(4-bromobenzyl)-1-(*tert*-butoxycarbonyl)pyrrolidine-2-carboxylic acid (83 mg, 0.22 mmol, prepared according to the procedure for Compound I-12 in DMF (2 mL) was added HATU (99 mg, 0.26 mmol) and DIEA (115 µL, 0.66 mmol). After stirring for 10 min at room temperature, methyl (*R*)-4,4-difluoropyrrolidine-2-carboxylate (43 mg, 0.26 mmol) was added and the resulting mixture allowed to stir for another 1.5 h. Upon completion, the reaction mixture was diluted in ethyl acetate and washed with 10% aq. $KHSO_4$, brine and sat. $NaHCO_3$, then dried over Na_2SO_4 and concentrated under vacuum. The resulting residue was purified by chromatography (30-60% ethyl acetate/hexanes) to afford *tert*-butyl (2*S*,4*R*)-4-(4-bromobenzyl)-2-((*R*)-4,4-difluoro-2-(methoxycarbonyl)pyrrolidine-1-carbonyl)pyrrolidine-1-carboxylate as a colorless oil (91 mg, 78% yield).



Step 2: To a solution of *tert*-butyl (2*S*,4*R*)-4-(4-bromobenzyl)-2-((*R*)-4,4-difluoro-2-(methoxycarbonyl)pyrrolidine-1-carbonyl)pyrrolidine-1-carboxylate (91 mg, 0.17 mmol) in THF (1.5 mL) and H_2O (1.5 mL) was added LiOH (11 mg, 0.43 mmol). After stirring for 4 h at room temperature, the reaction mixture was concentrated to remove THF. To the aq. solution was added 10% $KHSO_4$ solution, and the resulting ppt collected via vacuum filtration and washed with hexanes to afford (*R*)-1-((2*S*,4*R*)-4-(4-

bromobenzyl)-1-(*tert*-butoxycarbonyl)pyrrolidine-2-carbonyl)-4,4-difluoropyrrolidine-2-carboxylic acid as a white powder (84 mg, 95% yield).

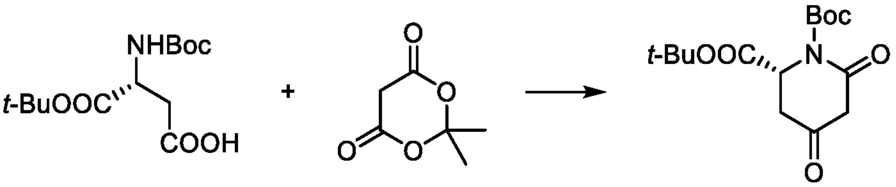


<u>Steps 3-4:</u> The title compound was prepared as a white, fluffy solid (22 mg, 48% yield) according to the procedure for Compound I-44, steps 4-5 using the appropriate starting materials.

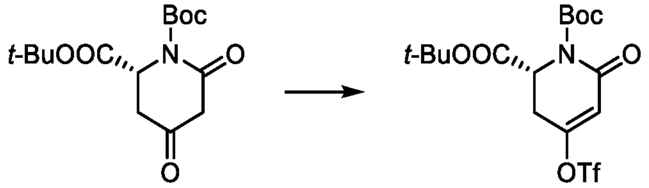
EXAMPLE 62

PREPARATION OF (2*R*,4*S*)-*N*-((*S*)-1-((4-CARBAMIMIDOYLBENZYL)AMINO)-1-OXOPROPAN-2-YL)-4-(4-FLUOROPHENYL)PIPERIDINE-2-CARBOXAMIDE DI-TRIFLUOROACETATE

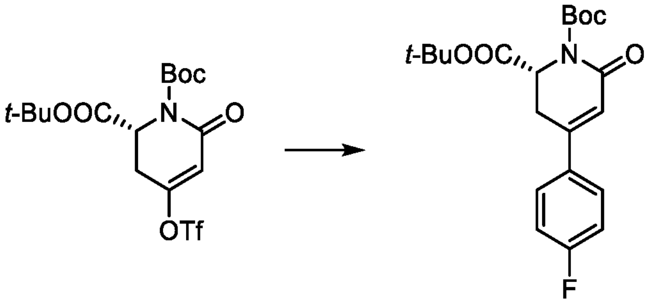
(COMPOUND I-67)



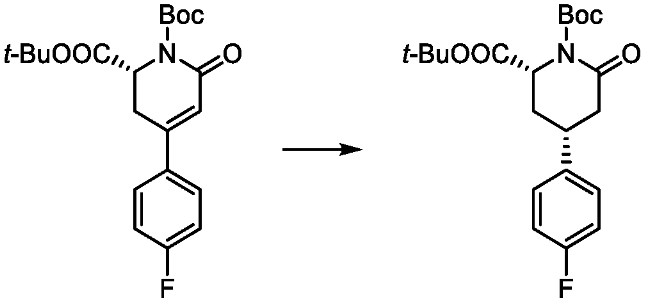
<u>Step 1</u>: To a solution of *N*-Boc-*D*-aspartic acid 1-(*tert*-butyl) ester (10 g, 35 mmol) and Meldrum's acid (5 g, 35 mmol) in anhydrous dichloromethane (140 mL, 0.25 M) at 0 °C, was added *N*,*N*-dimethylamino-4-pyridine (6.3 g, 52 mmol), followed by EDC (10 g, 52 mmol). Temperature was maintained at 0 °C for 1 h, then warmed to room temperature. Upon reaction completion (monitored by TLC), the reaction mixture was washed 4x with 1 N $KHSO_4$. The reaction mixture then dried over sodium sulfate, concentrated and rigorously dried under vacuum. The crude mixture was then dissolved in anhydrous toluene (350 mL, 0.1 M) and heated to reflux. Upon completion of reaction (monitored by TLC), the reaction mixture was cooled, and concentrated under vacuum to afford di-*tert*-butyl (*R*)-4,6-dioxopiperidine-1,2-dicarboxylate as a pale yellow solid (10.34 g, 95%).



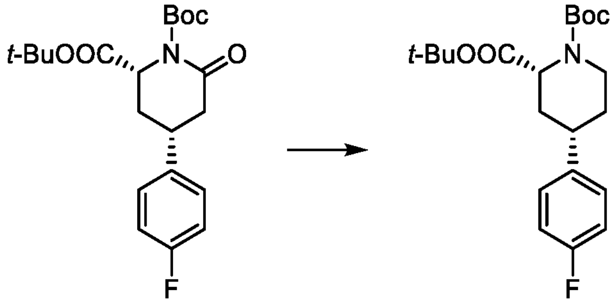
Step 2: To a solution of di-*tert*-butyl (*R*)-4,6-dioxopiperidine-1,2-dicarboxylate (10.34 g, 33 mmol,) in anhydrous dichloromethane (110 mL, 0.3 M) at 0 °C, was added *N*-phenyl-bis(trifluoromethanesulfonimide) (14 g, 40 mmol) followed by *N*,*N*-diisopropylethylamine (12 mL, 66 mmol). After stirring at 0 °C for 2 h, reaction mixture was concentrated and purified on a silica column using ethyl acetate/heptane to afford di-*tert*-butyl (*R*)-6-oxo-4-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydropyridine-1,2(2*H*)-dicarboxylate as a white solid (11.5 g, 78%).



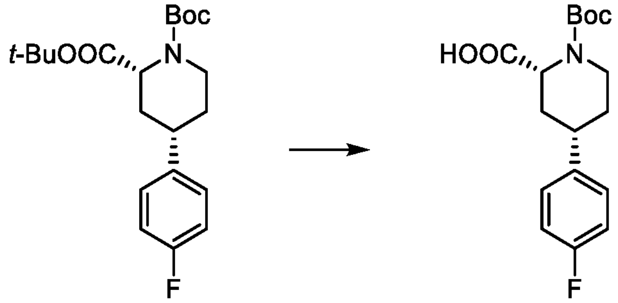
Step 3: To a solution of di-*tert*-butyl (*R*)-6-oxo-4-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydropyridine-1,2(2*H*)-dicarboxylate (500 mg, 1.1 mmol), 4-fluoroboronic acid (230 mg, 1.65 mmol) and bis(triphenylphosphine)palladium(II) chloride (40 mg, 0.055 mmol) in THF (28 mL, 0.04 M), was added potassium carbonate solution (2 N aqueous, 16 mL, 0.07 M). The solution was then sparged with argon for 10 minutes and heated to 40 °C until completion of reaction. The reaction mixture was then cooled to room temperature, diluted with ethyl acetate and partitioned. The organic solvent was then dried over sodium sulfate, concentrated and purified on a silica column using ethyl acetate/heptane to afford di-*tert*-butyl (*R*)-4-(4-fluorophenyl)-6-oxo-3,6-dihydropyridine-1,2(2*H*)-dicarboxylate as a white solid (410 mg, 93%).



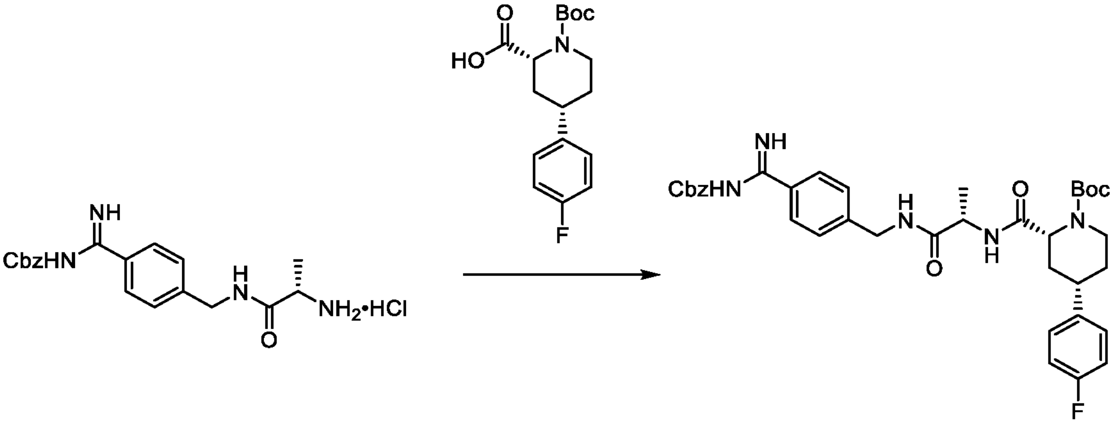
Step 4: A solution of di-*tert*-butyl (*R*)-4-(4-fluorophenyl)-6-oxo-3,6-dihydropyridine-1,2(2*H*)-dicarboxylate (410 mg, 1 mmol) and 10% Pd/C (41 mg) in ethyl acetate (5 mL, 0.2 M) was sparged with argon for 10 minutes, followed by hydrogen for 10 min. The reaction mixture was stirred under H_2 overnight. The reaction mixture then sparged with argon for 10 min and filtered over Celite. The filtrate was then concentrated under vacuum to afford di-*tert*-butyl (2*R*,4*R*)-4-(4-fluorophenyl)-6-oxopiperidine-1,2-dicarboxylate as a white solid which was carried forward without further purification.



Step 5: To a solution of crude di-*tert*-butyl (2*R*,4*R*)-4-(4-fluorophenyl)-6-oxopiperidine-1,2-dicarboxylate (395 mg, 1 mmol) in anhydrous THF (6.3 mL, 0.16 M) at 0 °C, was added borane-dimethylsulfide (2 M in THF, 2.6 mL, 5.2 mmol) dropwise and the reaction mixture was allowed to warm to room temperature overnight. The reaction mixture was then cooled to 0 °C and 1 mL methanol was added to quench the reaction. After 10 minutes stirring, the reaction mixture was concentrated and purified on a silica column using ethyl acetate/heptane to afford di-*tert*-butyl (2*R*,4*S*)-4-(4-fluorophenyl)piperidine-1,2-dicarboxylate (260 mg, 66% over two steps) as a white solid.

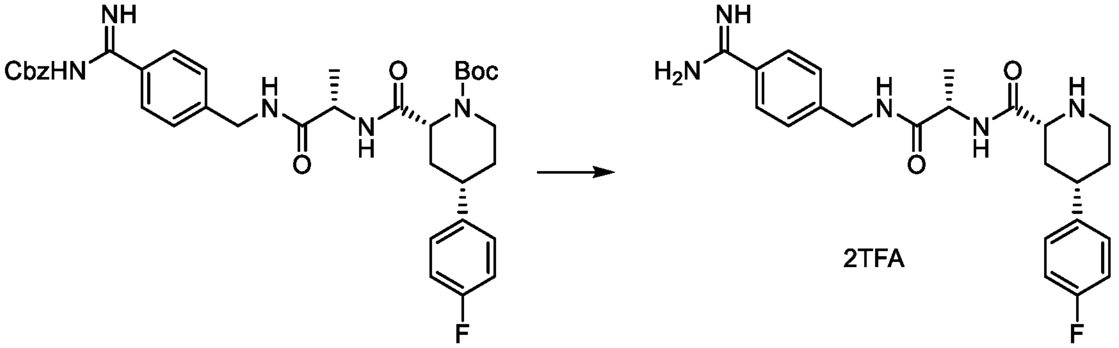


Step 6: To a solution of di-*tert*-butyl (2*R*,4*S*)-4-(4-fluorophenyl)piperidine-1,2-dicarboxylate (260 mg, 0.69 mmol), was added HCl (4 M in dioxane, 3.4 mL) to the reaction mixture stirred until reaction was complete as monitored by LCMS. The reaction mixture was then concentrated and re-dissolved in dioxane (1.3 mL, 0.5 M) and aqueous sodium hydroxide (1 N, 2.8 mL, 0.25 M). Boc$_2$O (160 mg, 0.72 mmol) was added and the mixture was stirred overnight. The reaction mixture was acidified with 1 M potassium bisulfate and extracted three times with ethyl acetate. The organic layer was then concentrated under vacuum to afford (2*R*,4*S*)-1-(*tert*-butoxycarbonyl)-4-(4-fluorophenyl)piperidine-2-carboxylic acid (159 mg, 71% over two steps) as a white solid.



Step 7: To a solution of (2*R*,4*S*)-1-(*tert*-butoxycarbonyl)-4-(4-fluorophenyl)piperidine-2-carboxylic acid (100 mg, 0.3 mmol) and (*S*)-1-((4-(*N*-((benzyloxy)carbonyl)carbamimidoyl)benzyl)amino)-1-oxopropan-2-aminium chloride (145 mg, 0.37 mmol, prepared according to Compound I-13, steps 5-11) in anhydrous *N*,*N*-dimethylformamide (7.4 mL, 0.05 M) was added diisopropylethylamine (220 µL, 1.2 mmol) followed by hydroxybenzotriazole (50 mg, 0.37 mmol) and 1-ethyl-3-(3-

dimethylaminopropyl)carbodiimide (71 mg, 0.37 mmol). After stirring overnight, the reaction mixture was diluted with ethyl acetate then extracted with sat. NH_4Cl, sat. $NaHCO_3$, water (2 times), and brine. The organic layer was then concentrated and purified on a silica column using ethyl acetate/heptane to afford *tert*-butyl (2*R*,4*S*)-2-(((*S*)-1-((4-(*N*-((benzyloxy)carbonyl)carbamimidoyl)benzyl)amino)-1-oxopropan-2-yl)carbamoyl)-4-(4-fluorophenyl)piperidine-1-carboxylate (110 mg, 54%).



Step 8: A solution of *tert*-butyl (2*R*,4*S*)-2-(((*S*)-1-((4-(*N*-((benzyloxy)carbonyl)carbamimidoyl)benzyl)amino)-1-oxopropan-2-yl)carbamoyl)-4-(4-fluorophenyl)piperidine-1-carboxylate (55 mg, 0.08 mmol) in dichloromethane (400 μL, 0.2 M) was added trifluoroacetic acid (130 μL, 1.7 mmol). After stirring for 1-3 h, the reaction was complete as monitored by LCMS. The reaction mixture was concentrated to dryness and re-dissolved in anhydrous methanol (800 μL, 0.1 M) to which 10% Pd/C (20 mg) was added. The reaction mixture was sparged with argon for 10 minutes, followed by H_2 for 10 minutes. The reaction mixture was stirred under H_2 for approximately 30 min until reaction completion which was monitored by LCMS. The reaction mixture was then sparged with argon for 10 minutes and filtered over Celite. The filtrate was then concentrated under vacuum to afford di-*tert*-butyl (2*R*,4*R*)-4-(4-fluorophenyl)-6-oxopiperidine-1,2-dicarboxylate (53.6 mg, quant. over 2 steps) as a white solid powder following lyophilization.

EXAMPLE 63

PREPARATION OF (2*R*,4*S*)-4-([1,1'-BIPHENYL]-3-YL)-*N*-((*S*)-1-((4-CARBAMIMIDOYLBENZYL)AMINO)-1-OXOPROPAN-2-YL)PIPERIDINE-2-CARBOXAMIDE DI-TRIFLUOROACETATE (COMPOUND I-68)

(2*R*,4*S*)-4-([1,1'-Biphenyl]-3-yl)-*N*-((*S*)-1-((4-carbamimidoylbenzyl)amino)-1-oxopropan-2-yl)piperidine-2-carboxamide di-trifluoroacetate was synthesized according to the procedures for Compound I-67.

EXAMPLE 64

PREPARATION OF (2*R*,4*S*)-4-([1,1'-BIPHENYL]-4-YL)-*N*-((*S*)-1-((4-CARBAMIMIDOYLBENZYL)AMINO)-1-OXOPROPAN-2-YL)PIPERIDINE-2-CARBOXAMIDE DI-TRIFLUOROACETATE (COMPOUND I-69)

(2*R*,4*S*)-4-([1,1'-Biphenyl]-4-yl)-*N*-((*S*)-1-((4-carbamimidoylbenzyl)amino)-1-oxopropan-2-yl)piperidine-2-carboxamide di-trifluoroacetate was synthesized according to the procedures for Compound I-67.

EXAMPLE 65

PREPARATION OF (2*R*,4*S*)-*N*-((*S*)-1-((4-CARBAMIMIDOYLBENZYL)AMINO)-1-OXOPROPAN-2-YL)-4-(NAPHTHALEN-2-YL)PIPERIDINE-2-CARBOXAMIDE DI-TRIFLUOROACETATE (COMPOUND I-70)

(2*R*,4*S*)-*N*-((*S*)-1-((4-Carbamimidoylbenzyl)amino)-1-oxopropan-2-yl)-4-(naphthalen-2-yl)piperidine-2-carboxamide di-trifluoroacetate was synthesized according to the procedures for Compound I-67.

EXAMPLE 66

PREPARATION OF (2*R*,4*S*)-4-(BENZO[B]THIOPHEN-2-YL)-*N*-((*S*)-1-((4-CARBAMIMIDOYLBENZYL)AMINO)-1-OXOPROPAN-2-YL)PIPERIDINE-2-CARBOXAMIDE DI-TRIFLUOROACETATE (COMPOUND I-71)

(2*R*,4*S*)-4-(Benzo[b]thiophen-2-yl)-*N*-((*S*)-1-((4-carbamimidoylbenzyl)amino)-1-oxopropan-2-yl)piperidine-2-carboxamide di-trifluoroacetate was synthesized according to the procedures for Compound I-67.

EXAMPLE 67

PREPARATION OF (2*R*,4*S*)-*N*-((*S*)-1-((4-CARBAMIMIDOYLBENZYL)AMINO)-1-OXOPROPAN-2-YL)-4-(4-(PYRIDIN-3-YL)PHENYL)PIPERIDINE-2-CARBOXAMIDE DI-TRIFLUOROACETATE (COMPOUND I-72)

(2*R*,4*S*)-*N*-((*S*)-1-((4-Carbamimidoylbenzyl)amino)-1-oxopropan-2-yl)-4-(4-(pyridin-3-yl)phenyl)piperidine-2-carboxamide di-trifluoroacetate was synthesized according to the procedures for Compound I-67.

EXAMPLE 68

PREPARATION OF (2*R*,4*S*)-*N*-((*S*)-1-(((1*H*-PYRROLO[3,2-C]PYRIDIN-2-YL)METHYL)AMINO)-1-OXOPROPAN-2-YL)-4-(4-(PYRIDIN-3-YL)PHENYL)PIPERIDINE-2-CARBOXAMIDE TRI-TRIFLUOROACETATE (COMPOUND I-73)

(2*R*,4*S*)-*N*-((*S*)-1-(((1*H*-Pyrrolo[3,2-c]pyridin-2-yl)methyl)amino)-1-oxopropan-2-yl)-4-(4-(pyridin-3-yl)phenyl)piperidine-2-carboxamide tri-trifluoroacetate was synthesized according to the procedures for Compound I-67 except that in step 7, (*S*)-*N*-((1*H*-pyrrolo[3,2-c]pyridin-2-yl)methyl)-2-aminopropanamide di-trifluoroacetate (prepared according to the procedures for synthesizing Compound I-2, steps 1-6) was used as the amine coupling partner. Additionally in step 8, no hydrogenation was performed.

EXAMPLE 69

PREPARATION OF (2*R*,4*S*)-*N*-((*S*)-1-(((1*H*-PYRROLO[3,2-C]PYRIDIN-2-YL)METHYL)AMINO)-1-OXOPROPAN-2-YL)-4-([1,1'-BIPHENYL]-4-YL)PIPERIDINE-2-CARBOXAMIDE DI-TRIFLUOROACETATE (COMPOUND I-74)

(2*R*,4*S*)-*N*-((*S*)-1-(((1*H*-Pyrrolo[3,2-c]pyridin-2-yl)methyl)amino)-1-oxopropan-2-yl)-4-([1,1'-biphenyl]-4-yl)piperidine-2-carboxamide di-trifluoroacetate was synthesized according to the procedures for Compound I-73.

EXAMPLE 70

PREPARATION OF (2*R*,4*S*)-*N*-((*S*)-1-((4-CARBAMIMIDOYLBENZYL)AMINO)-1-OXOPROPAN-2-YL)-4-(4-(3,5-DIMETHYL-1*H*-PYRAZOL-1-YL)PHENYL)PIPERIDINE-2-CARBOXAMIDE DIHYDROCHLORIDE (COMPOUND I-75)

(2*R*,4*S*)-*N*-((*S*)-1-((4-Carbamimidoylbenzyl)amino)-1-oxopropan-2-yl)-4-(4-(3,5-dimethyl-1*H*-pyrazol-1-yl)phenyl)piperidine-2-carboxamide dihydrochloride was synthesized according to the procedures for Compound I-67 except that in step 8, HCl in isopropanol was used in place of trifluoroacetic acid and anhydrous methanol was used as the solvent.

EXAMPLE 71

PREPARATION OF (2*R*,4*S*)-*N*-((*S*)-1-((4-CARBAMIMIDOYLBENZYL)AMINO)-1-OXOPROPAN-2-YL)-4-(4-MORPHOLINOPHENYL)PIPERIDINE-2-CARBOXAMIDE DIHYDROCHLORIDE (COMPOUND I-76)

(2*R*,4*S*)-*N*-((*S*)-1-((4-Carbamimidoylbenzyl)amino)-1-oxopropan-2-yl)-4-(4-morpholinophenyl)piperidine-2-carboxamide dihydrochloride was synthesized according to the procedures for Compound I-67.

EXAMPLE 72

PREPARATION OF (2*R*,4*S*)-4-(3-(1*H*-PYRAZOL-1-YL)PHENYL)-*N*-((*S*)-1-((4-CARBAMIMIDOYLBENZYL)AMINO)-1-OXOPROPAN-2-YL)PIPERIDINE-2-CARBOXAMIDE DIHYDROCHLORIDE (COMPOUND I-77)

(2*R*,4*S*)-4-(3-(1*H*-Pyrazol-1-yl)phenyl)-*N*-((*S*)-1-((4-carbamimidoylbenzyl)amino)-1-oxopropan-2-yl)piperidine-2-carboxamide dihydrochloride was synthesized according to the procedures for Compound I-67.

EXAMPLE 73

PREPARATION OF (2*R*,4*S*)-4-(3-(1*H*-PYRAZOL-1-YL)PHENYL)-*N*-((*S*)-1-(((6-AMINO-2-METHYLPYRIDIN-3-YL)METHYL)AMINO)-1-OXOPROPAN-2-YL)PIPERIDINE-2-CARBOXAMIDE DIHYDROCHLORIDE (COMPOUND I-78)

(2*R*,4*S*)-4-(3-(1*H*-Pyrazol-1-yl)phenyl)-*N*-((*S*)-1-(((6-amino-2-methylpyridin-3-yl)methyl)amino)-1-oxopropan-2-yl)piperidine-2-carboxamide dihydrochloride was synthesized according to the procedures for Compound I-67 except that in step 7, (*S*)-2-amino-*N*-((6-amino-2-methylpyridin-3-yl)methyl)propanamide di-trifluoroacetate (prepared according to the procedures for Compound I-44, step 4 and Compound I-1, step 7) was used as the amine coupling partner. Additionally, in step 8, no hydrogenation was performed.

EXAMPLE 74

PREPARATION OF (2*R*,4*S*)-4-(3-(1*H*-PYRAZOL-1-YL)PHENYL)-*N*-((*S*)-1-((5-CHLORO-2-(1*H*-TETRAZOL-1-YL)BENZYL)AMINO)-1-OXOPROPAN-2-YL)PIPERIDINE-2-CARBOXAMIDE DIHYDROCHLORIDE (COMPOUND I-79)

(2*R*,4*S*)-4-(3-(1*H*-Pyrazol-1-yl)phenyl)-*N*-((*S*)-1-((5-chloro-2-(1*H*-tetrazol-1-yl)benzyl)amino)-1-oxopropan-2-yl)piperidine-2-carboxamide dihydrochloride was synthesized according to the procedures for Compound I-67 except that in step 7, (*S*)-2-amino-*N*-(5-chloro-2-(1*H*-tetrazol-1-yl)benzyl)propanamide ditrifluoroacetate was used as the amine coupling partner. Additionally, in step 8, no hydrogenation was performed.

EXAMPLE 75

PREPARATION OF (2*R*,4*S*)-4-(3-(1*H*-PYRAZOL-1-YL)PHENYL)-*N*-((*S*)-1-(((1*H*-PYRROLO[3,2-C]PYRIDIN-2-YL)METHYL)AMINO)-1-OXOPROPAN-2-YL)PIPERIDINE-2-CARBOXAMIDE DIHYDROCHLORIDE (COMPOUND I-80)

(2*R*,4*S*)-4-(3-(1*H*-Pyrazol-1-yl)phenyl)-*N*-((*S*)-1-(((1*H*-pyrrolo[3,2-c]pyridin-2-yl)methyl)amino)-1-oxopropan-2-yl)piperidine-2-carboxamide dihydrochloride was synthesized according to the procedures for Compound I-67 except that in step 7, (*S*)-*N*-((1*H*-pyrrolo[3,2-c]pyridin-2-yl)methyl)-2-aminopropanamide di-trifluoroacetate (prepared according to Compound I-2, steps 1-6) was used as the amine coupling partner. Additionally, in step 8, no hydrogenation was performed.

EXAMPLE 76

PREPARATION OF (*S*)-*N*-((6-AMINO-2-METHYLPYRIDIN-3-YL)METHYL)-1-((2*R*,4*S*)-4-PHENYLPIPERIDINE-2-CARBONYL)AZETIDNE-2-CARBOXAMIDE DI-TRIFLUOROACETATE (COMPOUND I-63)

(*S*)-*N*-((6-amino-2-methylpyridin-3-yl)methyl)-1-((2*R*,4*S*)-4-phenylpiperidine-2-carbonyl)azetidine-2-carboxamide di-trifluoroacetate was synthesized according to the procedures for Compound I-67 except that in step 7, amide coupling was performed using HATU:

To (*S*)-*N*-((6-amino-2-methylpyridin-3-yl)methyl)azetidine-2-carboxamide hydrochloride (46 mg, 0.16 mmol, prepared according to the procedure for Compound I-44, step 4-5 using (*S*)-1-(*tert*-butoxycarbonyl)azetidine-2-carboxylic acid as the starting material) (2*R*,4*S*)-1-(*tert*-butoxycarbonyl)-4-phenylpiperidine-2-carboxylic acid (0.13 mmol), DIEA (120 µL, 0.7 mmol) in DMF (430 µL, 0.3 M) was added a HATU (74 mg, 0.2 mmol) with stirring at room temperature while monitoring for the consumption of starting material (16 h). The solution was diluted with ethyl acetate and washed with sat. aq NH_4Cl. The aqueous layer was extracted 2 additional times with ethyl acetate, then the organic layer was washed with H_2O and brine, dried over Na_2SO_4 and evaporated to dryness. The resulting residue was purified on an amine column using ethyl acetate, then MeOH/CH_2Cl_2 to yield *tert*-butyl (2*R*,4*S*)-2-((*S*)-2-(((6-amino-2-

methylpyridin-3-yl)methyl)carbamoyl)azetidine-1-carbonyl)-4-phenylpiperidine-1-carboxylate di-trifluoroacetate (43 mg, 53%) as an off-white film. This product was further deprotected following the procedure for Compound I-67 step 8, but without hydrogenation.

EXAMPLE 77

PREPARATION OF (*S*)-1-((2*R*,4*S*)-4-([1,1'-BIPHENYL]-4-YLMETHYL)PYRROLIDINE-2-CARBONYL)-*N*-((6-AMINO-2-METHYLPYRIDIN-3-YL)METHYL)AZETIDINE-2-CARBOXAMIDE DI-TRIFLUOROACETATE (COMPOUND I-62)

(*S*)-1-((2*R*,4*S*)-4-([1,1'-Biphenyl]-4-ylmethyl)pyrrolidine-2-carbonyl)-*N*-((6-amino-2-methylpyridin-3-yl)methyl)azetidine-2-carboxamide di-trifluoroacetate was synthesized according to the procedures from step 7 onward for Compound I-63 except that the acid used in the coupling in step 7 was (2*R*,4*S*)-4-([1,1'-biphenyl]-4-ylmethyl)pyrrolidine-2-carboxylic acid (prepared according to the procedures for Compound I-2, steps 1-4).

EXAMPLE 78

PREPARATION OF (*S*)-1-((2*R*,4*R*)-4-([1,1'-BIPHENYL]-3-YL)PYRROLIDINE-2-CARBONYL)-*N*-((6-AMINO-2-METHYLPYRIDIN-3-YL)METHYL)AZETIDINE-2-CARBOXAMIDE DI-TRIFLUOROACETATE (COMPOUND I-64)

(*S*)-1-((2*R*,4*R*)-4-([1,1'-Biphenyl]-3-yl)pyrrolidine-2-carbonyl)-*N*-((6-amino-2-methylpyridin-3-yl)methyl)azetidine-2-carboxamide di-trifluoroacetate was synthesized according to the procedures from step 7 onward Compound I-62 except that the acid used in the coupling in step 7 was (2*R*,4*R*)-4-([1,1'-biphenyl]-3-yl)pyrrolidine-2-carboxylic acid, (prepared according to the procedures for Compound I-13, steps 1-4).

EXAMPLE 79

PREPARATION OF (*S*)-*N*-(4-CARBAMIMIDOYLBENZYL)-1-((2*R*,4*S*)-4-PHENYLPIPERIDINE-2-CARBONYL)AZETIDINE-2-CARBOXAMIDE TRIFLUOROACETATE (COMPOUND I-66)

(*S*)-*N*-(4-Carbamimidoylbenzyl)-1-((2*R*,4*S*)-4-phenylpiperidine-2-carbonyl)azetidine-2-carboxamide trifluoroacetate was synthesized according to the procedures for Compound I-67 except that in step 7, benzyl (*S*)-((4-((azetidine-2-carboxamido)methyl)phenyl)(imino)methyl)carbamate hydrochloride (prepared according to the procedure for Compound I-13, steps 5-11 using (*S*)-1-(*tert*-butoxycarbonyl)azetidine-2-carboxylic acid as the starting material in step 10) was used as the coupling partner in step 7. The product was purified by reverse phase HPLC.

