

PPARG MODULATORS**CROSS-REFERENCE TO RELATED APPLICATIONS**

[0001] This application claims the benefit of and priority under 35 U.S.C. § 119(e) to U.S. Provisional Application Number 63/437,891, filed January 9, 2023, titled PPARG MODULATORS, the contents of which are incorporated herewith by reference in their entirety.

BACKGROUND OF THE INVENTION

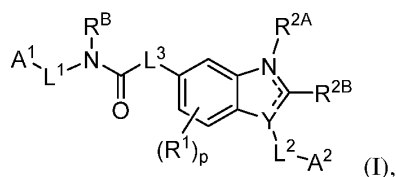
[0002] Peroxisome proliferator-activated receptor γ (PPAR γ) has been implicated in tumor initiation and progression in several major cancers, including both colorectal and pancreatic malignancies. Tumor type and genetic background are relevant factors, since PPAR γ displays tumor suppressor and oncogenic roles. It has also been shown that a genetic signature of PPAR γ phosphorylation is associated with worse outcomes in response to chemotherapy in human patients. Previous work has demonstrated that phosphorylation of S273 of PPAR γ occurs in cancer cells on exposure to DNA damaging agents, and that blocking this phosphorylation increases accumulation of DNA damage, resulting in apoptotic cell death. Additionally, a subset of bladder cancer cell lines representing some 10-20% of human bladder malignancies, along with esophageal and prostate lines, that over-express PPAR γ have been identified, and may represent a more targeted translational pathway in oncology.

SUMMARY OF THE INVENTION

[0003] Compounds that are non-activating (non-agonist) peroxisome proliferator-activated receptor γ (PPAR γ) modulators are useful in treatment of conditions wherein nonactivating modulation of PPAR γ is medically indicated, such as for treatment of a progressive bone disease and or selected cancers. Such compounds may block phosphorylation of PPAR γ at serine 273, but are not agonists of the receptor itself. By avoiding agonism of the receptor, the compounds may exhibit little or reduced side effects associated with administration of full and partial agonists of PPAR γ , which include significant weight gain, edema, impairment of bone growth or formation, cardiac hypertrophy, congestive heart failure, vascular leak syndrome, and/or hepatotoxicity. Non-agonist PPAR γ modulators may be used for the treatment of progressive bone diseases such as osteoporosis, Paget's Disease, multiple myeloma, and hyperparathyroidism.

[0004] The compounds disclosed herein may be antagonists or inverse agonists of PPAR γ modulators, and may have multiple applications in various disease pathologies. These include potential orphan diseases, especially in the therapeutic areas of bone, bone marrow, stem cells, obesity-metabolism, and reproductive endocrinology. The compounds may also be useful in a subset of bladder cancers and esophageal and prostate cancers that overexpress PPAR γ , and may represent a more targeted translational pathway in oncology.

[0005] Accordingly, in one aspect, the present disclosure provides compounds of Formula (I):



or a pharmaceutically acceptable salts or prodrugs thereof, wherein A^1 , A^2 , Y , L^1 , L^2 , L^3 , R^1 , R^{2A} , R^{2B} , R^B , and p are as defined herein.

[0006] In another aspect, the present disclosure provides pharmaceutical compositions comprising a compound disclosed herein. In some embodiments, the pharmaceutical composition comprises an excipient.

[0007] In another aspect, the present disclosure provides methods of treating or preventing a disease or disorder in a subject in need thereof, comprising administering to the subject in need thereof a provided compound or pharmaceutical composition. In certain embodiments, the disease or disorder is associated with peroxisome proliferator-activated receptor γ (PPAR γ) (*e.g.*, progressive bone disease, proliferative disease, metabolic disease).

[0008] In another aspect, the present disclosure provides methods of modulating (*e.g.*, upregulating, downregulating, increasing, decreasing) peroxisome proliferator-activated receptor γ (PPAR γ) in a subject in need thereof or in a cell, tissue, or biological sample, comprising administering to the subject in need thereof or contacting the cell, tissue, or biological sample with an effective amount of a provided compound or pharmaceutical composition. In certain embodiments, the cell, tissue, or biological sample is *in vivo*. In certain embodiments, the cell, tissue, or biological sample is *in vitro*.

[0009] In another aspect, the present disclosure provides kits comprising a provided compound or pharmaceutical composition disclosed herein and instructions for its use.

[0010] It should be appreciated that the foregoing concepts, and the additional concepts discussed below, may be arranged in any suitable combination, as the present disclosure is not limited in this respect. Further, other advantages and novel features of the present disclosure will become apparent from the following detailed description of various non-limiting embodiments.

DEFINITIONS

[0011] Unless defined otherwise, all technical and scientific terms used herein have the meaning commonly understood by a person skilled in the art to which this invention belongs. The following references provide one of skill with a general definition of many of the terms used in this invention: Singleton et al., *Dictionary of Microbiology and Molecular Biology* (2nd ed. 1994); *The Cambridge Dictionary of Science and Technology* (Walker ed., 1988); *The Glossary of Genetics*, 5th Ed., R. Rieger et al. (eds.), Springer Verlag (1991); and Hale & Marham, *The Harper Collins Dictionary of Biology* (1991). As used herein, the following terms have the meanings ascribed to them unless specified otherwise.

[0012] Definitions of specific functional groups and chemical terms are described in more detail below. The chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version,

Handbook of Chemistry and Physics, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in Thomas Sorrell, *Organic Chemistry*, University Science Books, Sausalito, 1999; Michael B. Smith, *March's Advanced Organic Chemistry*, 7th Edition, John Wiley & Sons, Inc., New York, 2013; Richard C. Larock, *Comprehensive Organic Transformations*, John Wiley & Sons, Inc., New York, 2018; and Carruthers, *Some Modern Methods of Organic Synthesis*, 3rd Edition, Cambridge University Press, Cambridge, 1987.

[0013] Compounds described herein can comprise one or more asymmetric centers, and thus can exist in various stereoisomeric forms, *e.g.*, enantiomers and/or diastereomers. For example, the compounds described herein can be in the form of an individual enantiomer, diastereomer or geometric isomer, or can be in the form of a mixture of stereoisomers, including racemic mixtures and mixtures enriched in one or more stereoisomer. Isomers can be isolated from mixtures by methods known to those skilled in the art, including chiral high-pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts; or preferred isomers can be prepared by asymmetric syntheses. See, for example, Jacques *et al.*, *Enantiomers, Racemates and Resolutions* (Wiley Interscience, New York, 1981); Wilen *et al.*, *Tetrahedron* 33:2725 (1977); Eliel, E.L. *Stereochemistry of Carbon Compounds* (McGraw-Hill, NY, 1962); and Wilen, S.H., *Tables of Resolving Agents and Optical Resolutions* p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN 1972). The invention additionally encompasses compounds as individual isomers substantially free of other isomers, and alternatively, as mixtures of various isomers. The term “isomers” is intended to include diastereoisomers, enantiomers, regioisomers, structural isomers, rotational isomers, tautomers, and the like. All such isomers of such compounds herein are expressly included in the present invention.

[0014] When a range of values (“range”) is listed, it encompasses each value and sub-range within the range. A range is inclusive of the values at the two ends of the range unless otherwise provided. For example “C₁₋₆ alkyl” encompasses, C₁, C₂, C₃, C₄, C₅, C₆, C₁₋₆, C₁₋₅, C₁₋₄, C₁₋₃, C₁₋₂, C₂₋₆, C₂₋₅, C₂₋₄, C₂₋₃, C₃₋₆, C₃₋₅, C₃₋₄, C₄₋₆, C₄₋₅, and C₅₋₆ alkyl.

[0015] The term “aliphatic” refers to alkyl, alkenyl, alkynyl, and carbocyclic groups. Likewise, the term “heteroaliphatic” refers to heteroalkyl, heteroalkenyl, heteroalkynyl, and heterocyclic groups.

[0016] The term “alkyl” refers to a radical of a straight-chain or branched saturated hydrocarbon group having from 1 to 20 carbon atoms (“C₁₋₂₀ alkyl”). In some embodiments, an alkyl group has 1 to 12 carbon atoms (“C₁₋₁₂ alkyl”). In some embodiments, an alkyl group has 1 to 10 carbon atoms (“C₁₋₁₀ alkyl”). In some embodiments, an alkyl group has 1 to 9 carbon atoms (“C₁₋₉ alkyl”). In some embodiments, an alkyl group has 1 to 8 carbon atoms (“C₁₋₈ alkyl”). In some embodiments, an alkyl group has 1 to 7 carbon atoms (“C₁₋₇ alkyl”). In some embodiments, an alkyl group has 1 to 6 carbon atoms (“C₁₋₆ alkyl”). In some embodiments, an alkyl group has 1 to 5 carbon atoms (“C₁₋₅ alkyl”). In some embodiments, an alkyl group has 1 to 4 carbon atoms (“C₁₋₄ alkyl”). In some embodiments, an alkyl group has 1 to 3 carbon atoms (“C₁₋₃ alkyl”). In some embodiments, an alkyl group has 1 to 2 carbon atoms (“C₁₋₂ alkyl”). In some embodiments, an alkyl group has 1 carbon atom (“C₁ alkyl”). In some

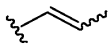
embodiments, an alkyl group has 2 to 6 carbon atoms (“C₂₋₆ alkyl”). Examples of C₁₋₆ alkyl groups include methyl (C₁), ethyl (C₂), propyl (C₃) (*e.g.*, *n*-propyl, isopropyl), butyl (C₄) (*e.g.*, *n*-butyl, *tert*-butyl, *sec*-butyl, isobutyl), pentyl (C₅) (*e.g.*, *n*-pentyl, 3-pentanyl, amyl, neopentyl, 3-methyl-2-butanyl, *tert*-amyl), and hexyl (C₆) (*e.g.*, *n*-hexyl). Additional examples of alkyl groups include *n*-heptyl (C₇), *n*-octyl (C₈), *n*-dodecyl (C₁₂), and the like. Unless otherwise specified, each instance of an alkyl group is independently unsubstituted (an “unsubstituted alkyl”) or substituted (a “substituted alkyl”) with one or more substituents (*e.g.*, halogen, such as F). In certain embodiments, the alkyl group is an unsubstituted C₁₋₁₂ alkyl (such as unsubstituted C₁₋₆ alkyl, *e.g.*, –CH₃ (Me), unsubstituted ethyl (Et), unsubstituted propyl (Pr, *e.g.*, unsubstituted *n*-propyl (*n*-Pr), unsubstituted isopropyl (*i*-Pr)), unsubstituted butyl (Bu, *e.g.*, unsubstituted *n*-butyl (*n*-Bu), unsubstituted *tert*-butyl (*tert*-Bu or *t*-Bu), unsubstituted *sec*-butyl (*sec*-Bu or *s*-Bu), unsubstituted isobutyl (*i*-Bu)). In certain embodiments, the alkyl group is a substituted C₁₋₁₂ alkyl (such as substituted C₁₋₆ alkyl, *e.g.*, –CH₂F, –CHF₂, –CF₃, –CH₂CH₂F, –CH₂CHF₂, –CH₂CF₃, or benzyl (Bn)).

[0017] The term “haloalkyl” is a substituted alkyl group, wherein one or more of the hydrogen atoms are independently replaced by a halogen, *e.g.*, fluoro, bromo, chloro, or iodo. “Perhaloalkyl” is a subset of haloalkyl and refers to an alkyl group wherein all of the hydrogen atoms are independently replaced by a halogen, *e.g.*, fluoro, bromo, chloro, or iodo. In some embodiments, the haloalkyl moiety has 1 to 20 carbon atoms (“C₁₋₂₀ haloalkyl”). In some embodiments, the haloalkyl moiety has 1 to 10 carbon atoms (“C₁₋₁₀ haloalkyl”). In some embodiments, the haloalkyl moiety has 1 to 9 carbon atoms (“C₁₋₉ haloalkyl”). In some embodiments, the haloalkyl moiety has 1 to 8 carbon atoms (“C₁₋₈ haloalkyl”). In some embodiments, the haloalkyl moiety has 1 to 7 carbon atoms (“C₁₋₇ haloalkyl”). In some embodiments, the haloalkyl moiety has 1 to 6 carbon atoms (“C₁₋₆ haloalkyl”). In some embodiments, the haloalkyl moiety has 1 to 5 carbon atoms (“C₁₋₅ haloalkyl”). In some embodiments, the haloalkyl moiety has 1 to 4 carbon atoms (“C₁₋₄ haloalkyl”). In some embodiments, the haloalkyl moiety has 1 to 3 carbon atoms (“C₁₋₃ haloalkyl”). In some embodiments, the haloalkyl moiety has 1 to 2 carbon atoms (“C₁₋₂ haloalkyl”). In some embodiments, all of the haloalkyl hydrogen atoms are independently replaced with fluoro to provide a “perfluoroalkyl” group. In some embodiments, all of the haloalkyl hydrogen atoms are independently replaced with chloro to provide a “perchloroalkyl” group. Examples of haloalkyl groups include –CHF₂, –CH₂F, –CF₃, –CH₂CF₃, –CF₂CF₃, –CF₂CF₂CF₃, –CCl₃, –CFC₂Cl, –CF₂Cl, and the like.

[0018] The term “heteroalkyl” refers to an alkyl group, which further includes at least one heteroatom (*e.g.*, 1, 2, 3, or 4 heteroatoms) selected from oxygen, nitrogen, or sulfur within (*e.g.*, inserted between adjacent carbon atoms of) and/or placed at one or more terminal position(s) of the parent chain. In certain embodiments, a heteroalkyl group refers to a saturated group having from 1 to 20 carbon atoms and 1 or more heteroatoms within the parent chain (“heteroC₁₋₂₀ alkyl”). In certain embodiments, a heteroalkyl group refers to a saturated group having from 1 to 12 carbon atoms and 1 or more heteroatoms within the parent chain (“heteroC₁₋₁₂ alkyl”). In some embodiments, a heteroalkyl group is a saturated group having 1 to 11 carbon atoms and 1 or more heteroatoms within the parent chain (“heteroC₁₋₁₁ alkyl”). In some embodiments, a heteroalkyl group is a saturated group having 1 to 10 carbon atoms and 1 or more

heteroatoms within the parent chain (“heteroC₁₋₁₀ alkyl”). In some embodiments, a heteroalkyl group is a saturated group having 1 to 9 carbon atoms and 1 or more heteroatoms within the parent chain (“heteroC₁₋₉ alkyl”). In some embodiments, a heteroalkyl group is a saturated group having 1 to 8 carbon atoms and 1 or more heteroatoms within the parent chain (“heteroC₁₋₈ alkyl”). In some embodiments, a heteroalkyl group is a saturated group having 1 to 7 carbon atoms and 1 or more heteroatoms within the parent chain (“heteroC₁₋₇ alkyl”). In some embodiments, a heteroalkyl group is a saturated group having 1 to 6 carbon atoms and 1 or more heteroatoms within the parent chain (“heteroC₁₋₆ alkyl”). In some embodiments, a heteroalkyl group is a saturated group having 1 to 5 carbon atoms and 1 or 2 heteroatoms within the parent chain (“heteroC₁₋₅ alkyl”). In some embodiments, a heteroalkyl group is a saturated group having 1 to 4 carbon atoms and 1 or 2 heteroatoms within the parent chain (“heteroC₁₋₄ alkyl”). In some embodiments, a heteroalkyl group is a saturated group having 1 to 3 carbon atoms and 1 heteroatom within the parent chain (“heteroC₁₋₃ alkyl”). In some embodiments, a heteroalkyl group is a saturated group having 1 to 2 carbon atoms and 1 heteroatom within the parent chain (“heteroC₁₋₂ alkyl”). In some embodiments, a heteroalkyl group is a saturated group having 1 carbon atom and 1 heteroatom (“heteroC₁ alkyl”). In some embodiments, a heteroalkyl group is a saturated group having 2 to 6 carbon atoms and 1 or 2 heteroatoms within the parent chain (“heteroC₂₋₆ alkyl”). Unless otherwise specified, each instance of a heteroalkyl group is independently unsubstituted (an “unsubstituted heteroalkyl”) or substituted (a “substituted heteroalkyl”) with one or more substituents. In certain embodiments, the heteroalkyl group is an unsubstituted heteroC₁₋₁₂ alkyl. In certain embodiments, the heteroalkyl group is a substituted heteroC₁₋₁₂ alkyl.

[0019] The term “alkenyl” refers to a radical of a straight-chain or branched hydrocarbon group having from 2 to 20 carbon atoms and one or more carbon-carbon double bonds (*e.g.*, 1, 2, 3, or 4 double bonds). In some embodiments, an alkenyl group has 2 to 20 carbon atoms (“C₂₋₂₀ alkenyl”). In some embodiments, an alkenyl group has 2 to 12 carbon atoms (“C₂₋₁₂ alkenyl”). In some embodiments, an alkenyl group has 2 to 11 carbon atoms (“C₂₋₁₁ alkenyl”). In some embodiments, an alkenyl group has 2 to 10 carbon atoms (“C₂₋₁₀ alkenyl”). In some embodiments, an alkenyl group has 2 to 9 carbon atoms (“C₂₋₉ alkenyl”). In some embodiments, an alkenyl group has 2 to 8 carbon atoms (“C₂₋₈ alkenyl”). In some embodiments, an alkenyl group has 2 to 7 carbon atoms (“C₂₋₇ alkenyl”). In some embodiments, an alkenyl group has 2 to 6 carbon atoms (“C₂₋₆ alkenyl”). In some embodiments, an alkenyl group has 2 to 5 carbon atoms (“C₂₋₅ alkenyl”). In some embodiments, an alkenyl group has 2 to 4 carbon atoms (“C₂₋₄ alkenyl”). In some embodiments, an alkenyl group has 2 to 3 carbon atoms (“C₂₋₃ alkenyl”). In some embodiments, an alkenyl group has 2 carbon atoms (“C₂ alkenyl”). The one or more carbon-carbon double bonds can be internal (such as in 2-butenyl) or terminal (such as in 1-butenyl). Examples of C₂₋₄ alkenyl groups include ethenyl (C₂), 1-propenyl (C₃), 2-propenyl (C₃), 1-butenyl (C₄), 2-butenyl (C₄), butadienyl (C₄), and the like. Examples of C₂₋₆ alkenyl groups include the aforementioned C₂₋₄ alkenyl groups as well as pentenyl (C₅), pentadienyl (C₅), hexenyl (C₆), and the like. Additional examples of alkenyl include heptenyl (C₇), octenyl (C₈), octatrienyl (C₈), and the like. Unless otherwise specified, each instance of an alkenyl group is independently unsubstituted (an “unsubstituted alkenyl”) or substituted (a “substituted

alkenyl”) with one or more substituents. In certain embodiments, the alkenyl group is an unsubstituted C₂₋₂₀ alkenyl. In certain embodiments, the alkenyl group is a substituted C₂₋₂₀ alkenyl. In an alkenyl group, a C=C double bond for which the stereochemistry is not specified (*e.g.*, $-\text{CH}=\text{CHCH}_3$ or ) may be in the (*E*)- or (*Z*)-configuration.

[0020] The term “heteroalkenyl” refers to an alkenyl group, which further includes at least one heteroatom (*e.g.*, 1, 2, 3, or 4 heteroatoms) selected from oxygen, nitrogen, or sulfur within (*e.g.*, inserted between adjacent carbon atoms of) and/or placed at one or more terminal position(s) of the parent chain. In certain embodiments, a heteroalkenyl group refers to a group having from 2 to 20 carbon atoms, at least one double bond, and 1 or more heteroatoms within the parent chain (“heteroC₂₋₂₀ alkenyl”). In certain embodiments, a heteroalkenyl group refers to a group having from 2 to 12 carbon atoms, at least one double bond, and 1 or more heteroatoms within the parent chain (“heteroC₂₋₁₂ alkenyl”). In certain embodiments, a heteroalkenyl group refers to a group having from 2 to 11 carbon atoms, at least one double bond, and 1 or more heteroatoms within the parent chain (“heteroC₂₋₁₁ alkenyl”). In certain embodiments, a heteroalkenyl group refers to a group having from 2 to 10 carbon atoms, at least one double bond, and 1 or more heteroatoms within the parent chain (“heteroC₂₋₁₀ alkenyl”). In some embodiments, a heteroalkenyl group has 2 to 9 carbon atoms at least one double bond, and 1 or more heteroatoms within the parent chain (“heteroC₂₋₉ alkenyl”). In some embodiments, a heteroalkenyl group has 2 to 8 carbon atoms, at least one double bond, and 1 or more heteroatoms within the parent chain (“heteroC₂₋₈ alkenyl”). In some embodiments, a heteroalkenyl group has 2 to 7 carbon atoms, at least one double bond, and 1 or more heteroatoms within the parent chain (“heteroC₂₋₇ alkenyl”). In some embodiments, a heteroalkenyl group has 2 to 6 carbon atoms, at least one double bond, and 1 or more heteroatoms within the parent chain (“heteroC₂₋₆ alkenyl”). In some embodiments, a heteroalkenyl group has 2 to 5 carbon atoms, at least one double bond, and 1 or 2 heteroatoms within the parent chain (“heteroC₂₋₅ alkenyl”). In some embodiments, a heteroalkenyl group has 2 to 4 carbon atoms, at least one double bond, and 1 or 2 heteroatoms within the parent chain (“heteroC₂₋₄ alkenyl”). In some embodiments, a heteroalkenyl group has 2 to 3 carbon atoms, at least one double bond, and 1 heteroatom within the parent chain (“heteroC₂₋₃ alkenyl”). In some embodiments, a heteroalkenyl group has 2 carbon atoms, at least one double bond, and 1 heteroatom within the parent chain (“heteroC₂ alkenyl”). In some embodiments, a heteroalkenyl group has 2 to 6 carbon atoms, at least one double bond, and 1 or 2 heteroatoms within the parent chain (“heteroC₂₋₆ alkenyl”). Unless otherwise specified, each instance of a heteroalkenyl group is independently unsubstituted (an “unsubstituted heteroalkenyl”) or substituted (a “substituted heteroalkenyl”) with one or more substituents. In certain embodiments, the heteroalkenyl group is an unsubstituted heteroC₂₋₂₀ alkenyl. In certain embodiments, the heteroalkenyl group is a substituted heteroC₂₋₂₀ alkenyl.