EXAMPLE 80

PREPARATION OF (*S*)-1-((2*R*,4*S*)-4-([1,1'-BIPHENYL]-3-YL)PIPERIDINE-2-CARBONYL)-*N*-((6-AMINO-2-METHYLPYRIDIN-3-YL)METHYL)AZETIDINE-2-CARBOXAMIDE DI-TRIFLUOROACETATE (COMPOUND I-65)

(*S*)-1-((2*R*,4*S*)-4-([1,1'-biphenyl]-3-yl)piperidine-2-carbonyl)-*N*-((6-amino-2-methylpyridin-3-yl)methyl)azetidine-2-carboxamide di-trifluoroacetate was synthesized according to the procedures for Compound I-67 except that in step 1, *N*-Boc-*D*-aspartic acid 1-methyl ester was used, and in step 7, benzyl (*S*)-((4-((azetidine-2-carboxamido)methyl)phenyl)(imino)methyl)carbamate hydrochloride (prepared according to the procedure for Compound I-44, step 4-5 using (*S*)-1-(*tert*-butoxycarbonyl)azetidine-2-carboxylic acid starting material in step 4) was used as the coupling partner in step 7. Additionally, in place of step 6, saponification was performed:

To 1-(*tert*-butyl) 2-methyl (2*R*,4*S*)-4-([1,1'-biphenyl]-3-yl)piperidine-1,2-dicarboxylate (43 mg, 0.11 mmol) in THF (2.2 mL, 0.05 M), MeOH (1.1 mL, 0.1 M), H_2O (1.1 mL, 0.1 M) was added $LiOH \cdot H_2O$ (68 mg, 1.6 mmol) with stirring at room temperature while monitoring for the consumption of starting material (16 h). The solution was brought to pH 3 with 1 N HCl, extracted 3× with ethyl acetate then dried over Na_2SO_4 and evaporated to dryness. The resulting residue was carried forward without further purification.

EXAMPLE 81

PREPARATION OF (2*R*,4*S*)-*N*-((*S*)-1-(((6-AMINO-2-METHYLPYRIDIN-3-YL)METHYL)AMINO)-1-OXOPROPAN-2-YL)-4-((4'-FLUORO-[1,1'-BIPHENYL]-3-YL)METHYL)PYRROLIDINE-2-CARBOXAMIDE DI-TRIFLUOROACETATE (COMPOUND I-81)

(2*R*,4*S*)-*N*-((*S*)-1-(((6-Amino-2-methylpyridin-3-yl)methyl)amino)-1-oxopropan-2-yl)-4-((4'-fluoro-[1,1'-biphenyl]-3-yl)methyl)pyrrolidine-2-carboxamide di-trifluoroacetate was synthesized according to the procedure for Compound I-44.

EXAMPLE 82

PREPARATION OF (2*R*,4*S*)-*N*-((*S*)-1-(((3-CHLORO-1*H*-PYRROLO[2,3-B]PYRIDIN-5-YL)METHYL)AMINO)-1-OXOPROPAN-2-YL)-4-(3-CHLOROBENZYL)PYRROLIDINE-2-CARBOXAMIDE DIHYDROCHLORIDE (COMPOUND I-82)

(2*R*,4*S*)-*N*-((*S*)-1-(((3-Chloro-1*H*-pyrrolo[2,3-b]pyridin-5-yl)methyl)amino)-1-oxopropan-2-yl)-4-(3-chlorobenzyl)pyrrolidine-2-carboxamide di-hydrochloride was synthesized according to the procedures for Compound I-25.

EXAMPLE 83

PREPARATION OF (2*R*,4*R*)-*N*-((*S*)-1-(((3-CHLORO-1*H*-PYRROLO[2,3-B]PYRIDIN-5-YL)METHYL)AMINO)-1-OXOPROPAN-2-YL)-4-((5-CHLOROTHIOPHEN-2-YL)METHYL)PYRROLIDINE-2-CARBOXAMIDE DIHYDROCHLORIDE (COMPOUND I-83)

(2*R*,4*R*)-*N*-((*S*)-1-(((3-Chloro-1*H*-pyrrolo[2,3-b]pyridin-5-yl)methyl)amino)-1-oxopropan-2-yl)-4-((5-chlorothiophen-2-yl)methyl)pyrrolidine-2-carboxamide dihydrochloride was synthesized according to the procedures for Compound I-25.

EXAMPLE 84

PREPARATION OF (2*R*,4*R*)-*N*-((*S*)-1-(((3-CHLORO-1-METHYL-1*H*-PYRROLO[2,3-B]PYRIDIN-5-YL)METHYL)AMINO)-1-OXOPROPAN-2-YL)-4-((5-CHLOROTHIOPHEN-2-YL)METHYL)PYRROLIDINE-2-CARBOXAMIDE DIHYDROCHLORIDE (COMPOUND I-84)

(2*R*,4*R*)-*N*-((*S*)-1-(((3-Chloro-1-methyl-1*H*-pyrrolo[2,3-b]pyridin-5-yl)methyl)amino)-1-oxopropan-2-yl)-4-((5-chlorothiophen-2-yl)methyl)pyrrolidine-2-carboxamide dihydrochloride was synthesized according to the procedures for Compound I-44 except using (*S*)-2-amino-*N*-((3-chloro-1-methyl-1*H*-pyrrolo[2,3-b]pyridin-5-yl)methyl)propenamide instead of (*S*)-2-amino-*N*-((6-amino-2-methylpyridin-3-yl)methyl)propanamide.

EXAMPLE 85

PREPARATION OF (2*R*,4*S*)-*N*-((*S*)-1-(((6-AMINO-2-METHYLPYRIDIN-3-YL)METHYL)AMINO)-1-OXOPROPAN-2-YL)-4-((5-METHYLNAPHTHALEN-2-YL)METHYL)PYRROLIDINE-2-CARBOXAMIDE DIHYDROCHLORIDE (COMPOUND I-80)

(2*R*,4*S*)-*N*-((*S*)-1-(((6-Amino-2-methylpyridin-3-yl)methyl)amino)-1-oxopropan-2-yl)-4-((5-methylnaphthalen-2-yl)methyl)pyrrolidine-2-carboxamide dihydrochloride was synthesized according to the procedures for Compound I-44.

EXAMPLE 86

PREPARATION OF (2*R*,4*R*)-*N*-((*S*)-1-(((6-AMINO-2-METHYLPYRIDIN-3-YL)METHYL)AMINO)-1-OXOPROPAN-2-YL)-4-((5-CYANOTHIOPHEN-2-YL)METHYL)PYRROLIDINE-2-CARBOXAMIDE DIHYDROCHLORIDE (COMPOUND I-86)

(2*R*,4*R*)-*N*-((*S*)-1-(((6-Amino-2-methylpyridin-3-yl)methyl)amino)-1-oxopropan-2-yl)-4-((5-cyanothiophen-2-yl)methyl)pyrrolidine-2-carboxamide dihydrochloride was synthesized according to the procedures for Compound I-44.

EXAMPLE 87

PREPARATION OF (2*R*,4*R*)-*N*-((S)-1-(((6-AMINO-2-METHYLPYRIDIN-3-YL)METHYL)AMINO)-1-OXOPROPAN-2-YL)-4-((4-CHLOROTHIOPHEN-2-YL)METHYL)PYRROLIDINE-2-CARBOXAMIDE DIHYDROCHLORIDE (COMPOUND I-87)

(2*R*,4*R*)-*N*-((*S*)-1-(((6-Amino-2-methylpyridin-3-yl)methyl)amino)-1-oxopropan-2-yl)-4-((4-chlorothiophen-2-yl)methyl)pyrrolidine-2-carboxamide dihydrochloride was synthesized according to the procedures for Compound I-44.

EXAMPLE 88

PREPARATION OF (2*R*,4*S*)-*N*-((*S*)-1-(((6-AMINO-2-METHYLPYRIDIN-3-YL)METHYL)AMINO)-1-OXOPROPAN-2-YL)-4-(3-CHLORO-2,4-DIFLUOROBENZYL)PYRROLIDINE-2-CARBOXAMIDE DIHYDROCHLORIDE (COMPOUND I-88)

(2*R*,4*S*)-*N*-((*S*)-1-(((6-Amino-2-methylpyridin-3-yl)methyl)amino)-1-oxopropan-2-yl)-4-(3-chloro-2,4-difluorobenzyl)pyrrolidine-2-carboxamide dihydrochloride was synthesized containing an approximately 13% unknown diastereomer according to the procedures for Compound I-44.

EXAMPLE 89

PREPARATION OF (2*R*,4*R*)-*N*-((*S*)-1-(((6-AMINO-2-METHYLPYRIDIN-3-YL)METHYL)AMINO)-1-OXOPROPAN-2-YL)-4-((5-(TRIFLUOROMETHYL)THIOPHEN-2-YL)METHYL)PYRROLIDINE-2-CARBOXAMIDE DIHYDROCHLORIDE (COMPOUND I-89)

(2*R*,4*R*)-*N*-((*S*)-1-(((6-Amino-2-methylpyridin-3-yl)methyl)amino)-1-oxopropan-2-yl)-4-((5-(trifluoromethyl)thiophen-2-yl)methyl)pyrrolidine-2-carboxamide dihydrochloride was synthesized according to the procedures for Compound I-44.

EXAMPLE 90

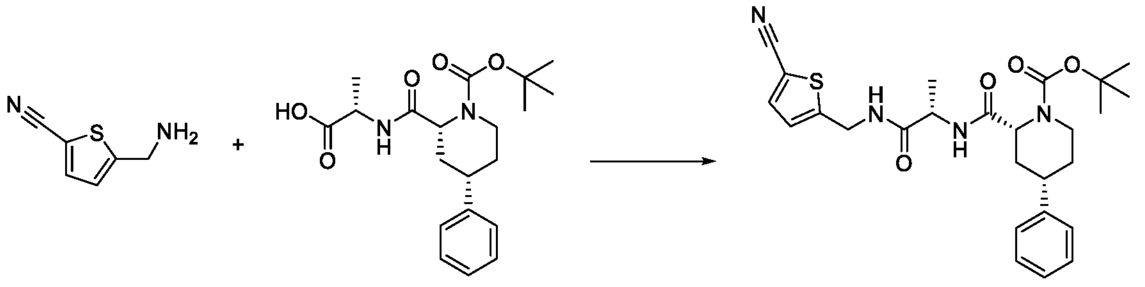
PREPARATION OF (2*R*,4*S*)-*N*-((*S*)-1-(((1*H*-PYRROLO[3,2-C]PYRIDIN-2-YL)METHYL)AMINO)-1-OXOPROPAN-2-YL)-4-PHENYLPIPERIDINE-2-CARBOXAMIDE DI-TRIFLUOROACETATE

(COMPOUND I-90)

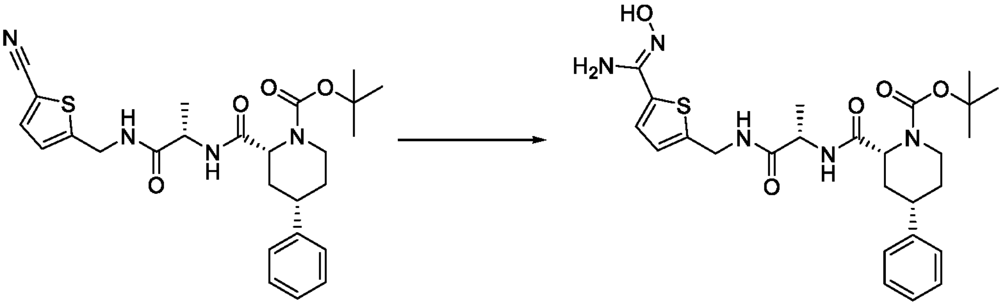
(2*R*,4*S*)-*N*-((*S*)-1-(((1*H*-Pyrrolo[3,2-c]pyridin-2-yl)methyl)amino)-1-oxopropan-2-yl)-4-phenylpiperidine-2-carboxamide di-trifluoroacetate was synthesized according to the procedures for Compound I-2, steps 5-7 and Compound I-39, steps 1-2.

EXAMPLE 91

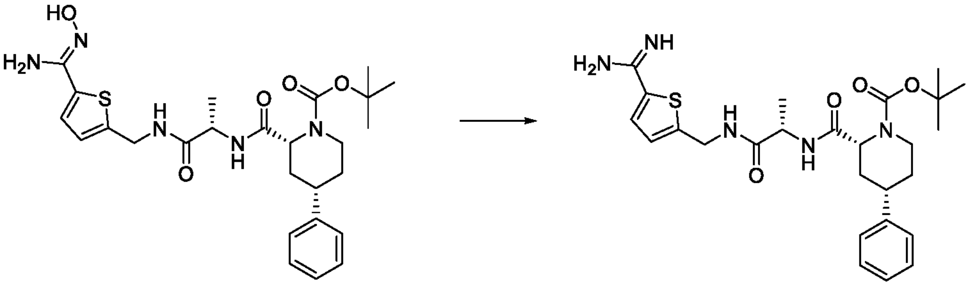
PREPARATION (2*R*,4*S*)-*N*-((*S*)-1-(((5-CARBAMIMIDOYLTHIOPHEN-2-YL)METHYL)AMINO)-1-OXOPROPAN-2-YL)-4-PHENYLPIPERIDINE-2-CARBOXAMIDE DI-TRIFLUOROACETATE SALT (COMPOUND I-91)



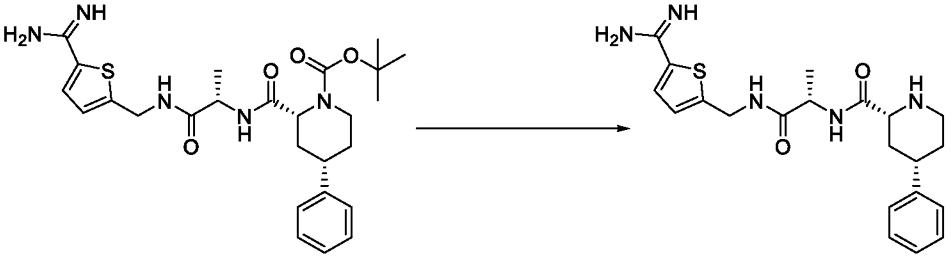
Step 1: A solution consisting of (*(2R,4S)*-1-(*tert*-butoxycarbonyl)-4-phenylpiperidine-2-carbonyl)-*L*-alanine (100 mg, 0.27 mmol) and DCC (60 mg, 0.29 mmol) in DCM (6 mL) was stirred for 1 h at RT. The resultant slurry was then added to a suspension of 5-(aminomethyl)thiophene-2-carbonitrile hydrochloride (60 mg, 0.33 mmol) in saturated aqueous $NaHCO_3$ (6 mL) and the mixture was stirred for 1 h at RT. The mixture was partitioned and the aqueous portion was extracted with DCM (3 × 40 mL). The organics layers were combined, dried over $MgSO_4$, filtered and concentrated. The crude material was purified via flash chromatography (SiO_2, 12 g) using a gradient of 0-100% heptane/ ethyl acetate to afford tert-butyl (2*R*,4*S*)-2-(((*S*)-1-(((5-cyanothiophen-2-yl)methyl)amino)-1-oxopropan-2-yl)carbamoyl)-4-phenylpiperidine-1-carboxylate (130 mg, 97%) as an off-white solid.



Step 2: To a suspension of tert-butyl (2*R*,4*S*)-2-(((*S*)-1-(((5-cyanothiophen-2-yl)methyl)amino)-1-oxopropan-2-yl)carbamoyl)-4-phenylpiperidine-1-carboxylate (100 mg, 0.2 mmol) and hydroxylamine hydrochloride (56 mg, 0.8 mmol) in methanol (2 mL) was added DIEA (139 µL, 0.8 mmol). The mixture was heated to 69 °C and stirred at this temperature overnight. After the reaction was allowed to cool to RT and concentrated *in vacuo*, the residue was triturated in water (5 mL) and the solid was collected via filtration. The solid was washed with water (2 × 5 mL) and dried *in vacuo* to afford *tert*-butyl (2*R*,4*S*)-2-(((*S*)-1-(((5-((*Z*)-*N*'-hydroxycarbamimidoyl)thiophen-2-yl)methyl)amino)-1-oxopropan-2-yl)carbamoyl)-4-phenylpiperidine-1-carboxylate (100 mg, 94%) as an off-white solid.



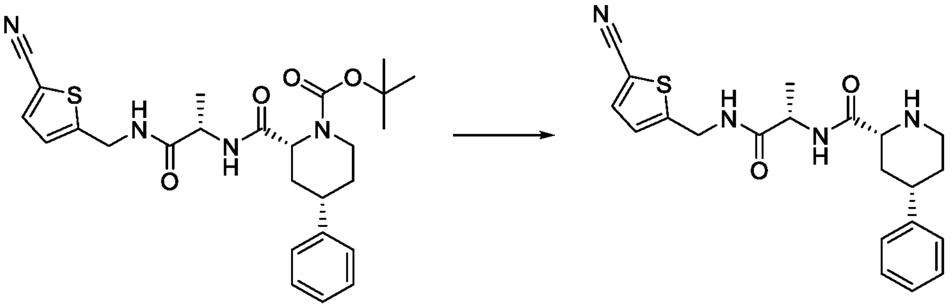
Step 3: A solution of *tert*-butyl (2*R*,4*S*)-2-(((*S*)-1-(((5-((*Z*)-*N*'-hydroxycarbamimidoyl)thiophen-2-yl)methyl)amino)-1-oxopropan-2-yl)carbamoyl)-4-phenylpiperidine-1-carboxylate (67 mg, 0.13 mmol) and acetic anhydride (19 µL, 0.20 mmol) in acetic acid (300 µL, 5.06 mmol) was combined with 10% Pd/C (7 mg) then kept under hydrogen (1 atm) overnight at RT. The reaction mixture was filtered through Celite, washed thoroughly with MeOH and the filtrate concentrated to dryness *in vacuo* to afford *tert*-butyl (2*R*,4*S*)-2-(((*S*)-1-(((5-carbamimidoylthiophen-2-yl)methyl)amino)-1-oxopropan-2-yl)carbamoyl)-4-phenylpiperidine-1-carboxylate acetate (40 mg, 53%) as an off-white solid.



Step 4: A solution of *tert*-butyl (2*R*,4*S*)-2-(((*S*)-1-(((5-carbamimidoylthiophen-2-yl)methyl)amino)-1-oxopropan-2-yl)carbamoyl)-4-phenylpiperidine-1-carboxylate acetate (40 mg, 0.07 mmol) in 6 M HCl/IPA (1 mL) was stirred at RT for 1.5 h. The reaction was concentrated and the residue purified via preparatory HPLC to afford (2*R*,4*S*)-*N*-((*S*)-1-(((5-carbamimidoylthiophen-2-yl)methyl)amino)-1-oxopropan-2-yl)-4-phenylpiperidine-2-carboxamide di-trifluoroacetate (9.9 mg, 29%) as an off-white solid.

EXAMPLE 92

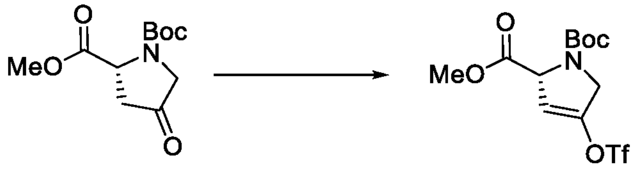
PREPARATION OF (2*R*,4*S*)-*N*-((*S*)-1-(((5-CYANOTHIOPHEN-2-YL)METHYL)AMINO)-1-OXOPROPAN-2-YL)-4-PHENYLPIPERIDINE-2-CARBOXAMIDE HYDROCHLORIDE SALT (COMPOUND I-92)



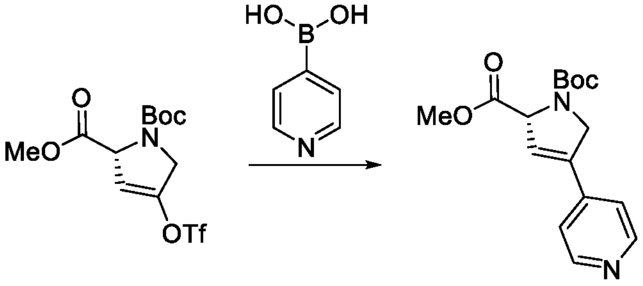
tert-butyl (2*R*,4*S*)-2-(((*S*)-1-(((5-cyanothiophen-2-yl)methyl)amino)-1-oxopropan-2-yl)carbamoyl)-4-phenylpiperidine-1-carboxylate was treated using the procedure described in Example 91 Step 4 to afford (2*R*,4*S*)-*N*-((*S*)-1-(((5-Cyanothiophen-2-yl)methyl)amino)-1-oxopropan-2-yl)-4-phenylpiperidine-2-carboxamide hydrochloride (20 mg, 76%).

EXAMPLE 93

PREPARATION OF (2*R*,4*S*)-*N*-((*S*)-1-((4-CARBAMIMIDOYLBENZYL)AMINO)-1-OXOPROPAN-2-YL)-4-(PYRIDIN-4-YL)PYRROLIDINE-2-CARBOXAMIDE DI-FLUOROACETATE (COMPOUND I-95)

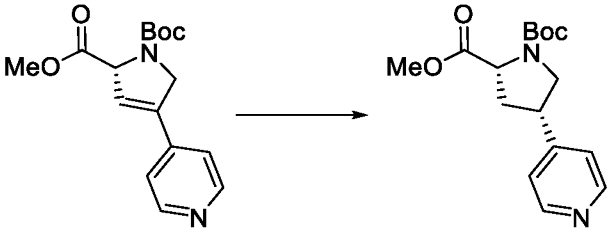


<u>Step 1</u>: To a −78 °C solution of 1-(*tert*-butyl) 2-methyl (*R*)-4-oxopyrrolidine-1,2-dicarboxylate (1.50 g, 6.16 mmol) in THF (15 mL, 0.4 M) was slowly added lithium bis(trimethylsilyl)amide (1.0 M in THF, 7.40 mL, 7.40 mmol) under Ar. After stirring for 1 h at the same temperature, Comins' reagent (2.99 g, 7.40 mmol) in THF (5 mL) was added and the stirring continued for an additional 1 h. After stirring for 18 h at −20 °C, the reaction was quenched by addition of 20 mL H_2O and extracted with diethyl ether. The combined extacts were washed with 2 N NaOH solution, dried over anhyd Na_2SO_4, filtered, and concd under vacuum. The residue was purified by chromatography (0-100% EtOAc-hexanes) to give 1-(*tert*-butyl) 2-methyl (*R*)-4-(((trifluoromethyl)sulfonyl)oxy)-2,5-dihydro-1*H*-pyrrole-1,2-dicarboxylate (1.85 g, 80% yield).

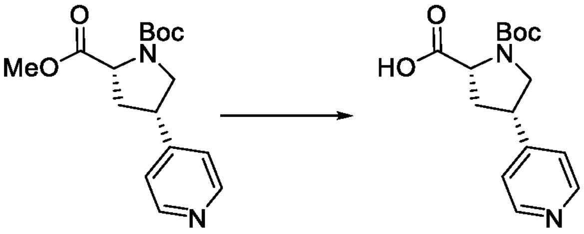


<u>Step 2</u>: To a solution of 1-(*tert*-butyl) 2-methyl (*R*)-4-(((trifluoromethyl)sulfonyl)oxy)-2,5-dihydro-1*H*-pyrrole-1,2-dicarboxylate (300 mg, 0.8 mmol) in dioxane (6 mL, 0.13 M) was added $Pd(PPh_3)_4$ (93 mg, 0.11 mmol) and pyridin-4-ylboronic acid (98 mg, 0.8 mmol) followed by K_2CO_3 (332 mg, 2.4 mmol) as an aqueous solution (in 1.2 mL H_2O). The mixture was heated to 80 °C and stirred for 30 min by which time the solution had turned from orange to dark black, indicating completion. The reaction mixture was cooled to RT and concd under vacuum. The residue

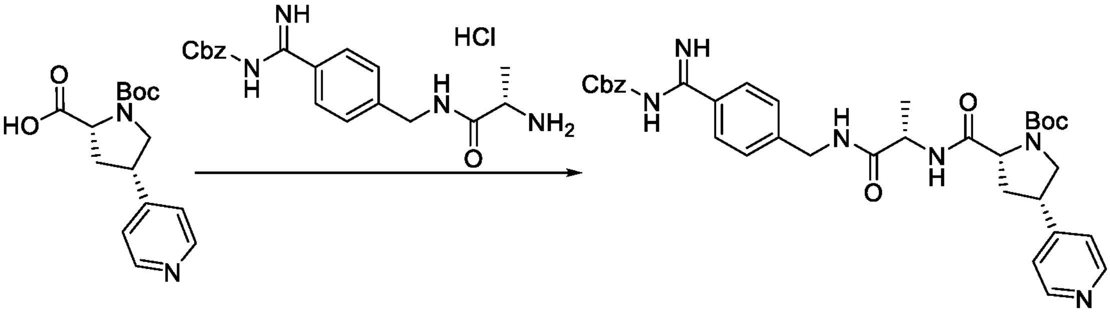
was diluted with H_2O and the aqueous layer was extracted with EtOAc. The combined organic extracts were dried over anhyd Na_2SO_4, filtered, and concd under vacuum. The residue was purified by chromatography (0-100% EtOAc-hexanes) to give 1-(*tert*-butyl) 2-methyl (*R*)-4-(pyridin-4-yl)-2,5-dihydro-1*H*-pyrrole-1,2-dicarboxylate (234 mg, 96% yield).



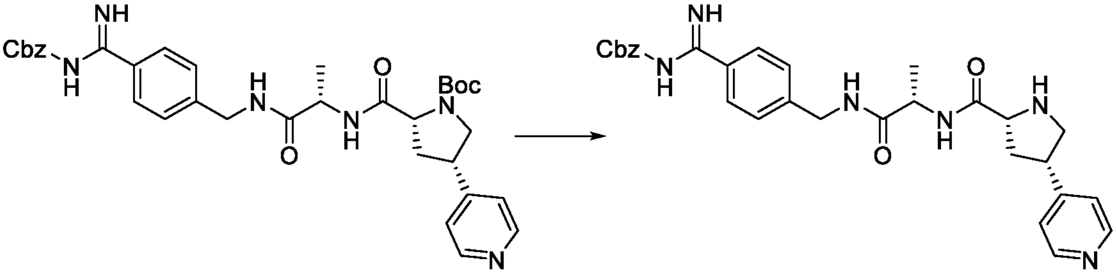
Step 3: 1-(*tert*-Butyl) 2-methyl (*R*)-4-(pyridin-4-yl)-2,5-dihydro-1*H*-pyrrole-1,2-dicarboxylate (234 mg, 0.77 mmol) in MeOH (50 mL, 0.07 M) was degassed with a stream of Ar for 2 min. 10% Pd/C (70 mg) was added, a vacuum was pulled for 1 min, and a balloon of H_2 was added. After stirring for 16 h at RT, the catalyst was removed by filtration and the solution was evaporated to give 1-(*tert*-butyl) 2-methyl (2*R*,4*S*)-4-(pyridin-4-yl)pyrrolidine-1,2-dicarboxylate, 235 mg, 99% yield).



Step 4: To a solution of 1-(*tert*-butyl) 2-methyl (2*R*,4*S*)-4-(pyridin-4-yl)pyrrolidine-1,2-dicarboxylate (235 mg, 0.76 mmol) in THF (20 mL), MeOH (10 mL) and H_2O (10 mL) was added LiOH (275 mg, 11.5 mmol). After stirring for 3 h at RT the pH was adjusted to approximately 3-4 using 11 mL of 1 N HCl and the mixture was concd. The aqueous mixture was first extracted with EtOAc then CH_2Cl_2. The combined extracts were washed with brine, dried over anhyd Na_2SO_4, filtered and concd under vacuum to give the crude (2*R*,4*S*)-1-(*tert*-butoxycarbonyl)-4-(pyridin-4-yl)pyrrolidine-2-carboxylic acid (7 mg, 3% yield) which was used in the next step without further purification.

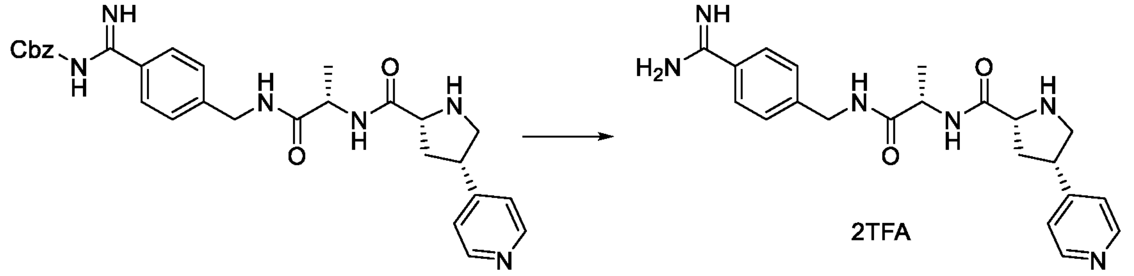


Step 5: To a solution of (2*R*,4*S*)-1-(*tert*-butoxycarbonyl)-4-(pyridin-4-yl)pyrrolidine-2-carboxylic acid (7 mg, 0.02 mmol) in DMF (2 mL, 0.01 M) were added HOBt (4 mg, 0.03 mmol), DIEA (0.014 mL, 0.08 mmol) and EDC·HCl (5 mg, 0.06 mmol). After stirring for 30 min, benzyl (*S*)-((4-((2-aminopropanamido)methyl)phenyl)(imino)methyl)carbamate hydrochloride (10 mg, 0.03 mmol, prepared according to the procedure described in PCT Publication No. WO2019/231935) was added. After stirring for 16 h at RT, the reaction mixture was concd and the residue was partitioned with EtOAc and 10% $KHSO_4$. The aqueous layer was extracted with CH_2Cl_2 and the organic layer was washed with H_2O, sat. $NaHCO_3$, and brine. After drying over anhyd Na_2SO_4, the organic layer was filtered, concd and the residue purified by chromatography (0-100% EtOAc-hexanes) to give *tert*-butyl (4*S*)-2-(((*S*)-1-((4-(*N*-((benzyloxy)carbonyl)carbamimidoyl)benzyl)amino)-1-oxopropan-2-yl)carbamoyl)-4-(pyridin-4-yl)pyrrolidine-1-carboxylate (12 mg, 95% yield).



Step 6: To a 0 °C solution of *tert*-butyl (4*S*)-2-(((*S*)-1-((4-(*N*-((benzyloxy)carbonyl)carbamimidoyl)benzyl)amino)-1-oxopropan-2-yl)carbamoyl)-4-(pyridin-4-yl)pyrrolidine-1-carboxylate (74 mg, 0.12 mmol) in CH_2Cl_2 (3 mL, 0.04 M) was added 20% TFA in CH_2Cl_2 (3 mL). After stirring for 3 h at RT, the reaction mixture was concd and the crude material purified by chromatography (0-100% [5% 7 N NH_3 in MeOH/CH_2Cl_2]-CH_2Cl_2) to give benzyl (imino(4-(((2*S*)-2-((4*S*)-4-(pyridin-4-

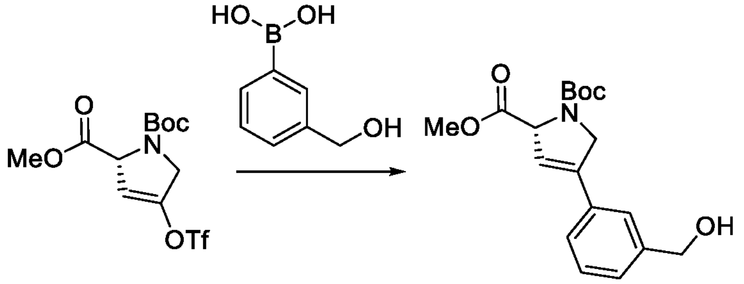
yl)pyrrolidine-2-carboxamido)propanamido)methyl)phenyl)methyl)carbamate (20 mg, 32% yield).



Step 7: A solution of benzyl (imino(4-(((2*S*)-2-((4*S*)-4-(pyridin-4-yl)pyrrolidine-2-carboxamido)propanamido)methyl)phenyl)methyl)carbamate (20 mg, 0.04 mmol) in MeOH (2 mL, 0.02 M) was degassed with a stream of Ar for 2 min. 10% Pd/C (3 mg) was added, a vacuum was pulled for 1 min and a balloon of H_2 was added. After stirring for 3 h, the catalyst was removed by filtration and the solution was evaporated. The crude material was purified using reverse-phase HPLC to give (2*R*,4*S*)-*N*-((*S*)-1-((4-carbamimidoylbenzyl)amino)-1-oxopropan-2-yl)-4-(pyridin-4-yl)pyrrolidine-2-carboxamide di-trifluoroacetate (15.1 mg, 67% yield).