[0021] The term “alkynyl” refers to a radical of a straight-chain or branched hydrocarbon group having from 2 to 20 carbon atoms and one or more carbon-carbon triple bonds (*e.g.*, 1, 2, 3, or 4 triple bonds) (“C₁₋₂₀ alkynyl”). In some embodiments, an alkynyl group has 2 to 10 carbon atoms (“C₂₋₁₀ alkynyl”). In

some embodiments, an alkynyl group has 2 to 9 carbon atoms (“C₂₋₉ alkynyl”). In some embodiments, an alkynyl group has 2 to 8 carbon atoms (“C₂₋₈ alkynyl”). In some embodiments, an alkynyl group has 2 to 7 carbon atoms (“C₂₋₇ alkynyl”). In some embodiments, an alkynyl group has 2 to 6 carbon atoms (“C₂₋₆ alkynyl”). In some embodiments, an alkynyl group has 2 to 5 carbon atoms (“C₂₋₅ alkynyl”). In some embodiments, an alkynyl group has 2 to 4 carbon atoms (“C₂₋₄ alkynyl”). In some embodiments, an alkynyl group has 2 to 3 carbon atoms (“C₂₋₃ alkynyl”). In some embodiments, an alkynyl group has 2 carbon atoms (“C₂ alkynyl”). The one or more carbon-carbon triple bonds can be internal (such as in 2-butyne) or terminal (such as in 1-butyne). Examples of C₂₋₄ alkynyl groups include, without limitation, ethynyl (C₂), 1-propynyl (C₃), 2-propynyl (C₃), 1-butyne (C₄), 2-butyne (C₄), and the like. Examples of C₂₋₆ alkynyl groups include the aforementioned C₂₋₄ alkynyl groups as well as pentynyl (C₅), hexynyl (C₆), and the like. Additional examples of alkynyl include heptyne (C₇), octynyl (C₈), and the like. Unless otherwise specified, each instance of an alkynyl group is independently unsubstituted (an “unsubstituted alkynyl”) or substituted (a “substituted alkynyl”) with one or more substituents. In certain embodiments, the alkynyl group is an unsubstituted C₂₋₂₀ alkynyl. In certain embodiments, the alkynyl group is a substituted C₂₋₂₀ alkynyl.

[0022] The term “heteroalkynyl” refers to an alkynyl group, which further includes at least one heteroatom (*e.g.*, 1, 2, 3, or 4 heteroatoms) selected from oxygen, nitrogen, or sulfur within (*e.g.*, inserted between adjacent carbon atoms of) and/or placed at one or more terminal position(s) of the parent chain. In certain embodiments, a heteroalkynyl group refers to a group having from 2 to 20 carbon atoms, at least one triple bond, and 1 or more heteroatoms within the parent chain (“heteroC₂₋₂₀ alkynyl”). In certain embodiments, a heteroalkynyl group refers to a group having from 2 to 10 carbon atoms, at least one triple bond, and 1 or more heteroatoms within the parent chain (“heteroC₂₋₁₀ alkynyl”). In some embodiments, a heteroalkynyl group has 2 to 9 carbon atoms, at least one triple bond, and 1 or more heteroatoms within the parent chain (“heteroC₂₋₉ alkynyl”). In some embodiments, a heteroalkynyl group has 2 to 8 carbon atoms, at least one triple bond, and 1 or more heteroatoms within the parent chain (“heteroC₂₋₈ alkynyl”). In some embodiments, a heteroalkynyl group has 2 to 7 carbon atoms, at least one triple bond, and 1 or more heteroatoms within the parent chain (“heteroC₂₋₇ alkynyl”). In some embodiments, a heteroalkynyl group has 2 to 6 carbon atoms, at least one triple bond, and 1 or more heteroatoms within the parent chain (“heteroC₂₋₆ alkynyl”). In some embodiments, a heteroalkynyl group has 2 to 5 carbon atoms, at least one triple bond, and 1 or 2 heteroatoms within the parent chain (“heteroC₂₋₅ alkynyl”). In some embodiments, a heteroalkynyl group has 2 to 4 carbon atoms, at least one triple bond, and 1 or 2 heteroatoms within the parent chain (“heteroC₂₋₄ alkynyl”). In some embodiments, a heteroalkynyl group has 2 to 3 carbon atoms, at least one triple bond, and 1 heteroatom within the parent chain (“heteroC₂₋₃ alkynyl”). In some embodiments, a heteroalkynyl group has 2 carbon atoms, at least one triple bond, and 1 heteroatom within the parent chain (“heteroC₂ alkynyl”). In some embodiments, a heteroalkynyl group has 2 to 6 carbon atoms, at least one triple bond, and 1 or 2 heteroatoms within the parent chain (“heteroC₂₋₆ alkynyl”). Unless otherwise specified, each instance of a heteroalkynyl group is independently unsubstituted (an “unsubstituted heteroalkynyl”) or substituted (a “substituted heteroalkynyl”) with one or more

substituents. In certain embodiments, the heteroalkynyl group is an unsubstituted heteroC₂₋₂₀ alkynyl. In certain embodiments, the heteroalkynyl group is a substituted heteroC₂₋₂₀ alkynyl.

[0023] The term “carbocyclyl” or “carbocyclic” refers to a radical of a non-aromatic cyclic hydrocarbon group having from 3 to 14 ring carbon atoms (“C₃₋₁₄ carbocyclyl”) and zero heteroatoms in the non-aromatic ring system. In some embodiments, a carbocyclyl group has 3 to 14 ring carbon atoms (“C₃₋₁₄ carbocyclyl”). In some embodiments, a carbocyclyl group has 3 to 13 ring carbon atoms (“C₃₋₁₃ carbocyclyl”). In some embodiments, a carbocyclyl group has 3 to 12 ring carbon atoms (“C₃₋₁₂ carbocyclyl”). In some embodiments, a carbocyclyl group has 3 to 11 ring carbon atoms (“C₃₋₁₁ carbocyclyl”). In some embodiments, a carbocyclyl group has 3 to 10 ring carbon atoms (“C₃₋₁₀ carbocyclyl”). In some embodiments, a carbocyclyl group has 3 to 8 ring carbon atoms (“C₃₋₈ carbocyclyl”). In some embodiments, a carbocyclyl group has 3 to 7 ring carbon atoms (“C₃₋₇ carbocyclyl”). In some embodiments, a carbocyclyl group has 3 to 6 ring carbon atoms (“C₃₋₆ carbocyclyl”). In some embodiments, a carbocyclyl group has 4 to 6 ring carbon atoms (“C₄₋₆ carbocyclyl”). In some embodiments, a carbocyclyl group has 5 to 6 ring carbon atoms (“C₅₋₆ carbocyclyl”). In some embodiments, a carbocyclyl group has 5 to 10 ring carbon atoms (“C₅₋₁₀ carbocyclyl”). Exemplary C₃₋₆ carbocyclyl groups include cyclopropyl (C₃), cyclopropenyl (C₃), cyclobutyl (C₄), cyclobutenyl (C₄), cyclopentyl (C₅), cyclopentenyl (C₅), cyclohexyl (C₆), cyclohexenyl (C₆), cyclohexadienyl (C₆), and the like. Exemplary C₃₋₈ carbocyclyl groups include the aforementioned C₃₋₆ carbocyclyl groups as well as cycloheptyl (C₇), cycloheptenyl (C₇), cycloheptadienyl (C₇), cycloheptatrienyl (C₇), cyclooctyl (C₈), cyclooctenyl (C₈), bicyclo[2.2.1]heptanyl (C₇), bicyclo[2.2.2]octanyl (C₈), and the like. Exemplary C₃₋₁₀ carbocyclyl groups include the aforementioned C₃₋₈ carbocyclyl groups as well as cyclononyl (C₉), cyclononenyl (C₉), cyclodecyl (C₁₀), cyclodecenyl (C₁₀), octahydro-1*H*-indenyl (C₉), decahydronaphthalenyl (C₁₀), spiro[4.5]decanyl (C₁₀), and the like. Exemplary C₃₋₈ carbocyclyl groups include the aforementioned C₃₋₁₀ carbocyclyl groups as well as cycloundecyl (C₁₁), spiro[5.5]undecanyl (C₁₁), cyclododecyl (C₁₂), cyclododecenyl (C₁₂), cyclotridecane (C₁₃), cyclotetradecane (C₁₄), and the like. As the foregoing examples illustrate, in certain embodiments, the carbocyclyl group is either monocyclic (“monocyclic carbocyclyl”) or polycyclic (*e.g.*, containing a fused, bridged or spiro ring system such as a bicyclic system (“bicyclic carbocyclyl”) or tricyclic system (“tricyclic carbocyclyl”)) and can be saturated or can contain one or more carbon-carbon double or triple bonds. “Carbocyclyl” also includes ring systems wherein the carbocyclyl ring, as defined above, is fused with one or more aryl or heteroaryl groups wherein the point of attachment is on the carbocyclyl ring, and in such instances, the number of carbons continue to designate the number of carbons in the carbocyclic ring system. Unless otherwise specified, each instance of a carbocyclyl group is independently unsubstituted (an “unsubstituted carbocyclyl”) or substituted (a “substituted carbocyclyl”) with one or more substituents. In certain embodiments, the carbocyclyl group is an unsubstituted C₃₋₁₄ carbocyclyl. In certain embodiments, the carbocyclyl group is a substituted C₃₋₁₄ carbocyclyl.

[0024] In some embodiments, “carbocyclyl” is a monocyclic, saturated carbocyclyl group having from 3 to 14 ring carbon atoms (“C₃₋₁₄ cycloalkyl”). In some embodiments, a cycloalkyl group has 3 to 10 ring

carbon atoms (“C₃₋₁₀ cycloalkyl”). In some embodiments, a cycloalkyl group has 3 to 8 ring carbon atoms (“C₃₋₈ cycloalkyl”). In some embodiments, a cycloalkyl group has 3 to 6 ring carbon atoms (“C₃₋₆ cycloalkyl”). In some embodiments, a cycloalkyl group has 4 to 6 ring carbon atoms (“C₄₋₆ cycloalkyl”). In some embodiments, a cycloalkyl group has 5 to 6 ring carbon atoms (“C₅₋₆ cycloalkyl”). In some embodiments, a cycloalkyl group has 5 to 10 ring carbon atoms (“C₅₋₁₀ cycloalkyl”). Examples of C₅₋₆ cycloalkyl groups include cyclopentyl (C₅) and cyclohexyl (C₆). Examples of C₃₋₆ cycloalkyl groups include the aforementioned C₅₋₆ cycloalkyl groups as well as cyclopropyl (C₃) and cyclobutyl (C₄). Examples of C₃₋₈ cycloalkyl groups include the aforementioned C₃₋₆ cycloalkyl groups as well as cycloheptyl (C₇) and cyclooctyl (C₈). Unless otherwise specified, each instance of a cycloalkyl group is independently unsubstituted (an “unsubstituted cycloalkyl”) or substituted (a “substituted cycloalkyl”) with one or more substituents. In certain embodiments, the cycloalkyl group is an unsubstituted C₃₋₁₄ cycloalkyl. In certain embodiments, the cycloalkyl group is a substituted C₃₋₁₄ cycloalkyl. In certain embodiments, the carbocyclyl includes 0, 1, or 2 C=C double bonds in the carbocyclic ring system, as valency permits.

[0025] The term “heterocyclyl” or “heterocyclic” refers to a radical of a 3- to 14-membered non-aromatic ring system having ring carbon atoms and 1 to 4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur (“3–14 membered heterocyclyl”). In heterocyclyl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. A heterocyclyl group can either be monocyclic (“monocyclic heterocyclyl”) or polycyclic (*e.g.*, a fused, bridged or spiro ring system such as a bicyclic system (“bicyclic heterocyclyl”) or tricyclic system (“tricyclic heterocyclyl”)), and can be saturated or can contain one or more carbon-carbon double or triple bonds. Heterocyclyl polycyclic ring systems can include one or more heteroatoms in one or both rings. “Heterocyclyl” also includes ring systems wherein the heterocyclyl ring, as defined above, is fused with one or more carbocyclyl groups wherein the point of attachment is either on the carbocyclyl or heterocyclyl ring, or ring systems wherein the heterocyclyl ring, as defined above, is fused with one or more aryl or heteroaryl groups, wherein the point of attachment is on the heterocyclyl ring, and in such instances, the number of ring members continue to designate the number of ring members in the heterocyclyl ring system. Unless otherwise specified, each instance of heterocyclyl is independently unsubstituted (an “unsubstituted heterocyclyl”) or substituted (a “substituted heterocyclyl”) with one or more substituents. In certain embodiments, the heterocyclyl group is an unsubstituted 3–14 membered heterocyclyl. In certain embodiments, the heterocyclyl group is a substituted 3–14 membered heterocyclyl. In certain embodiments, the heterocyclyl is substituted or unsubstituted, 3- to 7-membered, monocyclic heterocyclyl, wherein 1, 2, or 3 atoms in the heterocyclic ring system are independently oxygen, nitrogen, or sulfur, as valency permits.

[0026] In some embodiments, a heterocyclyl group is a 5–10 membered non-aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur (“5–10 membered heterocyclyl”). In some embodiments, a heterocyclyl group is a 5–8 membered non-aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms,

wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur (“5–8 membered heterocyclyl”). In some embodiments, a heterocyclyl group is a 5–6 membered non-aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur (“5–6 membered heterocyclyl”). In some embodiments, the 5–6 membered heterocyclyl has 1–3 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5–6 membered heterocyclyl has 1–2 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5–6 membered heterocyclyl has 1 ring heteroatom selected from nitrogen, oxygen, and sulfur.

[0027] Exemplary 3-membered heterocyclyl groups containing 1 heteroatom include azirdinyl, oxiranyl, and thiiranyl. Exemplary 4-membered heterocyclyl groups containing 1 heteroatom include azetidiny, oxetanyl, and thietanyl. Exemplary 5-membered heterocyclyl groups containing 1 heteroatom include tetrahydrofuranyl, dihydrofuranyl, tetrahydrothiophenyl, dihydrothiophenyl, pyrrolidinyl, dihydropyrrolyl, and pyrrolyl-2,5-dione. Exemplary 5-membered heterocyclyl groups containing 2 heteroatoms include dioxolanyl, oxathiolanyl and dithiolanyl. Exemplary 5-membered heterocyclyl groups containing 3 heteroatoms include triazoliny, oxadiazoliny, and thiadiazoliny. Exemplary 6-membered heterocyclyl groups containing 1 heteroatom include piperidinyl, tetrahydropyranyl, dihydropyridiny, and thianyl. Exemplary 6-membered heterocyclyl groups containing 2 heteroatoms include piperazinyl, morpholinyl, dithianyl, and dioxanyl. Exemplary 6-membered heterocyclyl groups containing 3 heteroatoms include triazinyl. Exemplary 7-membered heterocyclyl groups containing 1 heteroatom include azepanyl, oxepanyl and thiepanyl. Exemplary 8-membered heterocyclyl groups containing 1 heteroatom include azocanyl, oxecanyl and thiocanyl. Exemplary bicyclic heterocyclyl groups include indolinyl, isoindolinyl, dihydrobenzofuranyl, dihydrobenzothieryl, tetrahydrobenzothieryl, tetrahydrobenzofuranyl, tetrahydroindolyl, tetrahydroquinoliny, tetrahydroisoquinoliny, decahydroquinoliny, decahydroisoquinoliny, octahydrochromenyl, octahydroisochromenyl, decahydronaphthyrindiny, decahydro-1,8-naphthyrindiny, octahydropyrrolo[3,2-b]pyrrole, indolinyl, phthalimidyl, naphthalimidyl, chromanyl, chromenyl, 1H-benzo[e][1,4]diazepiny, 1,4,5,7-tetrahydropyrano[3,4-b]pyrrolyl, 5,6-dihydro-4H-furo[3,2-b]pyrrolyl, 6,7-dihydro-5H-furo[3,2-b]pyranyl, 5,7-dihydro-4H-thieno[2,3-c]pyranyl, 2,3-dihydro-1H-pyrrolo[2,3-b]pyridiny, 2,3-dihydrofuro[2,3-b]pyridiny, 4,5,6,7-tetrahydro-1H-pyrrolo[2,3-b]pyridiny, 4,5,6,7-tetrahydrofuro[3,2-c]pyridiny, 4,5,6,7-tetrahydrothieno[3,2-b]pyridiny, 1,2,3,4-tetrahydro-1,6-naphthyrindiny, and the like.

[0028] The term “aryl” refers to a radical of a monocyclic or polycyclic (*e.g.*, bicyclic or tricyclic) $4n+2$ aromatic ring system (*e.g.*, having 6, 10, or 14 π electrons shared in a cyclic array) having 6–14 ring carbon atoms and zero heteroatoms provided in the aromatic ring system (“C₆₋₁₄ aryl”). In some embodiments, an aryl group has 6 ring carbon atoms (“C₆ aryl”; *e.g.*, phenyl). In some embodiments, an aryl group has 10 ring carbon atoms (“C₁₀ aryl”; *e.g.*, naphthyl such as 1-naphthyl and 2-naphthyl). In some embodiments, an aryl group has 14 ring carbon atoms (“C₁₄ aryl”; *e.g.*, anthracyl). “Aryl” also includes ring systems wherein the aryl ring, as defined above, is fused with one or more carbocyclyl or heterocyclyl groups wherein the radical or point of attachment is on the aryl ring, and in such instances,

the number of carbon atoms continue to designate the number of carbon atoms in the aryl ring system. Unless otherwise specified, each instance of an aryl group is independently unsubstituted (an “unsubstituted aryl”) or substituted (a “substituted aryl”) with one or more substituents. In certain embodiments, the aryl group is an unsubstituted C₆₋₁₄ aryl. In certain embodiments, the aryl group is a substituted C₆₋₁₄ aryl.

[0029] “Aralkyl” is a subset of “alkyl” and refers to an alkyl group substituted by an aryl group, wherein the point of attachment is on the alkyl moiety.

[0030] The term “heteroaryl” refers to a radical of a 5-14 membered monocyclic or polycyclic (*e.g.*, bicyclic, tricyclic) 4n+2 aromatic ring system (*e.g.*, having 6, 10, or 14 π electrons shared in a cyclic array) having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur (“5-14 membered heteroaryl”). In heteroaryl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. Heteroaryl polycyclic ring systems can include one or more heteroatoms in one or both rings. “Heteroaryl” includes ring systems wherein the heteroaryl ring, as defined above, is fused with one or more carbocyclyl or heterocyclyl groups wherein the point of attachment is on the heteroaryl ring, and in such instances, the number of ring members continue to designate the number of ring members in the heteroaryl ring system. “Heteroaryl” also includes ring systems wherein the heteroaryl ring, as defined above, is fused with one or more aryl groups wherein the point of attachment is either on the aryl or heteroaryl ring, and in such instances, the number of ring members designates the number of ring members in the fused polycyclic (aryl/heteroaryl) ring system. Polycyclic heteroaryl groups wherein one ring does not contain a heteroatom (*e.g.*, indolyl, quinolinyl, carbazolyl, and the like) the point of attachment can be on either ring, *e.g.*, either the ring bearing a heteroatom (*e.g.*, 2-indolyl) or the ring that does not contain a heteroatom (*e.g.*, 5-indolyl). In certain embodiments, the heteroaryl is substituted or unsubstituted, 5- or 6-membered, monocyclic heteroaryl, wherein 1, 2, 3, or 4 atoms in the heteroaryl ring system are independently oxygen, nitrogen, or sulfur. In certain embodiments, the heteroaryl is substituted or unsubstituted, 9- or 10-membered, bicyclic heteroaryl, wherein 1, 2, 3, or 4 atoms in the heteroaryl ring system are independently oxygen, nitrogen, or sulfur.

[0031] In some embodiments, a heteroaryl group is a 5-10 membered aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur (“5-10 membered heteroaryl”). In some embodiments, a heteroaryl group is a 5-8 membered aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur (“5-8 membered heteroaryl”). In some embodiments, a heteroaryl group is a 5-6 membered aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur (“5-6 membered heteroaryl”). In some embodiments, the 5-6 membered heteroaryl has 1–3 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the

5-6 membered heteroaryl has 1–2 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5-6 membered heteroaryl has 1 ring heteroatom selected from nitrogen, oxygen, and sulfur. Unless otherwise specified, each instance of a heteroaryl group is independently unsubstituted (an “unsubstituted heteroaryl”) or substituted (a “substituted heteroaryl”) with one or more substituents. In certain embodiments, the heteroaryl group is an unsubstituted 5-14 membered heteroaryl. In certain embodiments, the heteroaryl group is a substituted 5-14 membered heteroaryl.

[0032] Exemplary 5-membered heteroaryl groups containing 1 heteroatom include pyrrolyl, furanyl, and thiophenyl. Exemplary 5-membered heteroaryl groups containing 2 heteroatoms include imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, and isothiazolyl. Exemplary 5-membered heteroaryl groups containing 3 heteroatoms include triazolyl, oxadiazolyl, and thiadiazolyl. Exemplary 5-membered heteroaryl groups containing 4 heteroatoms include tetrazolyl. Exemplary 6-membered heteroaryl groups containing 1 heteroatom include pyridinyl. Exemplary 6-membered heteroaryl groups containing 2 heteroatoms include pyridazinyl, pyrimidinyl, and pyrazinyl. Exemplary 6-membered heteroaryl groups containing 3 or 4 heteroatoms include triazinyl and tetrazinyl, respectively. Exemplary 7-membered heteroaryl groups containing 1 heteroatom include azepinyl, oxepinyl, and thiepinyl. Exemplary 5,6-bicyclic heteroaryl groups include indolyl, isoindolyl, indazolyl, benzotriazolyl, benzothiophenyl, isobenzothiophenyl, benzofuranyl, benzoisofuranyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzoxadiazolyl, benzthiazolyl, benzisothiazolyl, benzthiadiazolyl, indolizinyl, and purinyl. Exemplary 6,6-bicyclic heteroaryl groups include naphthyridinyl, pteridinyl, quinolinyl, isoquinolinyl, cinnolinyl, quinoxalinyl, phthalazinyl, and quinazolinyl. Exemplary tricyclic heteroaryl groups include phenanthridinyl, dibenzofuranyl, carbazolyl, acridinyl, phenothiazinyl, phenoxazinyl, and phenazinyl.

[0033] “Heteroaralkyl” is a subset of “alkyl” and refers to an alkyl group substituted by a heteroaryl group, wherein the point of attachment is on the alkyl moiety.

[0034] The term “unsaturated bond” refers to a double or triple bond.

[0035] The term “unsaturated” or “partially unsaturated” refers to a moiety that includes at least one double or triple bond.

[0036] The term “saturated” or “fully saturated” refers to a moiety that does not contain a double or triple bond, *e.g.*, the moiety only contains single bonds.

[0037] Affixing the suffix “-ene” to a group indicates the group is a divalent moiety, *e.g.*, alkylene is the divalent moiety of alkyl, alkenylene is the divalent moiety of alkenyl, alkynylene is the divalent moiety of alkynyl, heteroalkylene is the divalent moiety of heteroalkyl, heteroalkenylene is the divalent moiety of heteroalkenyl, heteroalkynylene is the divalent moiety of heteroalkynyl, carbocyclylene is the divalent moiety of carbocyclyl, heterocyclylene is the divalent moiety of heterocyclyl, arylene is the divalent moiety of aryl, and heteroarylene is the divalent moiety of heteroaryl.

[0038] A group is optionally substituted unless expressly provided otherwise. The term “optionally substituted” refers to being substituted or unsubstituted. In certain embodiments, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl groups are optionally substituted. “Optionally substituted” refers to a group which is substituted or unsubstituted

(*e.g.*, “substituted” or “unsubstituted” alkyl, “substituted” or “unsubstituted” alkenyl, “substituted” or “unsubstituted” alkynyl, “substituted” or “unsubstituted” heteroalkyl, “substituted” or “unsubstituted” heteroalkenyl, “substituted” or “unsubstituted” heteroalkynyl, “substituted” or “unsubstituted” carbocyclyl, “substituted” or “unsubstituted” heterocyclyl, “substituted” or “unsubstituted” aryl or “substituted” or “unsubstituted” heteroaryl group). In general, the term “substituted” means that at least one hydrogen present on a group is replaced with a permissible substituent, *e.g.*, a substituent which upon substitution results in a stable compound, *e.g.*, a compound which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, or other reaction. Unless otherwise indicated, a “substituted” group has a substituent at one or more substitutable positions of the group, and when more than one position in any given structure is substituted, the substituent is either the same or different at each position. The term “substituted” is contemplated to include substitution with all permissible substituents of organic compounds and includes any of the substituents described herein that results in the formation of a stable compound. The present invention contemplates any and all such combinations in order to arrive at a stable compound. For purposes of this invention, heteroatoms such as nitrogen may have hydrogen substituents and/or any suitable substituent as described herein which satisfy the valencies of the heteroatoms and results in the formation of a stable moiety. The invention is not limited in any manner by the exemplary substituents described herein.

[0039] In certain embodiments, a “substituted” group (*e.g.*, “substituted” alkyl, “substituted” alkenyl, “substituted” alkynyl, “substituted” heteroalkyl, “substituted” heteroalkenyl, “substituted” heteroalkynyl, “substituted” carbocyclyl, “substituted” heterocyclyl, “substituted” aryl or “substituted” heteroaryl group) is substituted with one or more of halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroalkenyl, substituted or unsubstituted heteroalkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-\text{CN}$, $-\text{OR}^A$, $-\text{SCN}$, $-\text{SR}^A$, $-\text{SSR}^A$, $-\text{N}_3$, $-\text{NO}$, $-\text{N}(\text{R}^A)_2$, $-\text{NO}_2$, $-\text{C}(=\text{O})\text{R}^A$, $-\text{C}(=\text{O})\text{OR}^A$, $-\text{C}(=\text{O})\text{SR}^A$, $-\text{C}(=\text{O})\text{N}(\text{R}^A)_2$, $-\text{C}(=\text{NR}^A)\text{R}^A$, $-\text{C}(=\text{NR}^A)\text{OR}^A$, $-\text{C}(=\text{NR}^A)\text{SR}^A$, $-\text{C}(=\text{NR}^A)\text{N}(\text{R}^A)_2$, $-\text{S}(=\text{O})\text{R}^A$, $-\text{S}(=\text{O})\text{OR}^A$, $-\text{S}(=\text{O})\text{SR}^A$, $-\text{S}(=\text{O})\text{N}(\text{R}^A)_2$, $-\text{S}(=\text{O})_2\text{R}^A$, $-\text{S}(=\text{O})_2\text{OR}^A$, $-\text{S}(=\text{O})_2\text{SR}^A$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^A)_2$, $-\text{OC}(=\text{O})\text{R}^A$, $-\text{OC}(=\text{O})\text{OR}^A$, $-\text{OC}(=\text{O})\text{SR}^A$, $-\text{OC}(=\text{O})\text{N}(\text{R}^A)_2$, $-\text{OC}(=\text{NR}^A)\text{R}^A$, $-\text{OC}(=\text{NR}^A)\text{OR}^A$, $-\text{OC}(=\text{NR}^A)\text{SR}^A$, $-\text{OC}(=\text{NR}^A)\text{N}(\text{R}^A)_2$, $-\text{OS}(=\text{O})\text{R}^A$, $-\text{OS}(=\text{O})\text{OR}^A$, $-\text{OS}(=\text{O})\text{SR}^A$, $-\text{OS}(=\text{O})\text{N}(\text{R}^A)_2$, $-\text{OS}(=\text{O})_2\text{R}^A$, $-\text{OS}(=\text{O})_2\text{OR}^A$, $-\text{OS}(=\text{O})_2\text{SR}^A$, $-\text{OS}(=\text{O})_2\text{N}(\text{R}^A)_2$, $-\text{ON}(\text{R}^A)_2$, $-\text{SC}(=\text{O})\text{R}^A$, $-\text{SC}(=\text{O})\text{OR}^A$, $-\text{SC}(=\text{O})\text{SR}^A$, $-\text{SC}(=\text{O})\text{N}(\text{R}^A)_2$, $-\text{SC}(=\text{NR}^A)\text{R}^A$, $-\text{SC}(=\text{NR}^A)\text{OR}^A$, $-\text{SC}(=\text{NR}^A)\text{SR}^A$, $-\text{SC}(=\text{NR}^A)\text{N}(\text{R}^A)_2$, $-\text{NR}^A\text{C}(=\text{O})\text{R}^A$, $-\text{NR}^A\text{C}(=\text{O})\text{OR}^A$, $-\text{NR}^A\text{C}(=\text{O})\text{SR}^A$, $-\text{NR}^A\text{C}(=\text{O})\text{N}(\text{R}^A)_2$, $-\text{NR}^A\text{C}(=\text{NR}^A)\text{R}^A$, $-\text{NR}^A\text{C}(=\text{NR}^A)\text{OR}^A$, $-\text{NR}^A\text{C}(=\text{NR}^A)\text{SR}^A$, $-\text{NR}^A\text{C}(=\text{NR}^A)\text{N}(\text{R}^A)_2$, $-\text{NR}^A\text{S}(=\text{O})\text{R}^A$, $-\text{NR}^A\text{S}(=\text{O})\text{OR}^A$, $-\text{NR}^A\text{S}(=\text{O})\text{SR}^A$, $-\text{NR}^A\text{S}(=\text{O})\text{N}(\text{R}^A)_2$, $-\text{NR}^A\text{S}(=\text{O})_2\text{R}^A$, $-\text{NR}^A\text{S}(=\text{O})_2\text{OR}^A$, $-\text{NR}^A\text{S}(=\text{O})_2\text{SR}^A$, $-\text{NR}^A\text{S}(=\text{O})_2\text{N}(\text{R}^A)_2$, $-\text{Si}(\text{R}^A)_3$, $-\text{Si}(\text{R}^A)_2\text{OR}^A$, $-\text{Si}(\text{R}^A)(\text{OR}^A)_2$, $-\text{Si}(\text{OR}^A)_3$, $-\text{OSi}(\text{R}^A)_3$, $-\text{OSi}(\text{R}^A)_2\text{OR}^A$, $-\text{OSi}(\text{R}^A)(\text{OR}^A)_2$, $-\text{OSi}(\text{OR}^A)_3$, and/or $-\text{B}(\text{OR}^A)_2$ groups.

[0040] Exemplary carbon atom substituents include halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{N}_3$, $-\text{SO}_2\text{H}$, $-\text{SO}_3\text{H}$, $-\text{OH}$, $-\text{OR}^{\text{aa}}$, $-\text{ON}(\text{R}^{\text{bb}})_2$, $-\text{N}(\text{R}^{\text{bb}})_2$, $-\text{N}(\text{R}^{\text{bb}})_3^+\text{X}^-$, $-\text{N}(\text{OR}^{\text{cc}})\text{R}^{\text{bb}}$, $-\text{SH}$, $-\text{SR}^{\text{aa}}$, $-\text{SSR}^{\text{cc}}$, $-\text{C}(=\text{O})\text{R}^{\text{aa}}$, $-\text{CO}_2\text{H}$,

$-\text{CHO}$, $-\text{C}(\text{OR}^{\text{cc}})_2$, $-\text{CO}_2\text{R}^{\text{aa}}$, $-\text{OC}(=\text{O})\text{R}^{\text{aa}}$, $-\text{OCO}_2\text{R}^{\text{aa}}$, $-\text{C}(=\text{O})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{OC}(=\text{O})\text{N}(\text{R}^{\text{bb}})_2$,
 $-\text{NR}^{\text{bb}}\text{C}(=\text{O})\text{R}^{\text{aa}}$, $-\text{NR}^{\text{bb}}\text{CO}_2\text{R}^{\text{aa}}$, $-\text{NR}^{\text{bb}}\text{C}(=\text{O})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{C}(=\text{NR}^{\text{bb}})\text{R}^{\text{aa}}$, $-\text{C}(=\text{NR}^{\text{bb}})\text{OR}^{\text{aa}}$, $-\text{OC}(=\text{NR}^{\text{bb}})\text{R}^{\text{aa}}$,
 $-\text{OC}(=\text{NR}^{\text{bb}})\text{OR}^{\text{aa}}$, $-\text{C}(=\text{NR}^{\text{bb}})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{OC}(=\text{NR}^{\text{bb}})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{NR}^{\text{bb}}\text{C}(=\text{NR}^{\text{bb}})\text{N}(\text{R}^{\text{bb}})_2$,
 $-\text{C}(=\text{O})\text{NR}^{\text{bb}}\text{SO}_2\text{R}^{\text{aa}}$, $-\text{NR}^{\text{bb}}\text{SO}_2\text{R}^{\text{aa}}$, $-\text{SO}_2\text{N}(\text{R}^{\text{bb}})_2$, $-\text{SO}_2\text{R}^{\text{aa}}$, $-\text{SO}_2\text{OR}^{\text{aa}}$, $-\text{OSO}_2\text{R}^{\text{aa}}$, $-\text{S}(=\text{O})\text{R}^{\text{aa}}$,
 $-\text{OS}(=\text{O})\text{R}^{\text{aa}}$, $-\text{Si}(\text{R}^{\text{aa}})_3$, $-\text{OSi}(\text{R}^{\text{aa}})_3$, $-\text{C}(=\text{S})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{C}(=\text{O})\text{SR}^{\text{aa}}$, $-\text{C}(=\text{S})\text{SR}^{\text{aa}}$, $-\text{SC}(=\text{S})\text{SR}^{\text{aa}}$,
 $-\text{SC}(=\text{O})\text{SR}^{\text{aa}}$, $-\text{OC}(=\text{O})\text{SR}^{\text{aa}}$, $-\text{SC}(=\text{O})\text{OR}^{\text{aa}}$, $-\text{SC}(=\text{O})\text{R}^{\text{aa}}$, $-\text{P}(=\text{O})(\text{R}^{\text{aa}})_2$, $-\text{P}(=\text{O})(\text{OR}^{\text{cc}})_2$, $-\text{OP}(=\text{O})(\text{R}^{\text{aa}})_2$,
 $-\text{OP}(=\text{O})(\text{OR}^{\text{cc}})_2$, $-\text{P}(=\text{O})(\text{N}(\text{R}^{\text{bb}})_2)_2$, $-\text{OP}(=\text{O})(\text{N}(\text{R}^{\text{bb}})_2)_2$, $-\text{NR}^{\text{bb}}\text{P}(=\text{O})(\text{R}^{\text{aa}})_2$, $-\text{NR}^{\text{bb}}\text{P}(=\text{O})(\text{OR}^{\text{cc}})_2$,
 $-\text{NR}^{\text{bb}}\text{P}(=\text{O})(\text{N}(\text{R}^{\text{bb}})_2)_2$, $-\text{P}(\text{R}^{\text{cc}})_2$, $-\text{P}(\text{OR}^{\text{cc}})_2$, $-\text{P}(\text{R}^{\text{cc}})_3^+\text{X}^-$, $-\text{P}(\text{OR}^{\text{cc}})_3^+\text{X}^-$, $-\text{P}(\text{R}^{\text{cc}})_4$, $-\text{P}(\text{OR}^{\text{cc}})_4$, $-\text{OP}(\text{R}^{\text{cc}})_2$,
 $-\text{OP}(\text{R}^{\text{cc}})_3^+\text{X}^-$, $-\text{OP}(\text{OR}^{\text{cc}})_2$, $-\text{OP}(\text{OR}^{\text{cc}})_3^+\text{X}^-$, $-\text{OP}(\text{R}^{\text{cc}})_4$, $-\text{OP}(\text{OR}^{\text{cc}})_4$, $-\text{B}(\text{R}^{\text{aa}})_2$, $-\text{B}(\text{OR}^{\text{cc}})_2$, $-\text{BR}^{\text{aa}}(\text{OR}^{\text{cc}})$,
 C_{1-20} alkyl, C_{1-20} perhaloalkyl, C_{1-20} alkenyl, C_{1-20} alkynyl, hetero C_{1-20} alkyl, hetero C_{1-20} alkenyl,
hetero C_{1-20} alkynyl, C_{3-10} carbocyclyl, 3-14 membered heterocyclyl, C_{6-14} aryl, and 5-14 membered
heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl,
heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups; wherein
 X^- is a counterion;

or two geminal hydrogens on a carbon atom are replaced with the group $=\text{O}$, $=\text{S}$, $=\text{NN}(\text{R}^{\text{bb}})_2$,
 $=\text{NNR}^{\text{bb}}\text{C}(=\text{O})\text{R}^{\text{aa}}$, $=\text{NNR}^{\text{bb}}\text{C}(=\text{O})\text{OR}^{\text{aa}}$, $=\text{NNR}^{\text{bb}}\text{S}(=\text{O})_2\text{R}^{\text{aa}}$, $=\text{NR}^{\text{bb}}$, or $=\text{NOR}^{\text{cc}}$;

wherein:

each instance of R^{aa} is, independently, selected from C_{1-20} alkyl, C_{1-20} perhaloalkyl, C_{1-20} alkenyl,
 C_{1-20} alkynyl, hetero C_{1-20} alkyl, hetero C_{1-20} alkenyl, hetero C_{1-20} alkynyl, C_{3-10} carbocyclyl, 3-14 membered
heterocyclyl, C_{6-14} aryl, and 5-14 membered heteroaryl, or two R^{aa} groups are joined to form a 3-14
membered heterocyclyl or 5-14 membered heteroaryl ring, wherein each of the alkyl, alkenyl, alkynyl,
heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently
substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

each instance of R^{bb} is, independently, selected from hydrogen, $-\text{OH}$, $-\text{OR}^{\text{aa}}$, $-\text{N}(\text{R}^{\text{cc}})_2$, $-\text{CN}$,
 $-\text{C}(=\text{O})\text{R}^{\text{aa}}$, $-\text{C}(=\text{O})\text{N}(\text{R}^{\text{cc}})_2$, $-\text{CO}_2\text{R}^{\text{aa}}$, $-\text{SO}_2\text{R}^{\text{aa}}$, $-\text{C}(=\text{NR}^{\text{cc}})\text{OR}^{\text{aa}}$, $-\text{C}(=\text{NR}^{\text{cc}})\text{N}(\text{R}^{\text{cc}})_2$, $-\text{SO}_2\text{N}(\text{R}^{\text{cc}})_2$,
 $-\text{SO}_2\text{R}^{\text{cc}}$, $-\text{SO}_2\text{OR}^{\text{cc}}$, $-\text{SOR}^{\text{aa}}$, $-\text{C}(=\text{S})\text{N}(\text{R}^{\text{cc}})_2$, $-\text{C}(=\text{O})\text{SR}^{\text{cc}}$, $-\text{C}(=\text{S})\text{SR}^{\text{cc}}$, $-\text{P}(=\text{O})(\text{R}^{\text{aa}})_2$, $-\text{P}(=\text{O})(\text{OR}^{\text{cc}})_2$,
 $-\text{P}(=\text{O})(\text{N}(\text{R}^{\text{cc}})_2)_2$, C_{1-20} alkyl, C_{1-20} perhaloalkyl, C_{1-20} alkenyl, C_{1-20} alkynyl, hetero C_{1-20} alkyl, hetero C_{1-20}
alkenyl, hetero C_{1-20} alkynyl, C_{3-10} carbocyclyl, 3-14 membered heterocyclyl, C_{6-14} aryl, and 5-14
membered heteroaryl, or two R^{bb} groups are joined to form a 3-14 membered heterocyclyl or 5-14
membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl,
carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd}
groups;

each instance of R^{cc} is, independently, selected from hydrogen, C_{1-20} alkyl, C_{1-20} perhaloalkyl, C_{1-20}
alkenyl, C_{1-20} alkynyl, hetero C_{1-20} alkyl, hetero C_{1-20} alkenyl, hetero C_{1-20} alkynyl, C_{3-10} carbocyclyl, 3-14
membered heterocyclyl, C_{6-14} aryl, and 5-14 membered heteroaryl, or two R^{cc} groups are joined to form a
3-14 membered heterocyclyl or 5-14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl,
heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently
substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

each instance of R^{dd} is, independently, selected from halogen, $-CN$, $-NO_2$, $-N_3$, $-SO_2H$, $-SO_3H$, $-OH$, $-OR^{ee}$, $-ON(R^{ff})_2$, $-N(R^{ff})_2$, $-N(R^{ff})_3^+X^-$, $-N(OR^{ee})R^{ff}$, $-SH$, $-SR^{ee}$, $-SSR^{ee}$, $-C(=O)R^{ee}$, $-CO_2H$, $-CO_2R^{ee}$, $-OC(=O)R^{ee}$, $-OCO_2R^{ee}$, $-C(=O)N(R^{ff})_2$, $-OC(=O)N(R^{ff})_2$, $-NR^{ff}C(=O)R^{ee}$, $-NR^{ff}CO_2R^{ee}$, $-NR^{ff}C(=O)N(R^{ff})_2$, $-C(=NR^{ff})OR^{ee}$, $-OC(=NR^{ff})R^{ee}$, $-OC(=NR^{ff})OR^{ee}$, $-C(=NR^{ff})N(R^{ff})_2$, $-OC(=NR^{ff})N(R^{ff})_2$, $-NR^{ff}C(=NR^{ff})N(R^{ff})_2$, $-NR^{ff}SO_2R^{ee}$, $-SO_2N(R^{ff})_2$, $-SO_2R^{ee}$, $-SO_2OR^{ee}$, $-OSO_2R^{ee}$, $-S(=O)R^{ee}$, $-Si(R^{ee})_3$, $-OSi(R^{ee})_3$, $-C(=S)N(R^{ff})_2$, $-C(=O)SR^{ee}$, $-C(=S)SR^{ee}$, $-SC(=S)SR^{ee}$, $-P(=O)(OR^{ee})_2$, $-P(=O)(R^{ee})_2$, $-OP(=O)(R^{ee})_2$, $-OP(=O)(OR^{ee})_2$, C_{1-10} alkyl, C_{1-10} perhaloalkyl, C_{1-10} alkenyl, C_{1-10} alkynyl, hetero C_{1-10} alkyl, hetero C_{1-10} alkenyl, hetero C_{1-10} alkynyl, C_{3-10} carbocyclyl, 3-10 membered heterocyclyl, C_{6-10} aryl, and 5-10 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{eg} groups, or two geminal R^{dd} substituents are joined to form $=O$ or $=S$; wherein X^- is a counterion;

each instance of R^{ee} is, independently, selected from C_{1-10} alkyl, C_{1-10} perhaloalkyl, C_{1-10} alkenyl, C_{1-10} alkynyl, hetero C_{1-10} alkyl, hetero C_{1-10} alkenyl, hetero C_{1-10} alkynyl, C_{3-10} carbocyclyl, C_{6-10} aryl, 3-10 membered heterocyclyl, and 3-10 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{eg} groups;

each instance of R^{ff} is, independently, selected from hydrogen, C_{1-10} alkyl, C_{1-10} perhaloalkyl, C_{1-10} alkenyl, C_{1-10} alkynyl, hetero C_{1-10} alkyl, hetero C_{1-10} alkenyl, hetero C_{1-10} alkynyl, C_{3-10} carbocyclyl, 3-10 membered heterocyclyl, C_{6-10} aryl, and 5-10 membered heteroaryl, or two R^{ff} groups are joined to form a 3-10 membered heterocyclyl or 5-10 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{eg} groups;

each instance of R^{eg} is, independently, halogen, $-CN$, $-NO_2$, $-N_3$, $-SO_2H$, $-SO_3H$, $-OH$, $-OC_{1-6}$ alkyl, $-ON(C_{1-6} \text{ alkyl})_2$, $-N(C_{1-6} \text{ alkyl})_2$, $-N(C_{1-6} \text{ alkyl})_3^+X^-$, $-NH(C_{1-6} \text{ alkyl})_2^+X^-$, $-NH_2(C_{1-6} \text{ alkyl})^+X^-$, $-NH_3^+X^-$, $-N(OC_{1-6} \text{ alkyl})(C_{1-6} \text{ alkyl})$, $-N(OH)(C_{1-6} \text{ alkyl})$, $-NH(OH)$, $-SH$, $-SC_{1-6} \text{ alkyl}$, $-SS(C_{1-6} \text{ alkyl})$, $-C(=O)(C_{1-6} \text{ alkyl})$, $-CO_2H$, $-CO_2(C_{1-6} \text{ alkyl})$, $-OC(=O)(C_{1-6} \text{ alkyl})$, $-OCO_2(C_{1-6} \text{ alkyl})$, $-C(=O)NH_2$, $-C(=O)N(C_{1-6} \text{ alkyl})_2$, $-OC(=O)NH(C_{1-6} \text{ alkyl})$, $-NHC(=O)(C_{1-6} \text{ alkyl})$, $-N(C_{1-6} \text{ alkyl})C(=O)(C_{1-6} \text{ alkyl})$, $-NHCO_2(C_{1-6} \text{ alkyl})$, $-NHC(=O)N(C_{1-6} \text{ alkyl})_2$, $-NHC(=O)NH(C_{1-6} \text{ alkyl})$, $-NHC(=O)NH_2$, $-C(=NH)O(C_{1-6} \text{ alkyl})$, $-OC(=NH)(C_{1-6} \text{ alkyl})$, $-OC(=NH)OC_{1-6} \text{ alkyl}$, $-C(=NH)N(C_{1-6} \text{ alkyl})_2$, $-C(=NH)NH(C_{1-6} \text{ alkyl})$, $-C(=NH)NH_2$, $-OC(=NH)N(C_{1-6} \text{ alkyl})_2$, $-OC(NH)NH(C_{1-6} \text{ alkyl})$, $-OC(NH)NH_2$, $-NHC(NH)N(C_{1-6} \text{ alkyl})_2$, $-NHC(=NH)NH_2$, $-NHSO_2(C_{1-6} \text{ alkyl})$, $-SO_2N(C_{1-6} \text{ alkyl})_2$, $-SO_2NH(C_{1-6} \text{ alkyl})$, $-SO_2NH_2$, $-SO_2C_{1-6} \text{ alkyl}$, $-SO_2OC_{1-6} \text{ alkyl}$, $-OSO_2C_{1-6} \text{ alkyl}$, $-SOC_{1-6} \text{ alkyl}$, $-Si(C_{1-6} \text{ alkyl})_3$, $-OSi(C_{1-6} \text{ alkyl})_3$, $-C(=S)N(C_{1-6} \text{ alkyl})_2$, $C(=S)NH(C_{1-6} \text{ alkyl})$, $C(=S)NH_2$, $-C(=O)S(C_{1-6} \text{ alkyl})$, $-C(=S)SC_{1-6} \text{ alkyl}$, $-SC(=S)SC_{1-6} \text{ alkyl}$, $-P(=O)(OC_{1-6} \text{ alkyl})_2$, $-P(=O)(C_{1-6} \text{ alkyl})_2$, $-OP(=O)(C_{1-6} \text{ alkyl})_2$, $-OP(=O)(OC_{1-6} \text{ alkyl})_2$, C_{1-10} alkyl, C_{1-10} perhaloalkyl, C_{1-10} alkenyl, C_{1-10} alkynyl, hetero C_{1-10} alkyl, hetero C_{1-10} alkenyl, hetero C_{1-10} alkynyl, C_{3-10} carbocyclyl, C_{6-10} aryl, 3-10 membered heterocyclyl, or 5-10 membered heteroaryl; or two geminal R^{eg} substituents can be joined to form $=O$ or $=S$; and

each X^- is a counterion.