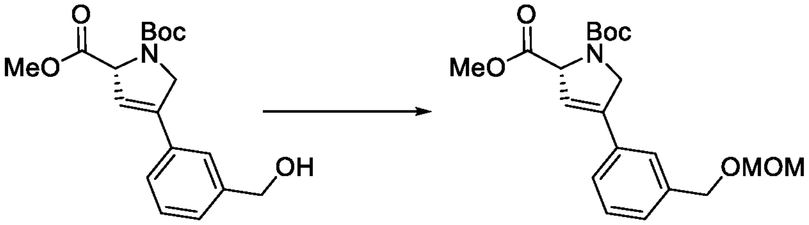
EXAMPLE 94

PREPARATION OF (2*R*,4*R*)-*N*-((*S*)-1-((4-CARBAMIMIDOYLBENZYL)AMINO)-1-OXOPROPAN-2-YL)-4-(3-(HYDROXYMETHYL)PHENYL)PYRROLIDINE-2-CARBOXAMIDE DI-TRIFLUOROACETATE (COMPOUND I-94)

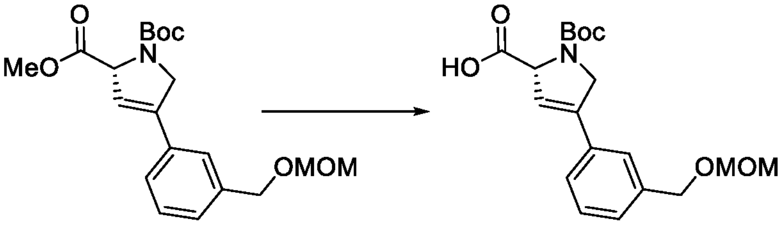


Step 1: 1-(*tert*-Butyl) 2-methyl (*R*)-4-(3-(hydroxymethyl)phenyl)-2,5-dihydro-1*H*-pyrrole-1,2-dicarboxylate was synthesized (107 mg, 72% yield) from 1-(*tert*-butyl) 2-methyl (*R*)-4-(((trifluoromethyl)sulfonyl)oxy)-2,5-dihydro-1*H*-pyrrole-1,2-dicarboxylate (167 mg, 0.45 mmol, prepared according to Example 93, step 1) and (3-

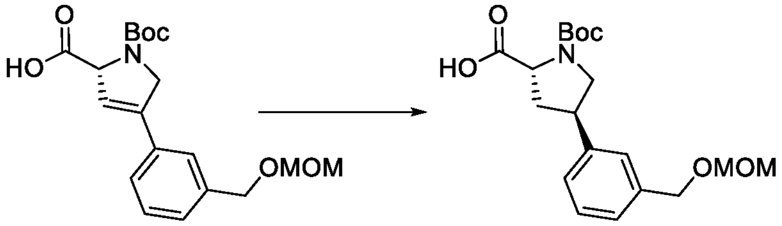
(hydroxymethyl)phenyl)boronic acid (67 mg, 0.45 mmol) according to Example 93, step 2.



Step 2: To a 0 °C solution of 1-(*tert*-butyl) 2-methyl (*R*)-4-(3-(hydroxymethyl)phenyl)-2,5-dihydro-1*H*-pyrrole-1,2-dicarboxylate (107 mg, 0.32 mmol) in CH_2Cl_2 (3 mL, 0.1 M) was added DIEA (0.11 mL, 0.64 mmol) and chloromethyl methyl ether (0.03 mL, 0.38 mmol). After stirring for 16 h at RT, the reaction mixture was washed with H_2O and extracted with CH_2Cl_2 to give the crude 1-(*tert*-butyl) 2-methyl (*R*)-4-(3-((methoxymethoxy)methyl)phenyl)-2,5-dihydro-1*H*-pyrrole-1,2-dicarboxylate (120 mg, 100% yield) which was used in the next step without further purification.

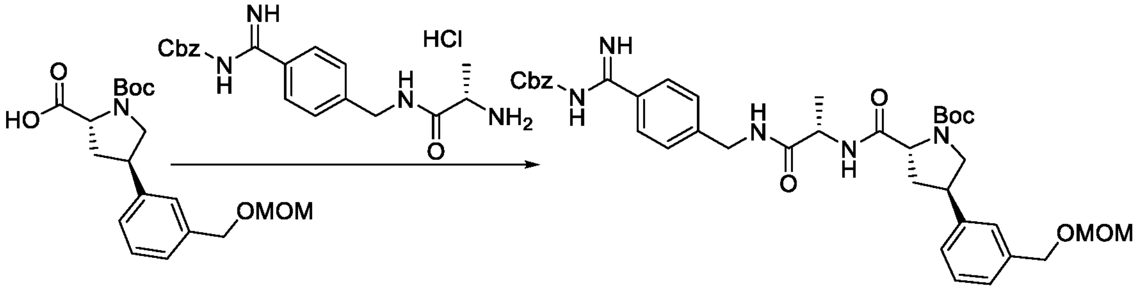


Step 3: (*R*)-1-(*tert*-Butoxycarbonyl)-4-(3-((methoxymethoxy)methyl)phenyl)-2,5-dihydro-1*H*-pyrrole-2-carboxylic acid (115 mg, 92% yield) was synthesized from 1-(*tert*-butyl) 2-methyl (*R*)-4-(3-((methoxymethoxy)methyl)phenyl)-2,5-dihydro-1*H*-pyrrole-1,2-dicarboxylate (120mg, 0.32 mmol) according to Example 93, step 4.

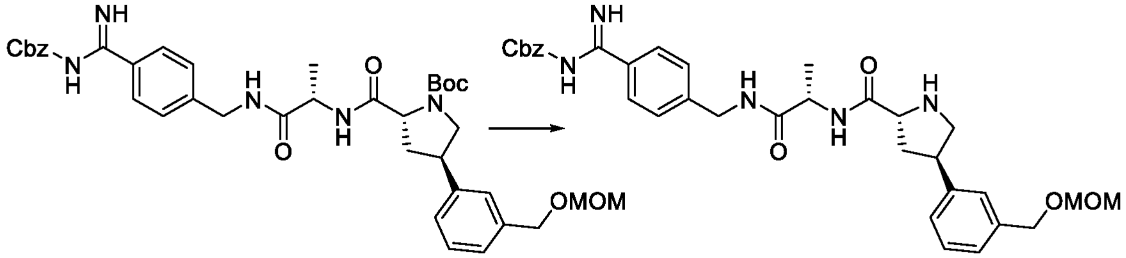


Step 4: To a solution of (*R*)-1-(*tert*-butoxycarbonyl)-4-(3-((methoxymethoxy)methyl)phenyl)-2,5-dihydro-1*H*-pyrrole-2-carboxylic acid (115 mg, 0.32 mmol) in THF (2.5 mL) and MeOH (2.5 mL) was added Et_3N (0.04 mL, 0.32 mmol)

and degassed with a stream of Ar for 2 min. Chlorotris(triphenylphosphine)rhodium (28 mg, 0.03 mmol) was added, a vacuum was pulled for 1 min and a balloon of H_2 was added. The reaction was monitored for the consumption of starting material for 3 days. After evaporating the volatiles, the residue was diluted with sat. aq $NaHCO_3$ and the pH was adjusted to approximately 10 with 1 N NaOH. The mixture was washed with EtOAc and the organic layer was washed with sat. aq $NaHCO_3$ and the combined aqueous layers were brought to pH 3-4 using 1 N HCl. The aqueous layer was subsequently back-extracted with EtOAc and the combined organic extracts were dried over anhyd Na_2SO_4, filtered and concd under vacuum to give (2*R*,4*R*)-1-(*tert*-butoxycarbonyl)-4-(3-((methoxymethoxy)methyl)phenyl)pyrrolidine-2-carboxylic acid (107 mg, 96% yield). The crude material was used in the next step without further purification.

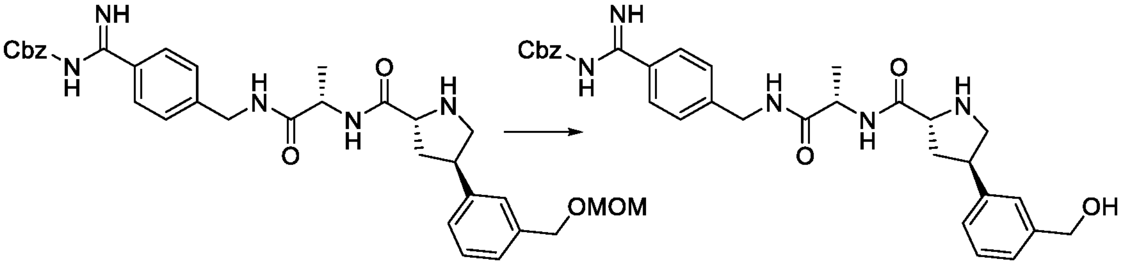


<u>Step 5</u>: *tert*-Butyl (4*R*)-2-(((*S*)-1-((4-(*N*-((benzyloxy)carbonyl)carbamimidoyl)benzyl)amino)-1-oxopropan-2-yl)carbamoyl)-4-(3-((methoxymethoxy)methyl)phenyl)pyrrolidine-1-carboxylate (77 mg, 37% yield) was synthesized from (2*R*,4*R*)-1-(*tert*-butoxycarbonyl)-4-(3-((methoxymethoxy)methyl)phenyl)pyrrolidine-2-carboxylic acid (107 mg, 0.3 mmol) according to Example 93, step 5.

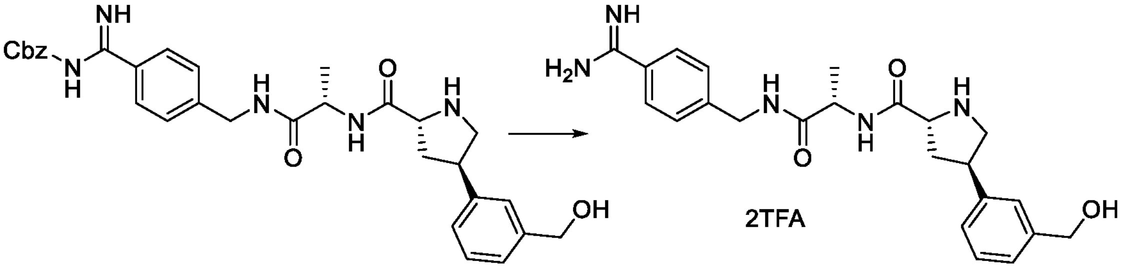


<u>Step 6</u>: Benzyl (imino(4-(((2*S*)-2-((4*R*)-4-(3-((methoxymethoxy)methyl)phenyl)pyrrolidine-2-carboxamido)propanamido)methyl)phenyl)methyl)carbamate (67 mg, 100% yield) was synthesized from *tert*-butyl (4*R*)-2-(((*S*)-1-((4-(*N*-

((benzyloxy)carbonyl)carbamimidoyl)benzyl)amino)-1-oxopropan-2-yl)carbamoyl)-4-(3-((methoxymethoxy)methyl)phenyl)pyrrolidine-1-carboxylate (77 mg, 0.11 mmol) according to Example 93, step 6.



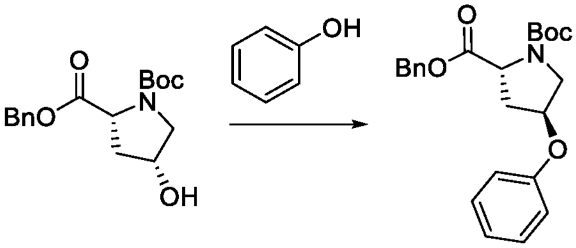
Step 7: Benzyl (imino(4-(((2*S*)-2-((4*R*)-4-(3-((methoxymethoxy)methyl)phenyl)pyrrolidine-2-carboxamido)propanamido)methyl)phenyl)methyl)carbamate (67 mg, 0.11 mmol) was dissolved in 6 N HCl in 2-propanol. After stirring for 4 h at RT, the reaction mixture was concd to give the crude benzyl ((4-(((2*S*)-2-((4*R*)-4-(3-(hydroxymethyl)phenyl)pyrrolidine-2-carboxamido)propanamido)methyl)phenyl)(imino)methyl)carbamate which was used in the next step without further purification.



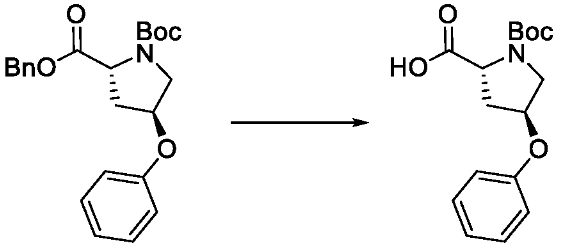
Step 8: (4*R*)-*N*-((*S*)-1-((4-Carbamimidoylbenzyl)amino)-1-oxopropan-2-yl)-4-(3-(hydroxymethyl)phenyl)pyrrolidine-2-carboxamide di-trifluoroacetate (12 mg, 26% yield) was synthesized from benzyl ((4-(((2*S*)-2-((4*R*)-4-(3-(hydroxymethyl)phenyl)pyrrolidine-2-carboxamido)propanamido)methyl)phenyl)(imino)methyl)carbamate (67 mg, 0.11 mmol) according to Example 93, step 7.

EXAMPLE 95

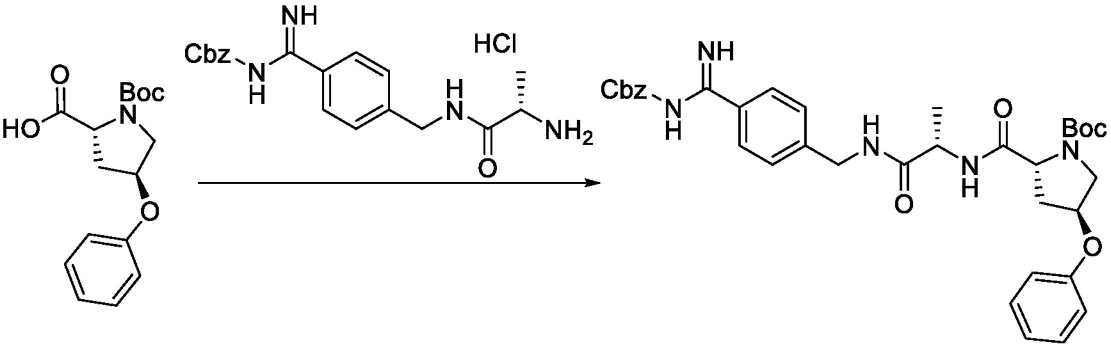
PREPARATION OF (2*R*,4*S*)-*N*-((*S*)-1-((4-CARBAMIMIDOYLBENZYL)AMINO)-1-OXOPROPAN-2-YL)-4-PHENOXYPYRROLIDINE-2-CARBOXAMIDE DI-TRIFLUOROACETATE (COMPOUND I-96)



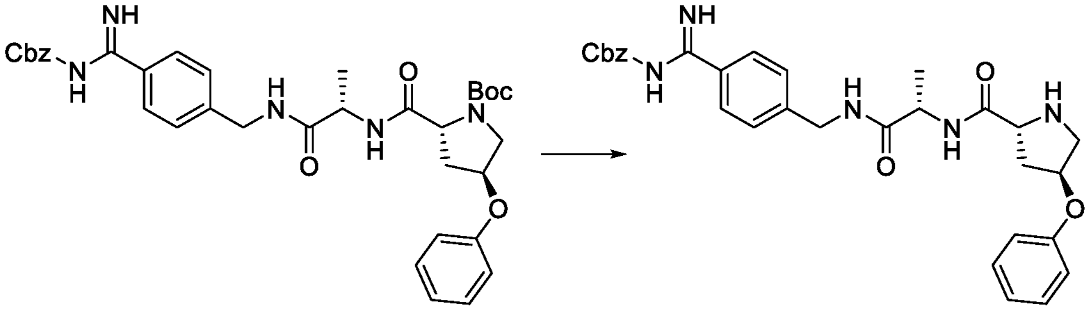
Step 1: To a solution of 2-benzyl 1-(*tert*-butyl) (2*R*,4*R*)-4-hydroxypyrrolidine-1,2-dicarboxylate (400 mg, 1.24 mmol) in THF (6 mL, 0.2 M) was added phenol (104 mg, 1.37 mmol), TPP (359 mg, 1.37 mmol), and DIAD (0.27 mL, 1.37 mmol). After stirring for 16 h at RT, the reaction mixture was concd and the residue purified by chromatography (0-100% EtOAc-hexanes) to give 2-benzyl 1-(*tert*-butyl) (2*R*,4*S*)-4-phenoxypyrrolidine-1,2-dicarboxylate (372 mg, 75% yield).



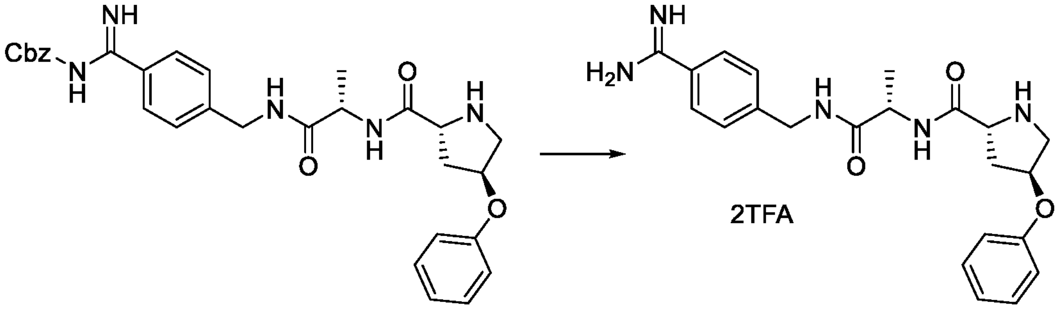
Step 2: (2*R*,4*S*)-1-(*tert*-Butoxycarbonyl)-4-phenoxypyrrolidine-2-carboxylic acid (268 mg, 93% yield) was synthesized from 2-benzyl 1-(*tert*-butyl) (2*R*,4*S*)-4-phenoxypyrrolidine-1,2-dicarboxylate (372 mg, 0.94 mmol) according to Example 93, step 7 except that the crude material was used in the next step without further purification.



Step 3: *tert*-Butyl (2*R*,4*S*)-2-(((*S*)-1-((4-(*N*-((benzyloxy)carbonyl)carbamimidoyl)benzyl)amino)-1-oxopropan-2-yl)carbamoyl)-4-phenoxypyrrolidine-1-carboxylate (60mg, 75% yield) was synthesized from (2*R*,4*S*)-1-(*tert*-butoxycarbonyl)-4-phenoxypyrrolidine-2-carboxylic acid (38 mg, 0.12 mmol) according to Example 93, step 5.



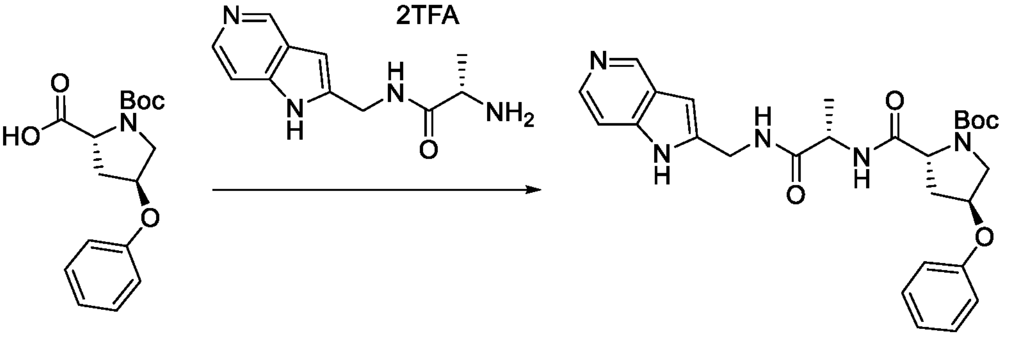
Step 4: Benzyl (imino(4-(((2*S*)-2-((4*S*)-4-phenoxypyrrolidine-2-carboxamido)propanamido)methyl)phenyl)methyl)carbamate (60 mg, 100% yield) was synthesized from *tert*-butyl (2*R*,4*S*)-2-(((*S*)-1-((4-(*N*-((benzyloxy)carbonyl)carbamimidoyl)benzyl)amino)-1-oxopropan-2-yl)carbamoyl)-4-phenoxypyrrolidine-1-carboxylate (60 mg, 0.09 mmol) according to Example 93, step 6.



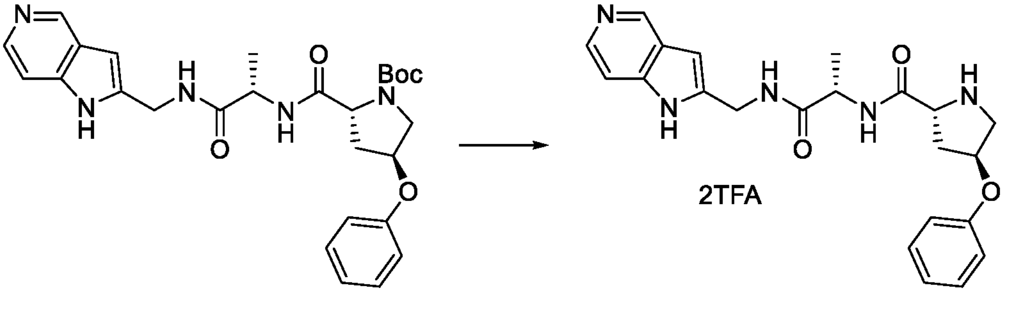
Step 5: (2*R*,4*S*)-*N*-((*S*)-1-((4-Carbamimidoylbenzyl)amino)-1-oxopropan-2-yl)-4-phenoxypyrrolidine-2-carboxamide di-trifluoroacetate (20 mg, 36% yield) was synthesized from benzyl (imino(4-(((2*S*)-2-((4*S*)-4-phenoxypyrrolidine-2-carboxamido)propanamido)methyl)phenyl)methyl)carbamate (60 mg, 0.09 mmol) according to Example 93, step 7.

EXAMPLE 96

PREPARATION OF (2*R*,4*S*)-*N*-((*S*)-1-(((1*H*-PYRROLO[3,2-C]PYRIDIN-2-YL)METHYL)AMINO)-1-OXOPROPAN-2-YL)-4-PHENOXYPYRROLIDINE-2-CARBOXAMIDE DI-TRIFLUOROACETATE (COMPOUND I-97)



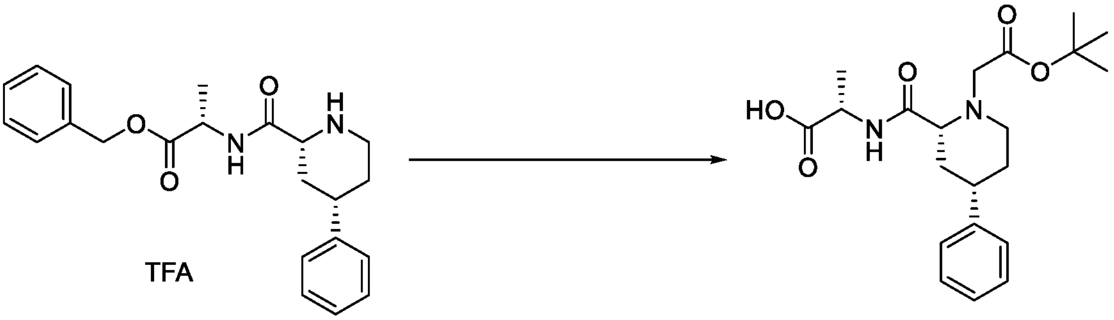
Step 1: *tert*-Butyl (4*S*)-2-(((*S*)-1-(((1*H*-pyrrolo[3,2-c]pyridin-2-yl)methyl)amino)-1-oxopropan-2-yl)carbamoyl)-4-phenoxypyrrolidine-1-carboxylate (110 mg, 52% yield) was synthesized from (2*R*,4*S*)-1-(*tert*-butoxycarbonyl)-4-phenoxypyrrolidine-2-carboxylic acid (127 mg, 0.41 mmol) and (*S*)-*N*-((1*H*-pyrrolo[3,2-c]pyridin-2-yl)methyl)-2-aminopropanamide di-trifluoroacetate (230 mg, 0.5 mmol, prepared using the procedure given for Example 3, step 5-6) according to Example 93, step 5.



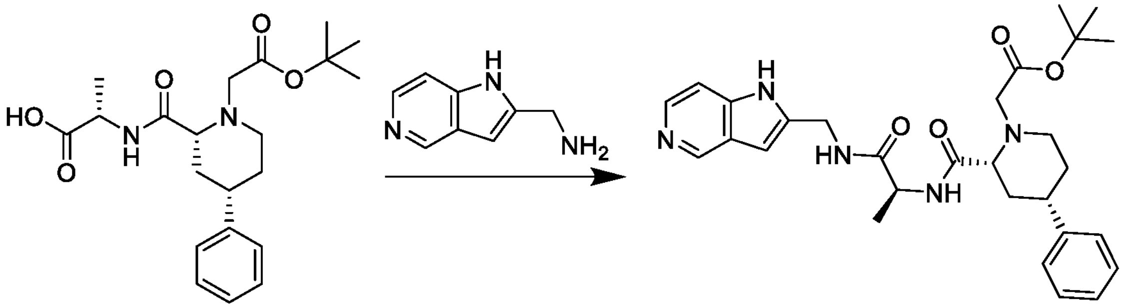
Step 2: (2*R*,4*S*)-*N*-((*S*)-1-(((1*H*-Pyrrolo[3,2-c]pyridin-2-yl)methyl)amino)-1-oxopropan-2-yl)-4-phenoxypyrrolidine-2-carboxamide di-trifluoroacetate (19 mg, 15% yield) was synthesized from *tert*-butyl (4*S*)-2-(((*S*)-1-(((1*H*-pyrrolo[3,2-c]pyridin-2-yl)methyl)amino)-1-oxopropan-2-yl)carbamoyl)-4-phenoxypyrrolidine-1-carboxylate (110 mg, 0.22 mmol) according to Example 93, step 6.

EXAMPLE 97

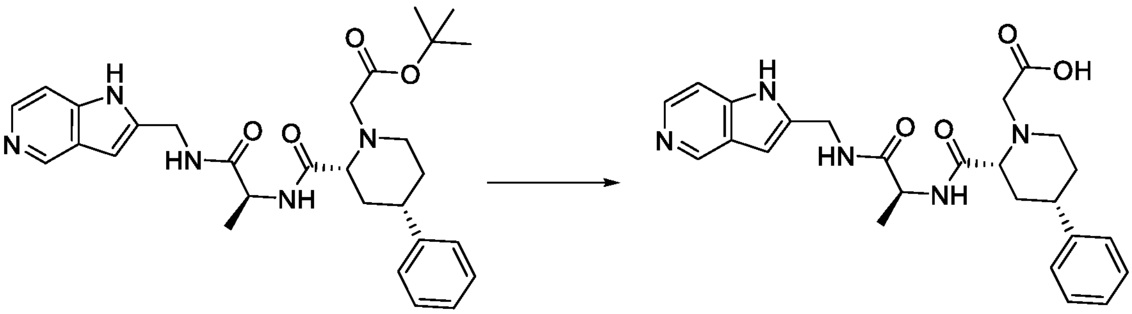
PREPARATION OF 2-((2*R*,4*S*)-2-(((*S*)-1-(((1*H*-PYRROLO[3,2-C]PYRIDIN-2-YL)METHYL)AMINO)-1-OXOPROPAN-2-YL)CARBAMOYL)-4-PHENYLPIPERIDIN-1-YL)ACETIC ACID DI-TRIFLUOROACETATE (COMPOUND I-105)



Step 1: To (2*R*,4*S*)-4-phenylpiperidine-2-carbonyl)-*L*-alaninate trifluoroacetate (100 mg, 0.21 mmol) synthesized according to procedures described in Example 30, steps 1-2 dissolved in DCM (2 mL) was added NEt_3 (0.1 mL) followed by *tert*-butyl 2-bromoacetate (82 mg, 0.42 mmol) and stirred for 14 h. The reaction was monitored by LCMS. The crude reaction mixture was diluted with water and extracted with EtOAc (2 × 20 mL) and concentrated *in vacuo*. To the crude material dissolved in MeOH was added 10% Pd/C (10 mg). After stirring under an H_2 atmosphere for 1h, the reaction mixture was filtered and used in the next reaction without further purification.



Step 2: *tert*-butyl 2-((2*R*,4*S*)-2-(((*S*)-1-(((1*H*-pyrrolo[3,2-c]pyridin-2-yl)methyl)amino)-1-oxopropan-2-yl)carbamoyl)-4-phenylpiperidin-1-yl)acetate was synthesized using the procedure described in step 2 to synthesize Compound I-41. The purification was performed using an amine column to yield *tert*-butyl 2-((2*R*,4*S*)-2-(((*S*)-1-(((1*H*-pyrrolo[3,2-c]pyridin-2-yl)methyl)amino)-1-oxopropan-2-yl)carbamoyl)-4-phenylpiperidin-1-yl)acetate in 46% yield over two steps.



Step 3: 2-((2*R*,4*S*)-2-(((*S*)-1-(((1*H*-pyrrolo[3,2-c]pyridin-2-yl)methyl)amino)-1-oxopropan-2-yl)carbamoyl)-4-phenylpiperidin-1-yl)acetic acid di-trifluoroacetate was synthesized from *tert*-butyl 2-((2*R*,4*S*)-2-(((*S*)-1-(((1*H*-pyrrolo[3,2-c]pyridin-2-yl)methyl)amino)-1-oxopropanyl)carbamoyl)-4-phenylpiperidin-1-yl)acetate according to Example 94. 1 mL MeOH was used as a cosolvent to accelerate the hydrolysis of *tert*-butylester.

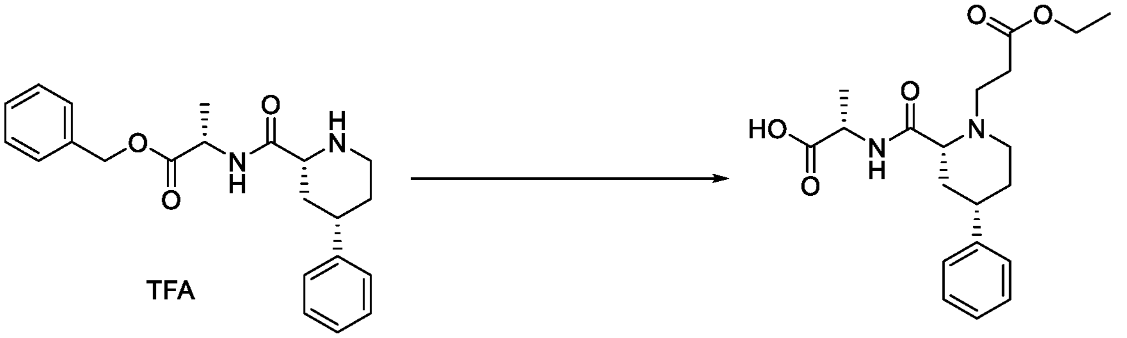
EXAMPLE 98

PREPERATION OF 2-((2*R*,4*S*)-2-(((*R*)-1-(((1*H*-PYRROLO[3,2-C]PYRIDIN-2-YL)METHYL)AMINO)-1-OXOPROPAN-2-YL)CARBAMOYL)-4-PHENYLPIPERIDIN-1-YL)ACETIC ACID DI-TRIFLUOROACETATE (COMPOUND I-104)

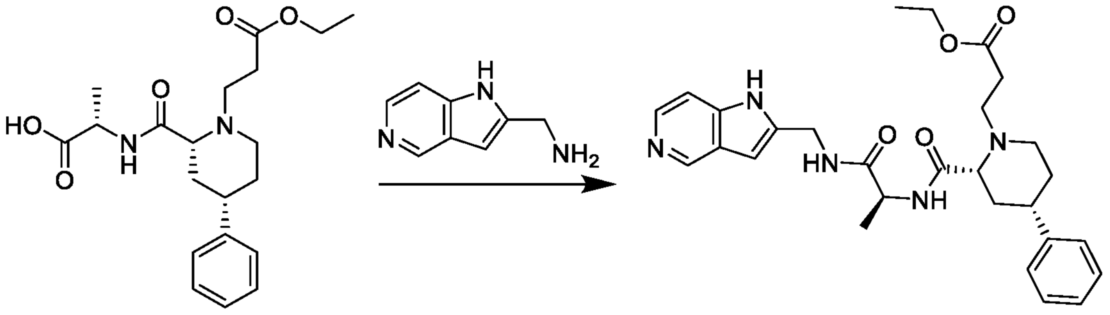
2-((2*R*,4*S*)-2-(((*R*)-1-(((1*H*-pyrrolo[3,2-c]pyridin-2-yl)methyl)amino)-1-oxopropan-2-yl)carbamoyl)-4-phenylpiperidin-1-yl)acetic acid di-trifluoroacetate was obtained as a side product due to isomerization during the synthesis of Compound I-105.