[0041] In certain embodiments, each carbon atom substituent is independently halogen, substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C_{1-6} alkyl, $-OR^{aa}$, $-SR^{aa}$, $-N(R^{bb})_2$, $-CN$, $-SCN$, $-NO_2$, $-C(=O)R^{aa}$, $-CO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, $-OC(=O)R^{aa}$, $-OCO_2R^{aa}$, $-OC(=O)N(R^{bb})_2$, $-NR^{bb}C(=O)R^{aa}$, $-NR^{bb}CO_2R^{aa}$, or $-NR^{bb}C(=O)N(R^{bb})_2$. In certain embodiments, each carbon atom substituent is independently halogen, substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C_{1-10} alkyl, $-OR^{aa}$, $-SR^{aa}$, $-N(R^{bb})_2$, $-CN$, $-SCN$, $-NO_2$, $-C(=O)R^{aa}$, $-CO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, $-OC(=O)R^{aa}$, $-OCO_2R^{aa}$, $-OC(=O)N(R^{bb})_2$, $-NR^{bb}C(=O)R^{aa}$, $-NR^{bb}CO_2R^{aa}$, or $-NR^{bb}C(=O)N(R^{bb})_2$, wherein R^{aa} is hydrogen, substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C_{1-10} alkyl, an oxygen protecting group (*e.g.*, silyl, TBDPS, TBDMS, TIPS, TES, TMS, MOM, THP, *t*-Bu, Bn, allyl, acetyl, pivaloyl, or benzoyl) when attached to an oxygen atom, or a sulfur protecting group (*e.g.*, acetamidomethyl, *t*-Bu, 3-nitro-2-pyridine sulfenyl, 2-pyridine-sulfenyl, or triphenylmethyl) when attached to a sulfur atom; and each R^{bb} is independently hydrogen, substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C_{1-10} alkyl, or a nitrogen protecting group (*e.g.*, Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts). In certain embodiments, each carbon atom substituent is independently halogen, substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C_{1-6} alkyl, $-OR^{aa}$, $-SR^{aa}$, $-N(R^{bb})_2$, $-CN$, $-SCN$, or $-NO_2$. In certain embodiments, each carbon atom substituent is independently halogen, substituted (*e.g.*, substituted with one or more halogen moieties) or unsubstituted C_{1-10} alkyl, $-OR^{aa}$, $-SR^{aa}$, $-N(R^{bb})_2$, $-CN$, $-SCN$, or $-NO_2$, wherein R^{aa} is hydrogen, substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C_{1-10} alkyl, an oxygen protecting group (*e.g.*, silyl, TBDPS, TBDMS, TIPS, TES, TMS, MOM, THP, *t*-Bu, Bn, allyl, acetyl, pivaloyl, or benzoyl) when attached to an oxygen atom, or a sulfur protecting group (*e.g.*, acetamidomethyl, *t*-Bu, 3-nitro-2-pyridine sulfenyl, 2-pyridine-sulfenyl, or triphenylmethyl) when attached to a sulfur atom; and each R^{bb} is independently hydrogen, substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C_{1-10} alkyl, or a nitrogen protecting group (*e.g.*, Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts).

[0042] In certain embodiments, the molecular weight of a carbon atom substituent is lower than 250, lower than 200, lower than 150, lower than 100, or lower than 50 g/mol. In certain embodiments, a carbon atom substituent consists of carbon, hydrogen, fluorine, chlorine, bromine, iodine, oxygen, sulfur, nitrogen, and/or silicon atoms. In certain embodiments, a carbon atom substituent consists of carbon, hydrogen, fluorine, chlorine, bromine, iodine, oxygen, sulfur, and/or nitrogen atoms. In certain embodiments, a carbon atom substituent consists of carbon, hydrogen, fluorine, chlorine, bromine, and/or iodine atoms. In certain embodiments, a carbon atom substituent consists of carbon, hydrogen, fluorine, and/or chlorine atoms.

[0043] The term “halo” or “halogen” refers to fluorine (fluoro, $-F$), chlorine (chloro, $-Cl$), bromine (bromo, $-Br$), or iodine (iodo, $-I$).

[0044] The term “hydroxyl” or “hydroxy” refers to the group $-OH$. The term “substituted hydroxyl” or “substituted hydroxyl,” by extension, refers to a hydroxyl group wherein the oxygen atom directly

attached to the parent molecule is substituted with a group other than hydrogen, and includes groups selected from $-\text{OR}^{\text{aa}}$, $-\text{ON}(\text{R}^{\text{bb}})_2$, $-\text{OC}(=\text{O})\text{SR}^{\text{aa}}$, $-\text{OC}(=\text{O})\text{R}^{\text{aa}}$, $-\text{OCO}_2\text{R}^{\text{aa}}$, $-\text{OC}(=\text{O})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{OC}(=\text{NR}^{\text{bb}})\text{R}^{\text{aa}}$, $-\text{OC}(=\text{NR}^{\text{bb}})\text{OR}^{\text{aa}}$, $-\text{OC}(=\text{NR}^{\text{bb}})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{OS}(=\text{O})\text{R}^{\text{aa}}$, $-\text{OSO}_2\text{R}^{\text{aa}}$, $-\text{OSi}(\text{R}^{\text{aa}})_3$, $-\text{OP}(\text{R}^{\text{cc}})_2$, $-\text{OP}(\text{R}^{\text{cc}})_3^+\text{X}^-$, $-\text{OP}(\text{OR}^{\text{cc}})_2$, $-\text{OP}(\text{OR}^{\text{cc}})_3^+\text{X}^-$, $-\text{OP}(=\text{O})(\text{R}^{\text{aa}})_2$, $-\text{OP}(=\text{O})(\text{OR}^{\text{cc}})_2$, and $-\text{OP}(=\text{O})(\text{N}(\text{R}^{\text{bb}})_2)_2$, wherein X^- , R^{aa} , R^{bb} , and R^{cc} are as defined herein.

[0045] The term “thiol” or “thio” refers to the group $-\text{SH}$. The term “substituted thiol” or “substituted thio,” by extension, refers to a thiol group wherein the sulfur atom directly attached to the parent molecule is substituted with a group other than hydrogen, and includes groups selected from $-\text{SR}^{\text{aa}}$, $-\text{S}=\text{SR}^{\text{cc}}$, $-\text{SC}(=\text{S})\text{SR}^{\text{aa}}$, $-\text{SC}(=\text{S})\text{OR}^{\text{aa}}$, $-\text{SC}(=\text{S})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{SC}(=\text{O})\text{SR}^{\text{aa}}$, $-\text{SC}(=\text{O})\text{OR}^{\text{aa}}$, $-\text{SC}(=\text{O})\text{N}(\text{R}^{\text{bb}})_2$, and $-\text{SC}(=\text{O})\text{R}^{\text{aa}}$, wherein R^{aa} and R^{cc} are as defined herein.

[0046] The term “amino” refers to the group $-\text{NH}_2$. The term “substituted amino,” by extension, refers to a monosubstituted amino, a disubstituted amino, or a trisubstituted amino. In certain embodiments, the “substituted amino” is a monosubstituted amino or a disubstituted amino group.

[0047] The term “monosubstituted amino” refers to an amino group wherein the nitrogen atom directly attached to the parent molecule is substituted with one hydrogen and one group other than hydrogen, and includes groups selected from $-\text{NH}(\text{R}^{\text{bb}})$, $-\text{NHC}(=\text{O})\text{R}^{\text{aa}}$, $-\text{NHCO}_2\text{R}^{\text{aa}}$, $-\text{NHC}(=\text{O})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{NHC}(=\text{NR}^{\text{bb}})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{NHSO}_2\text{R}^{\text{aa}}$, $-\text{NHP}(=\text{O})(\text{OR}^{\text{cc}})_2$, and $-\text{NHP}(=\text{O})(\text{N}(\text{R}^{\text{bb}})_2)_2$, wherein R^{aa} , R^{bb} and R^{cc} are as defined herein, and wherein R^{bb} of the group $-\text{NH}(\text{R}^{\text{bb}})$ is not hydrogen.

[0048] The term “disubstituted amino” refers to an amino group wherein the nitrogen atom directly attached to the parent molecule is substituted with two groups other than hydrogen, and includes groups selected from $-\text{N}(\text{R}^{\text{bb}})_2$, $-\text{NR}^{\text{bb}}\text{C}(=\text{O})\text{R}^{\text{aa}}$, $-\text{NR}^{\text{bb}}\text{CO}_2\text{R}^{\text{aa}}$, $-\text{NR}^{\text{bb}}\text{C}(=\text{O})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{NR}^{\text{bb}}\text{C}(=\text{NR}^{\text{bb}})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{NR}^{\text{bb}}\text{SO}_2\text{R}^{\text{aa}}$, $-\text{NR}^{\text{bb}}\text{P}(=\text{O})(\text{OR}^{\text{cc}})_2$, and $-\text{NR}^{\text{bb}}\text{P}(=\text{O})(\text{N}(\text{R}^{\text{bb}})_2)_2$, wherein R^{aa} , R^{bb} , and R^{cc} are as defined herein, with the proviso that the nitrogen atom directly attached to the parent molecule is not substituted with hydrogen.

[0049] The term “trisubstituted amino” refers to an amino group wherein the nitrogen atom directly attached to the parent molecule is substituted with three groups, and includes groups selected from $-\text{N}(\text{R}^{\text{bb}})_3$ and $-\text{N}(\text{R}^{\text{bb}})_3^+\text{X}^-$, wherein R^{bb} and X^- are as defined herein.

[0050] The term “sulfonyl” refers to a group selected from $-\text{SO}_2\text{N}(\text{R}^{\text{bb}})_2$, $-\text{SO}_2\text{R}^{\text{aa}}$, and $-\text{SO}_2\text{OR}^{\text{aa}}$, wherein R^{aa} and R^{bb} are as defined herein.

[0051] The term “sulfinyl” refers to the group $-\text{S}(=\text{O})\text{R}^{\text{aa}}$, wherein R^{aa} is as defined herein.

[0052] The term “acyl” refers to a group having the general formula $-\text{C}(=\text{O})\text{R}^{\text{X1}}$, $-\text{C}(=\text{O})\text{OR}^{\text{X1}}$, $-\text{C}(=\text{O})-\text{O}-\text{C}(=\text{O})\text{R}^{\text{X1}}$, $-\text{C}(=\text{O})\text{SR}^{\text{X1}}$, $-\text{C}(=\text{O})\text{N}(\text{R}^{\text{X1}})_2$, $-\text{C}(=\text{S})\text{R}^{\text{X1}}$, $-\text{C}(=\text{S})\text{N}(\text{R}^{\text{X1}})_2$, and $-\text{C}(=\text{S})\text{S}(\text{R}^{\text{X1}})$, $-\text{C}(=\text{NR}^{\text{X1}})\text{R}^{\text{X1}}$, $-\text{C}(=\text{NR}^{\text{X1}})\text{OR}^{\text{X1}}$, $-\text{C}(=\text{NR}^{\text{X1}})\text{SR}^{\text{X1}}$, and $-\text{C}(=\text{NR}^{\text{X1}})\text{N}(\text{R}^{\text{X1}})_2$, wherein R^{X1} is hydrogen; halogen; substituted or unsubstituted hydroxyl; substituted or unsubstituted thiol; substituted or unsubstituted amino; substituted or unsubstituted acyl, cyclic or acyclic, substituted or unsubstituted, branched or unbranched aliphatic; cyclic or acyclic, substituted or unsubstituted, branched or unbranched heteroaliphatic; cyclic or acyclic, substituted or unsubstituted, branched or unbranched alkyl; cyclic or acyclic, substituted or unsubstituted, branched or unbranched alkenyl; substituted or unsubstituted

alkynyl; substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, aliphaticoxy, heteroaliphaticoxy, alkyloxy, heteroalkyloxy, aryloxy, heteroaryloxy, aliphaticthioxy, heteroaliphaticthioxy, alkylthioxy, heteroalkylthioxy, arylthioxy, heteroarylthioxy, mono- or di-aliphaticamino, mono- or di- heteroaliphaticamino, mono- or di- alkylamino, mono- or di- heteroalkylamino, mono- or di-arylamino, or mono- or di-heteroarylamino; or two R^{X1} groups taken together form a 5- to 6-membered heterocyclic ring. Exemplary acyl groups include aldehydes (–CHO), carboxylic acids (–CO₂H), ketones, acyl halides, esters, amides, imines, carbonates, carbamates, and ureas. Acyl substituents include, but are not limited to, any of the substituents described herein, that result in the formation of a stable moiety (*e.g.*, aliphatic, alkyl, alkenyl, alkynyl, heteroaliphatic, heterocyclic, aryl, heteroaryl, acyl, oxo, imino, thiooxo, cyano, isocyano, amino, azido, nitro, hydroxyl, thiol, halo, aliphaticamino, heteroaliphaticamino, alkylamino, heteroalkylamino, arylamino, heteroarylamino, alkylaryl, arylalkyl, aliphaticoxy, heteroaliphaticoxy, alkyloxy, heteroalkyloxy, aryloxy, heteroaryloxy, aliphaticthioxy, heteroaliphaticthioxy, alkylthioxy, heteroalkylthioxy, arylthioxy, heteroarylthioxy, acyloxy, and the like, each of which may or may not be further substituted).

[0053] The term “carbonyl” refers to a group wherein the carbon directly attached to the parent molecule is sp² hybridized, and is substituted with an oxygen, nitrogen or sulfur atom, *e.g.*, a group selected from ketones (–C(=O)R^{aa}), carboxylic acids (–CO₂H), aldehydes (–CHO), esters (–CO₂R^{aa}, –C(=O)SR^{aa}, –C(=S)SR^{aa}), amides (–C(=O)N(R^{bb})₂, –C(=O)NR^{bb}SO₂R^{aa}, –C(=S)N(R^{bb})₂), and imines (–C(=NR^{bb})R^{aa}, –C(=NR^{bb})OR^{aa}, –C(=NR^{bb})N(R^{bb})₂), wherein R^{aa} and R^{bb} are as defined herein.

[0054] The term “silyl” refers to the group –Si(R^{aa})₃, wherein R^{aa} is as defined herein.

[0055] The term “phosphino” refers to the group –P(R^{cc})₂, wherein R^{cc} is as defined herein.

[0056] The term “phosphono” refers to the group –(P=O)(OR^{cc})₂, wherein R^{aa} and R^{cc} are as defined herein.

[0057] The term “phosphoramido” refers to the group –O(P=O)(N(R^{bb})₂)₂, wherein each R^{bb} is as defined herein.

[0058] The term “oxo” refers to the group =O, and the term “thiooxo” refers to the group =S.

[0059] Nitrogen atoms can be substituted or unsubstituted as valency permits, and include primary, secondary, tertiary, and quaternary nitrogen atoms. Exemplary nitrogen atom substituents include hydrogen, –OH, –OR^{aa}, –N(R^{cc})₂, –CN, –C(=O)R^{aa}, –C(=O)N(R^{cc})₂, –CO₂R^{aa}, –SO₂R^{aa}, –C(=NR^{bb})R^{aa}, –C(=NR^{cc})OR^{aa}, –C(=NR^{cc})N(R^{cc})₂, –SO₂N(R^{cc})₂, –SO₂R^{cc}, –SO₂OR^{cc}, –SOR^{aa}, –C(=S)N(R^{cc})₂, –C(=O)SR^{cc}, –C(=S)SR^{cc}, –P(=O)(OR^{cc})₂, –P(=O)(R^{aa})₂, –P(=O)(N(R^{cc})₂)₂, C_{1–20} alkyl, C_{1–20} perhaloalkyl, C_{1–20} alkenyl, C_{1–20} alkynyl, hetero C_{1–20} alkyl, hetero C_{1–20} alkenyl, hetero C_{1–20} alkynyl, C_{3–10} carbocyclyl, 3-14 membered heterocyclyl, C_{6–14} aryl, and 5-14 membered heteroaryl, or two R^{cc} groups attached to an N atom are joined to form a 3-14 membered heterocyclyl or 5-14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups, and wherein R^{aa}, R^{bb}, R^{cc} and R^{dd} are as defined above.

[0060] In certain embodiments, each nitrogen atom substituent is independently substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C₁₋₆ alkyl, $-\text{C}(=\text{O})\text{R}^{\text{aa}}$, $-\text{CO}_2\text{R}^{\text{aa}}$, $-\text{C}(=\text{O})\text{N}(\text{R}^{\text{bb}})_2$, or a nitrogen protecting group. In certain embodiments, each nitrogen atom substituent is independently substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C₁₋₁₀ alkyl, $-\text{C}(=\text{O})\text{R}^{\text{aa}}$, $-\text{CO}_2\text{R}^{\text{aa}}$, $-\text{C}(=\text{O})\text{N}(\text{R}^{\text{bb}})_2$, or a nitrogen protecting group, wherein R^{aa} is hydrogen, substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C₁₋₁₀ alkyl, or an oxygen protecting group when attached to an oxygen atom; and each R^{bb} is independently hydrogen, substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C₁₋₁₀ alkyl, or a nitrogen protecting group. In certain embodiments, each nitrogen atom substituent is independently substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C₁₋₆ alkyl or a nitrogen protecting group.

[0061] In certain embodiments, the substituent present on the nitrogen atom is a nitrogen protecting group (also referred to herein as an “amino protecting group”). Nitrogen protecting groups include $-\text{OH}$, $-\text{OR}^{\text{aa}}$, $-\text{N}(\text{R}^{\text{cc}})_2$, $-\text{C}(=\text{O})\text{R}^{\text{aa}}$, $-\text{C}(=\text{O})\text{N}(\text{R}^{\text{cc}})_2$, $-\text{CO}_2\text{R}^{\text{aa}}$, $-\text{SO}_2\text{R}^{\text{aa}}$, $-\text{C}(=\text{NR}^{\text{cc}})\text{R}^{\text{aa}}$, $-\text{C}(=\text{NR}^{\text{cc}})\text{OR}^{\text{aa}}$, $-\text{C}(=\text{NR}^{\text{cc}})\text{N}(\text{R}^{\text{cc}})_2$, $-\text{SO}_2\text{N}(\text{R}^{\text{cc}})_2$, $-\text{SO}_2\text{R}^{\text{cc}}$, $-\text{SO}_2\text{OR}^{\text{cc}}$, $-\text{SOR}^{\text{aa}}$, $-\text{C}(=\text{S})\text{N}(\text{R}^{\text{cc}})_2$, $-\text{C}(=\text{O})\text{SR}^{\text{cc}}$, $-\text{C}(=\text{S})\text{SR}^{\text{cc}}$, C₁₋₁₀ alkyl (*e.g.*, aralkyl, heteroaralkyl), C₁₋₂₀ alkenyl, C₁₋₂₀ alkynyl, hetero C₁₋₂₀ alkyl, hetero C₁₋₂₀ alkenyl, hetero C₁₋₂₀ alkynyl, C₃₋₁₀ carbocyclyl, 3-14 membered heterocyclyl, C₆₋₁₄ aryl, and 5-14 membered heteroaryl groups, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aralkyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups, and wherein R^{aa}, R^{bb}, R^{cc} and R^{dd} are as defined herein. Nitrogen protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, incorporated herein by reference.

[0062] For example, in certain embodiments, at least one nitrogen protecting group is an amide group (*e.g.*, a moiety that include the nitrogen atom to which the nitrogen protecting groups (*e.g.*, $-\text{C}(=\text{O})\text{R}^{\text{aa}}$) is directly attached). In certain such embodiments, each nitrogen protecting group, together with the nitrogen atom to which the nitrogen protecting group is attached, is independently selected from the group consisting of formamide, acetamide, chloroacetamide, trichloroacetamide, trifluoroacetamide, phenylacetamide, 3-phenylpropanamide, picolinamide, 3-pyridylcarboxamide, *N*-benzoylphenylalanyl derivatives, benzamide, *p*-phenylbenzamide, *o*-nitrophenylacetamide, *o*-nitrophenoxyacetamide, acetoacetamide, (*N'*-dithiobenzoyloxyacylamino)acetamide, 3-(*p*-hydroxyphenyl)propanamide, 3-(*o*-nitrophenyl)propanamide, 2-methyl-2-(*o*-nitrophenoxy)propanamide, 2-methyl-2-(*o*-phenylazophenoxy)propanamide, 4-chlorobutanamide, 3-methyl-3-nitrobutanamide, *o*-nitrocinnamide, *N*-acetylmethionine derivatives, *o*-nitrobenzamide, and *o*-(benzoyloxymethyl)benzamide.

[0063] In certain embodiments, at least one nitrogen protecting group is a carbamate group (*e.g.*, a moiety that includes the nitrogen atom to which the nitrogen protecting groups (*e.g.*, $-\text{C}(=\text{O})\text{OR}^{\text{aa}}$) is directly attached). In certain such embodiments, each nitrogen protecting group, together with the nitrogen atom to which the nitrogen protecting group is attached, is independently selected from the group consisting of methyl carbamate, ethyl carbamate, 9-fluorenylmethyl carbamate (Fmoc), 9-(2-

sulfo)fluorenylmethyl carbamate, 9-(2,7-dibromo)fluorenylmethyl carbamate, 2,7-di-*t*-butyl-[9-(10,10-dioxo-10,10,10,10-tetrahydrothioxanthyl)]methyl carbamate (DBD-Tmoc), 4-methoxyphenacyl carbamate (Phenoc), 2,2,2-trichloroethyl carbamate (Troc), 2-trimethylsilylethyl carbamate (Teoc), 2-phenylethyl carbamate (hZ), 1-(1-adamantyl)-1-methylethyl carbamate (Adpoc), 1,1-dimethyl-2-haloethyl carbamate, 1,1-dimethyl-2,2-dibromoethyl carbamate (DB-t-BOC), 1,1-dimethyl-2,2,2-trichloroethyl carbamate (TCBOC), 1-methyl-1-(4-biphenyl)ethyl carbamate (Bpoc), 1-(3,5-di-*t*-butylphenyl)-1-methylethyl carbamate (t-Bumeoc), 2-(2'- and 4'-pyridyl)ethyl carbamate (Pyoc), 2-(*N,N*-dicyclohexylcarboxamido)ethyl carbamate, *t*-butyl carbamate (BOC or Boc), 1-adamantyl carbamate (Adoc), vinyl carbamate (Voc), allyl carbamate (Alloc), 1-isopropylallyl carbamate (Ipaoc), cinnamyl carbamate (Coc), 4-nitrocinnamyl carbamate (Noc), 8-quinolyl carbamate, *N*-hydroxypiperidinyl carbamate, alkylthio carbamate, benzyl carbamate (Cbz), *p*-methoxybenzyl carbamate (Moz), *p*-nitrobenzyl carbamate, *p*-bromobenzyl carbamate, *p*-chlorobenzyl carbamate, 2,4-dichlorobenzyl carbamate, 4-methylsulfinylbenzyl carbamate (MsZ), 9-anthrylmethyl carbamate, diphenylmethyl carbamate, 2-methylthioethyl carbamate, 2-methylsulfonylethyl carbamate, 2-(*p*-toluenesulfonyl)ethyl carbamate, [2-(1,3-dithianyl)]methyl carbamate (Dmoc), 4-methylthiophenyl carbamate (Mtpc), 2,4-dimethylthiophenyl carbamate (Bmpc), 2-phosphonioethyl carbamate (Peoc), 2-triphenylphosphonioisopropyl carbamate (Ppoc), 1,1-dimethyl-2-cyanoethyl carbamate, *m*-chloro-*p*-acyloxybenzyl carbamate, *p*-(dihydroxyboryl)benzyl carbamate, 5-benzisoxazolylmethyl carbamate, 2-(trifluoromethyl)-6-chromonylmethyl carbamate (Tcroc), *m*-nitrophenyl carbamate, 3,5-dimethoxybenzyl carbamate, *o*-nitrobenzyl carbamate, 3,4-dimethoxy-6-nitrobenzyl carbamate, phenyl(*o*-nitrophenyl)methyl carbamate, *t*-amyl carbamate, *S*-benzyl thiocarbamate, *p*-cyanobenzyl carbamate, cyclobutyl carbamate, cyclohexyl carbamate, cyclopentyl carbamate, cyclopropylmethyl carbamate, *p*-decyloxybenzyl carbamate, 2,2-dimethoxyacetylvinyl carbamate, *o*-(*N,N*-dimethylcarboxamido)benzyl carbamate, 1,1-dimethyl-3-(*N,N*-dimethylcarboxamido)propyl carbamate, 1,1-dimethylpropynyl carbamate, di(2-pyridyl)methyl carbamate, 2-furanylmethyl carbamate, 2-iodoethyl carbamate, isoborynl carbamate, isobutyl carbamate, isonicotinyl carbamate, *p*-(*p*'-methoxyphenylazo)benzyl carbamate, 1-methylcyclobutyl carbamate, 1-methylcyclohexyl carbamate, 1-methyl-1-cyclopropylmethyl carbamate, 1-methyl-1-(3,5-dimethoxyphenyl)ethyl carbamate, 1-methyl-1-(*p*-phenylazophenyl)ethyl carbamate, 1-methyl-1-phenylethyl carbamate, 1-methyl-1-(4-pyridyl)ethyl carbamate, phenyl carbamate, *p*-(phenylazo)benzyl carbamate, 2,4,6-tri-*t*-butylphenyl carbamate, 4-(trimethylammonium)benzyl carbamate, and 2,4,6-trimethylbenzyl carbamate.

[0064] In certain embodiments, at least one nitrogen protecting group is a sulfonamide group (*e.g.*, a moiety that include the nitrogen atom to which the nitrogen protecting groups (*e.g.*, $-S(=O)_2R^{aa}$) is directly attached). In certain such embodiments, each nitrogen protecting group, together with the nitrogen atom to which the nitrogen protecting group is attached, is independently selected from the group consisting of *p*-toluenesulfonamide (Ts), benzenesulfonamide, 2,3,6-trimethyl-4-methoxybenzenesulfonamide (Mtr), 2,4,6-trimethoxybenzenesulfonamide (Mtb), 2,6-dimethyl-4-methoxybenzenesulfonamide (Pme), 2,3,5,6-tetramethyl-4-methoxybenzenesulfonamide (Mte), 4-

methoxybenzenesulfonamide (Mbs), 2,4,6-trimethylbenzenesulfonamide (Mts), 2,6-dimethoxy-4-methylbenzenesulfonamide (iMds), 2,2,5,7,8-pentamethylchroman-6-sulfonamide (Pmc), methanesulfonamide (Ms), β -trimethylsilylethanesulfonamide (SES), 9-anthracenesulfonamide, 4-(4',8'-dimethoxynaphthylmethyl)benzenesulfonamide (DNMBS), benzylsulfonamide, trifluoromethylsulfonamide, and phenaclysulfonamide.

[0065] In certain embodiments, each nitrogen protecting group, together with the nitrogen atom to which the nitrogen protecting group is attached, is independently selected from the group consisting of phenothiazinyl-(10)-acyl derivatives, *N'*-*p*-toluenesulfonylaminoacyl derivatives, *N'*-phenylaminothioacyl derivatives, *N*-benzoylphenylalanyl derivatives, *N*-acetylmethionine derivatives, 4,5-diphenyl-3-oxazolin-2-one, *N*-phthalimide, *N*-dithiasuccinimide (Dts), *N*-2,3-diphenylmaleimide, *N*-2,5-dimethylpyrrole, *N*-1,1,4,4-tetramethyldisilylazacyclopentane adduct (STABASE), 5-substituted 1,3-dimethyl-1,3,5-triazacyclohexan-2-one, 5-substituted 1,3-dibenzyl-1,3,5-triazacyclohexan-2-one, 1-substituted 3,5-dinitro-4-pyridone, *N*-methylamine, *N*-allylamine, *N*-[2-(trimethylsilyl)ethoxy]methylamine (SEM), *N*-3-acetoxypyrrolamine, *N*-(1-isopropyl-4-nitro-2-oxo-3-pyrroline-3-yl)amine, quaternary ammonium salts, *N*-benzylamine, *N*-di(4-methoxyphenyl)methylamine, *N*-5-dibenzosuberylamine, *N*-triphenylmethylamine (Tr), *N*-[(4-methoxyphenyl)diphenylmethyl]amine (MMTr), *N*-9-phenylfluorenylamine (PhF), *N*-2,7-dichloro-9-fluorenylmethyleneamine, *N*-ferrocenylmethylamino (Fcm), *N*-2-picolylamino *N'*-oxide, *N*-1,1-dimethylthiomethyleneamine, *N*-benzylideneamine, *N*-*p*-methoxybenzylideneamine, *N*-diphenylmethyleneamine, *N*-[(2-pyridyl)mesityl]methyleneamine, *N*-(*N'*,*N'*-dimethylaminomethylene)amine, *N*-*p*-nitrobenzylideneamine, *N*-salicylideneamine, *N*-5-chlorosalicylideneamine, *N*-(5-chloro-2-hydroxyphenyl)phenylmethyleneamine, *N*-cyclohexylideneamine, *N*-(5,5-dimethyl-3-oxo-1-cyclohexenyl)amine, *N*-borane derivatives, *N*-diphenylborinic acid derivatives, *N*-[phenyl(pentaacylchromium- or tungsten)acyl]amine, *N*-copper chelate, *N*-zinc chelate, *N*-nitroamine, *N*-nitrosoamine, amine *N*-oxide, diphenylphosphinamide (Dpp), dimethylthiophosphinamide (Mpt), diphenylthiophosphinamide (Ppt), dialkyl phosphoramidates, dibenzyl phosphoramidate, diphenyl phosphoramidate, benzenesulfenamide, *o*-nitrobenzenesulfenamide (Nps), 2,4-dinitrobenzenesulfenamide, pentachlorobenzenesulfenamide, 2-nitro-4-methoxybenzenesulfenamide, triphenylmethylsulfenamide, and 3-nitropyridinesulfenamide (Npys). In some embodiments, two instances of a nitrogen protecting group together with the nitrogen atoms to which the nitrogen protecting groups are attached are *N,N'*-isopropylidenediamine.

[0066] In certain embodiments, at least one nitrogen protecting group is Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts.

[0067] In certain embodiments, each oxygen atom substituent is independently substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C₁₋₁₀ alkyl, -C(=O)R^{aa}, -CO₂R^{aa}, -C(=O)N(R^{bb})₂, or an oxygen protecting group. In certain embodiments, each oxygen atom substituents is independently substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C₁₋₆ alkyl, -C(=O)R^{aa}, -CO₂R^{aa}, -C(=O)N(R^{bb})₂, or an oxygen protecting group, wherein R^{aa} is hydrogen, substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C₁₋₁₀ alkyl, or an oxygen protecting group when attached to an

oxygen atom; and each R^{bb} is independently hydrogen, substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C_{1-10} alkyl, or a nitrogen protecting group. In certain embodiments, each oxygen atom substituent is independently substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C_{1-6} alkyl or an oxygen protecting group.

[0068] In certain embodiments, the substituent present on an oxygen atom is an oxygen protecting group (also referred to herein as an “hydroxyl protecting group”). Oxygen protecting groups include $-R^{aa}$, $-N(R^{bb})_2$, $-C(=O)SR^{aa}$, $-C(=O)R^{aa}$, $-CO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, $-C(=NR^{bb})R^{aa}$, $-C(=NR^{bb})OR^{aa}$, $-C(=NR^{bb})N(R^{bb})_2$, $-S(=O)R^{aa}$, $-SO_2R^{aa}$, $-Si(R^{aa})_3$, $-P(R^{cc})_2$, $-P(R^{cc})_3^+X^-$, $-P(OR^{cc})_2$, $-P(OR^{cc})_3^+X^-$, $-P(=O)(R^{aa})_2$, $-P(=O)(OR^{cc})_2$, and $-P(=O)(N(R^{bb})_2)_2$, wherein X^- , R^{aa} , R^{bb} , and R^{cc} are as defined herein. Oxygen protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, incorporated herein by reference.

[0069] In certain embodiments, each oxygen protecting group, together with the oxygen atom to which the oxygen protecting group is attached, is selected from the group consisting of methyl, methoxymethyl (MOM), methylthiomethyl (MTM), *t*-butylthiomethyl, (phenyldimethylsilyl)methoxymethyl (SMOM), benzyloxymethyl (BOM), *p*-methoxybenzyloxymethyl (PMBM), (4-methoxyphenoxy)methyl (p-AOM), guaiacolmethyl (GUM), *t*-butoxymethyl, 4-pentenylloxymethyl (POM), siloxymethyl, 2-methoxyethoxymethyl (MEM), 2,2,2-trichloroethoxymethyl, bis(2-chloroethoxy)methyl, 2-(trimethylsilyl)ethoxymethyl (SEMOR), tetrahydropyranyl (THP), 3-bromotetrahydropyranyl, tetrahydrothiopyranyl, 1-methoxycyclohexyl, 4-methoxytetrahydropyranyl (MTHP), 4-methoxytetrahydrothiopyranyl, 4-methoxytetrahydrothiopyranyl *S,S*-dioxide, 1-[(2-chloro-4-methyl)phenyl]-4-methoxypiperidin-4-yl (CTMP), 1,4-dioxan-2-yl, tetrahydrofuranyl, tetrahydrothiofuranyl, 2,3,3a,4,5,6,7,7a-octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-yl, 1-ethoxyethyl, 1-(2-chloroethoxy)ethyl, 1-methyl-1-methoxyethyl, 1-methyl-1-benzyloxyethyl, 1-methyl-1-benzyloxy-2-fluoroethyl, 2,2,2-trichloroethyl, 2-trimethylsilyl ethyl, 2-(phenylselenyl)ethyl, *t*-butyl, allyl, *p*-chlorophenyl, *p*-methoxyphenyl, 2,4-dinitrophenyl, benzyl (Bn), *p*-methoxybenzyl (PMB), 3,4-dimethoxybenzyl, *o*-nitrobenzyl, *p*-nitrobenzyl, *p*-halobenzyl, 2,6-dichlorobenzyl, *p*-cyanobenzyl, *p*-phenylbenzyl, 2-picolyl, 4-picolyl, 3-methyl-2-picolyl *N*-oxido, diphenylmethyl, *p,p'*-dinitrobenzhydriyl, 5-dibenzosuberyl, triphenylmethyl, α -naphthyl diphenylmethyl, *p*-methoxyphenyl diphenylmethyl, di(*p*-methoxyphenyl)phenylmethyl, tri(*p*-methoxyphenyl)methyl, 4-(4'-bromophenacyloxyphenyl)diphenylmethyl, 4,4',4''-tris(4,5-dichlorophthalimidophenyl)methyl, 4,4',4''-tris(levulinoyloxyphenyl)methyl, 4,4',4''-tris(benzoyloxyphenyl)methyl, 4,4'-Dimethoxy-3'''-[N-(imidazolylmethyl)]trityl Ether (IDTr-OR), 4,4'-Dimethoxy-3'''-[N-(imidazolylethyl)carbamoil]trityl Ether (IETr-OR), 1,1-bis(4-methoxyphenyl)-1'-pyrenylmethyl, 9-anthryl, 9-(9-phenyl)xanthenyl, 9-(9-phenyl-10-oxo)anthryl, 1,3-benzodithiolan-2-yl, benzisothiazolyl *S,S*-dioxido, trimethylsilyl (TMS), triethylsilyl (TES), triisopropylsilyl (TIPS), dimethylisopropylsilyl (IPDMS), diethylisopropylsilyl (DEIPS), dimethylhexylsilyl, *t*-butyldimethylsilyl (TBDMS), *t*-butyldiphenylsilyl (TBDPS), tribenzylsilyl, tri-*p*-xylylsilyl, triphenylsilyl, diphenylmethylsilyl (DPMS), *t*-butylmethoxyphenylsilyl

(TBMPS), formate, benzoylformate, acetate, chloroacetate, dichloroacetate, trichloroacetate, trifluoroacetate, methoxyacetate, triphenylmethoxyacetate, phenoxyacetate, *p*-chlorophenoxyacetate, 3-phenylpropionate, 4-oxopentanoate (levulinate), 4,4-(ethylenedithio)pentanoate (levulinoyldithioacetal), pivaloate, adamantate, crotonate, 4-methoxycrotonate, benzoate, *p*-phenylbenzoate, 2,4,6-trimethylbenzoate (mesitoate), methyl carbonate, 9-fluorenylmethyl carbonate (Fmoc), ethyl carbonate, 2,2,2-trichloroethyl carbonate (Troc), 2-(trimethylsilyl)ethyl carbonate (TMSEC), 2-(phenylsulfonyl)ethyl carbonate (Psec), 2-(triphenylphosphonio)ethyl carbonate (Peoc), isobutyl carbonate, vinyl carbonate, allyl carbonate, *t*-butyl carbonate (BOC or Boc), *p*-nitrophenyl carbonate, benzyl carbonate, *p*-methoxybenzyl carbonate, 3,4-dimethoxybenzyl carbonate, *o*-nitrobenzyl carbonate, *p*-nitrobenzyl carbonate, *S*-benzyl thiocarbonate, 4-ethoxy-1-naphthyl carbonate, methyl dithiocarbonate, 2-iodobenzoate, 4-azidobutyrate, 4-nitro-4-methylpentanoate, *o*-(dibromomethyl)benzoate, 2-formylbenzenesulfonate, 2-(methylthiomethoxy)ethyl carbonate (MTMEC-OR), 4-(methylthiomethoxy)butyrate, 2-(methylthiomethoxymethyl)benzoate, 2,6-dichloro-4-methylphenoxyacetate, 2,6-dichloro-4-(1,1,3,3-tetramethylbutyl)phenoxyacetate, 2,4-bis(1,1-dimethylpropyl)phenoxyacetate, chlorodiphenylacetate, isobutyrate, monosuccinoate, (*E*)-2-methyl-2-butenate, *o*-(methoxyacyl)benzoate, α -naphthoate, nitrate, alkyl *N,N,N',N'*-tetramethylphosphorodiamidate, alkyl *N*-phenylcarbamate, borate, dimethylphosphinothioyl, alkyl 2,4-dinitrophenylsulfonate, sulfate, methanesulfonate (mesylate), benzyisulfonate, and tosylate (Ts).

[0070] In certain embodiments, at least one oxygen protecting group is silyl, TBDPS, TBDMS, TIPS, TES, TMS, MOM, THP, *t*-Bu, Bn, allyl, acetyl, pivaloyl, or benzoyl.

[0071] In certain embodiments, each sulfur atom substituent is independently substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C₁₋₁₀ alkyl, $-\text{C}(=\text{O})\text{R}^{\text{aa}}$, $-\text{CO}_2\text{R}^{\text{aa}}$, $-\text{C}(=\text{O})\text{N}(\text{R}^{\text{bb}})_2$, or a sulfur protecting group. In certain embodiments, each sulfur atom substituent is independently substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C₁₋₁₀ alkyl, $-\text{C}(=\text{O})\text{R}^{\text{aa}}$, $-\text{CO}_2\text{R}^{\text{aa}}$, $-\text{C}(=\text{O})\text{N}(\text{R}^{\text{bb}})_2$, or a sulfur protecting group, wherein R^{aa} is hydrogen, substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C₁₋₁₀ alkyl, or an oxygen protecting group when attached to an oxygen atom; and each R^{bb} is independently hydrogen, substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C₁₋₁₀ alkyl, or a nitrogen protecting group. In certain embodiments, each sulfur atom substituent is independently substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C₁₋₆ alkyl or a sulfur protecting group.

[0072] In certain embodiments, the substituent present on a sulfur atom is a sulfur protecting group (also referred to as a “thiol protecting group”). In some embodiments, each sulfur protecting group is selected from the group consisting of $-\text{R}^{\text{aa}}$, $-\text{N}(\text{R}^{\text{bb}})_2$, $-\text{C}(=\text{O})\text{SR}^{\text{aa}}$, $-\text{C}(=\text{O})\text{R}^{\text{aa}}$, $-\text{CO}_2\text{R}^{\text{aa}}$, $-\text{C}(=\text{O})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{C}(=\text{NR}^{\text{bb}})\text{R}^{\text{aa}}$, $-\text{C}(=\text{NR}^{\text{bb}})\text{OR}^{\text{aa}}$, $-\text{C}(=\text{NR}^{\text{bb}})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{S}(=\text{O})\text{R}^{\text{aa}}$, $-\text{SO}_2\text{R}^{\text{aa}}$, $-\text{Si}(\text{R}^{\text{aa}})_3$, $-\text{P}(\text{R}^{\text{cc}})_2$, $-\text{P}(\text{R}^{\text{cc}})_3^+\text{X}^-$, $-\text{P}(\text{OR}^{\text{cc}})_2$, $-\text{P}(\text{OR}^{\text{cc}})_3^+\text{X}^-$, $-\text{P}(=\text{O})(\text{R}^{\text{aa}})_2$, $-\text{P}(=\text{O})(\text{OR}^{\text{cc}})_2$, and $-\text{P}(=\text{O})(\text{N}(\text{R}^{\text{bb}})_2)_2$, wherein R^{aa}, R^{bb}, and R^{cc} are as defined herein. Sulfur protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, incorporated herein by reference.

[0073] In certain embodiments, the molecular weight of a substituent is lower than 250, lower than 200, lower than 150, lower than 100, or lower than 50 g/mol. In certain embodiments, a substituent consists of carbon, hydrogen, fluorine, chlorine, bromine, iodine, oxygen, sulfur, nitrogen, and/or silicon atoms. In certain embodiments, a substituent consists of carbon, hydrogen, fluorine, chlorine, bromine, iodine, oxygen, sulfur, and/or nitrogen atoms. In certain embodiments, a substituent consists of carbon, hydrogen, fluorine, chlorine, bromine, and/or iodine atoms. In certain embodiments, a substituent consists of carbon, hydrogen, fluorine, and/or chlorine atoms. In certain embodiments, a substituent comprises 0, 1, 2, or 3 hydrogen bond donors. In certain embodiments, a substituent comprises 0, 1, 2, or 3 hydrogen bond acceptors.

[0074] A “counterion” or “anionic counterion” is a negatively charged group associated with a positively charged group in order to maintain electronic neutrality. An anionic counterion may be monovalent (*e.g.*, including one formal negative charge). An anionic counterion may also be multivalent (*e.g.*, including more than one formal negative charge), such as divalent or trivalent. Exemplary counterions include halide ions (*e.g.*, F[−], Cl[−], Br[−], I[−]), NO₃[−], ClO₄[−], OH[−], H₂PO₄[−], HCO₃[−], HSO₄[−], sulfonate ions (*e.g.*, methanesulfonate, trifluoromethanesulfonate, *p*-toluenesulfonate, benzenesulfonate, 10-camphor sulfonate, naphthalene-2-sulfonate, naphthalene-1-sulfonic acid-5-sulfonate, ethan-1-sulfonic acid-2-sulfonate, and the like), carboxylate ions (*e.g.*, acetate, propanoate, benzoate, glycerate, lactate, tartrate, glycolate, gluconate, and the like), BF₄[−], PF₄[−], PF₆[−], AsF₆[−], SbF₆[−], B[3,5-(CF₃)₂C₆H₃]₄[−], B(C₆F₅)₄[−], BPh₄[−], Al(OC(CF₃)₃)₄[−], and carborane anions (*e.g.*, CB₁₁H₁₂[−] or (HCB₁₁Me₅Br₆)[−]). Exemplary counterions which may be multivalent include CO₃^{2−}, HPO₄^{2−}, PO₄^{3−}, B₄O₇^{2−}, SO₄^{2−}, S₂O₃^{2−}, carboxylate anions (*e.g.*, tartrate, citrate, fumarate, maleate, malate, malonate, gluconate, succinate, glutarate, adipate, pimelate, suberate, azelate, sebacate, salicylate, phthalates, aspartate, glutamate, and the like), and carboranes.