EXAMPLE 99

PREPARATION OF ETHYL 3-((2*R*,4*S*)-2-(((*S*)-1-(((1*H*-PYRROLO[3,2-C]PYRIDIN-2-YL)METHYL)AMINO)-1-OXOPROPAN-2-YL)CARBAMOYL)-4-PHENYLPIPERIDIN-1-YL)PROPANOATE (COMPOUND I-106)



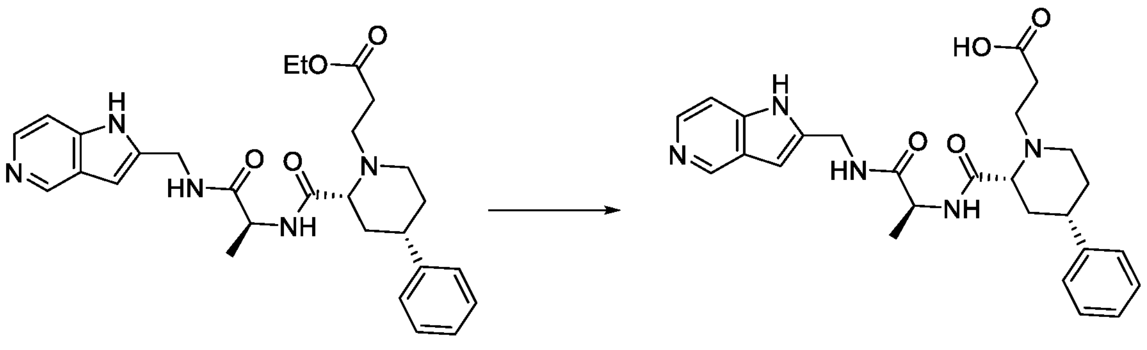
Step 1: To (2*R*,4*S*)-4-phenylpiperidine-2-carbonyl)-*L*-alaninate trifluoroacetate (100 mg, 0.21 mmol) synthesized according to procedures described in Example 30, steps 1-2 dissolved in DCM (2 mL) was added NEt_3 (0.5 mL) followed by ethyl 3-bromopropanoate (155 mg, 0.86 mmol) and stirred for 14 h. The reaction was monitored by LCMS. The crude reaction mixture was quenched with water and extracted with EtOAc (2 × 20 mL) and concentrated in vacuo. To the crude material dissolved in MeOH was added 10% Pd/C (10 mg) and stirred under H_2 atmosphere for 1h. The reaction mixture was filtered and used in the next reaction without further purification.



Step 2: Ethyl 3-((2*R*,4*S*)-2-(((*S*)-1-(((1*H*-pyrrolo[3,2-c]pyridin-2-yl)methyl)amino)-1-oxopropan-2-yl)carbamoyl)-4-phenylpiperidin-1-yl)propanoate was synthesized using the procedure described in step 2 of Example 42. The purification was performed using amine column instead of reverse phase HPLC.

EXAMPLE 100

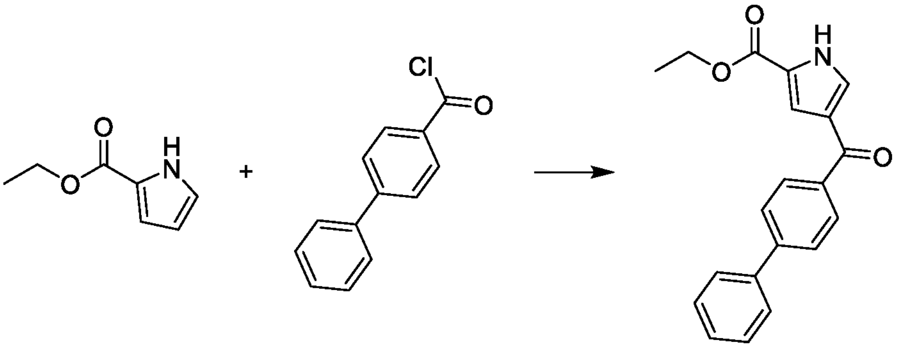
PREPARATION OF 3-((2*R*,4*S*)-2-(((*S*)-1-(((1H-PYRROLO[3,2-C]PYRIDIN-2-YL)METHYL)AMINO)-1-OXOPROPAN-2-YL)CARBAMOYL)-4-PHENYLPIPERIDIN-1-YL)PROPANOIC ACID DI-TRIFLUOROACETATE SALT (COMPOUND I-107)



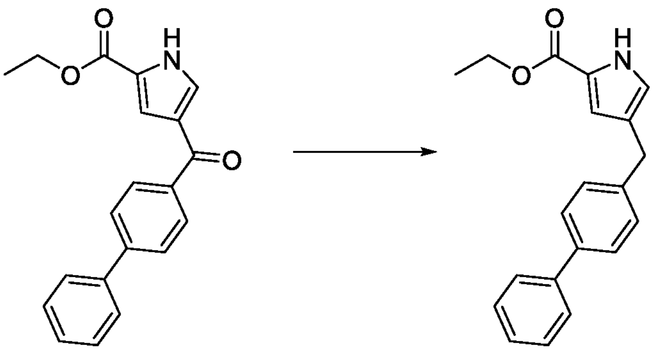
3-((2*R*,4*S*)-2-(((*S*)-1-(((1H-pyrrolo[3,2-c]pyridin-2-yl)methyl)amino)-1-oxopropan-2-yl)carbamoyl)-4-phenylpiperidin-1-yl)propanoic acid di-trifluoroacetate salt was synthesized from Compound I-106 using the procedure to synthesize Compound I-32.

EXAMPLE 101

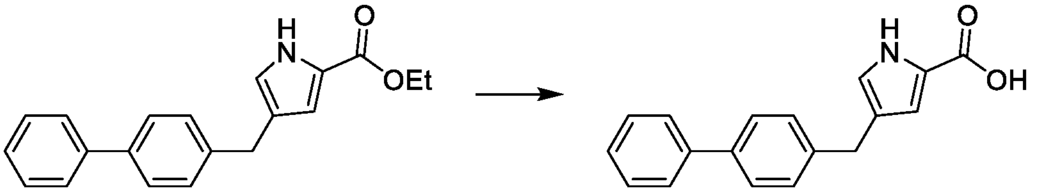
PREPARATION OF (*S*)-4-([1,1'-BIPHENYL]-4-YLMETHYL)-*N*-(1-((4-CARBAMIMIDOYLBENZYL)AMINO)-1-OXOPROPAN-2-YL)-1*H*-PYRROLE-2-CARBOXAMIDE TRIFLUOROACETATE (COMPOUND I-100)



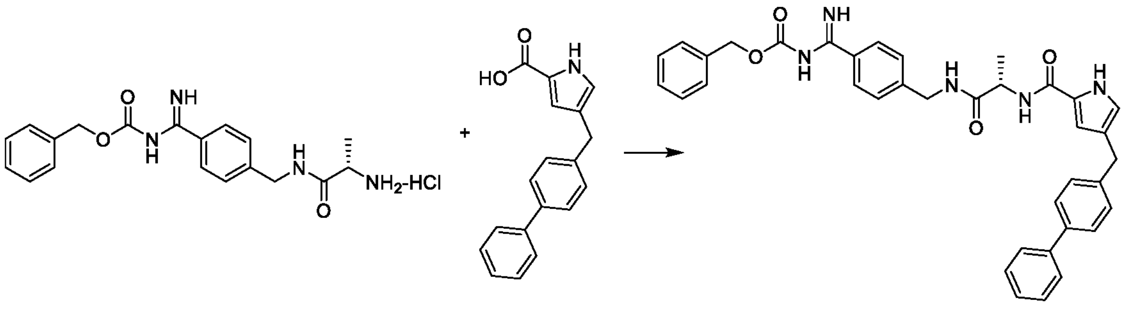
Step 1: A suspension of $AlCl_3$ (960 mg, 7.2 mmol) and [1,1'-biphenyl]-4-carbonyl chloride (1.56 g, 7.2 mmol) in anhydrous DCM (6.2 mL) was stirred under N_2 atmosphere at 0 °C for 15 minutes. Ethyl 1*H*-pyrrole-2-carboxylate (500 mg, 3.6 mmol) was added in portions at 0 °C to the suspension and the reaction was stirred overnight while allowing to warm to room temperature. The reaction was quenched with H_2O (20 mL) and extracted with DCM (3 × 20 mL). The organics were combined, washed with 1N aqueous NaOH (20 mL), H_2O (20 mL), brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified via flash chromatography using SiO_2 (24g) and an eluent of 0-100% EtOAc in heptane to afford ethyl 4-([1,1'-biphenyl]-4-carbonyl)-1*H*-pyrrole-2-carboxylate as an off-white solid (600 mg, 52%).



Step 2: Triethylsilane (681 µL, 4.26 mmol) was added to a solution of ethyl 4-([1,1'-biphenyl]-4-carbonyl)-1*H*-pyrrole-2-carboxylate (486 mg, 1.52 mmol) in TFA (3.23 mL). The reaction was heated to 40 °C and stirred at this temperature overnight. The reaction was concentrated *in vacuo* and the residue was taken up in EtOAc (60 mL), washed with saturated aqueous $NaHCO_3$ (40 mL), brine (40 mL), dried over $MgSO_4$, filtered and concentrated. Crude material was purified via flash chromatography using SiO_2 (24g) and an eluent of 0-100% EtOAc in heptanes to afford ethyl 4-([1,1'-biphenyl]-4-ylmethyl)-1*H*-pyrrole-2-carboxylate (370 mg, 80%) as an off-white solid.

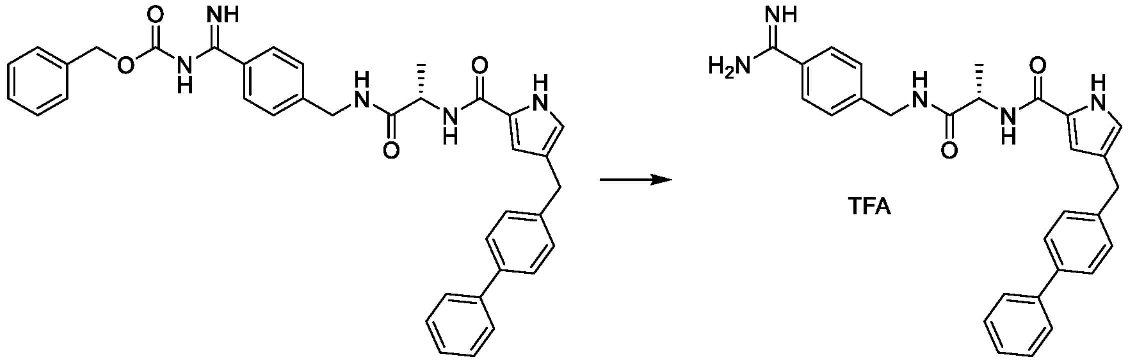


Step 3: Potassium hydroxide (680 mg, 12.1 mmol) was added to a mixture of ethyl 4-([1,1'-biphenyl]-4-ylmethyl)-1*H*-pyrrole-2-carboxylate (370 mg, 1.21 mmol) in THF:MeOH:H_2O (5 mL:5 mL:2.5 mL) and stirred overnight at room temperature. The organics solvents were removed in vacuo and the aqueous portion further diluted with H_2O (30 mL). After washing with diethyl ether (3 × 30 mL), the aqueous layer was acidified to a pH of 2-3 using 1N aqueous HCl and extracted with EtOAc (3 × 30 mL). The organic layers were combined, washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated to afford 4-([1,1'-biphenyl]-4-ylmethyl)-1*H*-pyrrole-2-carboxylic acid (315 mg, 94%).



Step 4: Benzyl (*S*)-((4-((2-(4-([1,1'-biphenyl]-4-ylmethyl)-1*H*-pyrrole-2-carboxamido)propanamido)methyl)phenyl)(imino)methyl)carbamate (59 mg, 44%) was obtained as an off-white solid from (*S*)-((4-((2-aminopropanamido)methyl)phenyl)(imino)methyl)carbamate hydrochloride (85 mg,

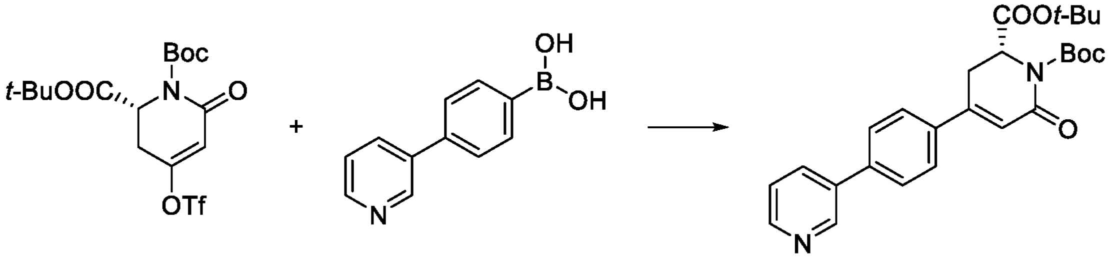
0.22 mmol) and 4-([1,1'-biphenyl]-4-ylmethyl)-1*H*-pyrrole-2-carboxylic acid (50 mg, 0.18 mmol) according to Example 93, Step 5.



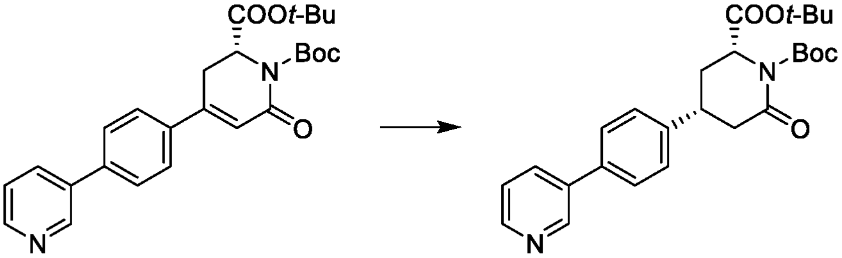
Step 5: (*S*)-4-([1,1'-Biphenyl]-4-ylmethyl)-*N*-(1-((4-carbamimidoylbenzyl)amino)-1-oxopropan-2-yl)-1*H*-pyrrole-2-carboxamide trifluoroacetate (22 mg, 39%) was obtained as an off-white solid from benzyl (*S*)-((4-((2-(4-([1,1'-biphenyl]-4-ylmethyl)-1*H*-pyrrole-2-carboxamido)propanamido)methyl)phenyl)(imino)methyl)carbamate (59 mg, 0.10 mmol) according to Example 93, Step 7.

EXAMPLE 102

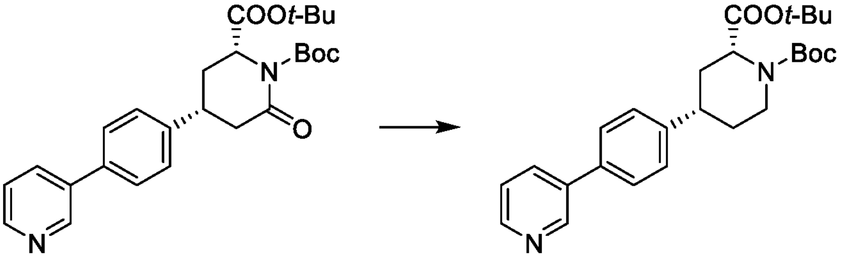
PREPARATION OF (2*R*,4*S*)-*N*-((*S*)-1-((5-CHLORO-2-(1*H*-TETRAZOL-1-YL)BENZYL)AMINO)-1-OXOPROPAN-2-YL)-4-(4-(PYRIDIN-3-YL)PHENYL)PIPERIDINE-2-CARBOXAMIDE TRIFLUOROACETATE (COMPOUND I-101)



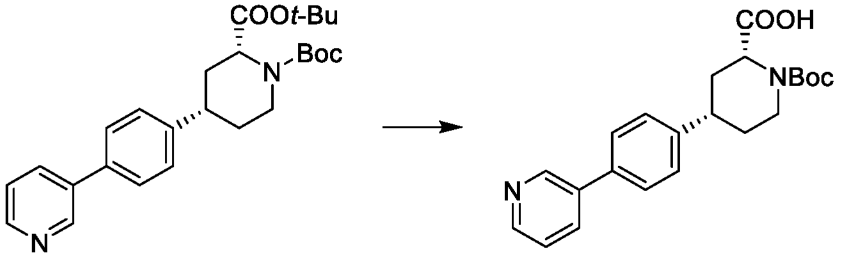
Step 1: Di-*tert*-butyl (*R*)-6-oxo-4-(4-(pyridin-3-yl)phenyl)-3,6-dihydropyridine-1,2(2*H*)-dicarboxylate (440 mg, 87%) was prepared as an orange solid from di-*tert*-butyl (*R*)-6-oxo-4-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydropyridine-1,2(2*H*)-dicarboxylate (500 mg, 1.12 mmol, prepared according to the procedure described in Synlett 2009(1): 71-74) and (4-(pyridin-3-yl)phenyl)boronic acid (335 mg, 1.68 mmol) using the procedure described in Example 62, Step 3.



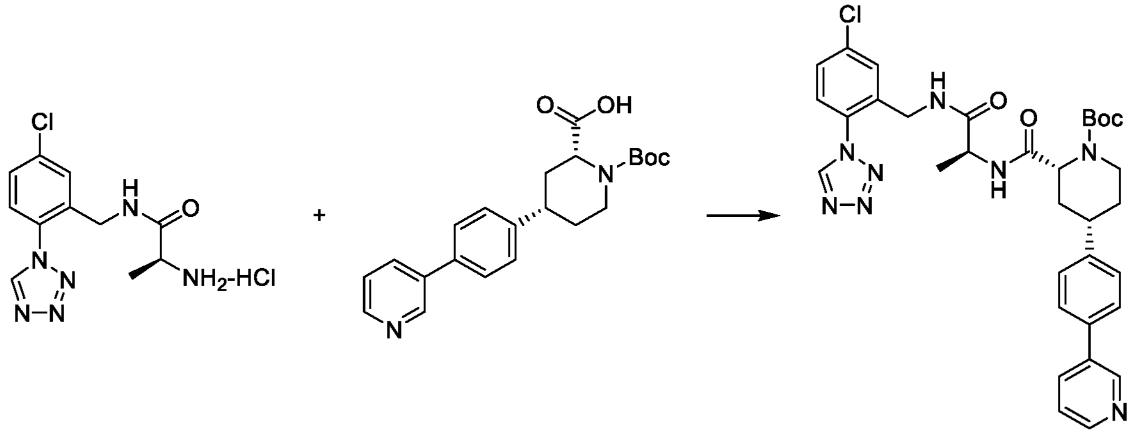
Step 2: Di-*tert*-butyl (2*R*,4*R*)-6-oxo-4-(4-(pyridin-3-yl)phenyl)piperidine-1,2-dicarboxylate (274 mg, 94%) was prepared as an off-white solid from di-*tert*-butyl (*R*)-6-oxo-4-(4-(pyridin-3-yl)phenyl)-3,6-dihydropyridine-1,2(2*H*)-dicarboxylate (288 mg, 0.64 mmol) using the procedure described in Example 62, Step 4.



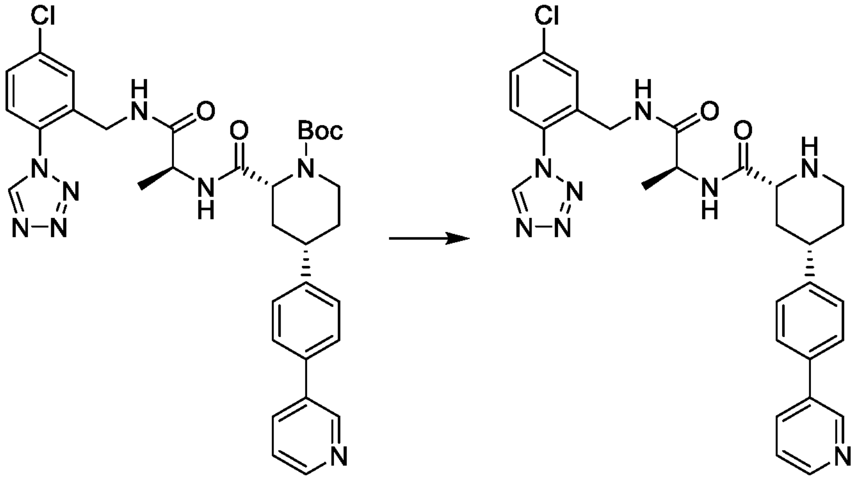
Step 3: Di-*tert*-butyl (2*R*,4*S*)-4-(4-(pyridin-3-yl)phenyl)piperidine-1,2-dicarboxylate (157 mg, 59%) was prepared as an off-white solid from di-*tert*-butyl (2*R*,4*R*)-6-oxo-4-(4-(pyridin-3-yl)phenyl)piperidine-1,2-dicarboxylate (274 mg, 0.61 mmol) using the procedure described in Example 62, Step 5.



Step 4: (2*R*,4*S*)-1-(*tert*-Butoxycarbonyl)-4-(4-(pyridin-3-yl)phenyl)piperidine-2-carboxylic acid (75 mg, 54% over two steps) was prepared as an off-white solid from di-*tert*-butyl (2*R*)-4-(4-(pyridin-3-yl)phenyl)piperidine-1,2-dicarboxylate (157 mg, 0.36 mmol) using the procedure described in Example 62, Step 6.



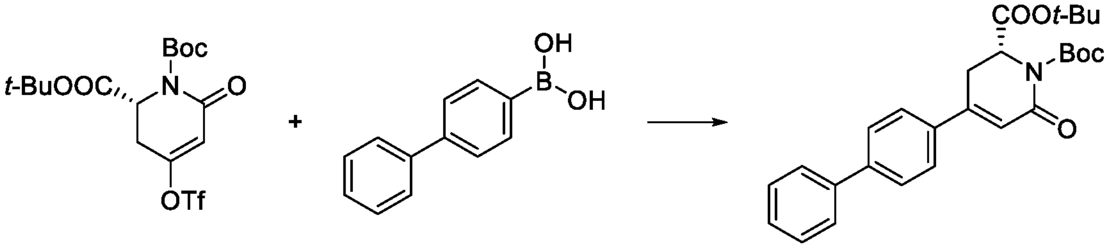
Step 5: *tert*-Butyl (2*R*,4*S*)-2-(((*S*)-1-((5-chloro-2-(1*H*-tetrazol-1-yl)benzyl)amino)-1-oxopropan-2-yl)carbamoyl)-4-(4-(pyridin-3-yl)phenyl)piperidine-1-carboxylate (39.4 mg, 69%) was prepared as an off-white solid from (*S*)-2-amino-*N*-(5-chloro-2-(1*H*-tetrazol-1-yl)benzyl)propanamide hydrochloride (34 mg, 0.11 mmol) and (2*R*,4*S*)-1-(*tert*-butoxycarbonyl)-4-(4-(pyridin-3-yl)phenyl)piperidine-2-carboxylic acid (34 mg, 0.09 mmol) using the procedure described in Example 62, step 7.



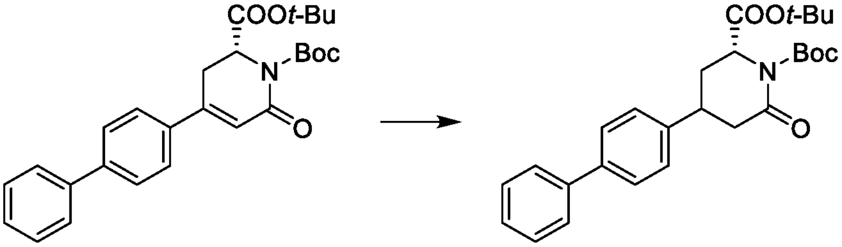
Step 6: (2*R*,4*S*)-*N*-((*S*)-1-((5-chloro-2-(1*H*-tetrazol-1-yl)benzyl)amino)-1-oxopropan-2-yl)-4-(4-(pyridin-3-yl)phenyl)piperidine-2-carboxamide trifluoroacetate (34 mg, 84%) was prepared as an off-white solid from tert-butyl (2*R*,4*S*)-2-(((*S*)-1-((5-chloro-2-(1*H*-tetrazol-1-yl)benzyl)amino)-1-oxopropan-2-yl)carbamoyl)-4-(4-(pyridin-3-yl)phenyl)piperidine-1-carboxylate (39 mg, 0.061 mmol) using the procedure described in Example 12, step 9.

EXAMPLE 103

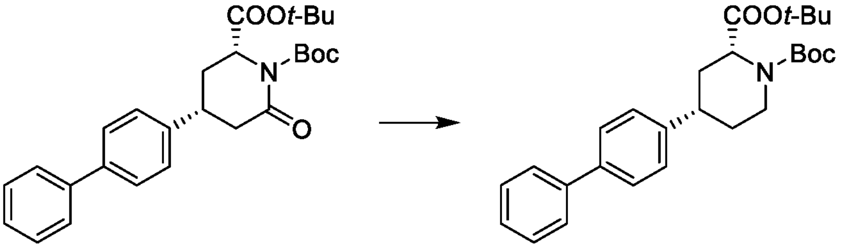
PREPARATION OF (2*R*,4*S*)-N-((*S*)-1-((5-CHLORO-2-(1*H*-TETRAZOL-1-YL)BENZYL)AMINO)-1-OXOPROPAN-2-YL)-4-(4-(PYRIDIN-3-YL)PHENYL)PIPERIDINE-2-CARBOXAMIDE TRIFLUOROACETATE (COMPOUND I-102)



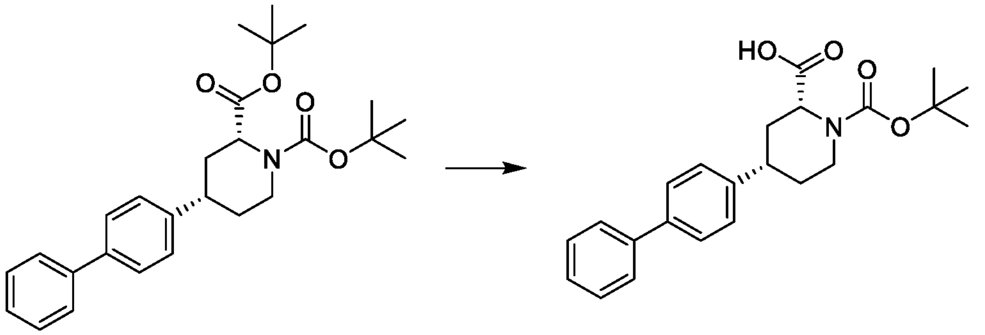
Step 1: Di-*tert*-butyl (*R*)-4-([1,1'-biphenyl]-4-yl)-6-oxo-3,6-dihydropyridine-1,2(2*H*)-dicarboxylate (415 mg, 83%) was prepared as an orange solid from di-*tert*-butyl (*R*)-6-oxo-4-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydropyridine-1,2(2*H*)-dicarboxylate (500 mg, 1.12 mmol) and [1,1'-biphenyl]-4-ylboronic acid (333 mg, 1.68 mmol) using the procedure described in Example 62, Step 3.



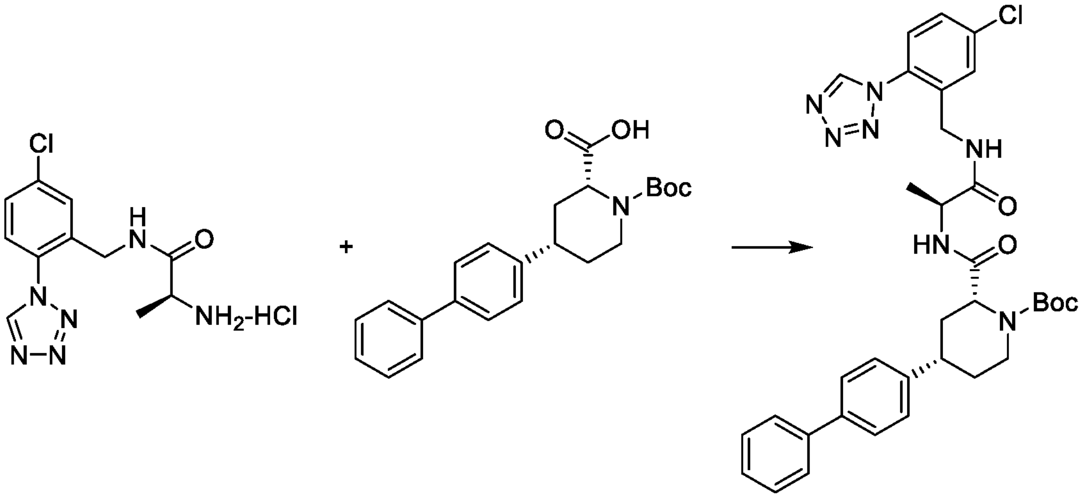
Step 2: Di-*tert*-butyl (2*R*)-4-([1,1'-biphenyl]-4-yl)-6-oxopiperidine-1,2-dicarboxylate (284 mg, 64%) was prepared as an off-white solid from di-*tert*-butyl (*R*)-4-([1,1'-biphenyl]-4-yl)-6-oxo-3,6-dihydropyridine-1,2(2*H*)-dicarboxylate (413 mg, 0.92 mmol) using the procedure described in Example 62, Step 4.



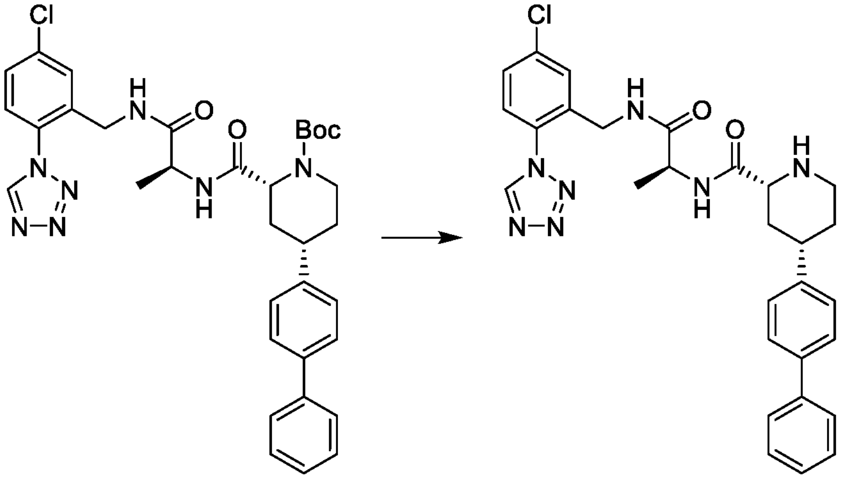
Step 3: Di-*tert*-butyl (2*R*,4*S*)-4-([1,1'-biphenyl]-4-yl)piperidine-1,2-dicarboxylate (189 mg, 69%) was prepared as an off-white solid from di-*tert*-butyl (2*R*,4*R*)-4-([1,1'-biphenyl]-4-yl)-6-oxopiperidine-1,2-dicarboxylate (284 mg, 0.63 mmol) using the procedure described in Example 62, Step 5.



Step 4: (2*R*,4*S*)-4-([1,1'-Biphenyl]-4-yl)-1-(*tert*-butoxycarbonyl)piperidine-2-carboxylic acid (36 mg, 23% over two steps) was obtained as an off-white solid from di-*tert*-butyl (2*R*,4*S*)-4-([1,1'-biphenyl]-4-yl)piperidine-1,2-dicarboxylate (189 mg, 0.43 mmol) using the procedure described in Example 62, Step 6.



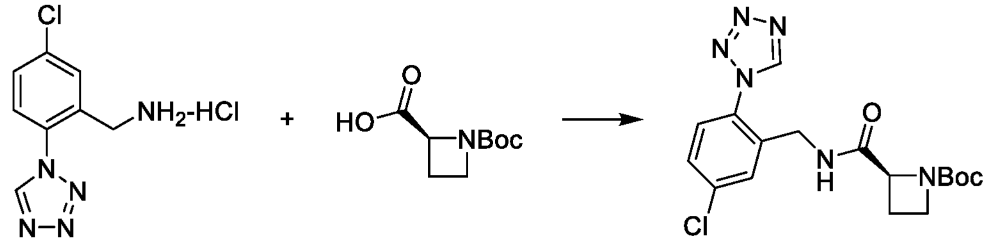
Step 5: *tert*-Butyl (2*R*,4*S*)-4-([1,1'-biphenyl]-4-yl)-2-(((*S*)-1-((5-chloro-2-(1*H*-tetrazol-1-yl)benzyl)amino)-1-oxopropan-2-yl)carbamoyl)piperidine-1-carboxylate (41 mg, 67%) was prepared as an off-white solid from (*S*)-2-amino-*N*-(5-chloro-2-(1*H*-tetrazol-1-yl)benzyl)propanamide hydrochloride (36 mg, 0.12 mmol) and (2*R*,4*S*)-4-([1,1'-biphenyl]-4-yl)-1-(*tert*-butoxycarbonyl)piperidine-2-carboxylic acid (36 mg, 0.01 mmol) using the procedure described in Example 62, step 7.



Step 6: (2*R*,4*S*)-4-([1,1'-Biphenyl]-4-yl)-*N*-((*S*)-1-((5-chloro-2-(1*H*-tetrazol-1-yl)benzyl)amino)-1-oxopropan-2-yl)piperidine-2-carboxamide trifluoroacetate (31 mg, 84%) was prepared as an off-white solid from *tert*-butyl (2*R*,4*S*)-4-([1,1'-biphenyl]-4-yl)-2-(((*S*)-1-((5-chloro-2-(1*H*-tetrazol-1-yl)benzyl)amino)-1-oxopropan-2-yl)carbamoyl)piperidine-1-carboxylate (41 mg, 0.06 mmol) using the procedure described in Example 12, Step 9.