[0075] A “leaving group” (LG) is an art-understood term referring to an atomic or molecular fragment that departs with a pair of electrons in heterolytic bond cleavage, wherein the molecular fragment is an anion or neutral molecule. As used herein, a leaving group can be an atom or a group capable of being displaced by a nucleophile. *See e.g.*, Smith, March Advanced Organic Chemistry 6th ed. (501–502). Exemplary leaving groups include, but are not limited to, halo (*e.g.*, fluoro, chloro, bromo, iodo) and activated substituted hydroxyl groups (*e.g.*, −OC(=O)SR^{aa}, −OC(=O)R^{aa}, −OCO₂R^{aa}, −OC(=O)N(R^{bb})₂, −OC(=NR^{bb})R^{aa}, −OC(=NR^{bb})OR^{aa}, −OC(=NR^{bb})N(R^{bb})₂, −OS(=O)R^{aa}, −OSO₂R^{aa}, −OP(R^{cc})₂, −OP(R^{cc})₃, −OP(=O)₂R^{aa}, −OP(=O)(R^{aa})₂, −OP(=O)(OR^{cc})₂, −OP(=O)₂N(R^{bb})₂, and −OP(=O)(NR^{bb})₂, wherein R^{aa}, R^{bb}, and R^{cc} are as defined herein). Additional examples of suitable leaving groups include, but are not limited to, halogen alkoxycarbonyloxy, aryloxy carbonyloxy, alkanesulfonyloxy, arenesulfonyloxy, alkyl-carbonyloxy (*e.g.*, acetoxy), arylcarbonyloxy, aryloxy, methoxy, *N,O*-dimethylhydroxylamino, pixyl, and haloformates. In some embodiments, the leaving group is a sulfonic acid ester, such as toluenesulfonate (tosylate, −OTs), methanesulfonate (mesylate, −OMs), *p*-bromobenzenesulfonyloxy (brosylate, −OBs), −OS(=O)₂(CF₂)₃CF₃ (nonaflate, −ONf), or trifluoromethanesulfonate (triflate, −OTf). In some embodiments, the leaving group is a brosylate, such as *p*-bromobenzenesulfonyloxy. In some embodiments, the leaving group is a nosylate, such as 2-nitrobenzenesulfonyloxy. In some embodiments,

the leaving group is a sulfonate-containing group. In some embodiments, the leaving group is a tosylate group. In some embodiments, the leaving group is a phosphineoxide (*e.g.*, formed during a Mitsunobu reaction) or an internal leaving group such as an epoxide or cyclic sulfate. Other non-limiting examples of leaving groups are water, ammonia, alcohols, ether moieties, thioether moieties, zinc halides, magnesium moieties, diazonium salts, and copper moieties.

[0076] Use of the phrase “at least one instance” refers to 1, 2, 3, 4, or more instances, but also encompasses a range, *e.g.*, for example, from 1 to 4, from 1 to 3, from 1 to 2, from 2 to 4, from 2 to 3, or from 3 to 4 instances, inclusive.

[0077] A “non-hydrogen group” refers to any group that is defined for a particular variable that is not hydrogen.

[0078] These and other exemplary substituents are described in more detail in the Detailed Description, Examples, and Claims. The invention is not limited in any manner by the above exemplary listing of substituents.

[0079] As used herein, the term “salt” refers to any and all salts and encompasses pharmaceutically acceptable salts. The term “salt” refers to ionic compounds that result from the neutralization reaction of an acid and a base. A salt is composed of one or more cations (positively charged ions) and one or more anions (negative ions) so that the salt is electrically neutral (without a net charge). Salts of the compounds of this disclosure include those derived from inorganic and organic acids and bases. Examples of acid addition salts are salts of an amino group formed with inorganic acids, such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, and perchloric acid, or with organic acids, such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid, or malonic acid or by using other methods known in the art such as ion exchange. Other salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, *p*-toluenesulfonate, undecanoate, valerate, hippurate, and the like. Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium, and $N^+(C_{1-4} \text{ alkyl})_4$ salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further salts include ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, lower alkyl sulfonate, and aryl sulfonate.

[0080] The term “pharmaceutically acceptable salt” refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, Berge *et al.*

describe pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences*, 1977, 66, 1–19, incorporated herein by reference. Pharmaceutically acceptable salts of the compounds of this disclosure include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids, such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, and perchloric acid or with organic acids, such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid, or malonic acid or by using other methods known in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like. Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium, and $N^+(C_{1-4} \text{ alkyl})_4^+$ salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, lower alkyl sulfonate, and aryl sulfonate.

[0081] The term “solvate” refers to forms of the compound, or a salt thereof, that are associated with a solvent, usually by a solvolysis reaction. This physical association may include hydrogen bonding. Conventional solvents include water, methanol, ethanol, acetic acid, DMSO, THF, diethyl ether, and the like. The compounds described herein may be prepared, *e.g.*, in crystalline form, and may be solvated. Suitable solvates include pharmaceutically acceptable solvates and further include both stoichiometric solvates and non-stoichiometric solvates. In certain instances, the solvate will be capable of isolation, for example, when one or more solvent molecules are incorporated in the crystal lattice of a crystalline solid. “Solvate” encompasses both solution-phase and isolatable solvates. Representative solvates include hydrates, ethanolates, and methanolates.

[0082] The term “hydrate” refers to a compound that is associated with water. Typically, the number of the water molecules contained in a hydrate of a compound is in a definite ratio to the number of the compound molecules in the hydrate. Therefore, a hydrate of a compound may be represented, for example, by the general formula $R \cdot x \text{ H}_2\text{O}$, wherein R is the compound, and x is a number greater than 0. A given compound may form more than one type of hydrate, including, *e.g.*, monohydrates (x is 1), lower hydrates (x is a number greater than 0 and smaller than 1, *e.g.*, hemihydrates ($R \cdot 0.5 \text{ H}_2\text{O}$)), and polyhydrates (x is a number greater than 1, *e.g.*, dihydrates ($R \cdot 2 \text{ H}_2\text{O}$) and hexahydrates ($R \cdot 6 \text{ H}_2\text{O}$)).

[0083] The term “polymorph” refers to a crystalline form of a compound (or a salt, hydrate, or solvate thereof). All polymorphs have the same elemental composition. Different crystalline forms usually have different X-ray diffraction patterns, infrared spectra, melting points, density, hardness, crystal shape, optical and electrical properties, stability, and solubility. Recrystallization solvent, rate of crystallization, storage temperature, and other factors may cause one crystal form to dominate. Various polymorphs of a compound can be prepared by crystallization under different conditions.

[0084] The term “co-crystal” refers to a crystalline structure comprising at least two different components (*e.g.*, a compound and an acid), wherein each of the components is independently an atom, ion, or molecule. In certain embodiments, none of the components is a solvent. In certain embodiments, at least one of the components is a solvent. A co-crystal of a compound and an acid is different from a salt formed from a compound and the acid. In the salt, a compound is complexed with the acid in a way that proton transfer (*e.g.*, a complete proton transfer) from the acid to a compound easily occurs at room temperature. In the co-crystal, however, a compound is complexed with the acid in a way that proton transfer from the acid to a herein does not easily occur at room temperature. In certain embodiments, in the co-crystal, there is substantially no proton transfer from the acid to a compound. In certain embodiments, in the co-crystal, there is partial proton transfer from the acid to a compound. Co-crystals may be useful to improve the properties (*e.g.*, solubility, stability, and ease of formulation) of a compound.

[0085] The term “tautomers” or “tautomeric” refers to two or more interconvertible compounds resulting from at least one formal migration of a hydrogen atom and at least one change in valency (*e.g.*, a single bond to a double bond, a triple bond to a single bond, or *vice versa*). The exact ratio of the tautomers depends on several factors, including temperature, solvent, and pH. Tautomerizations (*i.e.*, the reaction providing a tautomeric pair) may catalyzed by acid or base. Exemplary tautomerizations include keto-to-enol, amide-to-imide, lactam-to-lactim, enamine-to-imine, and enamine-to-(a different enamine) tautomerizations.

[0086] Compounds that have the same molecular formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space are termed “isomers.” Isomers that differ in the arrangement of their atoms in space are termed “stereoisomers.”

[0087] Stereoisomers that are not mirror images of one another are termed “diastereomers,” and those that are non-superimposable mirror images of each other are termed “enantiomers.” When a compound has an asymmetric center, for example, it is bonded to four different groups, a pair of enantiomers is possible. An enantiomer can be characterized by the absolute configuration of its asymmetric center and is described by the R- and S-sequencing rules of Cahn and Prelog, or by the manner in which the molecule rotates the plane of polarized light and designated as dextrorotatory or levorotatory (*i.e.*, as (+) or (-)-isomers respectively). A chiral compound can exist as either individual enantiomer or as a mixture thereof. A mixture containing equal proportions of the enantiomers is called a “racemic mixture.”

[0088] The term “isotopically labeled compound” refers to a derivative of a compound that only structurally differs from the compound in that at least one atom of the derivative includes at least one

isotope enriched above (*e.g.*, enriched 3-, 10-, 30-, 100-, 300-, 1,000-, 3,000- or 10,000-fold above) its natural abundance, whereas each atom of the compound includes isotopes at their natural abundances. In certain embodiments, the isotope enriched above its natural abundance is ^2H . In certain embodiments, the isotope enriched above its natural abundance is ^{13}C , ^{15}N , or ^{18}O .

[0089] The term “prodrugs” refers to compounds that have cleavable groups and become by solvolysis or under physiological conditions the compounds described herein, which are pharmaceutically active *in vivo*. Such examples include choline ester derivatives and the like, N-alkylmorpholine esters and the like. Other derivatives of the compounds described herein have activity in both their acid and acid derivative forms, but in the acid sensitive form often offer advantages of solubility, tissue compatibility, or delayed release in the mammalian organism (see, Bundgaard, H., *Design of Prodrugs*, pp. 7-9, 21-24, Elsevier, Amsterdam 1985). Prodrugs include, for example, esters prepared by reaction of the parent acid with a suitable alcohol, or amides prepared by reaction of the parent acid compound with a substituted or unsubstituted amine, or acid anhydrides, or mixed anhydrides.

[0090] The terms “pharmaceutical composition,” “composition,” and “formulation” are used interchangeably.

[0091] A “subject” to which administration is contemplated refers to a human (*i.e.*, male or female of any age group, *e.g.*, pediatric subject (*e.g.*, infant, child, or adolescent) or adult subject (*e.g.*, young adult, middle-aged adult, or senior adult)) or non-human animal. In certain embodiments, the non-human animal is a mammal (*e.g.*, primate (*e.g.*, cynomolgus monkey or rhesus monkey), commercially relevant mammal (*e.g.*, cattle, pig, horse, sheep, goat, cat, or dog), or bird (*e.g.*, commercially relevant bird, such as chicken, duck, goose, or turkey)). In certain embodiments, the non-human animal is a fish, reptile, or amphibian. The non-human animal may be a male or female at any stage of development. The non-human animal may be a transgenic animal or genetically engineered animal. The term “patient” refers to a human subject in need of treatment of a disease.

[0092] The term “biological sample” refers to any sample including tissue samples (such as tissue sections and needle biopsies of a tissue); cell samples (*e.g.*, cytological smears (such as Pap or blood smears) or samples of cells obtained by microdissection); samples of whole organisms (such as samples of yeasts or bacteria); or cell fractions, fragments or organelles (such as obtained by lysing cells and separating the components thereof by centrifugation or otherwise). Other examples of biological samples include blood, serum, urine, semen, fecal matter, cerebrospinal fluid, interstitial fluid, mucous, tears, sweat, pus, biopsied tissue (*e.g.*, obtained by a surgical biopsy or needle biopsy), nipple aspirates, milk, vaginal fluid, saliva, swabs (such as buccal swabs), or any material containing biomolecules that is derived from a first biological sample.

[0093] The term “administer,” “administering,” or “administration” refers to implanting, absorbing, ingesting, injecting, inhaling, or otherwise introducing a compound described herein, or a pharmaceutical composition thereof, in or on a subject.

[0094] The terms “treatment,” “treat,” and “treating” refer to reversing, alleviating, delaying the onset of, or inhibiting the progress of a disease described herein. In some embodiments, treatment may be

administered after one or more signs or symptoms of the disease have developed or have been observed. In other embodiments, treatment may be administered in the absence of signs or symptoms of the disease. For example, treatment may be administered to a susceptible subject prior to the onset of symptoms (*e.g.*, in light of a history of symptoms and/or in light of exposure to a pathogen). Treatment may also be continued after symptoms have resolved, for example, to delay or prevent recurrence.

[0095] The term “prevent,” “preventing,” or “prevention” refers to a prophylactic treatment of a subject who is not and was not with a disease but is at risk of developing the disease or who was with a disease, is not with the disease, but is at risk of regression of the disease. In certain embodiments, the subject is at a higher risk of developing the disease or at a higher risk of regression of the disease than an average healthy member of a population. In some embodiments, the subject is at risk of developing a disease or condition due to environmental factors (*e.g.*, exposure to the sun).

[0096] The terms “condition,” “disease,” and “disorder” are used interchangeably.

[0097] An “effective amount” of a compound described herein refers to an amount sufficient to elicit the desired biological response. An effective amount of a compound described herein may vary depending on such factors as the desired biological endpoint, severity of side effects, disease, or disorder, the identity, pharmacokinetics, and pharmacodynamics of the particular compound, the condition being treated, the mode, route, and desired or required frequency of administration, the species, age and health or general condition of the subject. In certain embodiments, an effective amount is a therapeutically effective amount. In certain embodiments, an effective amount is a prophylactic treatment. In certain embodiments, an effective amount is the amount of a compound described herein in a single dose. In certain embodiments, an effective amount is the combined amounts of a compound described herein in multiple doses. In certain embodiments, the desired dosage is delivered three times a day, two times a day, once a day, every other day, every third day, every week, every two weeks, every three weeks, or every four weeks. In certain embodiments, the desired dosage is delivered using multiple administrations (*e.g.*, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or more administrations).

[0098] In certain embodiments, an effective amount of a compound for administration one or more times a day to a 70 kg adult human comprises about 0.0001 mg to about 3000 mg, about 0.0001 mg to about 2000 mg, about 0.0001 mg to about 1000 mg, about 0.001 mg to about 1000 mg, about 0.01 mg to about 1000 mg, about 0.1 mg to about 1000 mg, about 1 mg to about 1000 mg, about 1 mg to about 100 mg, about 10 mg to about 1000 mg, or about 100 mg to about 1000 mg, of a compound per unit dosage form.

[0099] It will be appreciated that dose ranges as described herein provide guidance for the administration of provided pharmaceutical compositions to an adult. The amount to be administered to, for example, a child or an adolescent can be determined by a medical practitioner or person skilled in the art and can be lower or the same as that administered to an adult.

[0100] A “therapeutically effective amount” of a compound described herein is an amount sufficient to provide a therapeutic benefit in the treatment of a condition or to delay or minimize one or more symptoms associated with the condition. A therapeutically effective amount of a compound means an amount of therapeutic agent, alone or in combination with other therapies, which provides a therapeutic

benefit in the treatment of the condition. The term “therapeutically effective amount” can encompass an amount that improves overall therapy, reduces or avoids symptoms, signs, or causes of the condition, and/or enhances the therapeutic efficacy of another therapeutic agent. In certain embodiments, a therapeutically effective amount is an amount sufficient for treating a disease or disorder associated with associated with peroxisome proliferator-activated receptor γ (PPAR γ) (*e.g.*, progressive bone disease, proliferative disease, metabolic disease) in a subject in need thereof. In certain embodiments, a therapeutically effective amount is an amount sufficient for treating a disease or disorder associated with peroxisome proliferator-activated receptor γ (PPAR γ) (*e.g.*, progressive bone disease, proliferative disease, metabolic disease) in a subject in need thereof, wherein side effects (*e.g.*, weight gain, edema, impairment of bone growth or formation, cardiac hypertrophy, congestive heart failure, vascular leak syndrome, hepatotoxicity) experienced by the subject are reduced compared with administration of a PPAR γ agonist. In certain embodiments, a therapeutically effective amount is an amount sufficient for modulating (*e.g.*, upregulating, downregulating, increasing, decreasing) PPAR γ in a subject in need thereof or in a cell, tissue, or biological sample (*e.g.*, by at least about 10%, at least about 20%, at least about 30%, at least about 40%, 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 98%, at least about 99%, or at least about 100%). In certain embodiments, a therapeutically effective amount is an amount sufficient for acting as an antagonist PPAR γ in a subject in need thereof or in a cell, tissue, or biological sample (*e.g.*, by at least about 10%, at least about 20%, at least about 30%, at least about 40%, 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 98%, at least about 99%, or at least about 100%). In certain embodiments, a therapeutically effective amount is an amount sufficient for acting as an inverse agonist of PPAR γ in a subject in need thereof or in a cell, tissue, or biological sample (*e.g.*, by at least about 10%, at least about 20%, at least about 30%, at least about 40%, 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 98%, at least about 99%, or at least about 100%). In certain embodiments, a therapeutically effective amount is an amount not sufficient for activating PPAR γ . In certain embodiments, a therapeutically effective amount is an amount sufficient for reducing phosphorylation of PPAR γ at serine 273 (*e.g.*, by at least about 10%, at least about 20%, at least about 30%, at least about 40%, 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 98%, at least about 99%, or at least about 100%). In certain embodiments, a therapeutically effective amount is an amount sufficient for normalizing the functional remodeling activities of osteocytes, osteoblasts, and/or osteoclasts to result in healthy bone structure and/or strength. In certain embodiments, the functional remodeling activities are measured by increased bone cortical area, lower bone marrow adiposity, increased bone material strength, and/or increased bone turnover markers and circulating osteoprogenitors. *See, e.g.*, L. A. Stechschulte *et al.*, *EBioMedicine* **2016**, 10, 174-184. In certain embodiments, a therapeutically effective amount is an amount sufficient for decreasing marrow adiposity (*e.g.*, by at least about 10%, at least about 20%, at least about 30%, at least about 40%, 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 98%, at least about 99%, or at least about 100%). In certain embodiments, a therapeutically effective amount is an amount sufficient for increasing trabecular and/or cortical bone (*e.g.*, by at least about 10%, at least about 20%, at least about 30%, at least about 40%, 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 98%, at least about 99%, or at least about 100%). In certain embodiments, a therapeutically effective amount is an amount sufficient for improving metabolic parameters by reducing fasting plasma glucose into a normal range less than 100 mg/dl and HbA1c less than 6%.

[0101] A “prophylactically effective amount” of a compound is an amount sufficient to prevent a condition, or one or more signs and/or symptoms associated with the condition or prevent its recurrence. In certain embodiments, the prophylactically effective amount is an amount that improves overall prophylaxis and/or enhances the prophylactic efficacy of another prophylactic agent. In certain embodiments, a prophylactically effective amount is an amount sufficient for preventing a disease or disorder associated with peroxisome proliferator-activated receptor γ (PPAR γ) (*e.g.*, progressive bone disease, proliferative disease, metabolic disease) in a subject in need thereof. In certain embodiments, a prophylactically effective amount is an amount effective for reducing the risk of developing a disease or disorder associated with peroxisome proliferator-activated receptor γ (PPAR γ) (*e.g.*, progressive bone disease, proliferative disease, metabolic disease) in a subject in need thereof. In certain embodiments, a prophylactically effective amount is an amount sufficient for preventing or reducing the risk of developing a disease or disorder associated with peroxisome proliferator-activated receptor γ (PPAR γ) (*e.g.*, progressive bone disease, proliferative disease, metabolic disease) in a subject in need thereof, wherein side effects (*e.g.*, weight gain, edema, impairment of bone growth or formation, cardiac hypertrophy, congestive heart failure, vascular leak syndrome, hepatotoxicity) experienced by the subject are reduced compared with administration of a PPAR γ agonist. In certain embodiments, a prophylactically effective amount is an amount sufficient for modulating (*e.g.*, upregulating, downregulating, increasing, decreasing) PPAR γ in a subject in need thereof or in a cell, tissue, or biological sample (*e.g.*, by at least about 10%, at least about 20%, at least about 30%, at least about 40%, 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 98%, at least about 99%, or at least about 100%). In certain embodiments, a prophylactically effective amount is an amount sufficient for acting as an antagonist PPAR γ in a subject in need thereof or in a cell, tissue, or biological sample (*e.g.*, by at least about 10%, at least about 20%, at least about 30%, at least about 40%, 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 98%, at least about 99%, or at least about 100%). In certain embodiments, a prophylactically effective amount is an amount sufficient for acting as an inverse agonist of PPAR γ in a subject in need thereof or in a cell, tissue, or biological sample (*e.g.*, by at least about 10%, at least about 20%, at least about 30%, at least about 40%, 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 98%, at least about 99%, or at least about 100%). In certain embodiments, a prophylactically effective amount is an amount not sufficient for activating PPAR γ . In certain embodiments, a prophylactically effective amount is an amount sufficient for

reducing phosphorylation of PPAR γ at serine 273 (*e.g.*, by at least about 10%, at least about 20%, at least about 30%, at least about 40%, 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 98%, at least about 99%, or at least about 100%). In certain embodiments, a prophylactically effective amount is an amount sufficient for normalizing the functional remodeling activities of osteocytes, osteoblasts, and/or osteoclasts to result in healthy bone structure and/or strength. In certain embodiments, the functional remodeling activities are measured by increased bone cortical area, lower bone marrow adiposity, increased bone material strength, and/or increased bone turnover markers and circulating osteoprogenitors. *See, e.g.*, L. A. Stechschulte *et al.*, *EBioMedicine* **2016**, 10, 174-184.