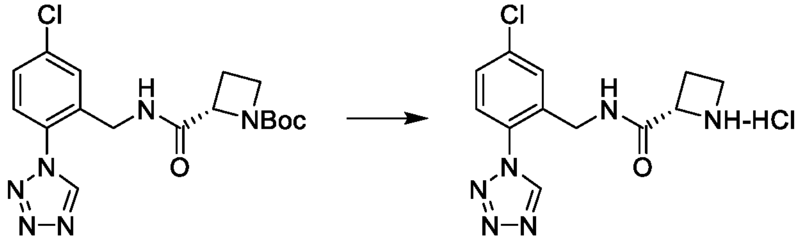
EXAMPLE 104

PREPARATION OF (*S*)-1-((2*R*,4*S*)-4-([1,1'-BIPHENYL]-4-YL)PIPERIDINE-2-CARBONYL)-*N*-(5-CHLORO-2-(1*H*-TETRAZOL-1-YL)BENZYL)AZETIDINE-2-CARBOXAMIDE TRIFLUOROACETATE (COMPOUND I-103)

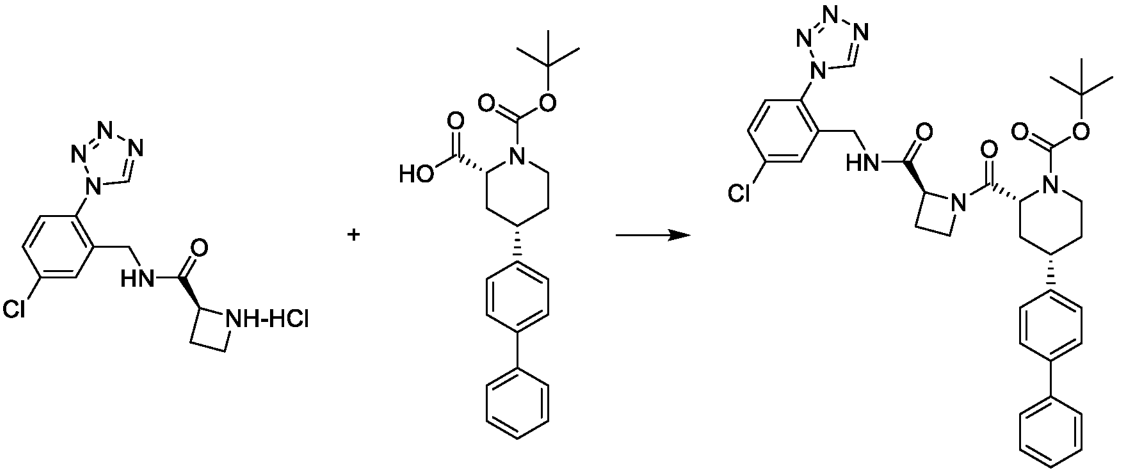


Step 3: To a solution of DCC (154 mg, 0.75 mmol) and (*S*)-1-(*tert*-butoxycarbonyl)azetidine-2-carboxylic acid (136 mg, 0.68 mmol) in DCM (11 mL) was added *N*-Hydroxysuccinimide (86 mg, 0.75 mmol). After stirring the reaction at rt for 1 h, the mixture was added to a suspension of (5-chloro-2-(1*H*-tetrazol-1-yl)phenyl)methanamine hydrochloride (200 mg, 0.81 mmol) in saturated aqueous $NaHCO_3$ (11 mL) and the resultant mixture was stirred at rt for an additional 1 h. The

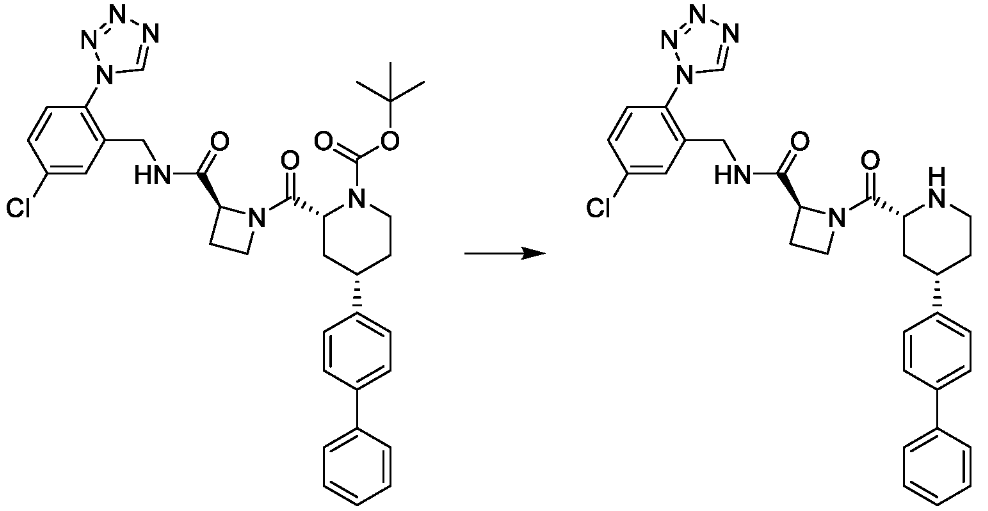
organic layer was partitioned and the aqueous layer extracted with DCM (2 × 20 mL). After the organic layers were combined, dried over $MgSO_4$, filtered and concentrated, the crude material was purified using flash chromatography (SiO_2) using an eluent of 0-100% EtOAc in heptane to afford *tert*-Butyl (*S*)-2-((5-chloro-2-(1*H*-tetrazol-1-yl)benzyl)carbamoyl)azetidine-1-carboxylate (242 mg, 91%) as an off-white solid.



<u>Step 4</u>: Hydrochloric acid (6N in IPA, 6.2 mL) was added to *tert*-butyl (*S*)-2-((5-chloro-2-(1*H*-tetrazol-1-yl)benzyl)carbamoyl)azetidine-1-carboxylate (242 mg, 0.62 mmol) and the reaction was stirred overnight. The reaction was concentrated to afford (*S*)-*N*-(5-chloro-2-(1*H*-tetrazol-1-yl)benzyl)azetidine-2-carboxamide hydrochloride (203 mg, 99.5%) as an off-white solid.



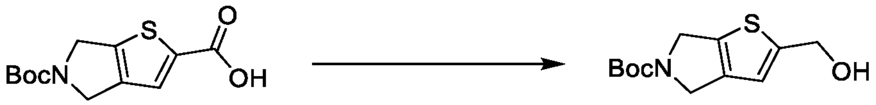
<u>Step 5</u>: *tert*-Butyl (2*R*,4*S*)-4-([1,1'-biphenyl]-4-yl)-2-((*S*)-2-((5-chloro-2-(1*H*-tetrazol-1-yl)benzyl)carbamoyl)azetidine-1-carbonyl)piperidine-1-carboxylate (60 mg, 74%) was prepared as an off-white solid from (*S*)-*N*-(5-chloro-2-(1*H*-tetrazol-1-yl)benzyl)azetidine-2-carboxamide hydrochloride (49 mg, 0.15 mmol) and (2*R*,4*S*)-4-([1,1'-biphenyl]-4-yl)-1-(tert-butoxycarbonyl)piperidine-2-carboxylic acid (47 mg, 0.12 mmol) using the procedure described in Example 62, step 7.



Step 6: (*S*)-1-((2*R*,4*S*)-4-([1,1'-Biphenyl]-4-yl)piperidine-2-carbonyl)-*N*-(5-chloro-2-(1*H*-tetrazol-1-yl)benzyl)azetidine-2-carboxamide trifluoroacetate (56 mg, 93%) was prepared as an off-white solid from *tert*-butyl (2*R*,4*S*)-4-([1,1'-biphenyl]-4-yl)-2-((*S*)-2-((5-chloro-2-(1*H*-tetrazol-1-yl)benzyl)carbamoyl)azetidine-1-carbonyl)piperidine-1-carboxylate (60 mg, 0.09 mmol) using the procedure described in Example 12, Step 9.

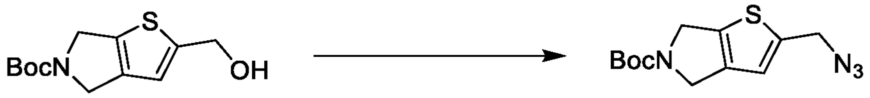
EXAMPLE 105

PREPARATION OF (2*R*,4*S*)-*N*-((*S*)-1-(((5,6-DIHYDRO-4*H*-THIENO[2,3-C]PYRROL-2-YL)METHYL)AMINO)-1-OXOPROPAN-2-YL)-4-PHENYLPIPERIDINE-2-CARBOXAMIDE DI-TRIFLUOROACETATE SALT (COMPOUND I-98)

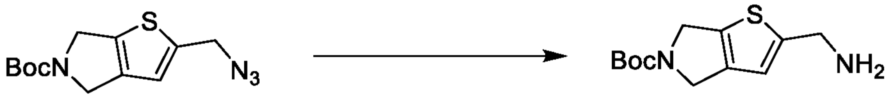


Step 1: Under a N_2 atmosphere, a stirred solution of 5-(*tert*-butoxycarbonyl)-5,6-dihydro-4*H*-thieno[2,3-c]pyrrole-2-carboxylic acid (100 mg, 0.35 mmol) and *N*-methylmorpholine (90 µL, 0.82 mmol) in THF (1.6 mL) was cooled to 0 °C in an ice bath. After isobutyl chloroformate (50 µL, 0.39 mmol) was added, the reaction was left to stir at room temp for 1 h before being filtered through a syringe filter. The collected filtrate was placed under a N_2 atmosphere, cooled to 0 °C before a solution of $NaBH_4$ (55 mg, 1.45 mmol) in water (300 µL) was added dropwise. After the mixture

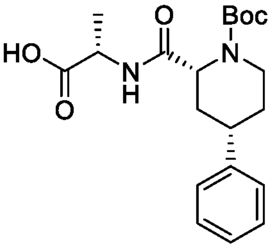
was stirred at 0 °C for 30 min and at room temp for 3 h, the reaction mixture was quenched with water and extracted with EtOAc (3×). The organic layers were combined, washed with brine, dried over Na_2SO_4, vacuum filtered and evaporated under reduced pressure. The crude product was dissolved in CH_2Cl_2 and adsorbed onto silica gel. Purification by chromatography (0-100% EtOAc-Hexane) afforded *tert*-butyl 2-(hydroxymethyl)-4,6-dihydro-5*H*-thieno[2,3-c]pyrrole-5-carboxylate (77.6 mg, 86% yield).



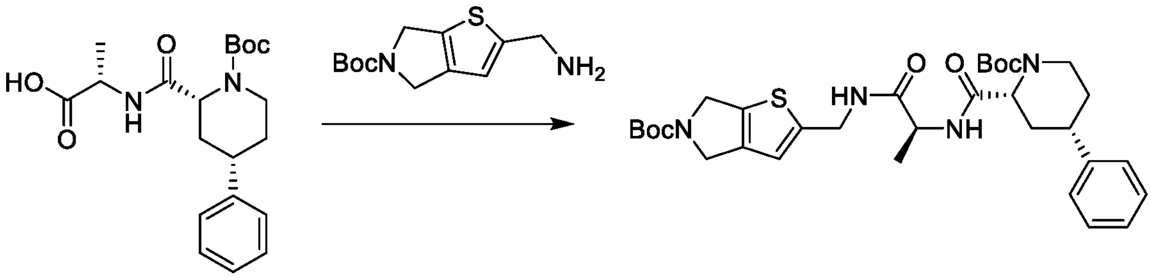
Step 2: To a stirred solution of *tert*-butyl 2-(hydroxymethyl)-4,6-dihydro-5*H*-thieno[2,3-c]pyrrole-5-carboxylate (77.6 mg, 0.30 mmol) in THF (1.5 mL) was added DIAD (130 µL, 0.66 mmol) and PPh_3 (170 mg, 0.65 mmol) at room temp. After cooling the mixture to 0°C, the solution was purging with N_2 before DPPA (140 µL, 0.65 mmol) was added. The reaction was stirred at room temp for 2 days, quenched with water then extracted with EtOAc (3×). The organic layers were combined, washed with brine, dried over Na_2SO_4, vacuum filtered, and evaporated under reduced pressure. The crude product was dissolved in CH_2Cl_2 and adsorbed onto silica gel. Purification by chromatography (0-10% EtOAc-Hexane) afforded *tert*-butyl 2-(azidomethyl)-4,6-dihydro-5*H*-thieno[2,3-*c*]pyrrole-5-carboxylate (48 mg, 56% yield).



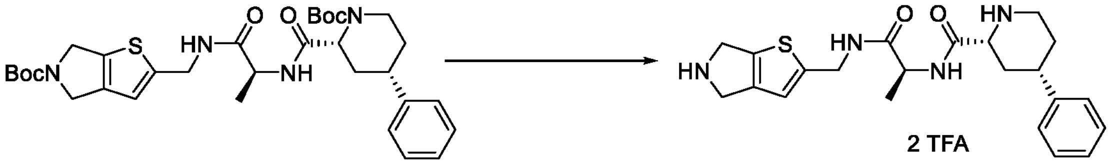
Step 3: To a stirred solution of *tert*-butyl 2-(azidomethyl)-4,6-dihydro-5*H*-thieno[2,3-c]pyrrole-5-carboxylate (48 mg, 0.17 mmol) in THF (1 mL) and water (0.12 mL) was added PPh_3 (68 mg, 0.26 mmol). After the reaction was stirred at room temperature for 16 h and quenched with 1 M $KHSO_4$, the resulting mixture was washed with diethyl ether (3×). The ethereal layers were discarded and the pH of the aqueous layer was adjusted to 12 by adding 5 M NaOH solution. The basic aqueous layer was extracted with EtOAc (3×). The organic layers were combined, washed with brine, dried over Na_2SO_4, vacuum filtered, and evaporated under reduced pressure. The crude product was dissolved in CH_2Cl_2 and adsorbed onto silica gel. Purification by chromatography (0-10% 7 N NH_3 in MeOH-CH_2Cl_2) afforded *tert*-butyl 2-(aminomethyl)-4,6-dihydro-5*H*-thieno[2,3-c]pyrrole-5-carboxylate (33 mg, 75% yield).



Step 4: ((2*R*,4*S*)-1-(*tert*-Butoxycarbonyl)-4-phenylpiperidine-2-carbonyl)-L-alanine was similarly synthesized according to the procedure for Compound I-31, step 1.



Step 5: To a solution of ((2*R*,4*S*)-1-(*tert*-butoxycarbonyl)-4-phenylpiperidine-2-carbonyl)-L-alanine (38 mg, 0.10 mmol) and *tert*-butyl 2-(aminomethyl)-4,6-dihydro-5*H*-thieno[2,3-c]pyrrole-5-carboxylate (32.5 mg, 0.13 mmol) in DMF (1.5 mL) was added DIEA (60 µL) at room temp. After purging with N_2, the solution was cooled to 0 °C in an ice bath and HATU (39 mg, 0.10 mmol) was added. The reaction was stirred at room temp for 16 h and evaporated under reduced pressure to dryness. The crude product was dissolved in CH_2Cl_2 and adsorbed onto silica gel. Purification by chromatography (0-10% MeOH-CH_2Cl_2) afforded *tert*-butyl 2-(((*S*)-2-((2*R*,4*S*)-1-(*tert*-butoxycarbonyl)-4-phenylpiperidine-2-carboxamido)propanamido)methyl)-4,6-dihydro-5*H*-thieno[2,3-c]pyrrole-5-carboxylate (70 mg, quant. yield)

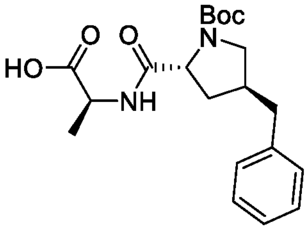


Step 6: To a solution of *tert*-butyl 2-(((*S*)-2-((2*R*,4*S*)-1-(*tert*-butoxycarbonyl)-4-phenylpiperidine-2-carboxamido)propanamido)methyl)-4,6-dihydro-5*H*-thieno[2,3-c]pyrrole-5-carboxylate (61 mg, 0.10 mmol) in DCM (3.2 mL) at

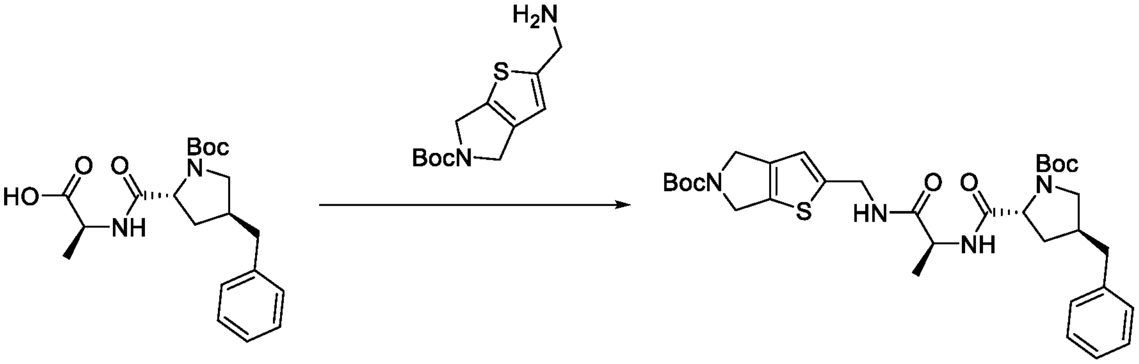
RT was added TES (80 μL, 0.5 mmol). After cooling the reaction mixture to ice-bath temperature, TFA (1.6 mL) was added and the solution was left to stir at room temp for 2 h. The solution was evaporated under reduced pressure to dryness and the crude product was purified by reverse-phase HPLC afforded the title compound (14.2 mg, 34% yield).

EXAMPLE 106

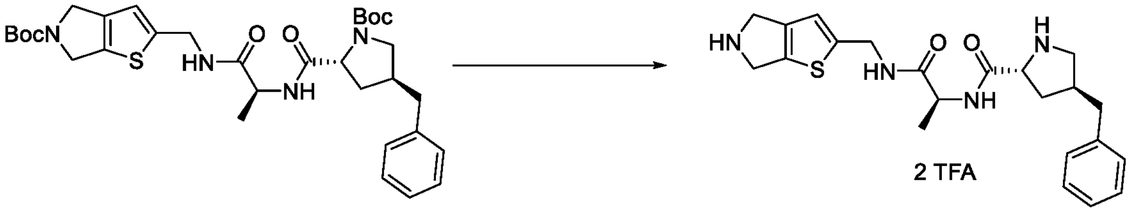
PREPARATION OF (2*R*,4*S*)-4-BENZYL-*N*-((*S*)-1-(((5,6-DIHYDRO-4*H*-THIENO[2,3-C]PYRROL-2-YL)METHYL)AMINO)-1-OXOPROPAN-2-YL)PYRROLIDINE-2-CARBOXAMIDE DI-TRIFLUOROACETATE SALT (COMPOUND I-99)



Step 1: ((2*R*,4*S*)-4-Benzyl-1-(*tert*-butoxycarbonyl)pyrrolidine-2-carbonyl)-L-alanine was similarly synthesized according to the procedure for Compound I-9, step 1-2.



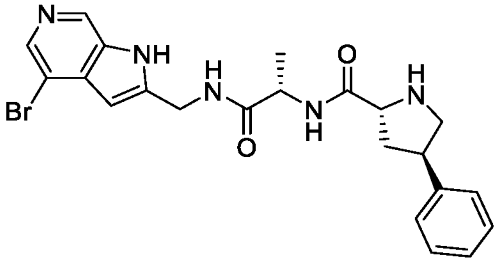
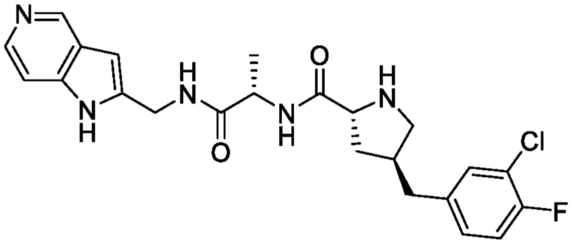
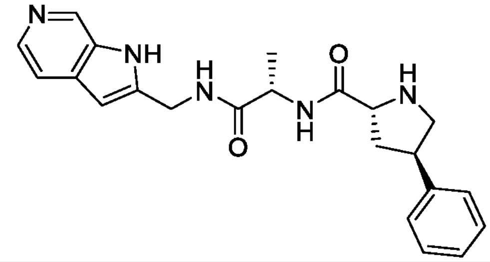
Step 2: *tert*-Butyl 2-(((*S*)-2-((2*R*,4*S*)-4-benzyl-1-(*tert*-butoxycarbonyl)pyrrolidine-2-carboxamido)propanamido)methyl)-4,6-dihydro-5*H*-thieno[2,3-c]pyrrole-5-carboxylate was similarly synthesized according to Example 105, step 5.

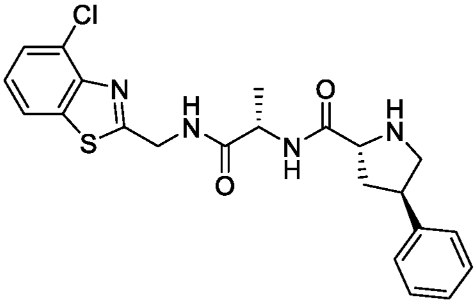
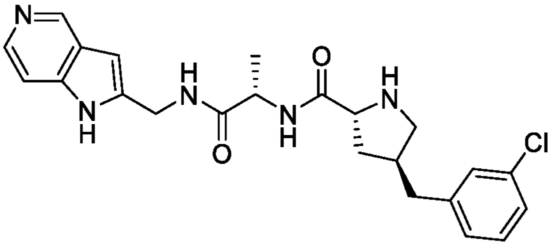
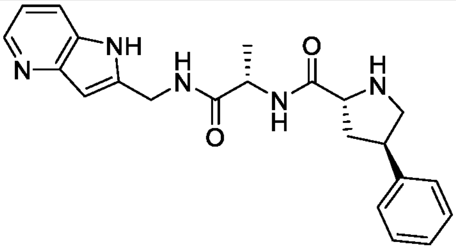
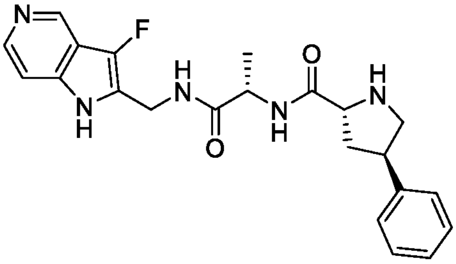
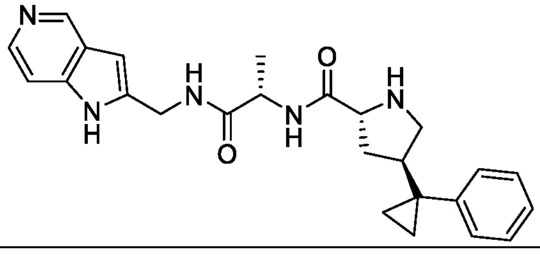


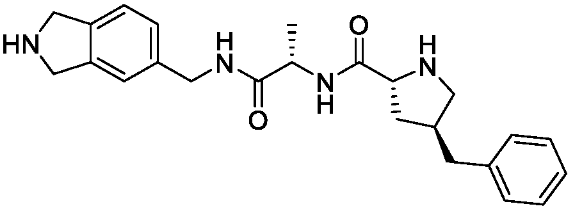
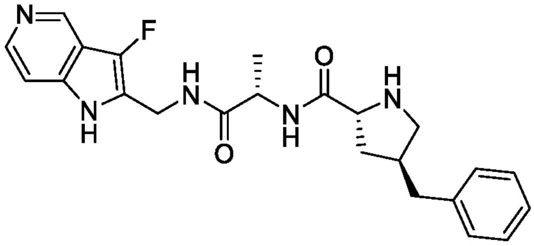
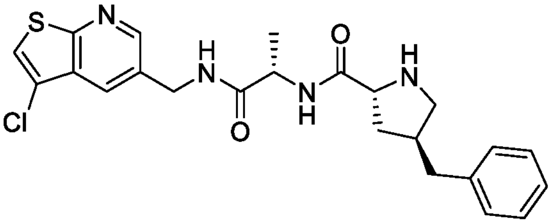
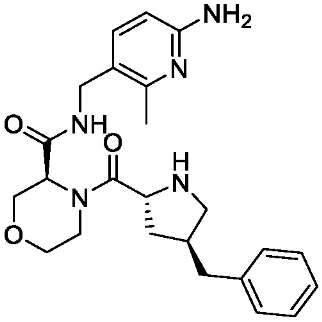
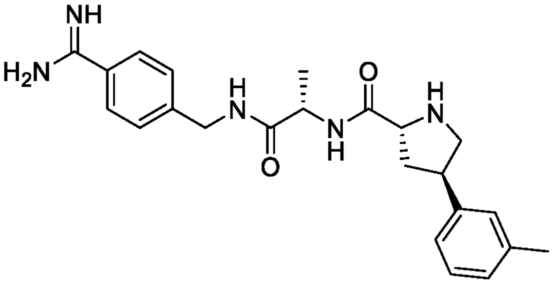
Step 3: The title compound was similarly synthesized according to Example 105, step 6.

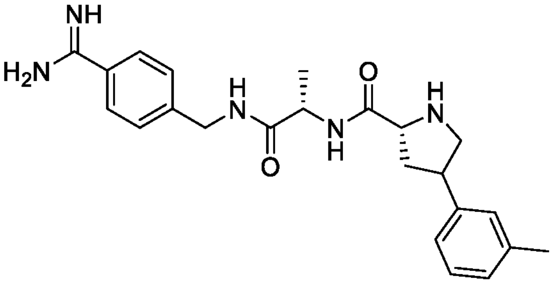
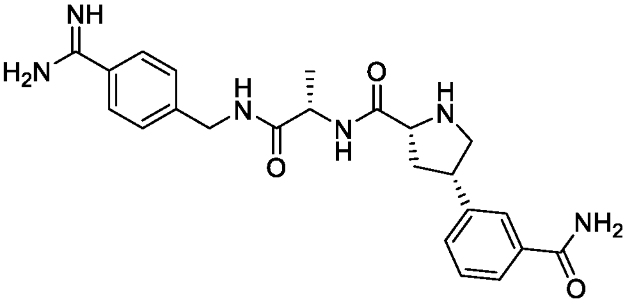
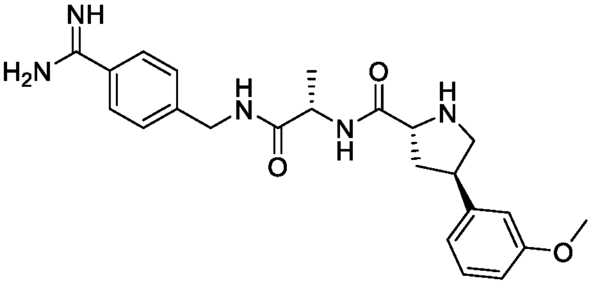
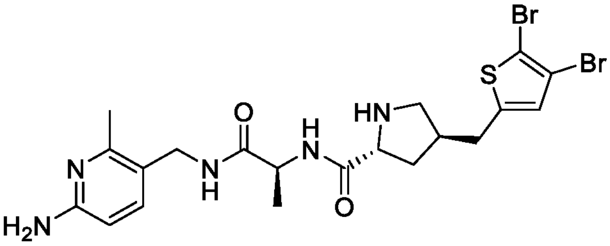
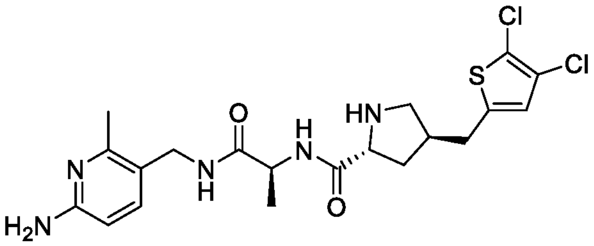
Table 1 lists compounds of the Examples described above, as well as additional compounds that may be prepared according to methods analogous to those described for the compounds above and other methods known to a person having skill in the art. In some embodiments, the compound is selected from Table 1 or is a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof.

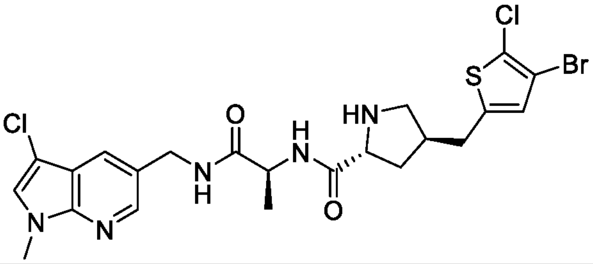
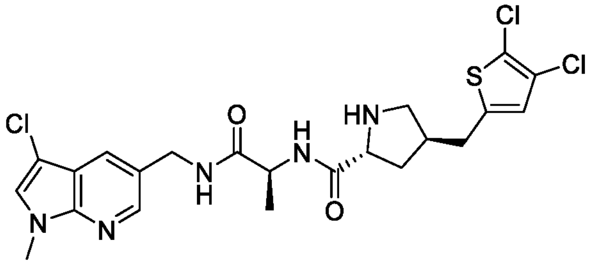
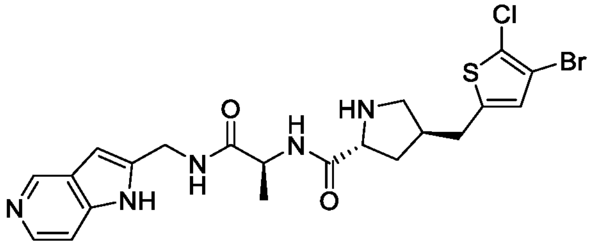
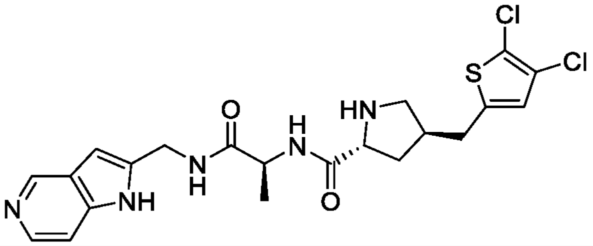
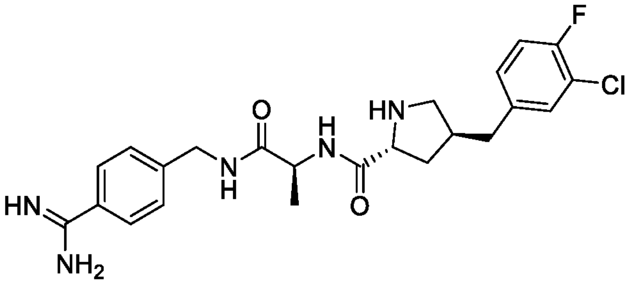
Table 1. Exemplary compounds of Structure (I)

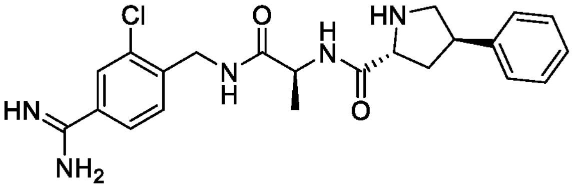
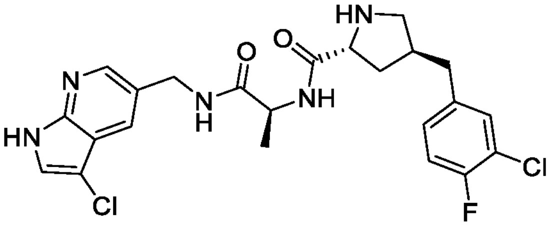
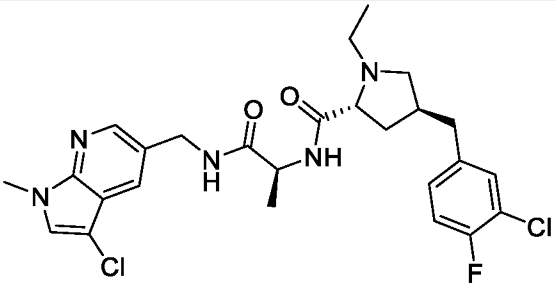
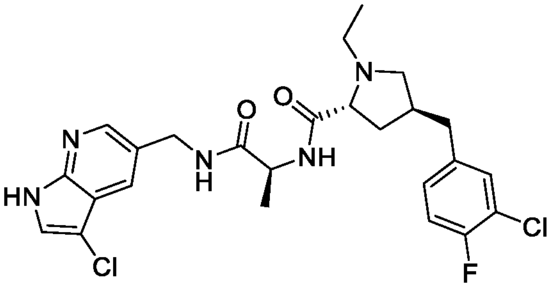
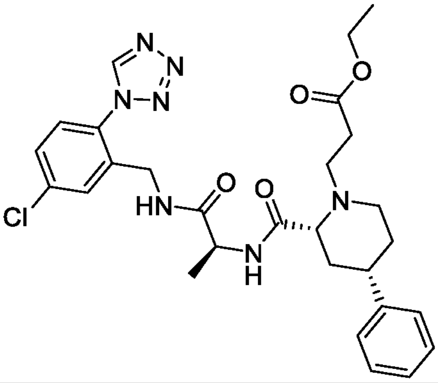
Cmp No.	Structure	Salt	Exact Observed Mass (ES+; M+H)	Exact Calc. Mass
I-1		2TFA	470.03	469.11
I-2		2TFA	458.08	457.17
I-3		2TFA	392.16	391.20

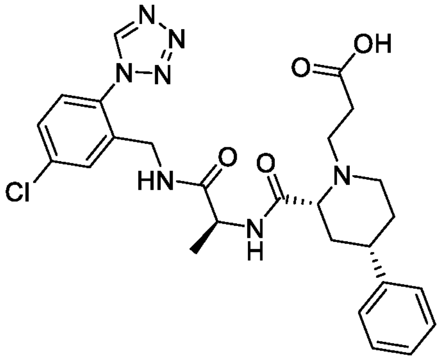
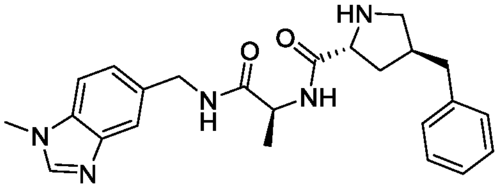
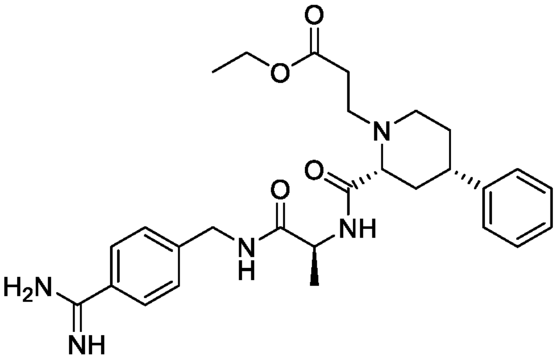
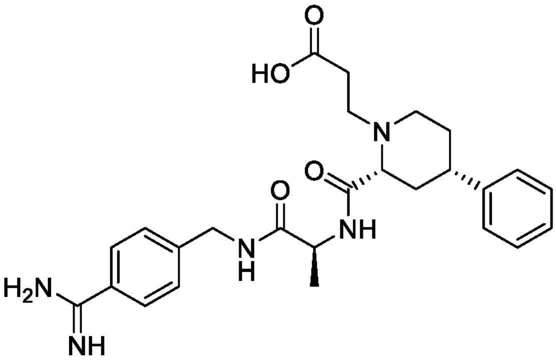
Cmp No.	Structure	Salt	Exact Observed Mass (ES+; M+H)	Exact Calc. Mass
I-4		TFA	443.05	442.12
I-5		2TFA	438.87 (ES-)	439.18
I-6		2TFA	392.14	391.20
I-7		2TFA	410.06	409.19
I-8		2TFA	432.15	431.23

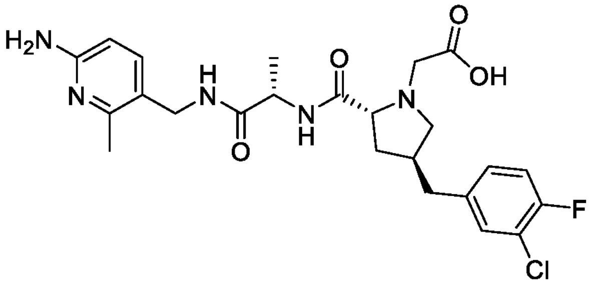
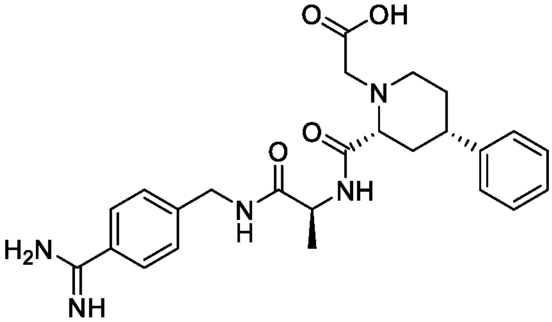
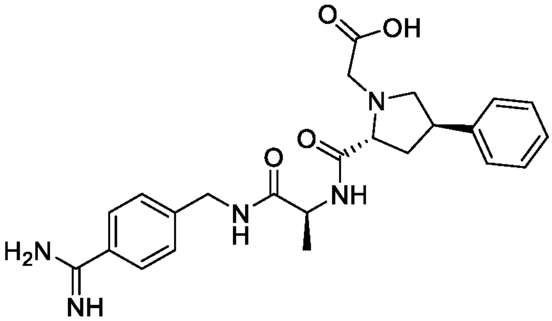
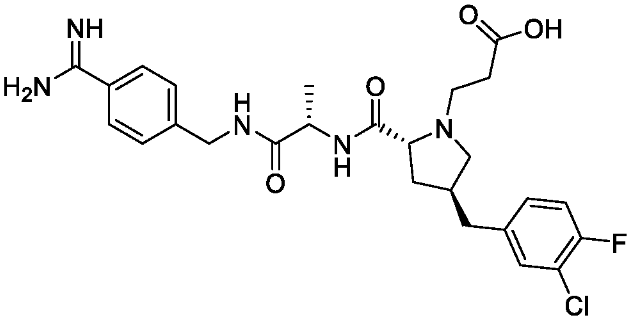
Cmp No.	Structure	Salt	Exact Observed Mass (ES+; M+H)	Exact Calc. Mass
I-9		2TFA	407.12	406.24
I-10		2TFA	424.09	423.21
I-11		TFA	457.01	456.14
I-12		2TFA	438.10	437.24
I-13		-	408.10	407.23

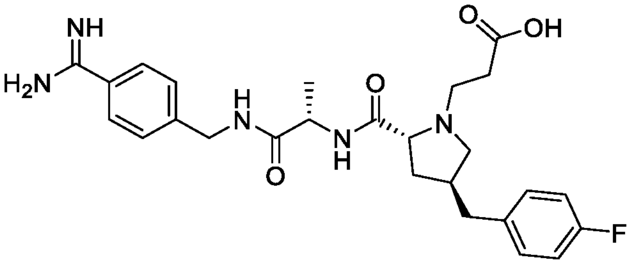
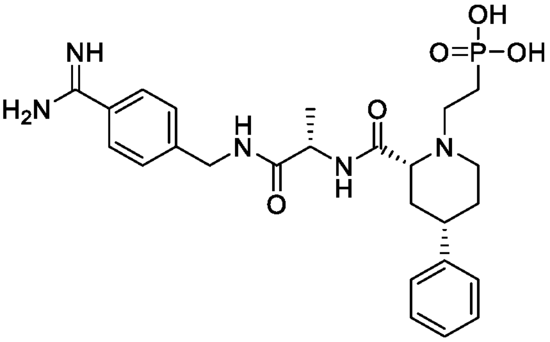
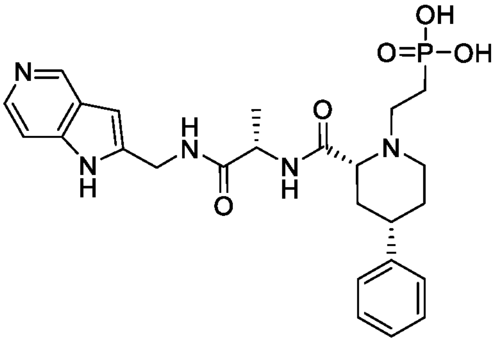
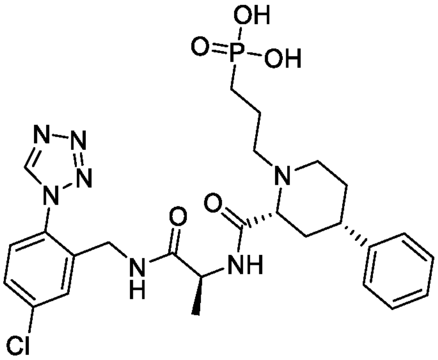
Cmp No.	Structure	Salt	Exact Observed Mass (ES+; M+H)	Exact Calc. Mass
I-14		-	408.08	407.23
I-15		2TFA	435.09 (ES-)	436.22
I-16		2HCl	424.17	423.23
I-17		2TFA	559.87	559.32
I-18		2TFA	470.01	470.41

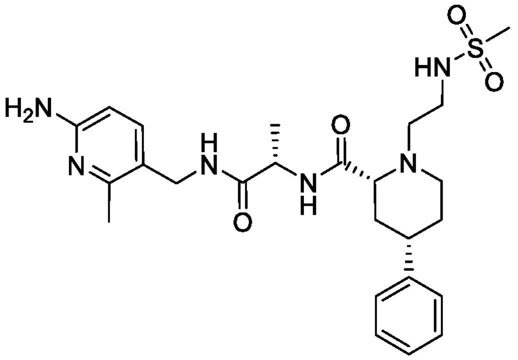
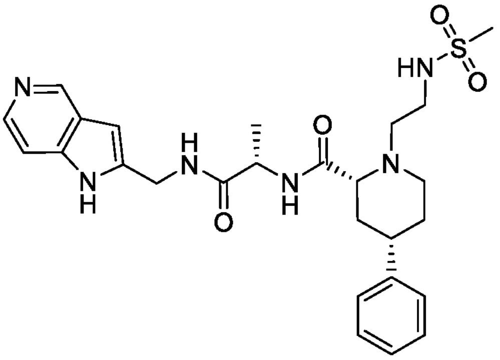
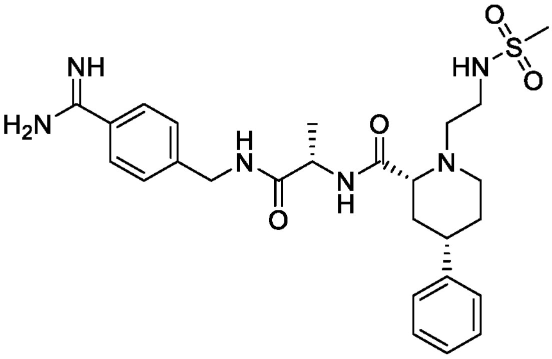
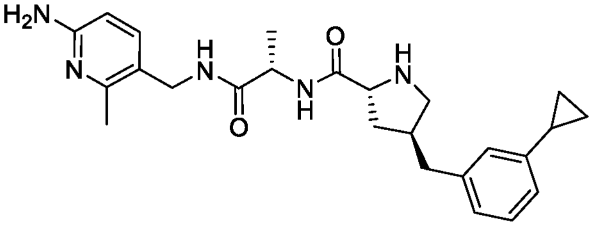
Cmp No.	Structure	Salt	Exact Observed Mass (ES+; M+H)	Exact Calc. Mass
I-19		TFA	573.90	573.33
I-20		TFA	529.92	528.88
I-21		2TFA	525.93	524.86
I-22		2TFA	481.97	480.41
I-23		2TFA	461.95	459.95

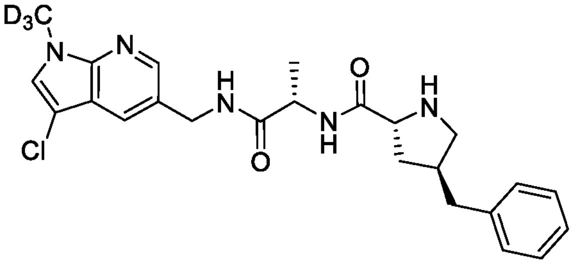
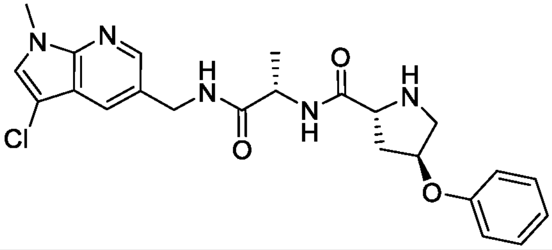
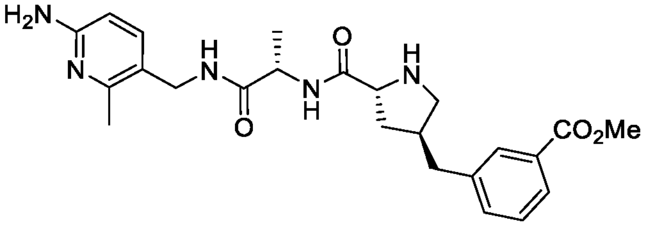
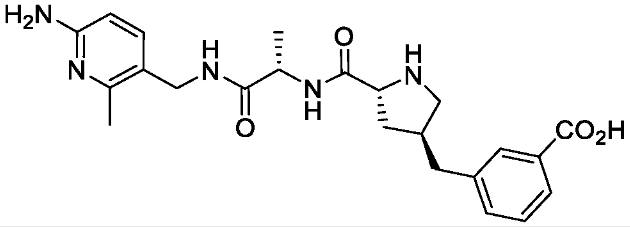
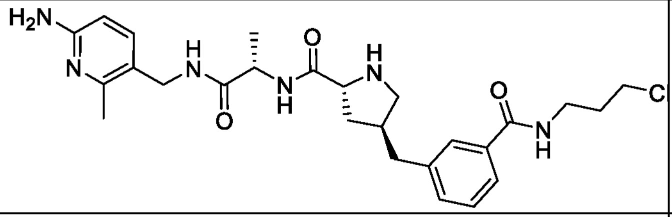
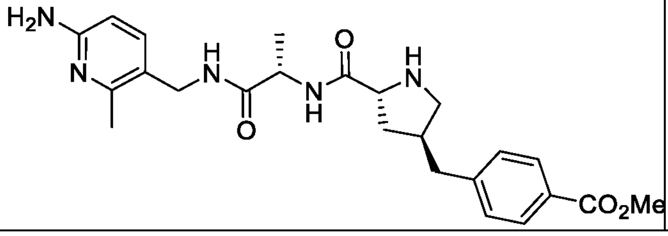
Cmp No.	Structure	Salt	Exact Observed Mass (ES+; M+H)	Exact Calc. Mass
I-24		2TFA	428.11	427.93
I-25		2TFA	492.40	491.13
I-26		-	534.48	533.18
I-27		-	520.45	519.16
I-28		-	568.52	567.24

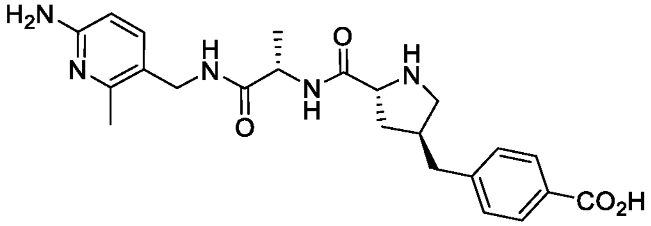
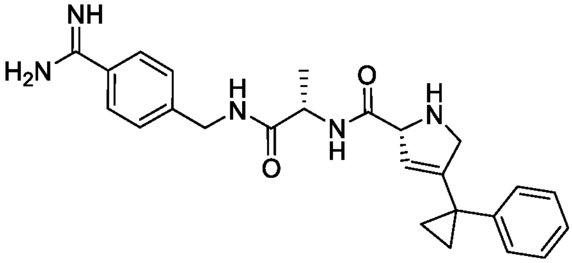
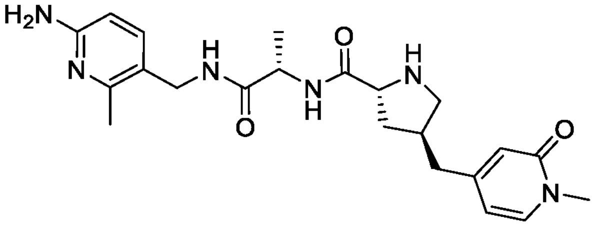
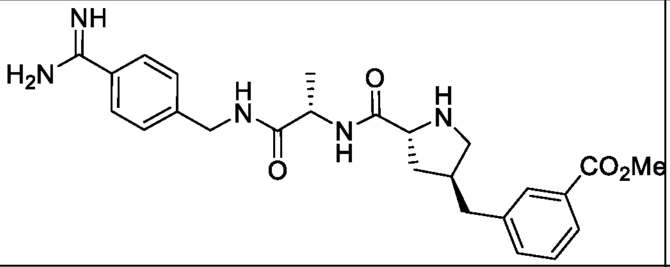
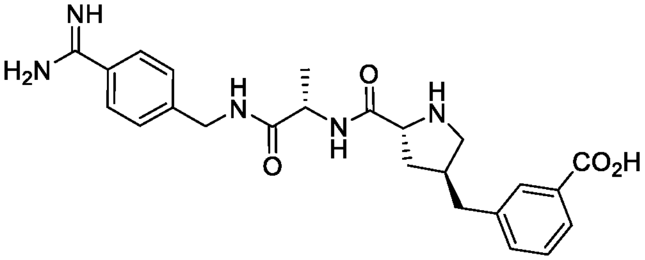
Cmp No.	Structure	Salt	Exact Observed Mass (ES+; M+H)	Exact Calc. Mass
I-29		TFA	540.47	539.20
I-30		TFA	420.16	419.23
I-31		-	508.56	507.28
I-32		2TFA	480.61	479.25

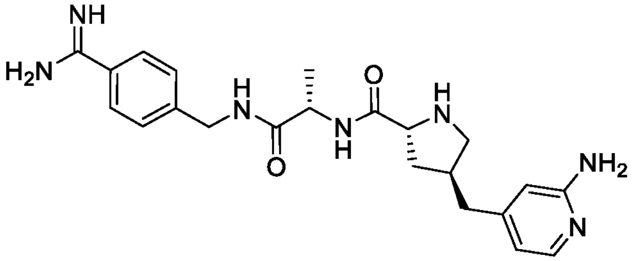
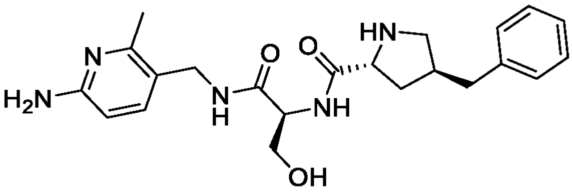
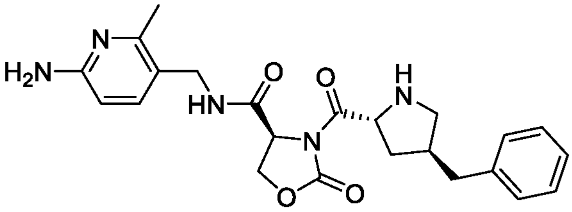
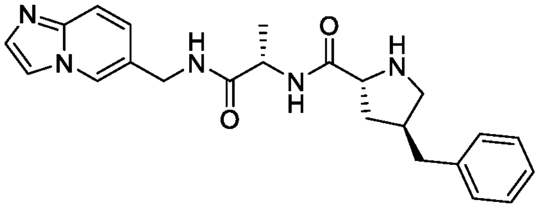
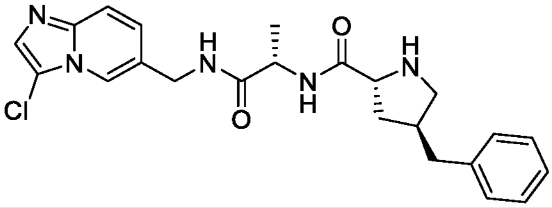
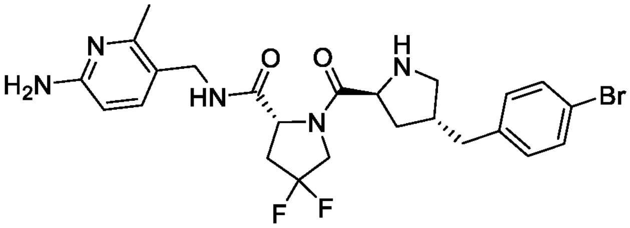
Cmp No.	Structure	Salt	Exact Observed Mass (ES+; M+H)	Exact Calc. Mass
I-33		2TFA	506.11	505.19
I-34		2TFA	466.20	465.24
I-35		2TFA	452.17	451.22
I-36		2TFA	532.14	531.20

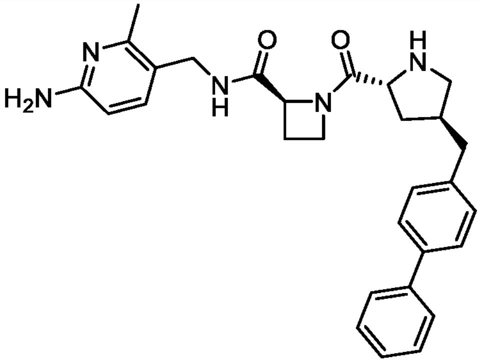
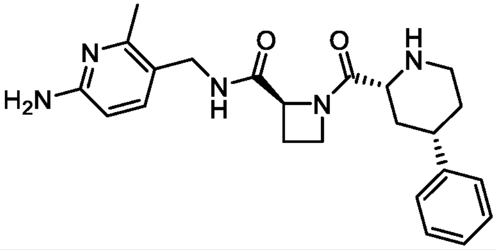
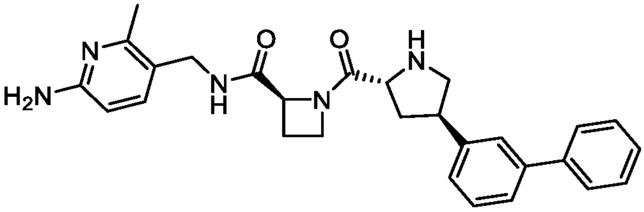
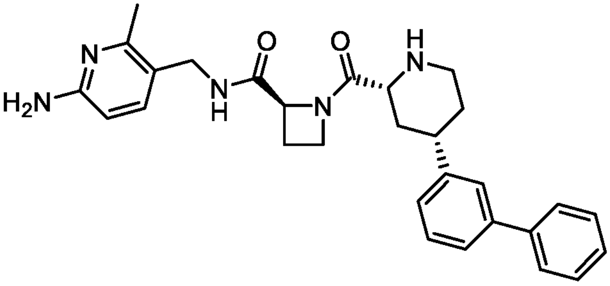
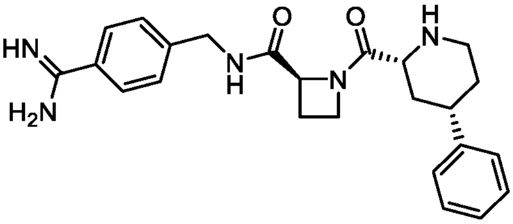
Cmp No.	Structure	Salt	Exact Observed Mass (ES+; M+H)	Exact Calc. Mass
I-37		2TFA	498.17	497.24
I-38		2TFA	516.17	515.23
I-39		2TFA	514.14	513.21
I-40		2TFA	590.15	589.20

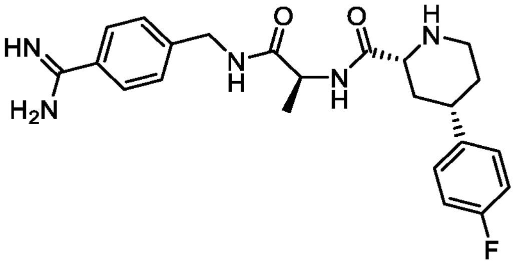
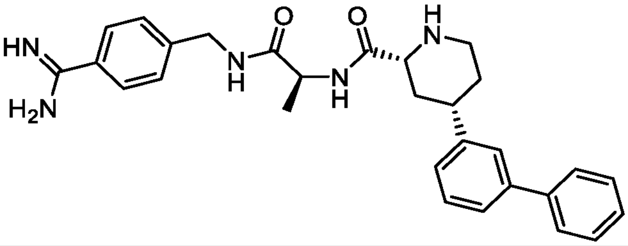
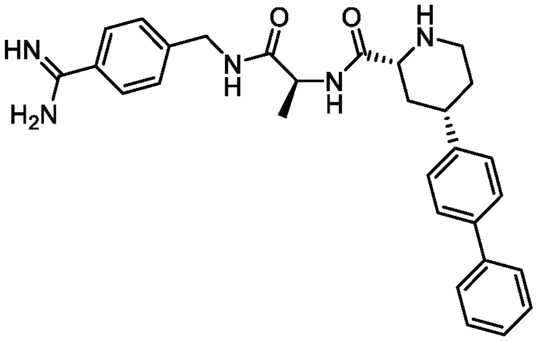
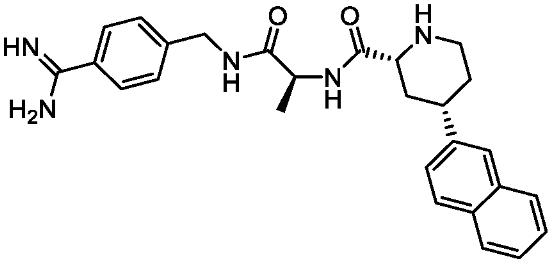
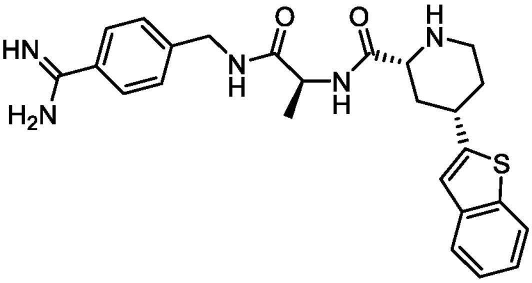
Cmp No.	Structure	Salt	Exact Observed Mass (ES+; M+H)	Exact Calc. Mass
I-41		2TFA	517.21	516.25
I-42		2TFA	527.21	526.24
I-43		2TFA	529.21	528.25
I-44		2TFA	436.14	435.26

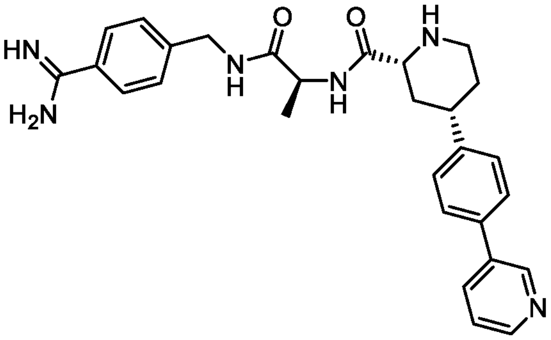
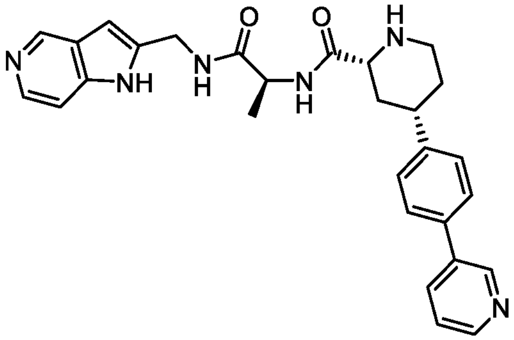
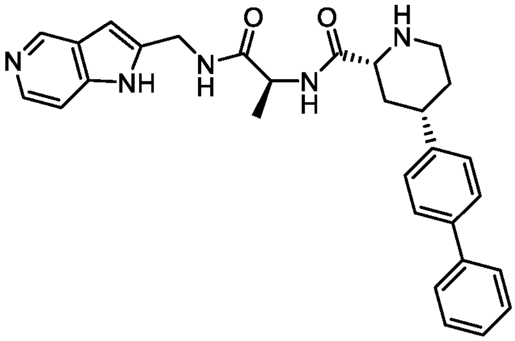
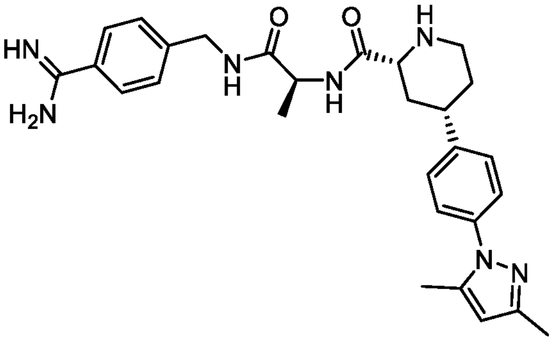
Cmp No.	Structure	Salt	Exact Observed Mass (ES+; M+H)	Exact Calc. Mass
I-45		HCl	457.18	456.21
I-46		TFA	456.10	455.17
I-47		2HCl	454.13	453.24
I-48		2TFA	440.13	439.22
I-49		2TFA	515.12	514.25
I-50		2HCl	454.14	453.24

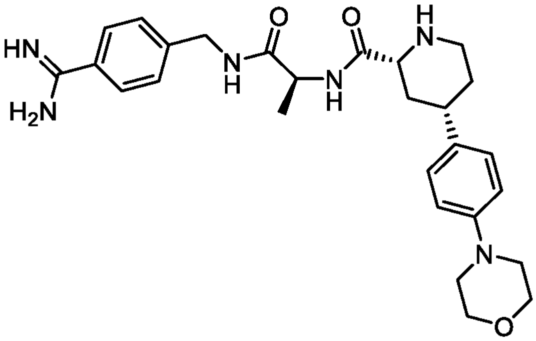
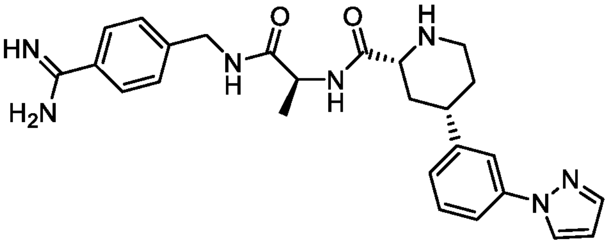
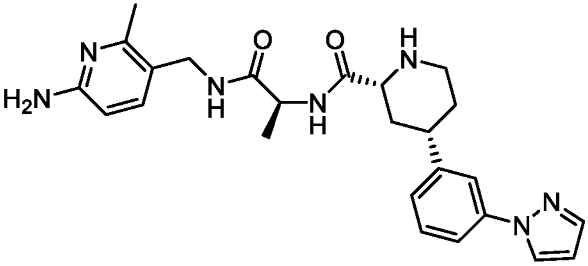
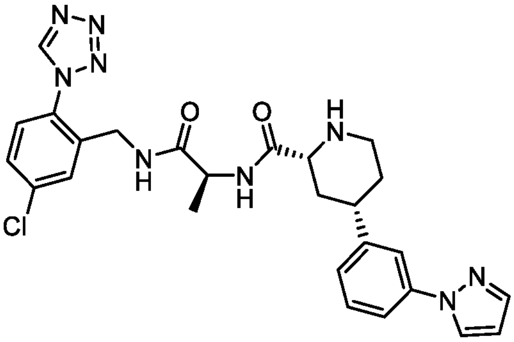
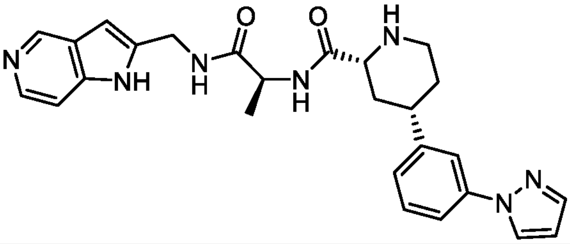
Cmp No.	Structure	Salt	Exact Observed Mass (ES+; M+H)	Exact Calc. Mass
I-51		2TFA	440.14	439.22
I-52		2HCl	432.16	431.23
I-53		2TFA	427.13	426.24
I-54		2TFA	466.12	465.24
I-55		2TFA	452.14	451.22