[0102] In certain embodiments, a prophylactically effective amount is an amount sufficient for decreasing marrow adiposity (*e.g.*, by at least about 10%, at least about 20%, at least about 30%, at least about 40%, 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 98%, at least about 99%, or at least about 100%). In certain embodiments, a prophylactically effective amount is an amount sufficient for increasing trabecular and/or cortical bone (*e.g.*, by at least about 10%, at least about 20%, at least about 30%, at least about 40%, 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 98%, at least about 99%, or at least about 100%). In certain embodiments, a prophylactically effective amount is an amount sufficient for improving metabolic parameters by reducing fasting plasma glucose into a normal range less than 100 mg/dl and HbA1c less than 6%.

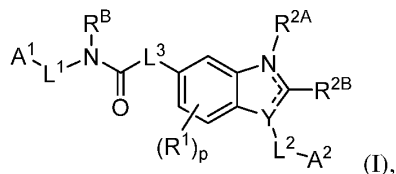
[0103] The terms “metabolic disease” and “metabolic disorder” refer to any disorder that involves an alteration in the normal metabolism of carbohydrates, lipids, proteins, nucleic acids, or a combination thereof. A metabolic disorder is associated with either a deficiency or excess in a metabolic pathway resulting in an imbalance in metabolism of nucleic acids, proteins, lipids, and/or carbohydrates. Factors affecting metabolism include, and are not limited to, the endocrine (hormonal) control system (*e.g.*, the insulin pathway, the enteroendocrine hormones including GLP-1, PYY or the like), the neural control system (*e.g.*, GLP-1 in the brain), or the like. Examples of metabolic disorders include, but are not limited to, diabetes (*e.g.*, Type I diabetes, Type II diabetes, gestational diabetes), hyperglycemia, hyperinsulinemia, insulin resistance, hypertriglyceridemia, metabolic syndrome, hyperinsulinemia, acidemia, and obesity. In some embodiments, the metabolic disease is obesity, hypertriglyceridemia, metabolic syndrome, insulin resistance, hyperinsulinemia, diabetes, or acidemia.

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS

[0104] The aspects described herein are not limited to specific embodiments, systems, compositions, methods, or configurations, and as such can, of course, vary. The terminology used herein is for the purpose of describing particular aspects only and, unless specifically defined herein, is not intended to be limiting.

Compounds

[0105] In one aspect, the present disclosure provides a compound of Formula (I):



or a pharmaceutically acceptable salt or prodrug thereof, wherein:

A¹ is substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

A² is substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl;

each of L¹, L², and L³ is independently a bond or substituted or unsubstituted alkylene;

Y is C or N;

each occurrence of R¹ is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroalkenyl, substituted or unsubstituted heteroalkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -CN, -OR^A, -SCN, -SR^A, -SSR^A, -N₃, -NO, -N(R^A)₂, -NO₂, -C(=O)R^A, -C(=O)OR^A, -C(=O)SR^A, -C(=O)N(R^A)₂, -C(=NR^A)R^A, -C(=NR^A)OR^A, -C(=NR^A)SR^A, -C(=NR^A)N(R^A)₂, -S(=O)R^A, -S(=O)OR^A, -S(=O)SR^A, -S(=O)N(R^A)₂, -S(=O)₂R^A, -S(=O)₂OR^A, -S(=O)₂SR^A, -S(=O)₂N(R^A)₂, -OC(=O)R^A, -OC(=O)OR^A, -OC(=O)SR^A, -OC(=O)N(R^A)₂, -OC(=NR^A)R^A, -OC(=NR^A)OR^A, -OC(=NR^A)SR^A, -OC(=NR^A)N(R^A)₂, -OS(=O)R^A, -OS(=O)OR^A, -OS(=O)SR^A, -OS(=O)N(R^A)₂, -OS(=O)₂R^A, -OS(=O)₂OR^A, -OS(=O)₂SR^A, -OS(=O)₂N(R^A)₂, -ON(R^A)₂, -SC(=O)R^A, -SC(=O)OR^A, -SC(=O)SR^A, -SC(=O)N(R^A)₂, -SC(=NR^A)R^A, -SC(=NR^A)OR^A, -SC(=NR^A)SR^A, -SC(=NR^A)N(R^A)₂, -NR^AC(=O)R^A, -NR^AC(=O)OR^A, -NR^AC(=O)SR^A, -NR^AC(=O)N(R^A)₂, -NR^AC(=NR^A)R^A, -NR^AC(=NR^A)OR^A, -NR^AC(=NR^A)SR^A, -NR^AC(=NR^A)N(R^A)₂, -NR^AS(=O)R^A, -NR^AS(=O)OR^A, -NR^AS(=O)SR^A, -NR^AS(=O)N(R^A)₂, -NR^AS(=O)₂R^A, -NR^AS(=O)₂OR^A, -NR^AS(=O)₂SR^A, -NR^AS(=O)₂N(R^A)₂, -Si(R^A)₃, -Si(R^A)₂OR^A, -Si(R^A)(OR^A)₂, -Si(OR^A)₃, -OSi(R^A)₃, -OSi(R^A)₂OR^A, -OSi(R^A)(OR^A)₂, -OSi(OR^A)₃, or -B(OR^A)₂;

R^{2A} is absent, hydrogen, substituted or unsubstituted alkyl, or a nitrogen protecting group, provided that when Y is N, R^{2A} is absent;

R^{2B} is hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroalkenyl, substituted or unsubstituted heteroalkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -CN, -OR^A, -SCN, -SR^A, -SSR^A, -N₃, -NO, -N(R^A)₂, -NO₂, -C(=O)R^A, -C(=O)OR^A, -C(=O)SR^A, -C(=O)N(R^A)₂, -C(=NR^A)R^A, -C(=NR^A)OR^A, -C(=NR^A)SR^A, -C(=NR^A)N(R^A)₂, -S(=O)R^A, -S(=O)OR^A, -S(=O)SR^A, -S(=O)N(R^A)₂, -S(=O)₂R^A, -S(=O)₂OR^A, -S(=O)₂SR^A, -S(=O)₂N(R^A)₂, -

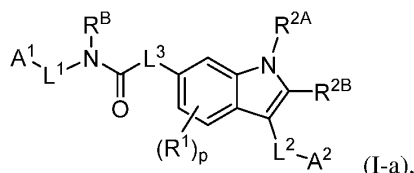
OC(=O)R^A, -OC(=O)OR^A, -OC(=O)SR^A, -OC(=O)N(R^A)₂, -OC(=NR^A)R^A, -OC(=NR^A)OR^A, -OC(=NR^A)SR^A, -OC(=NR^A)N(R^A)₂, -OS(=O)R^A, -OS(=O)OR^A, -OS(=O)SR^A, -OS(=O)N(R^A)₂, -OS(=O)₂R^A, -OS(=O)₂OR^A, -OS(=O)₂SR^A, -OS(=O)₂N(R^A)₂, -ON(R^A)₂, -SC(=O)R^A, -SC(=O)OR^A, -SC(=O)SR^A, -SC(=O)N(R^A)₂, -SC(=NR^A)R^A, -SC(=NR^A)OR^A, -SC(=NR^A)SR^A, -SC(=NR^A)N(R^A)₂, -NR^AC(=O)R^A, -NR^AC(=O)OR^A, -NR^AC(=O)SR^A, -NR^AC(=O)N(R^A)₂, -NR^AC(=NR^A)R^A, -NR^AC(=NR^A)OR^A, -NR^AC(=NR^A)SR^A, -NR^AC(=NR^A)N(R^A)₂, -NR^AS(=O)R^A, -NR^AS(=O)OR^A, -NR^AS(=O)SR^A, -NR^AS(=O)N(R^A)₂, -NR^AS(=O)₂R^A, -NR^AS(=O)₂OR^A, -NR^AS(=O)₂SR^A, -NR^AS(=O)₂N(R^A)₂, -Si(R^A)₃, -Si(R^A)₂OR^A, -Si(R^A)(OR^A)₂, -Si(OR^A)₃, -OSi(R^A)₃, -OSi(R^A)₂OR^A, -OSi(R^A)(OR^A)₂, -OSi(OR^A)₃, or -B(OR^A)₂;

each occurrence of R^A is independently hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroalkenyl, substituted or unsubstituted heteroalkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, a nitrogen protecting group when attached to a nitrogen atom, an oxygen protecting group when attached to an oxygen atom, or a sulfur protecting group when attached to a sulfur atom, or two occurrences of R^A are joined together with their intervening atom(s) to form an substituted or unsubstituted heterocyclic ring or substituted or unsubstituted heteroaryl ring;

R^B is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted acyl, or a nitrogen protecting group; and

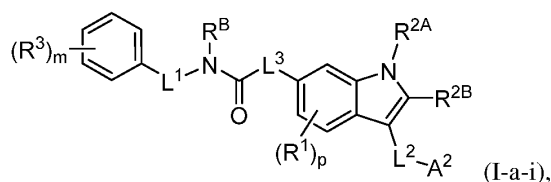
p is 0, 1, 2, or 3.

[0106] In certain embodiments, the compound of Formula (I) is of Formula (I-a):



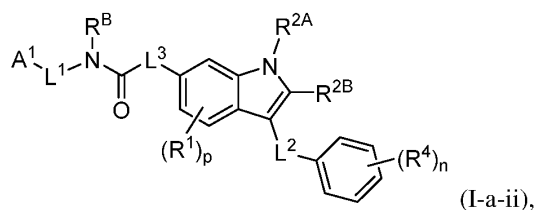
or a pharmaceutically acceptable salt or prodrug thereof.

[0107] In certain embodiments, the compound of Formula (I) is of Formula (I-a-i):



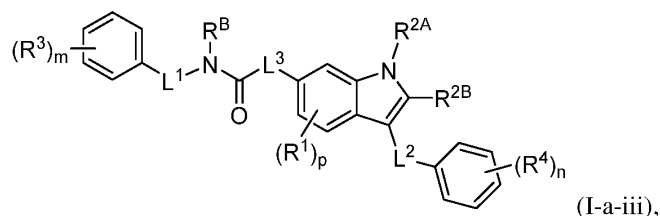
or a pharmaceutically acceptable salt or prodrug thereof.

[0108] In certain embodiments, the compound of Formula (I) is of Formula (I-a-ii):



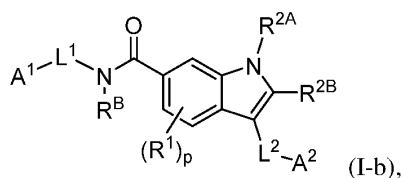
or a pharmaceutically acceptable salt or prodrug thereof.

[0109] In certain embodiments, the compound of Formula (I) is of Formula (I-a-iii):



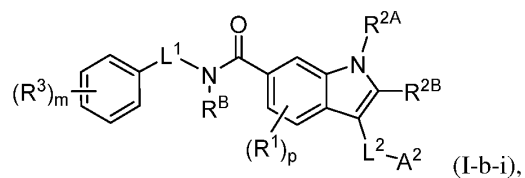
or a pharmaceutically acceptable salt or prodrug thereof.

[0110] In certain embodiments, the compound of Formula (I) is of Formula (I-b):



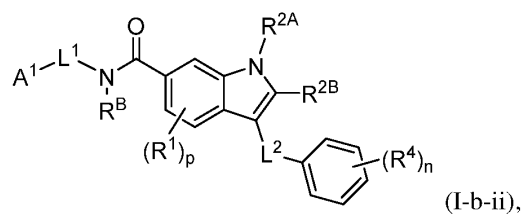
or a pharmaceutically acceptable salt or prodrug thereof.

[0111] In certain embodiments, the compound of Formula (I) is of Formula (I-b-i):



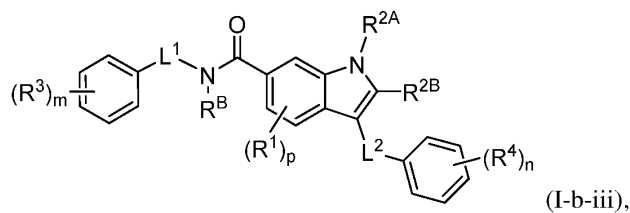
or a pharmaceutically acceptable salt or prodrug thereof.

[0112] In certain embodiments, the compound of Formula (I) is of Formula (I-b-ii):



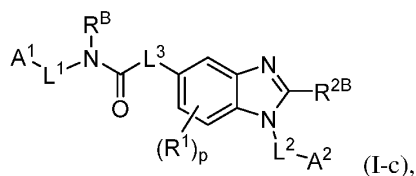
or a pharmaceutically acceptable salt or prodrug thereof.

[0113] In certain embodiments, the compound of Formula (I) is of Formula (I-b-iii):



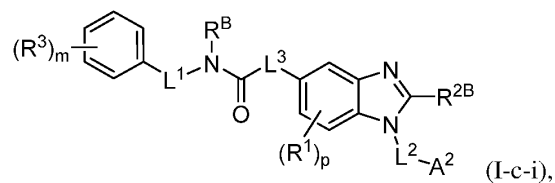
or a pharmaceutically acceptable salt or prodrug thereof.

[0114] In certain embodiments, the compound of Formula (I) is of Formula (I-c):



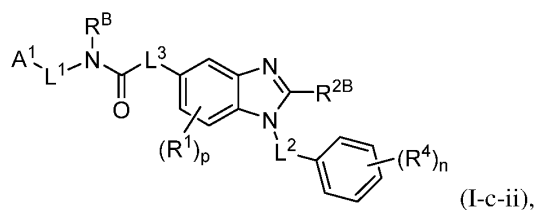
or a pharmaceutically acceptable salt or prodrug thereof.

[0115] In certain embodiments, the compound of Formula (I) is of Formula (I-c-i):



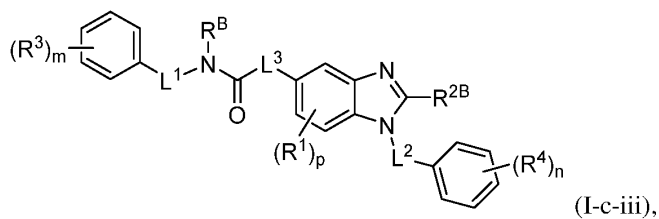
or a pharmaceutically acceptable salt or prodrug thereof.

[0116] In certain embodiments, the compound of Formula (I) is of Formula (I-c-ii):



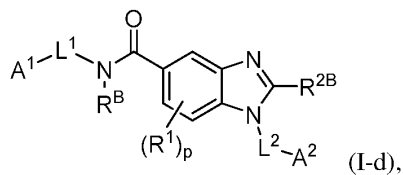
or a pharmaceutically acceptable salt or prodrug thereof.

[0117] In certain embodiments, the compound of Formula (I) is of Formula (I-c-iii):



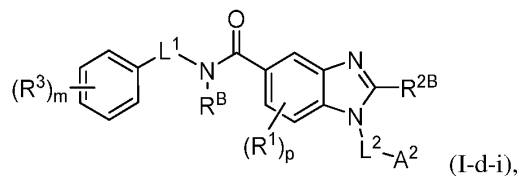
or a pharmaceutically acceptable salt or prodrug thereof.

[0118] In certain embodiments, the compound of Formula (I) is of Formula (I-d):



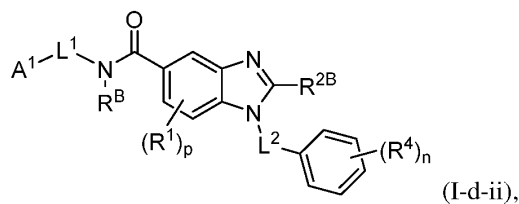
or a pharmaceutically acceptable salt or prodrug thereof.

[0119] In certain embodiments, the compound of Formula (I) is of Formula (I-d-i):



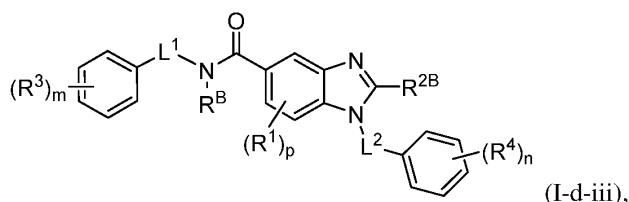
or a pharmaceutically acceptable salt or prodrug thereof.

[0120] In certain embodiments, the compound of Formula (I) is of Formula (I-d-ii):



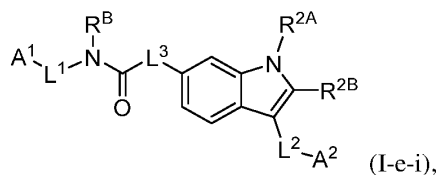
or a pharmaceutically acceptable salt or prodrug thereof.

[0121] In certain embodiments, the compound of Formula (I) is of Formula (I-d-iii):



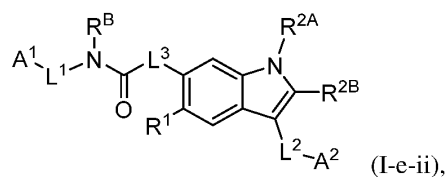
or a pharmaceutically acceptable salt or prodrug thereof.

[0122] In certain embodiments, the compound of Formula (I) is of Formula (I-e-i):



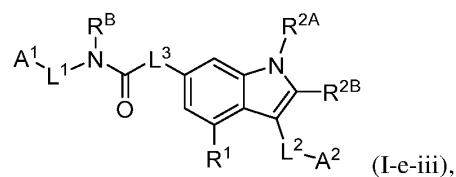
or a pharmaceutically acceptable salt or prodrug thereof.

[0123] In certain embodiments, the compound of Formula (I) is of Formula (I-e-ii):



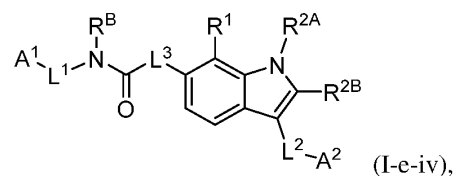
or a pharmaceutically acceptable salt or prodrug thereof.

[0124] In certain embodiments, the compound of Formula (I) is of Formula (I-e-iii):



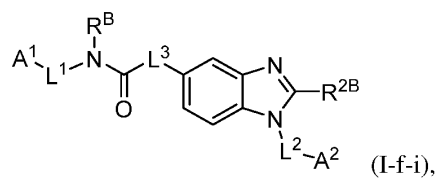
or a pharmaceutically acceptable salt or prodrug thereof.

[0125] In certain embodiments, the compound of Formula (I) is of Formula (I-e-iv):



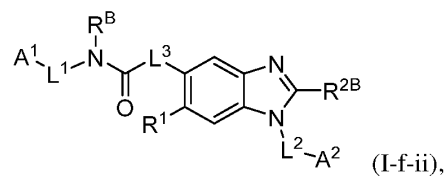
or a pharmaceutically acceptable salt or prodrug thereof.

[0126] In certain embodiments, the compound of Formula (I) is of Formula (I-f-i):



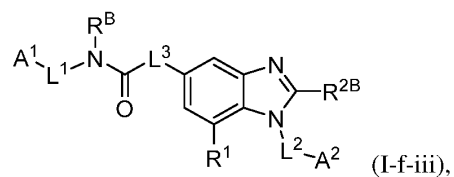
or a pharmaceutically acceptable salt or prodrug thereof.

[0127] In certain embodiments, the compound of Formula (I) is of Formula (I-f-ii):



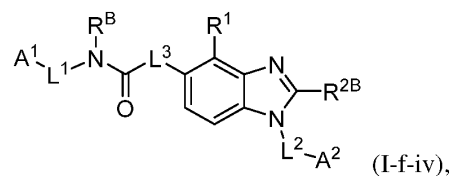
or a pharmaceutically acceptable salt or prodrug thereof.

[0128] In certain embodiments, the compound of Formula (I) is of Formula (I-f-iii):



or a pharmaceutically acceptable salt or prodrug thereof.

[0129] In certain embodiments, the compound of Formula (I) is of Formula (I-f-iv):



or a pharmaceutically acceptable salt or prodrug thereof.

A¹

[0130] In certain embodiments, A¹ is substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0131] In certain embodiments, A¹ is substituted or unsubstituted carbocyclyl. In certain embodiments, A¹ is substituted or unsubstituted, monocyclic carbocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 3- to 10-membered carbocyclyl). In certain embodiments, A¹ is substituted or unsubstituted, polycyclic carbocyclyl (*e.g.*, substituted or unsubstituted, bicyclic or tricyclic, 3- to 14-membered carbocyclyl). In certain embodiments, A¹ is substituted or unsubstituted saturated carbocyclyl. In certain embodiments, A¹ is substituted or unsubstituted cyclopropyl, substituted or unsubstituted cyclobutyl, substituted or unsubstituted cyclopentyl, substituted or unsubstituted cyclohexyl, substituted or unsubstituted cycloheptyl, substituted or unsubstituted cyclooctyl, substituted or unsubstituted cyclononyl, or substituted or unsubstituted cyclodecyl. In certain embodiments, A¹ is substituted carbocyclyl. In certain embodiments, A¹ is substituted saturated carbocyclyl. In certain embodiments, A¹ is substituted cyclopropyl, substituted cyclobutyl, substituted cyclopentyl, substituted cyclohexyl, substituted cycloheptyl, substituted cyclooctyl, substituted cyclononyl, or substituted cyclodecyl.