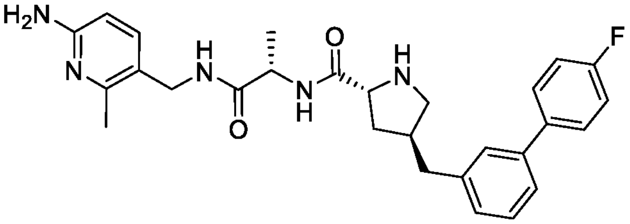
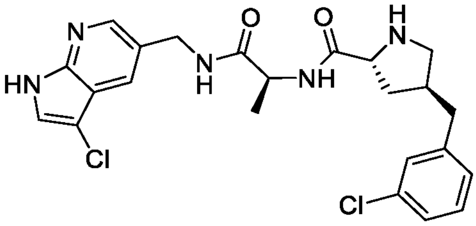
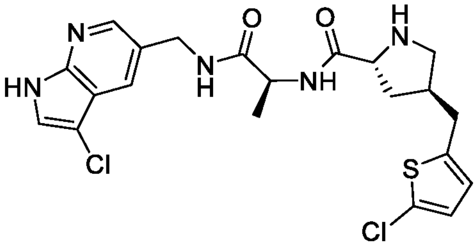
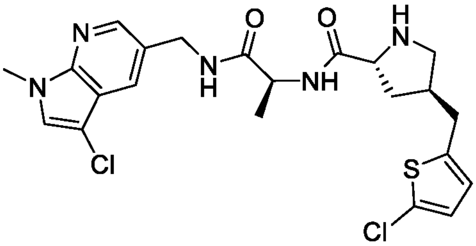
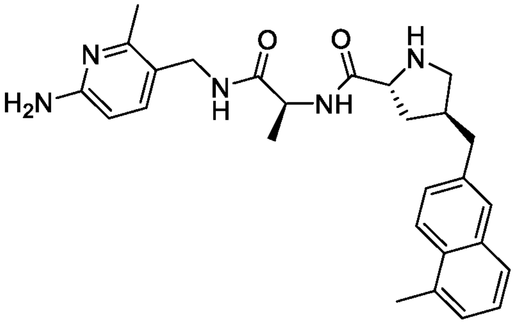
Cmp No.	Structure	Salt	Exact Observed Mass (ES+; M+H)	Exact Calc. Mass
I-56		2TFA	424.19	423.24
I-57		2HCl	412.15	411.23
I-58		2TFA	438.11	437.21
I-59		TFA	406.13	405.22
I-60		HCl	440.08	439.18
I-61		2HCl	536.05	535.14

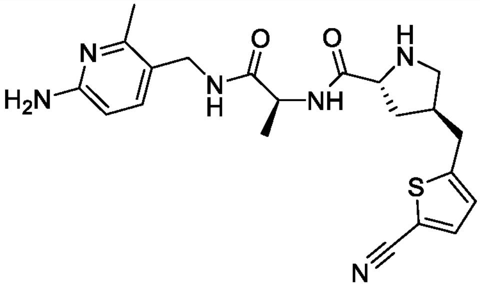
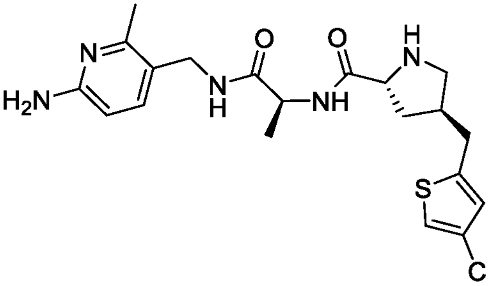
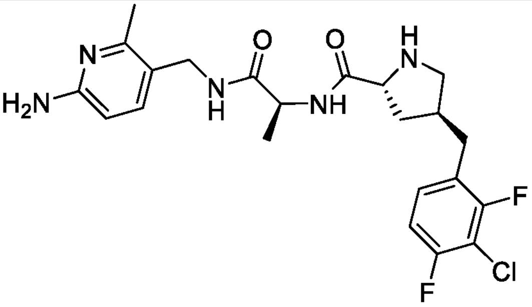
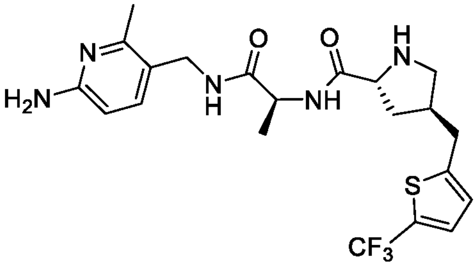
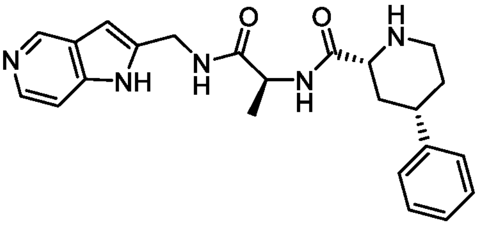
Cmp No.	Structure	Salt	Exact Observed Mass (ES+; M+H)	Exact Calc. Mass
I-62		2TFA	484.41	483.26
I-63		2TFA	408.47	407.23
I-64		2TFA	470.17	469.25
I-65		2TFA	484.24	483.26
I-66		2TFA	420.40	419.23

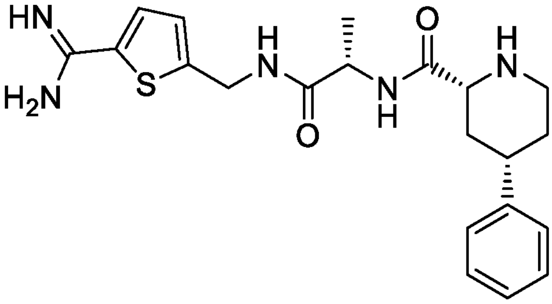
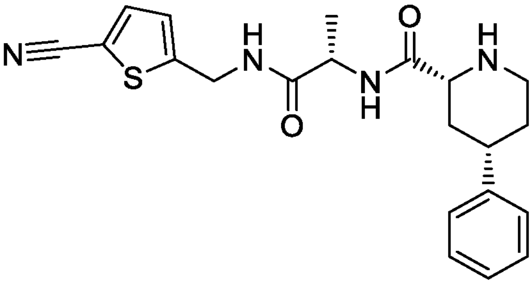
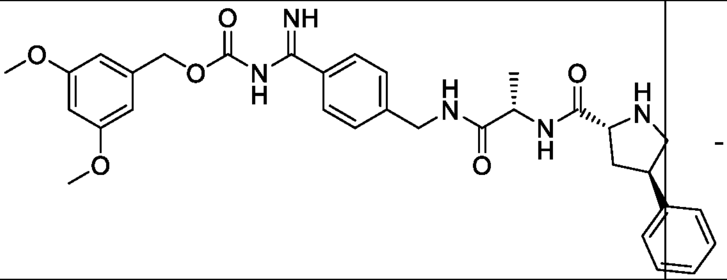
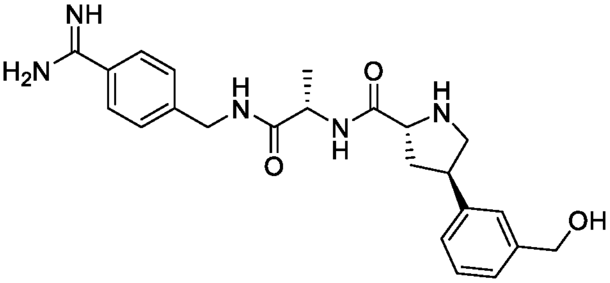
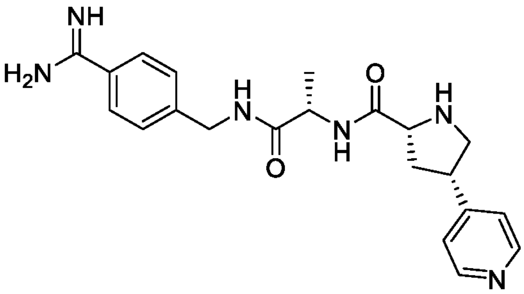
Cmp No.	Structure	Salt	Exact Observed Mass (ES+; M+H)	Exact Calc. Mass
I-67		2TFA	426.40	425.22
I-68		2TFA	484.51	483.26
I-69		2TFA	484.46	483.26
I-70		2TFA	458.40	457.25
I-71		2TFA	464.34	463.20

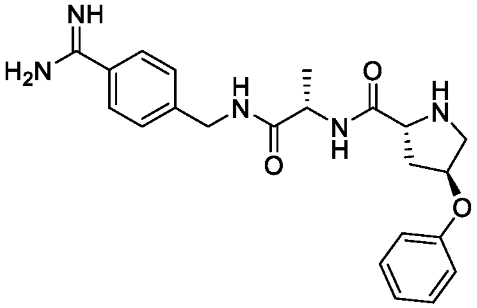
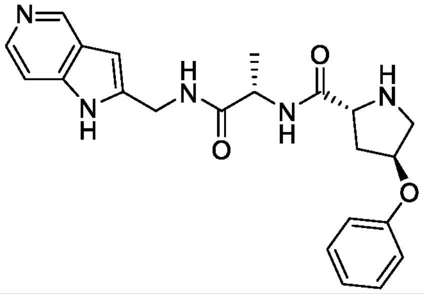
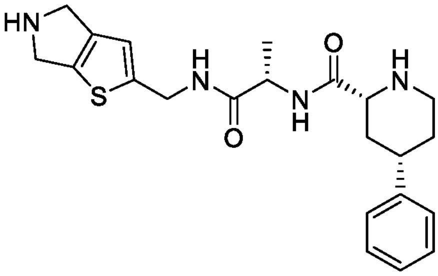
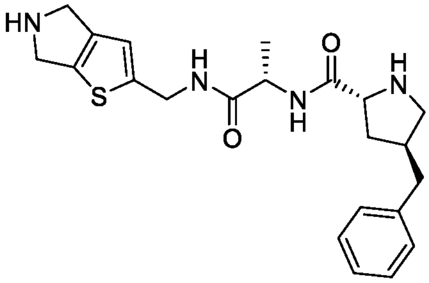
Cmp No.	Structure	Salt	Exact Observed Mass (ES+; M+H)	Exact Calc. Mass
I-72		2TFA	485.36	484.26
I-73		2TFA	483.46	482.24
I-74		2TFA	482.56	481.25
I-75		2HCl	502.53	501.29

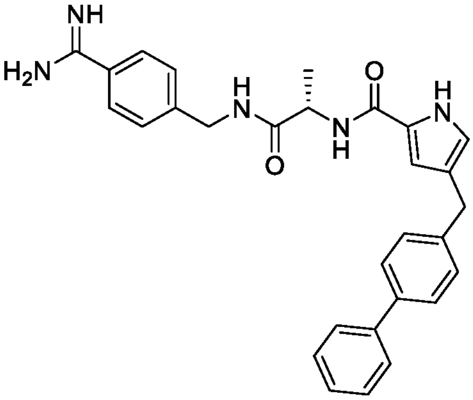
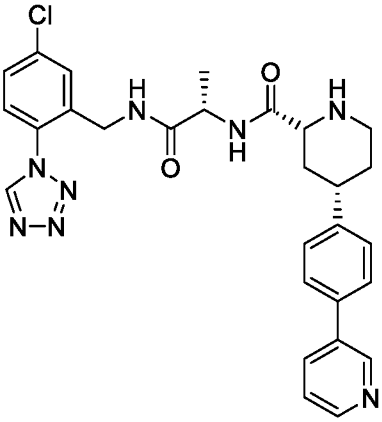
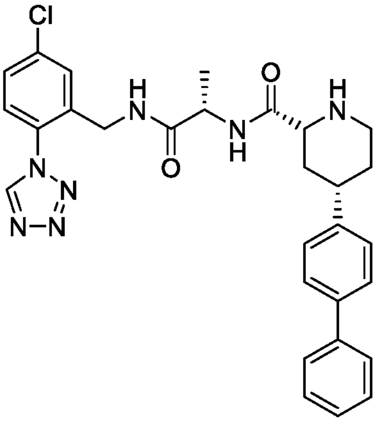
Cmp No.	Structure	Salt	Exact Observed Mass (ES+; M+H)	Exact Calc. Mass
I-76		2HCl	493.39	492.28
I-77		2HCl	474.57	473.25
I-78		2HCl	462.49	461.25
I-79		HCl	534.43	533.21
I-80		2HCl	472.53	471.24

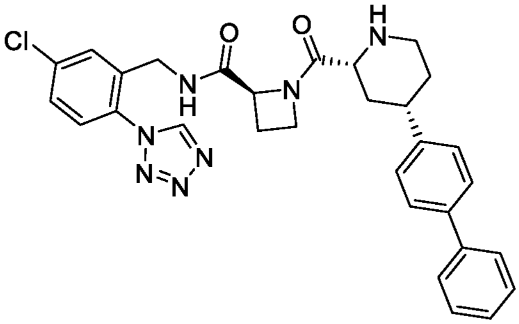
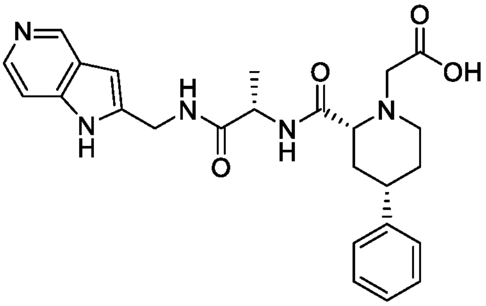
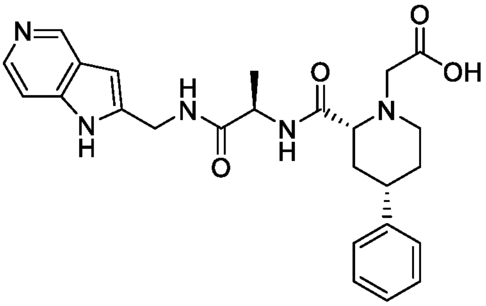
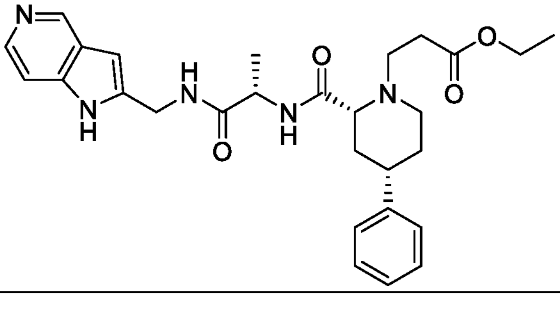
Cmp No.	Structure	Salt	Exact Observed Mass (ES+; M+H)	Exact Calc. Mass
I-81		2TFA	490.49	489.58
I-82		2HCl	474.02	473.14
I-83		2HCl	480.01	479.09
I-84		2HCl	494.02	493.11
I-85		2HCl	460.17	459.26

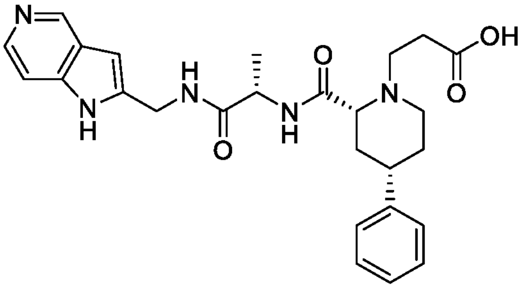
Cmp No.	Structure	Salt	Exact Observed Mass (ES+; M+H)	Exact Calc. Mass
I-86		2HCl	427.06	426.18
I-87		2HCl	436.04	435.15
I-88		2HCl	466.02	465.17
I-89		2HCl	470.04	469.18
I-90		2TFA	406.19	405.22

Cmp No.	Structure	Salt	Exact Observed Mass (ES+; M+H)	Exact Calc. Mass
I-91		2TFA	414.46	413.54
I-92		HCl	397.44	396.51
I-93		-	-	587.67
I-94		2TFA	424.25	423.23
I-95		2TFA	395.34	394.21

Cmp No.	Structure	Salt	Exact Observed Mass (ES+; M+H)	Exact Calc. Mass
I-96		2TFA	410.20	409.21
I-97		2TFA	408.14	407.20
I-98		2TFA	413.09	412.19
I-99		2TFA	413.17	412.19

Cmp No.	Structure	Salt	Exact Observed Mass (ES+; M+H)	Exact Calc. Mass
I-100		TFA	480.32	479.23
I-101		TFA	545.54	544.21
I-102		TFA	544.58	543.21

Cmp No.	Structure	Salt	Exact Observed Mass (ES+; M+H)	Exact Calc. Mass
I-103		TFA	556.47	555.21
I-104		2TFA	464.5	463.2
I-105		2TFA	464.5	463.2
I-106		-	506.5	505.3

Cmp No.	Structure	Salt	Exact Observed Mass (ES+; M+H)	Exact Calc. Mass
I-107		2TFA	478.5	477.2

EXAMPLE 107

ENZYMATIC ASSAY FOR MASP-2

The MASP-2 assay utilizes a fluorogenic substrate, based on the cleavage site for its natural substrate C2. The assay is run at room temperature in an assay buffer containing 20 mM HEPES, pH 7.4, 140 mM NaCl and 0.1% Tween 20. Assay parameters are adjusted such that the assay is linear with respect to time, enzyme, and substrate concentrations. Under these optimized assays conditions, IC_{50} values are equivalent to Ki values, except in a few cases of "tight binding" inhibitors. Cases of "tight binding" or possible "slow binding" inhibitors are handled by the methods described in Copeland R.A. (2013) Evaluation of Enzyme Inhibitors in Drug Discovery. 2nd Ed., John Wiley and Sons, Inc., Chapters 5-7.

The MASP-2 assay protocol is carried out as follows. Test compounds are serially diluted in DMSO and then 100 nL of each dilution is transferred to the assay plate(s). 10 µL of Assay Buffer is added, followed by 15 µL of Enzyme MASP-2 (CCP1-CCP2-SP) in Assay Buffer. 15 µL of Substrate in Assay Buffer is then added and mixed to start the reactions. After 20 min at room temperature, 15 µL of a stop solution (0.1 M acetic acid) is added, mixed and the plates are read on a SpectraMax i3x Microplate Reader and exported as Excel files. Each assay plate included a "no inhibitor" (DMSO Only) control, a "no enzyme" control and a reference inhibitor control. % Activity values = 100*(average test comp. fluorescence – average "no enzyme" fluorescence) / (average

"DMSO only" fluorescence – average "no enzyme" fluorescence). IC_{50} and Ki values are very reproducible, falling well within ± 2-fold.

The results of biological assays for the compounds listed in Table 1 are listed in Table 2, below.

Table 2. MASP-2 Inhibition for exemplary compound of Structure (I)

Compound	**MASP-2 K_i (μM)**	**Compound**	**MASP-2 K_i (μM)**	**Compound**	**MASP-2 K_i (μM)**
I-1	*	I-2	****	I-3	**
I-4	***	I-5	****	I-6	***
I-7	****	I-8	****	I-9	****
I-10	****	I-11	****	I-12	***
I-13	****	I-14	****	I-15	****
I-16	****	I-17	****	I-18	****
I-19	****	I-20	****	I-21	****
I-22	****	I-23	****	I-24	****
I-25	****	I-26	****	I-27	****
I-28	**	I-29	**	I-30	**
I-31	****	I-32	****	I-33	****
I-34	****	I-35	****	I-36	****
I-37	****	I-38	****	I-39	****
I-40	***	I-41	**	I-42	****
I-43	****	I-44	****	I-45	****
I-46	****	I-47	****	I-48	****
I-49	****	I-50	****	I-51	****
I-52	****	I-53	****	I-54	****
I-55	****	I-56	****	I-57	****
I-58	****	I-59	*	I-60	*
I-61	****	I-62	****	I-63	****
I-64	****	I-65	****	I-66	****
I-67	****	I-68	****	I-69	****
I-70	****	I-71	****	I-72	****
I-73	****	I-74	****	I-75	****
I-76	****	I-77	****	I-78	****
I-79	****	I-80	****	I-81	****
I-82	****	I-83	****	I-84	****
I-85	****	I-86	****	I-87	****
I-88	****	I-89	****	I-90	****
I-91	****	I-92	**	I-93	--
I-94	****	I-95	***	I-96	****
I-97	****	I-98	****	I-99	****
I-100	****	I-101	****	I-102	****
I-103	****	I-104	****	I-105	****
I-106	****	I-107	****	-	--

MASP-2 Inhibition K_i Values:

*	K_i greater than 10 µM
**	K_i between 2.5 - 10 µM
***	K_i between 0.5 - 2.5 µM
****	K_i of less than 0.5 µM
--	not tested

It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims. Each reference, including without limitation all patent, patent applications, and publications, cited in the present application is incorporated herein by reference in its entirety for all purposes.

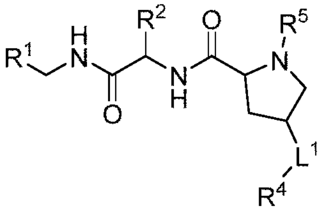
This application claims the benefit of priority to U.S. Provisional Application No. 62/943,611, filed December 4, 2019, which application is hereby incorporated by reference in its entirety.

Reference to any prior art in the specification is not an acknowledgement or suggestion that this prior art forms part of the common general knowledge in any jurisdiction or that this prior art could reasonably be expected to be combined with any other piece of prior art by a skilled person in the art.

By way of clarification and for avoidance of doubt, as used herein and except where the context requires otherwise, the term "comprise" and variations of the term, such as "comprising", "comprises" and "comprised", are not intended to exclude further additions, components, integers or steps.

CLAIMS

1. A compound having the following Structure (I):



(I)

or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein:

R^1 is a substituted aryl or a substituted or unsubstituted heteroaryl;

R^2 is methyl;

R^4 is a substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocyclyl;

R^5 is hydrogen, alkyl, haloalkyl, cycloalkyl, phosphonalkyl, $(CH_2)_mC(=O)OR^6$, $C(=O)R^6$, $C(=O)OR^6$, $(CH_2)_mNR^6S(O)_2R^7$, or $C(=O)NR^6R^7$;

R^6 and R^7 are, at each occurrence, independently hydrogen, alkyl, haloalkyl, cycloalkyl, or arylalkyl;

L^1 is a direct bond, $-CR^{8a}R^{8b}-$, $-S(O)_t-$, NR^{8c}, or -O-;

R^{8a} and R^{8b} are each independently hydrogen or alkyl, or R^{8a} and R^{8b}, together with the carbon to which they are attached form an optionally substituted 3-6 membered cycloalkyl;

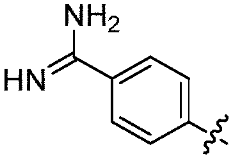
R^{8c} is hydrogen, alkyl, haloalkyl, (C=O)alkyl, (C=O)Oalkyl, (C=O)cycloalkyl, (C=O)Ocycloalkyl, (C=O)aryl, (C=O)Oaryl, (C=O)heteroaryl, (C=O)Oheteroaryl, (C=O)heterocyclyl, (C=O)O heterocyclyl, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted heterocyclyl, a substituted or unsubstituted arylalkyl, a substituted or unsubstituted heteroarylalkyl, a substituted or unsubstituted cycloalkylalkyl, or a substituted or unsubstituted heterocyclylalkyl;

m is 1, 2, 3, 4, 5, or 6; and

t is 0, 1, or 2.

2. The compound of claim 1, wherein R^1 is phenyl.

3. The compound of claim 1, wherein R^1 has one of the following structures: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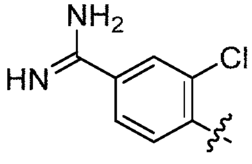
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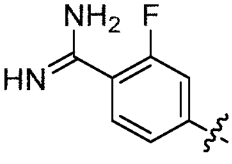
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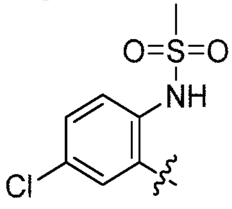
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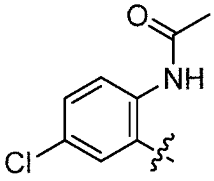
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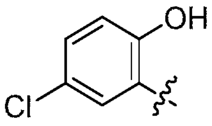
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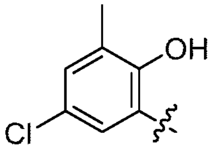
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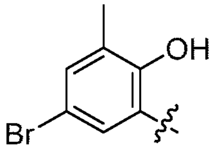
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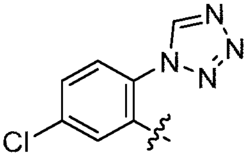
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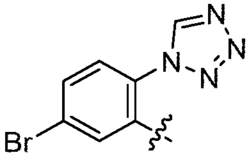
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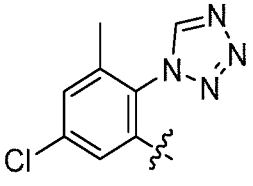
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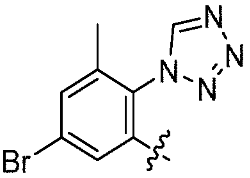
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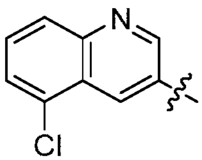
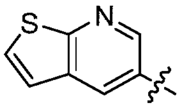
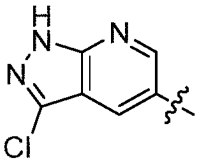
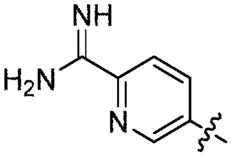
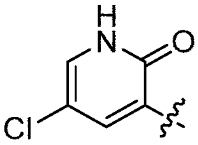
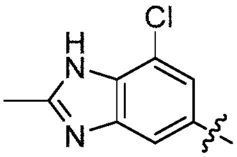
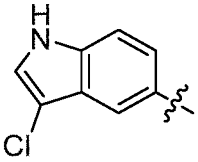
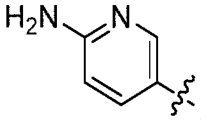
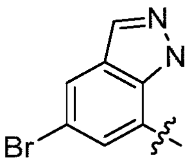
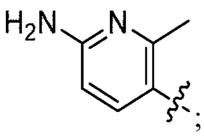
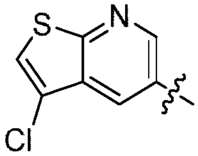
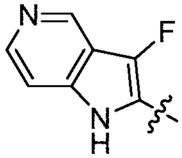
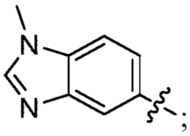
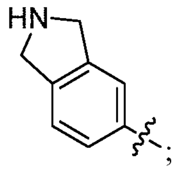
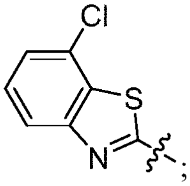
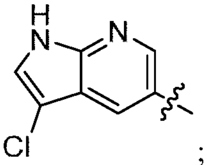
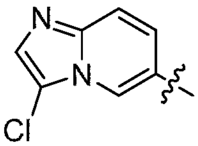
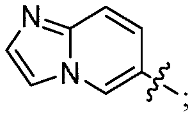
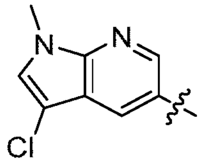
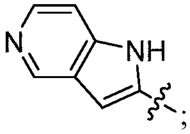
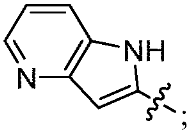
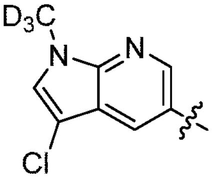
4. The compound of claim 1, wherein R^1 is a substituted or unsubstituted heteroaryl.

5. The compound of claim 1, wherein R^1 has one of the following structures:

;
;
;
;
;
;
;
;
;
;
;
;
;
;
;
;
;
;
;
;
;

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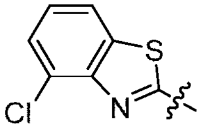
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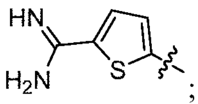
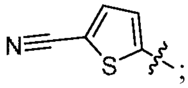
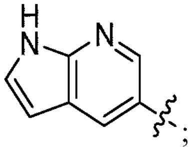
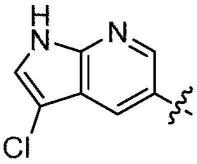
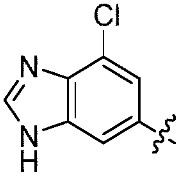
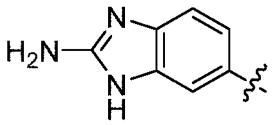
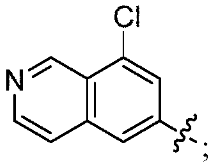
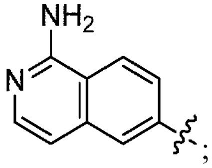
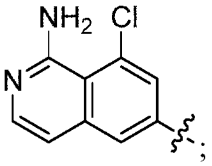
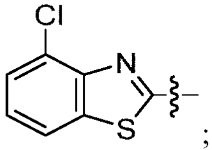
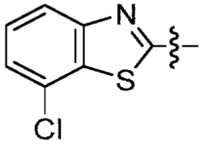
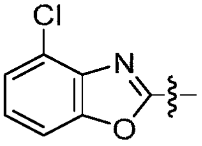
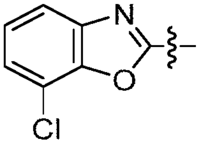
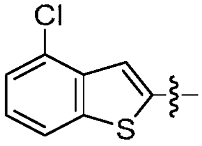
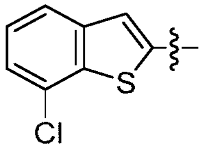
6. The compound of claim 1, wherein R^1 has one of the following structures:

;
;
;
;
;
;
;
;
;
;
;
;
;
;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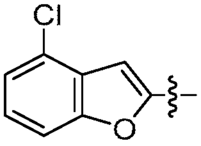
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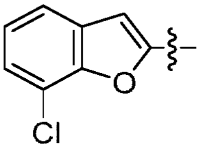
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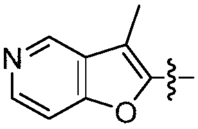
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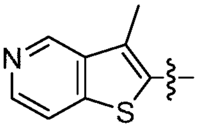
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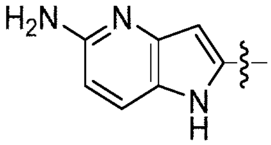
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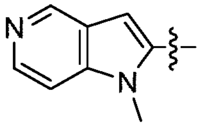
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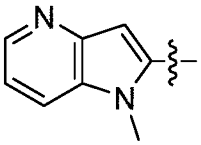
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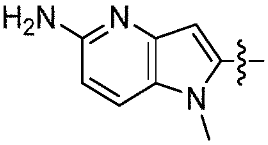
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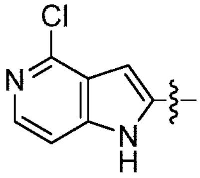
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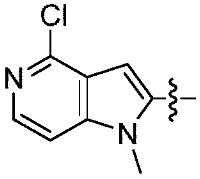
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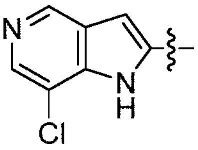
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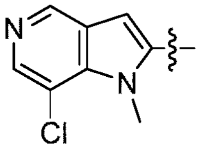
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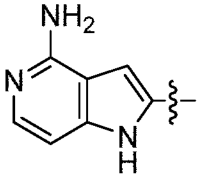
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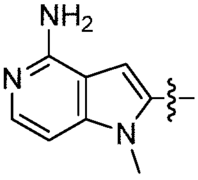
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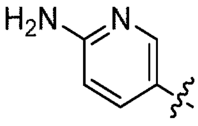
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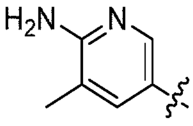
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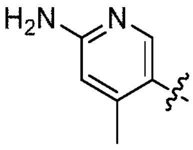
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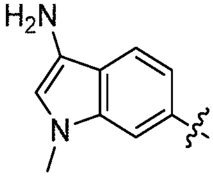
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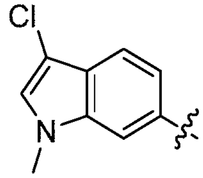
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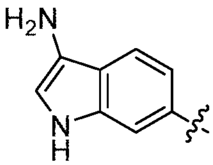
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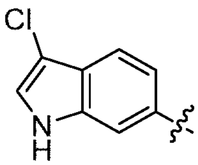
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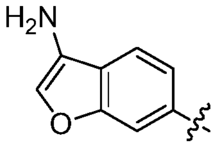
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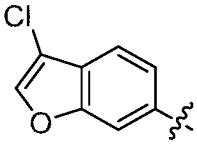
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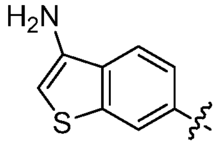
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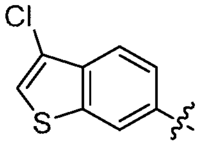
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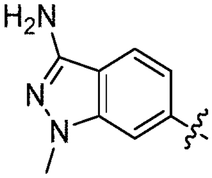
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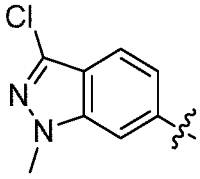
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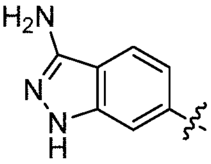
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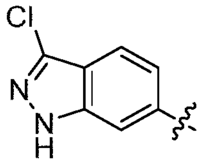
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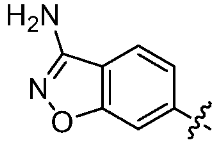
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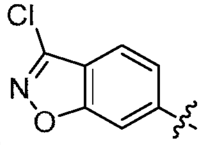

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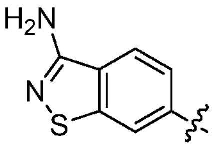
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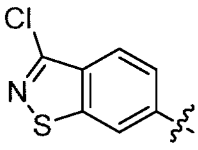
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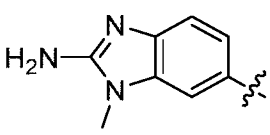
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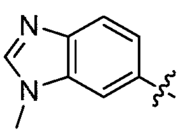
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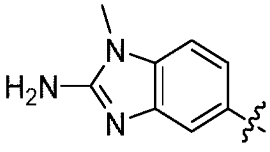
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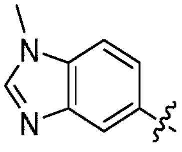
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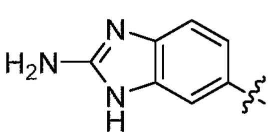
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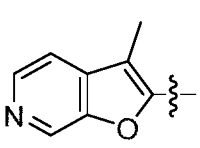
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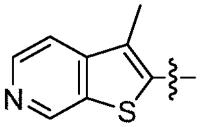
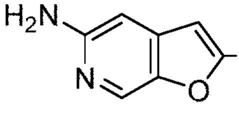
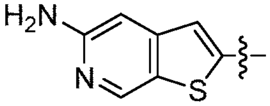
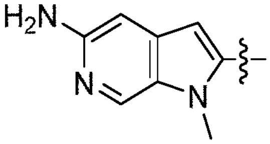
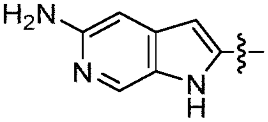
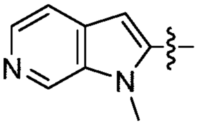
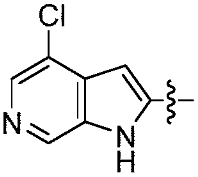
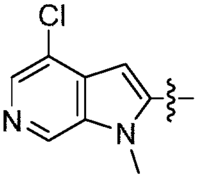
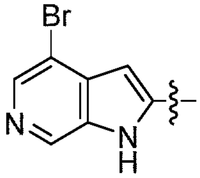
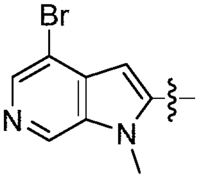
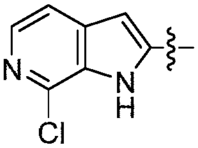
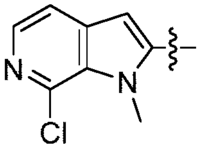
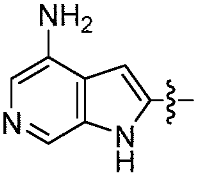
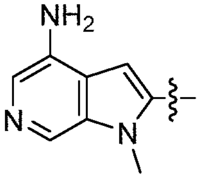
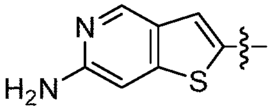
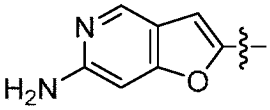
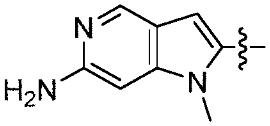
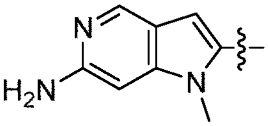
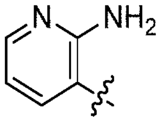
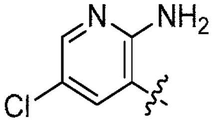
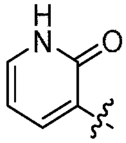
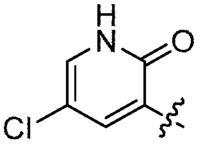
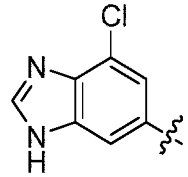
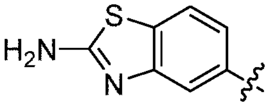
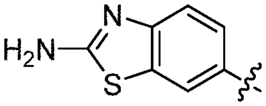
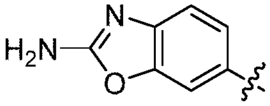
 ;  ;  ;  ;

 ;  ;  ;  ;

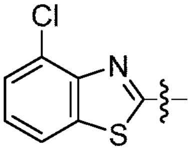
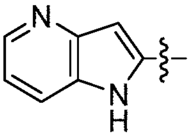
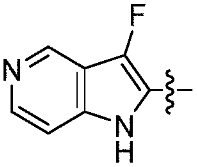
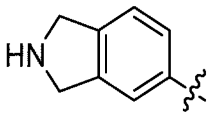
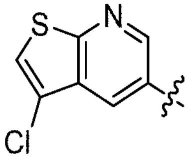
 ;  ;  ;  ;  ;

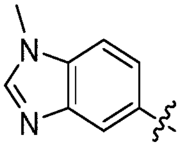
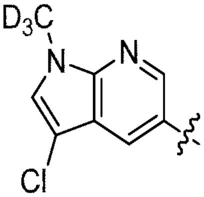
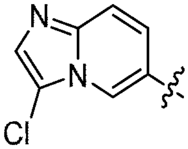
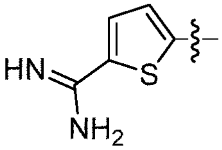
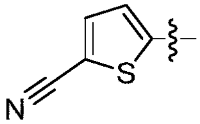
 ;  ;  ;  ;

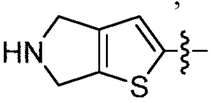
 ;  ;  ;  ;  ;

 ;  ;  or  .

7. The compound of claim 1, wherein R^1 has one of the following structures:

 ;  ;  ;  ;  ;

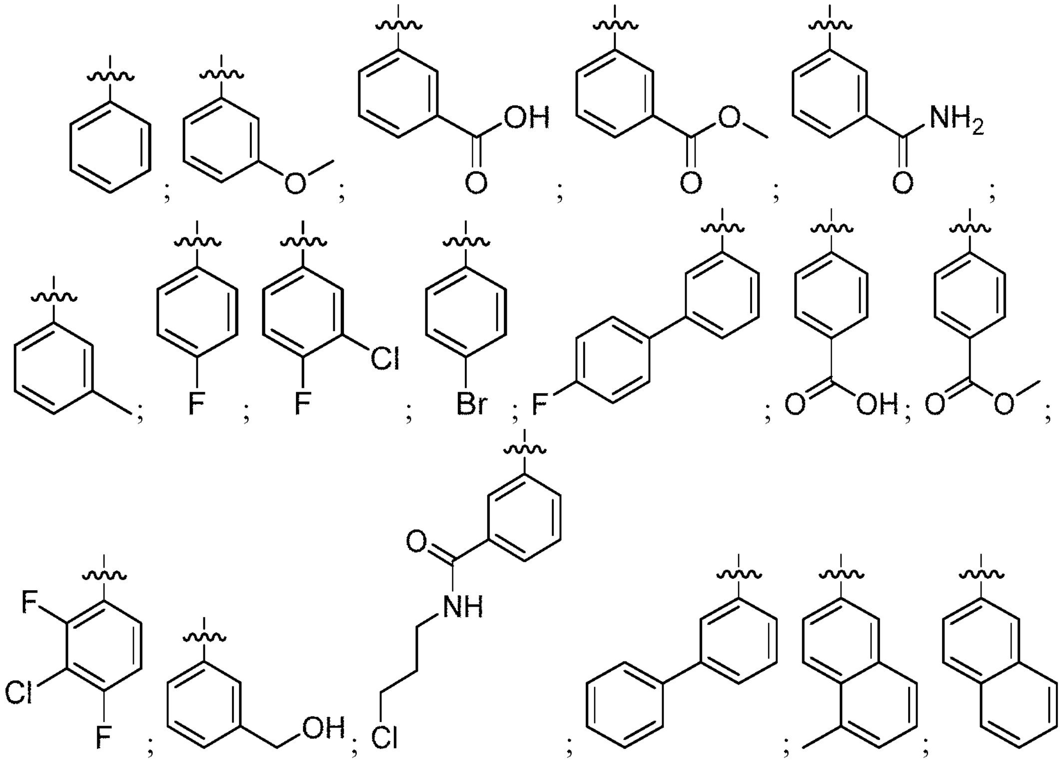
 ;  ;  ;  ; 

or  .

8. The compound of any one of claims 1 to 7, wherein R^4 is a substituted or unsubstituted aryl.

9. The compound of any one of claims 1 to 7, wherein R^4 is a substituted or unsubstituted phenyl.

10. The compound of any one of claims 1 to 7, wherein R^4 has one of the following structures:



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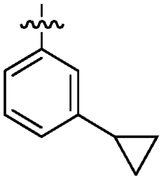
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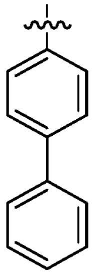
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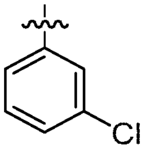
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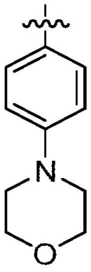
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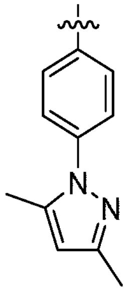
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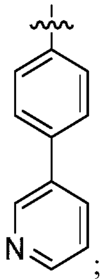
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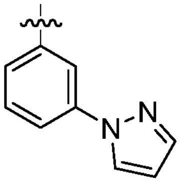
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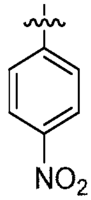
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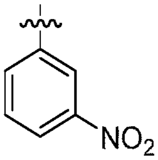
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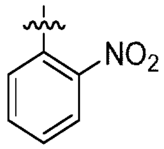
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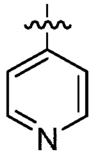
11. The compound of any one of claims 1 to 7, wherein R^4 is a substituted or unsubstituted heteroaryl.

12. The compound of any one of claims 1 to 7, wherein R^4 has one of the following structures: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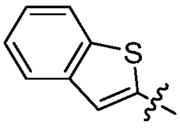
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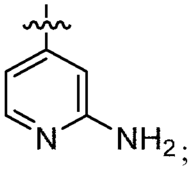
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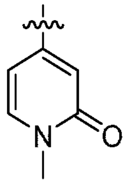
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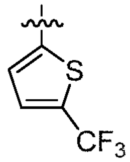
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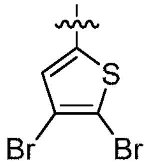
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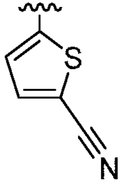
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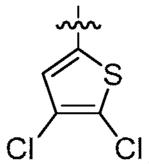
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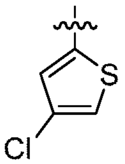
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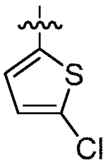
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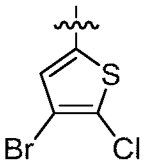
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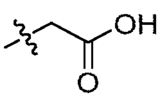
13. The compound of any one of claims 1 to 12, wherein R^5 is hydrogen, alkyl, phosphonalkyl, $(CH_2)_mNR^6S(O)_2R^7$, or $(CH_2)_mC(=O)OR^6$.

14. The compound of claim 13, wherein R^5 has one of the following structures: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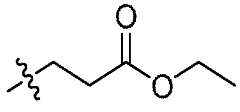
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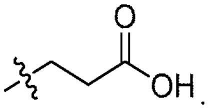
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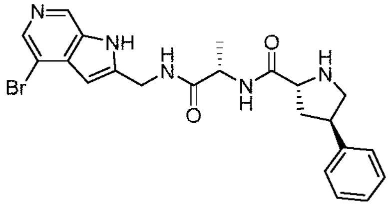
15. The compound of any one of claims 1 to 14, wherein L^1 is a direct bond, -O-, or $-CH_2-$.

16. The compound of any one of claims 1 to 14, wherein L^1 is $-CR^{8a}R^{8b}-$ and R^{8a} and R^{8b} together with the carbon to which they are attached form an optionally substituted 3, 4, or 5 membered cycloalkyl.

17. A compound having one of the structures: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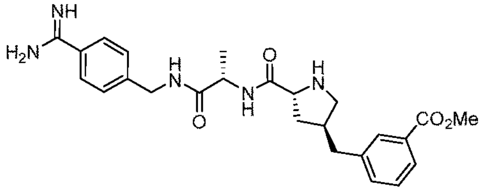
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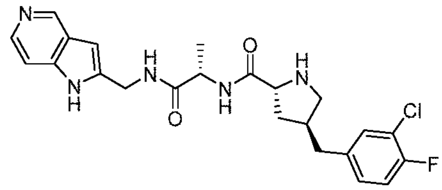
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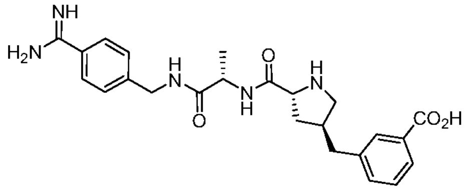
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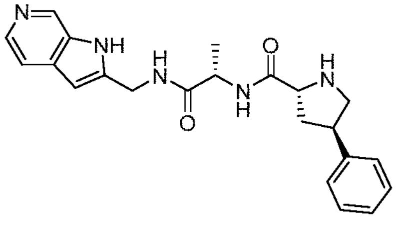
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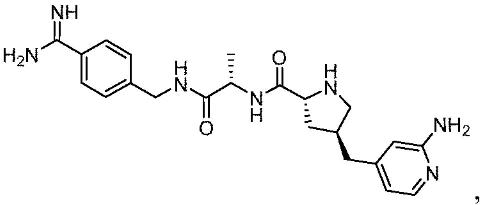
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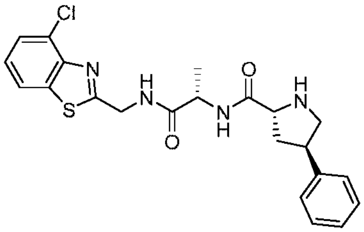
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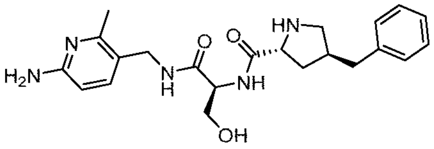
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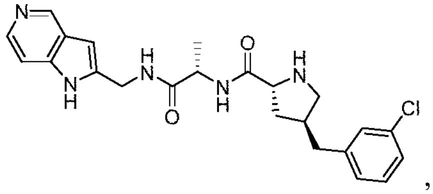
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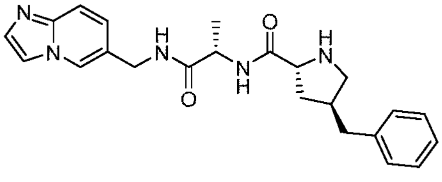
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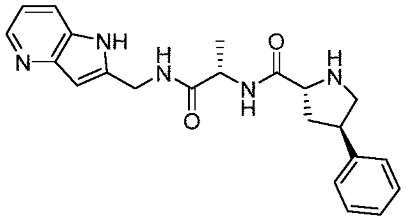
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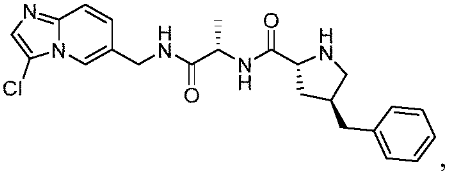
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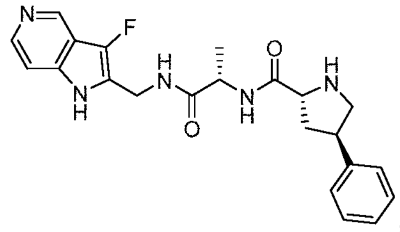
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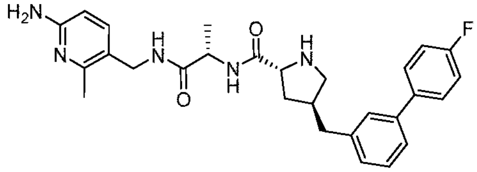
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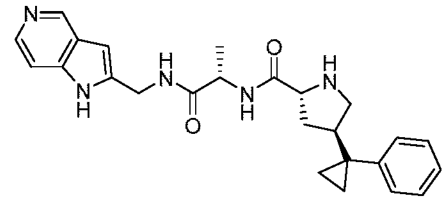
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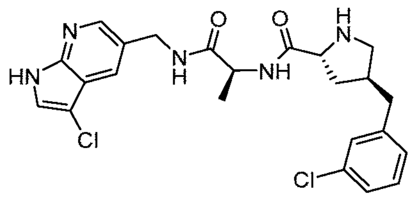
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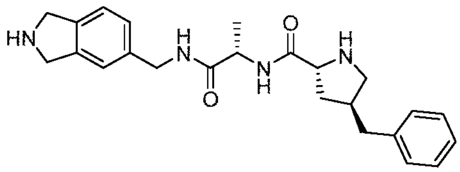
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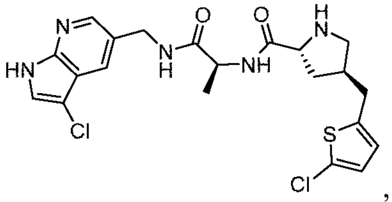
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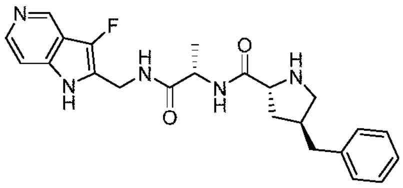
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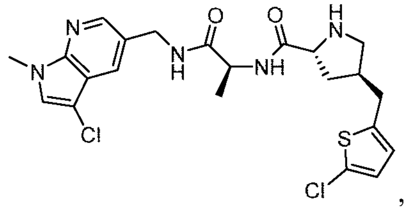
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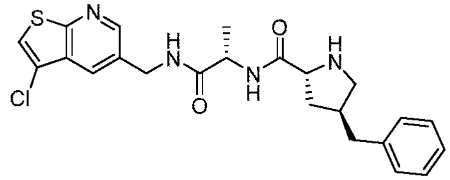
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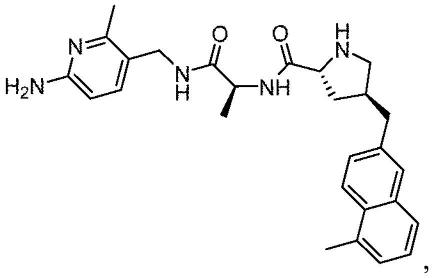
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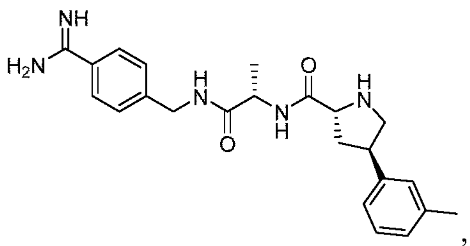
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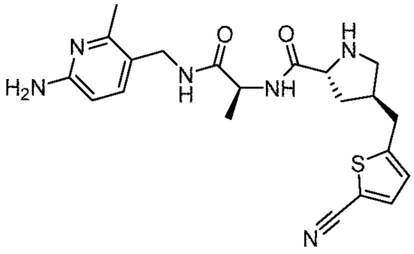
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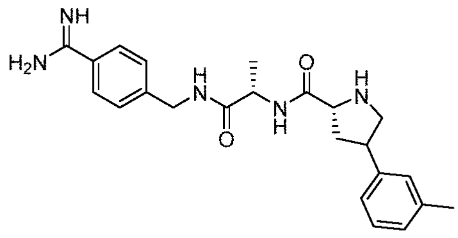
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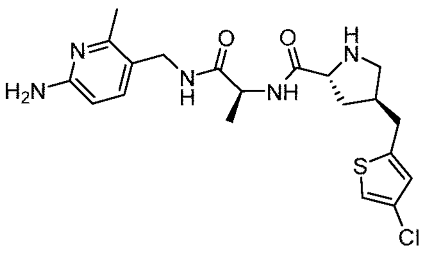
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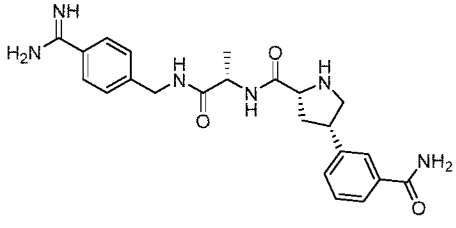
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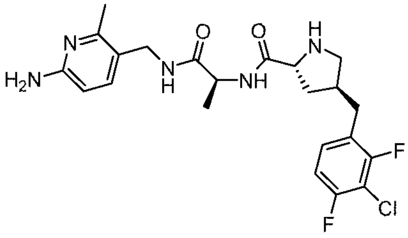
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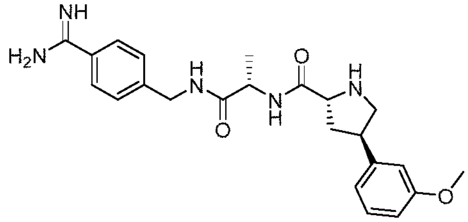
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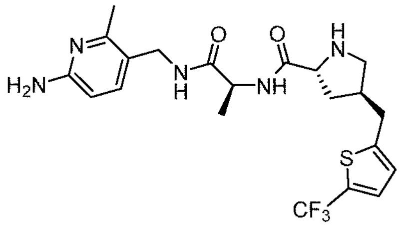
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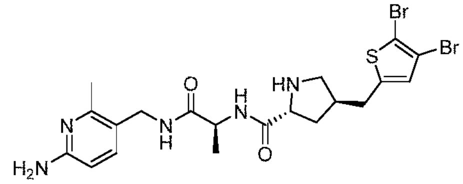
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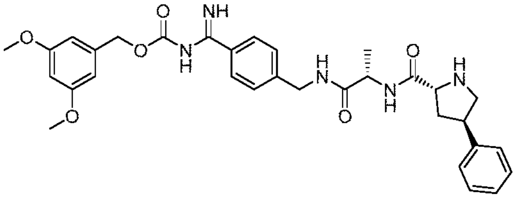
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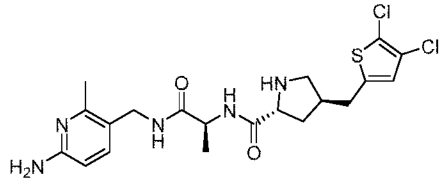
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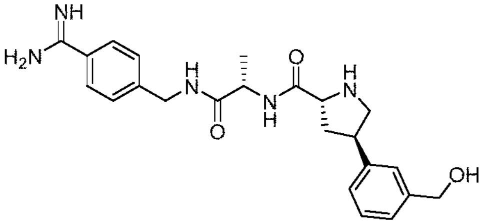
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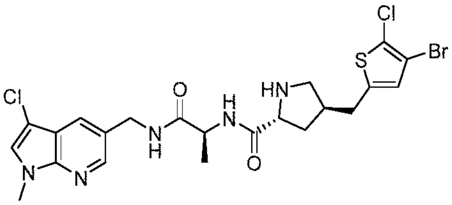
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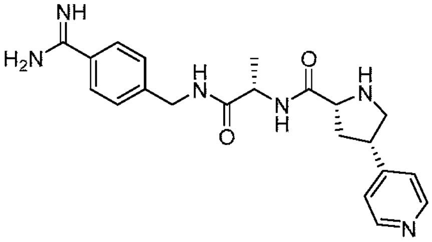
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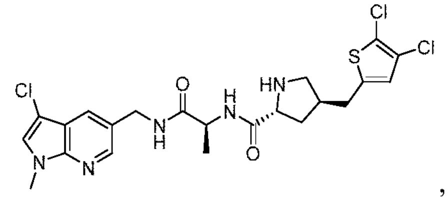
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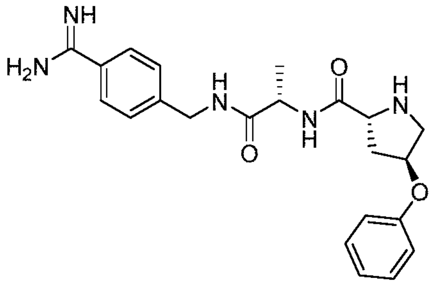
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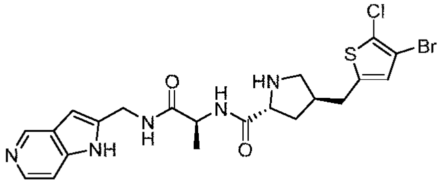
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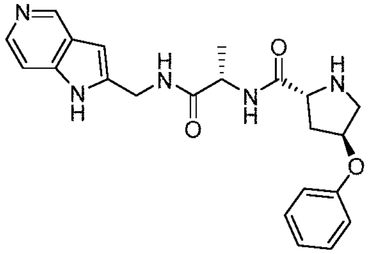
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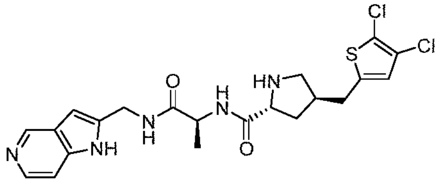
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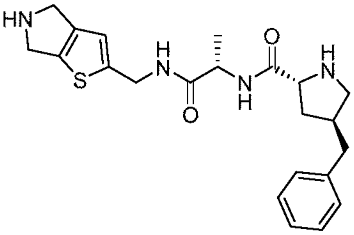
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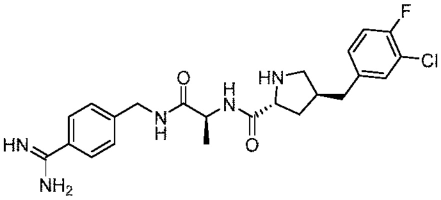
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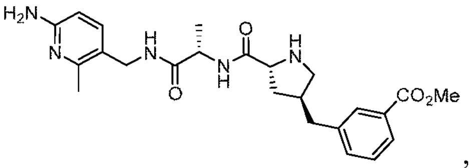
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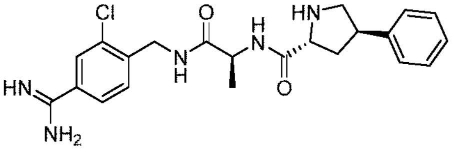
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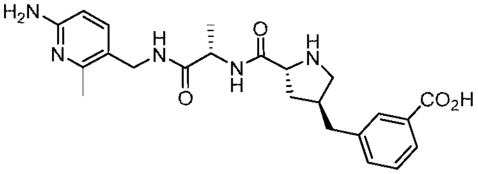
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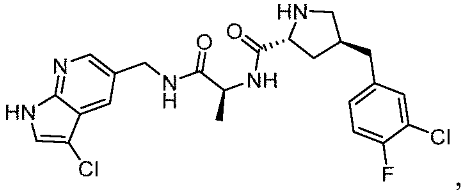
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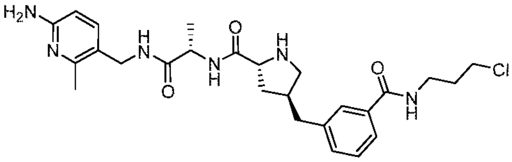
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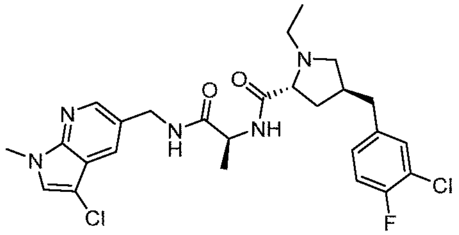
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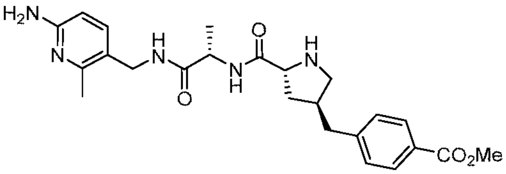
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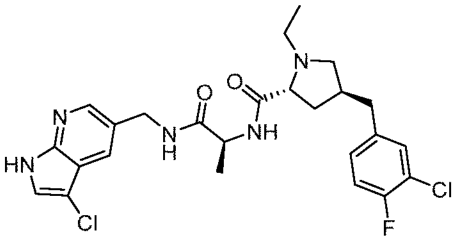
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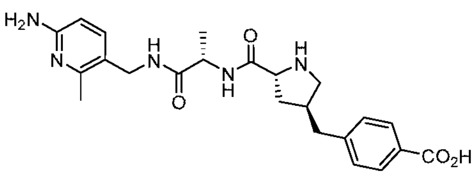
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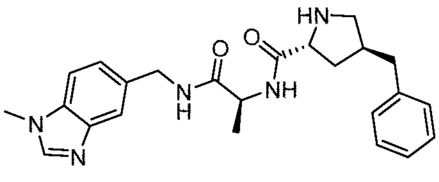
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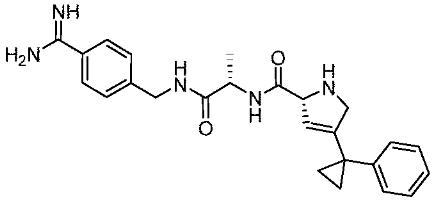
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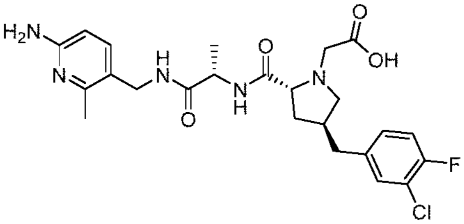
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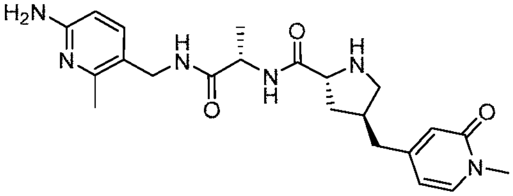
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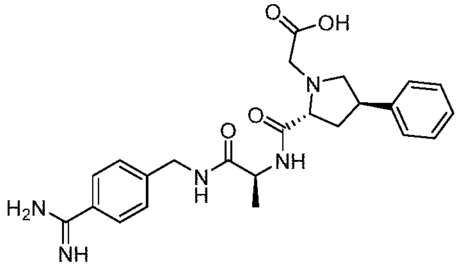
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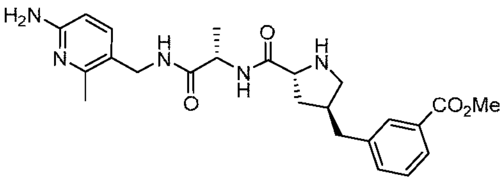
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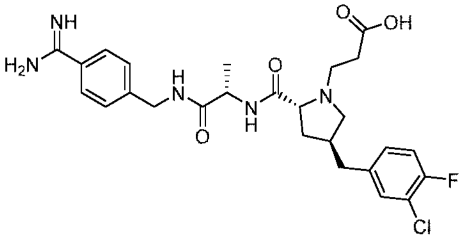
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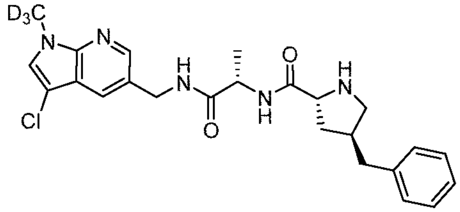
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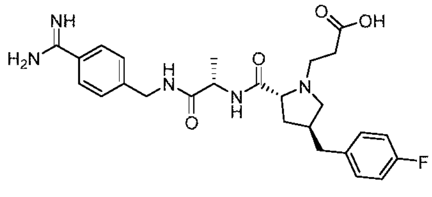
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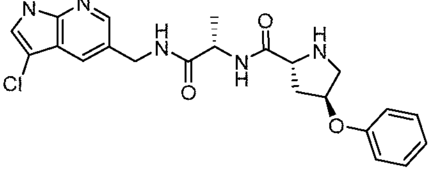
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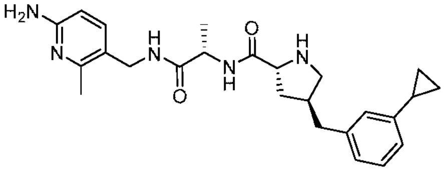
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or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof.

18. A pharmaceutical composition comprising a compound or pharmaceutically acceptable salt thereof of any one of claims 1-17 and a pharmaceutically acceptable carrier or excipient.

19. A method for relieving the symptoms from a MASP-2-associated disease or disorder in a subject in need thereof, the method comprising administering to the subject an effective amount of a compound of any one of claims 1-17, or a pharmaceutical composition according to claim 18.

20. Use of an effective amount of a compound of any one of claims 1-17, or a pharmaceutical composition according to claim 18, in the manufacture of a medicament for relieving the symptoms from a MASP-2-associated disease or disorder in a subject in need thereof.

SEQUENCE LISTING

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<130> 700128.423WO

<140> PCT
<141> 2020-12-04

<150> US 62/943,611
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Asp Ser Glu Thr Glu Arg Trp Phe Val Gly Gly Ile Val Ser Trp Gly
                645                 650                 655

Ser Met Asn Cys Gly Glu Ala Gly Gln Tyr Gly Val Tyr Thr Lys Val
            660                 665                 670

Ile Asn Tyr Ile Pro Trp Ile Glu Asn Ile Ile Ser Asp Phe
        675                 680                 685
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