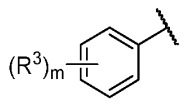
[0132] In certain embodiments, A¹ is substituted or unsubstituted heterocyclyl. In certain embodiments, A¹ is substituted or unsubstituted, monocyclic heterocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 3- to 10-membered heterocyclyl). In certain embodiments, A¹ is substituted or unsubstituted, polycyclic heterocyclyl (*e.g.*, substituted or unsubstituted, bicyclic or tricyclic, 3- to 14-membered heterocyclyl). In certain embodiments, A¹ is substituted or unsubstituted saturated heterocyclyl. In certain embodiments, A¹ is substituted or unsubstituted azirdinyl, substituted or unsubstituted oxiranyl, substituted or unsubstituted thiiiranyl, substituted or unsubstituted azetidyl, substituted or unsubstituted oxetanyl, substituted or unsubstituted thietanyl, substituted or unsubstituted tetrahydrofuranyl, substituted or unsubstituted dihydrofuranyl, substituted or unsubstituted tetrahydrothiophenyl, substituted or unsubstituted dihydrothiophenyl, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted dihydropyrrolyl, substituted or unsubstituted pyrrolyl-2,5-dione, substituted or unsubstituted dioxolanyl, substituted or unsubstituted oxathiolanyl, substituted or unsubstituted dithiolanyl, substituted or unsubstituted triazolanyl, substituted or unsubstituted oxadiazolanyl, substituted or unsubstituted thiadiazolanyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted tetrahydropyranlyl, substituted or unsubstituted dihydropyridinyl, substituted or unsubstituted thianyl, substituted or unsubstituted piperazinyl, substituted or unsubstituted morpholinyl, substituted or unsubstituted dithianyl, substituted or unsubstituted dioxanyl, substituted or unsubstituted triazinyl, substituted or unsubstituted azepanyl, substituted or unsubstituted oxepanyl, substituted or unsubstituted thiepanyl, substituted or unsubstituted azocanyl, substituted or unsubstituted oxecanyl, substituted or unsubstituted thiocanyl, substituted or unsubstituted indolinyl, substituted or unsubstituted isoindolinyl, substituted or unsubstituted dihydrobenzofuranyl, substituted or unsubstituted dihydrobenzothieryl, substituted or unsubstituted tetrahydrobenzothieryl, substituted or unsubstituted tetrahydrobenzofuranyl, substituted or unsubstituted tetrahydroindolyl, substituted or unsubstituted tetrahydroquinolyl, substituted or unsubstituted

tetrahydroisoquinoliny], substituted or unsubstituted decahydroquinoliny], substituted or unsubstituted decahydroisoquinoliny], substituted or unsubstituted octahydrochromenyl, substituted or unsubstituted octahydroisochromenyl, substituted or unsubstituted decahydronaphthyridiny], substituted or unsubstituted decahydro-1,8-naphthyridiny], substituted or unsubstituted octahydropyrrolo[3,2-b]pyrrole, substituted or unsubstituted indoliny], substituted or unsubstituted phthalimidyl, substituted or unsubstituted naphthalimidyl, substituted or unsubstituted chromanyl, substituted or unsubstituted chromenyl, substituted or unsubstituted 1H-benzo[e][1,4]diazepiny], substituted or unsubstituted 1,4,5,7-tetrahydropyrano[3,4-b]pyrroly], substituted or unsubstituted 5,6-dihydro-4H-furo[3,2-b]pyrroly], substituted or unsubstituted 6,7-dihydro-5H-furo[3,2-b]pyranyl, substituted or unsubstituted 5,7-dihydro-4H-thieno[2,3-c]pyranyl, substituted or unsubstituted 2,3-dihydro-1H-pyrrolo[2,3-b]pyridiny], substituted or unsubstituted 2,3-dihydrofuro[2,3-b]pyridiny], substituted or unsubstituted 4,5,6,7-tetrahydro-1H-pyrrolo[2,3-b]pyridiny], substituted or unsubstituted 4,5,6,7-tetrahydrofuro[3,2-c]pyridiny], substituted or unsubstituted 4,5,6,7-tetrahydrothieno[3,2-b]pyridiny], or substituted or unsubstituted 1,2,3,4-tetrahydro-1,6-naphthyridiny]. In certain embodiments, A¹ is substituted heterocyclyl. In certain embodiments, A¹ is substituted saturated heterocyclyl.

[0133] In certain embodiments, A¹ is substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl. In certain embodiments, A¹ is substituted or unsubstituted aryl. In certain embodiments, A¹ is substituted or unsubstituted C₆₋₁₄ aryl. In certain embodiments, A¹ is substituted or unsubstituted phenyl. In certain embodiments, A¹ is substituted phenyl. In certain embodiments, A¹ is phenyl substituted with halogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, -CN, and/or -OR^A. In certain embodiments, A¹ is phenyl substituted with -F, -Cl, -Br, -I, -OMe, -OCF₃, and/or -CN. In certain embodiments, A¹ is phenyl substituted with -F, -Cl, -Br, and/or -I. In certain embodiments, A¹ is phenyl substituted with -OMe, -OCF₃, and/or -CN. In certain embodiments, A¹ is phenyl substituted with substituted or unsubstituted alkyl. In certain embodiments, A¹ is phenyl substituted with substituted or unsubstituted C₁₋₁₂ alkyl. In certain embodiments, A¹ is phenyl substituted with substituted or unsubstituted C₁₋₆ alkyl. In certain embodiments, A¹ is phenyl substituted with unsubstituted C₁₋₆ alkyl. In certain embodiments, A¹ is phenyl substituted with substituted C₁₋₆ alkyl. In certain embodiments, A¹ is phenyl substituted with substituted or unsubstituted methyl, substituted or unsubstituted ethyl, substituted or unsubstituted *n*-propyl, substituted or unsubstituted isopropyl, substituted or unsubstituted *n*-butyl, substituted or unsubstituted *tert*-butyl, substituted or unsubstituted *sec*-butyl, substituted or unsubstituted isobutyl, substituted or unsubstituted *n*-pentyl, substituted or unsubstituted 3-pentanyl, substituted or unsubstituted amyl, substituted or unsubstituted neopentyl, substituted or unsubstituted 3-methyl-2-butanyl, substituted or unsubstituted *tert*-amyl, or substituted or unsubstituted *n*-hexyl. In certain embodiments, A¹ is phenyl substituted with methyl or trifluoromethyl. In certain embodiments, A¹ is phenyl substituted with methyl, trifluoromethyl, ethyl, isopropyl, or *tert*-butyl. In certain embodiments, A¹ is phenyl substituted with substituted or unsubstituted carbocyclyl. In certain embodiments, A¹ is phenyl substituted with C₁₋₆ cycloalkyl. In certain embodiments, A¹ is phenyl substituted with substituted or unsubstituted, monocyclic carbocyclyl (e.g., substituted or unsubstituted, monocyclic, 3- to 10-

membered carbocyclyl). In certain embodiments, A¹ is phenyl substituted with substituted or unsubstituted, polycyclic carbocyclyl (*e.g.*, substituted or unsubstituted, bicyclic or tricyclic, 3- to 14-membered carbocyclyl). In certain embodiments, A¹ is phenyl substituted with substituted or unsubstituted saturated carbocyclyl. In certain embodiments, A¹ is phenyl substituted with substituted or unsubstituted cyclopropyl, substituted or unsubstituted cyclobutyl, substituted or unsubstituted cyclopentyl, substituted or unsubstituted cyclohexyl, substituted or unsubstituted cycloheptyl, substituted or unsubstituted cyclooctyl, substituted or unsubstituted cyclononyl, or substituted or unsubstituted cyclodecyl. In certain embodiments, A¹ is phenyl substituted with substituted or unsubstituted cyclopropyl. In certain embodiments, A¹ is phenyl substituted with substituted cyclopropyl. In certain embodiments, A¹ is phenyl substituted with unsubstituted cyclopropyl. In certain embodiments, A¹ is unsubstituted phenyl.

[0134] In certain embodiments, A¹ is of formula:

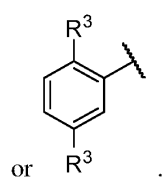
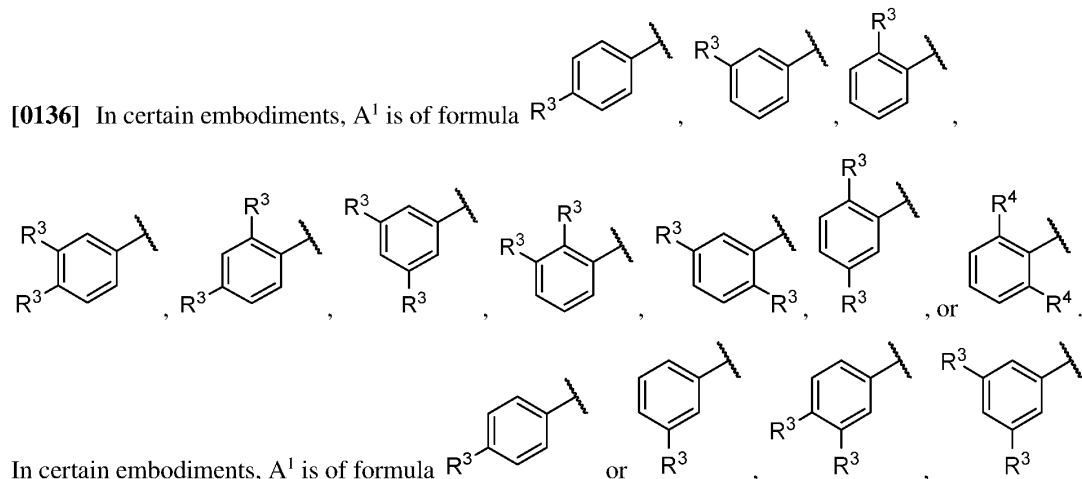


wherein:

each occurrence of R³ is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroalkenyl, substituted or unsubstituted heteroalkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -CN, -OR^A, -SCN, -SR^A, -SSR^A, -N₃, -NO, -N(R^A)₂, -NO₂, -C(=O)R^A, -C(=O)OR^A, -C(=O)SR^A, -C(=O)N(R^A)₂, -C(=NR^A)R^A, -C(=NR^A)OR^A, -C(=NR^A)SR^A, -C(=NR^A)N(R^A)₂, -S(=O)R^A, -S(=O)OR^A, -S(=O)SR^A, -S(=O)N(R^A)₂, -S(=O)₂R^A, -S(=O)₂OR^A, -S(=O)₂SR^A, -S(=O)₂N(R^A)₂, -OC(=O)R^A, -OC(=O)OR^A, -OC(=O)SR^A, -OC(=O)N(R^A)₂, -OC(=NR^A)R^A, -OC(=NR^A)OR^A, -OC(=NR^A)SR^A, -OC(=NR^A)N(R^A)₂, -OS(=O)R^A, -OS(=O)OR^A, -OS(=O)SR^A, -OS(=O)N(R^A)₂, -OS(=O)₂R^A, -OS(=O)₂OR^A, -OS(=O)₂SR^A, -OS(=O)₂N(R^A)₂, -ON(R^A)₂, -SC(=O)R^A, -SC(=O)OR^A, -SC(=O)SR^A, -SC(=O)N(R^A)₂, -SC(=NR^A)R^A, -SC(=NR^A)OR^A, -SC(=NR^A)SR^A, -SC(=NR^A)N(R^A)₂, -NR^AC(=O)R^A, -NR^AC(=O)OR^A, -NR^AC(=O)SR^A, -NR^AC(=O)N(R^A)₂, -NR^AC(=NR^A)R^A, -NR^AC(=NR^A)OR^A, -NR^AC(=NR^A)SR^A, -NR^AC(=NR^A)N(R^A)₂, -NR^AS(=O)R^A, -NR^AS(=O)OR^A, -NR^AS(=O)SR^A, -NR^AS(=O)N(R^A)₂, -NR^AS(=O)₂R^A, -NR^AS(=O)₂OR^A, -NR^AS(=O)₂SR^A, -NR^AS(=O)₂N(R^A)₂, -Si(R^A)₃, -Si(R^A)₂OR^A, -Si(R^A)(OR^A)₂, -Si(OR^A)₃, -OSi(R^A)₂OR^A, -OSi(R^A)(OR^A)₂, -OSi(OR^A)₃, or -B(OR^A)₂; and

m is 0, 1, 2, 3, 4, or 5.

[0135] In certain embodiments, m is 0. In certain embodiments, m is 1. In certain embodiments, m is 2. In certain embodiments, m is 3. In certain embodiments, m is 4. In certain embodiments, m is 5.



[0137] In certain embodiments, at least one occurrence of R³ is halogen. In certain embodiments, at least one occurrence of R³ is substituted or unsubstituted alkyl. In certain embodiments, at least one occurrence of R³ is substituted or unsubstituted alkenyl. In certain embodiments, at least one occurrence of R³ is substituted or unsubstituted alkynyl. In certain embodiments, at least one occurrence of R³ is substituted or unsubstituted heteroalkyl. In certain embodiments, at least one occurrence of R³ is substituted or unsubstituted heteroalkenyl. In certain embodiments, at least one occurrence of R³ is substituted or unsubstituted heteroalkynyl. In certain embodiments, at least one occurrence of R³ is substituted or unsubstituted carbocyclyl. In certain embodiments, at least one occurrence of R³ is substituted or unsubstituted heterocyclyl. In certain embodiments, at least one occurrence of R³ is substituted or unsubstituted aryl. In certain embodiments, at least one occurrence of R³ is substituted or unsubstituted heteroaryl. In certain embodiments, at least one occurrence of R³ is -CN. In certain embodiments, at least one occurrence of R³ is -OR^A. In certain embodiments, at least one occurrence of R³ is -SCN. In certain embodiments, at least one occurrence of R³ is -SR^A. In certain embodiments, at least one occurrence of R³ is -SSR^A. In certain embodiments, at least one occurrence of R³ is -N₃. In certain embodiments, at least one occurrence of R³ is -NO. In certain embodiments, at least one occurrence of R³ is -N(R^A)₂. In certain embodiments, at least one occurrence of R³ is -NO₂. In certain embodiments, at least one occurrence of R³ is -C(=O)R^A. In certain embodiments, at least one occurrence of R³ is -C(=O)OR^A. In certain embodiments, at least one occurrence of R³ is -C(=O)SR^A. In certain embodiments, at least one occurrence of R³ is -C(=O)N(R^A)₂. In certain embodiments, at least one occurrence of R³ is -C(=NR^A)R^A. In certain embodiments, at least one occurrence of R³ is -C(=NR^A)OR^A. In certain embodiments, at least one occurrence of R³ is -C(=NR^A)SR^A. In certain embodiments, at least one occurrence of R³ is -C(=NR^A)N(R^A)₂. In certain embodiments, at least one

43

one occurrence of R^3 is $-\text{Si}(\text{OR}^A)_3$. In certain embodiments, at least one occurrence of R^3 is $-\text{OSi}(\text{R}^A)_3$. In certain embodiments, at least one occurrence of R^3 is $-\text{OSi}(\text{R}^A)_2\text{OR}^A$. In certain embodiments, at least one occurrence of R^3 is $-\text{OSi}(\text{R}^A)(\text{OR}^A)_2$. In certain embodiments, at least one occurrence of R^3 is $-\text{OSi}(\text{OR}^A)_3$. In certain embodiments, at least one occurrence of R^3 is $-\text{B}(\text{OR}^A)_2$.

[0138] In certain embodiments, each occurrence of R^3 is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, $-\text{CN}$, or $-\text{OR}^A$. In certain embodiments, at least one occurrence of R^3 is $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{OMe}$, $-\text{OCF}_3$, or $-\text{CN}$. In certain embodiments, at least one occurrence of R^3 is $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, or $-\text{I}$. In certain embodiments, at least one occurrence of R^3 is substituted or unsubstituted alkyl. In certain embodiments, at least one occurrence of R^3 is substituted or unsubstituted C_{1-12} alkyl. In certain embodiments, at least one occurrence of R^3 is substituted or unsubstituted C_{1-6} alkyl. In certain embodiments, at least one occurrence of R^3 is unsubstituted C_{1-6} alkyl. In certain embodiments, at least one occurrence of R^3 is substituted C_{1-6} alkyl. In certain embodiments, at least one occurrence of R^3 is substituted or unsubstituted methyl, substituted or unsubstituted ethyl, substituted or unsubstituted *n*-propyl, substituted or unsubstituted isopropyl, substituted or unsubstituted *n*-butyl, substituted or unsubstituted *tert*-butyl, substituted or unsubstituted *sec*-butyl, substituted or unsubstituted isobutyl, substituted or unsubstituted *n*-pentyl, substituted or unsubstituted 3-pentanyl, substituted or unsubstituted amyl, substituted or unsubstituted neopentyl, substituted or unsubstituted 3-methyl-2-butanyl, substituted or unsubstituted *tert*-amyl, or substituted or unsubstituted *n*-hexyl. In certain embodiments, at least one occurrence of R^3 is methyl or trifluoromethyl. In certain embodiments, at least one occurrence of R^3 is methyl, trifluoromethyl, ethyl, isopropyl, or *tert*-butyl. In certain embodiments, at least one occurrence of R^3 is substituted or unsubstituted carbocyclyl. In certain embodiments, at least one occurrence of R^3 is substituted or unsubstituted C_{1-6} cycloalkyl. In certain embodiments, at least one occurrence of R^3 is substituted or unsubstituted, monocyclic carbocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 3- to 10-membered carbocyclyl). In certain embodiments, at least one occurrence of R^3 is substituted or unsubstituted, polycyclic carbocyclyl (*e.g.*, substituted or unsubstituted, bicyclic or tricyclic, 3- to 14-membered carbocyclyl). In certain embodiments, at least one occurrence of R^3 is substituted or unsubstituted saturated carbocyclyl. In certain embodiments, at least one occurrence of R^3 is substituted or unsubstituted cyclopropyl, substituted or unsubstituted cyclobutyl, substituted or unsubstituted cyclopentyl, substituted or unsubstituted cyclohexyl, substituted or unsubstituted cycloheptyl, substituted or unsubstituted cyclooctyl, substituted or unsubstituted cyclononyl, or substituted or unsubstituted cyclodecyl. In certain embodiments, at least one occurrence of R^3 is substituted or unsubstituted cyclopropyl. In certain embodiments, at least one occurrence of R^3 is substituted cyclopropyl. In certain embodiments, at least one occurrence of R^3 is unsubstituted cyclopropyl.

[0139] In certain embodiments, A^1 is substituted or unsubstituted heteroaryl. In certain embodiments, A^1 is substituted or unsubstituted 5–14 membered heteroaryl. In certain embodiments, A^1 is substituted or unsubstituted monocyclic heteroaryl. In certain embodiments, A^1 is substituted or unsubstituted 5- to 6-membered, monocyclic heteroaryl. In certain embodiments, A^1 is substituted or unsubstituted pyrrolyl,

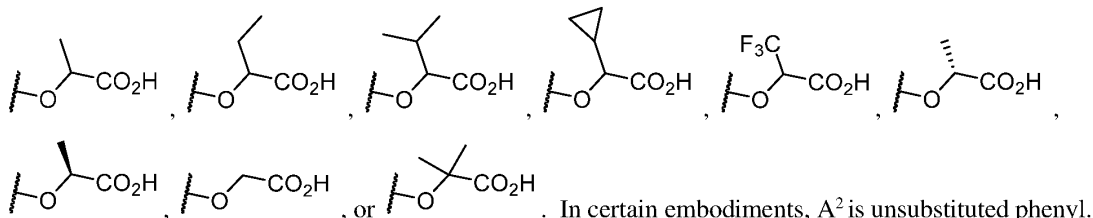
substituted or unsubstituted furanyl, substituted or unsubstituted thiophenyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted triazolyl, substituted or unsubstituted oxadiazolyl, substituted or unsubstituted thiadiazolyl, or substituted or unsubstituted tetrazolyl. In certain embodiments, A¹ is substituted or unsubstituted pyridinyl, substituted or unsubstituted pyridazinyl, substituted or unsubstituted pyrimidinyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted triazinyl, substituted or unsubstituted tetrazinyl, substituted or unsubstituted oxepinyl, or substituted or unsubstituted thiepinyl. In certain embodiments, A¹ is substituted or unsubstituted bicyclic heteroaryl (*e.g.* substituted or unsubstituted bicyclic, 9- or 10-membered heteroaryl, wherein 1, 2, 3, or 4 atoms in the heteroaryl ring system are independently oxygen, nitrogen, or sulfur). In certain embodiments, A¹ is substituted or unsubstituted indolyl, substituted or unsubstituted isoindolyl, substituted or unsubstituted indazolyl, substituted or unsubstituted benzotriazolyl, substituted or unsubstituted benzothiophenyl, substituted or unsubstituted isobenzothiophenyl, substituted or unsubstituted benzofuranyl, substituted or unsubstituted benzoisofuranyl, substituted or unsubstituted benzimidazolyl, substituted or unsubstituted benzoxazolyl, substituted or unsubstituted benzisoxazolyl, substituted or unsubstituted benzoxadiazolyl, substituted or unsubstituted benzthiazolyl, substituted or unsubstituted benzisothiazolyl, substituted or unsubstituted benzthiadiazolyl, substituted or unsubstituted indolizinyl, substituted or unsubstituted purinyl. In certain embodiments, A¹ is substituted or unsubstituted naphthyridinyl, substituted or unsubstituted pteridinyl, substituted or unsubstituted quinolinyl, substituted or unsubstituted isoquinolinyl, substituted or unsubstituted cinnolinyl, substituted or unsubstituted quinoxalinyl, substituted or unsubstituted phthalazinyl, or substituted or unsubstituted quinazolinyl. In certain embodiments, A¹ is heteroaryl substituted with halogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, –CN, and/or –OR^A. In certain embodiments, A¹ is heteroaryl substituted with substituted or unsubstituted C₁₋₆ alkyl. In certain embodiments, A¹ is heteroaryl substituted with methyl, trifluoromethyl, ethyl, isopropyl, or *tert*-butyl. In certain embodiments, A¹ is heteroaryl substituted with substituted or unsubstituted C₁₋₆ cycloalkyl. In certain embodiments, A¹ is heteroaryl substituted with substituted or unsubstituted cyclopropyl. In certain embodiments, A¹ is heteroaryl substituted with –F, –Cl, –Br, –OMe, –OCF₃, or –CN. In certain embodiments, A¹ is unsubstituted heteroaryl.

A²

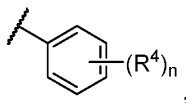
[0140] In certain embodiments, A² is substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl.

[0141] In certain embodiments, A² is substituted or unsubstituted aryl. In certain embodiments, A² is substituted or unsubstituted C₆₋₁₄ aryl. In certain embodiments, A² is substituted or unsubstituted phenyl. In certain embodiments, A² is substituted phenyl. In certain embodiments, A² is phenyl substituted with halogen, substituted or unsubstituted alkyl, and/or –OR^A. In certain embodiments, A² is phenyl substituted with –F, –Cl, –Br, and/or –I. In certain embodiments, A² is phenyl substituted with substituted

or unsubstituted alkyl. In certain embodiments, A² is phenyl substituted with substituted or unsubstituted C₁₋₁₂ alkyl. In certain embodiments, A² is phenyl substituted with substituted or unsubstituted C₁₋₆ alkyl. In certain embodiments, A² is phenyl substituted with unsubstituted C₁₋₆ alkyl. In certain embodiments, A² is phenyl substituted with substituted C₁₋₆ alkyl. In certain embodiments, A² is phenyl substituted with substituted or unsubstituted methyl, substituted or unsubstituted ethyl, substituted or unsubstituted *n*-propyl, substituted or unsubstituted isopropyl, substituted or unsubstituted *n*-butyl, substituted or unsubstituted *tert*-butyl, substituted or unsubstituted *sec*-butyl, substituted or unsubstituted isobutyl, substituted or unsubstituted *n*-pentyl, substituted or unsubstituted 3-pentanyl, substituted or unsubstituted amyl, substituted or unsubstituted neopentyl, substituted or unsubstituted 3-methyl-2-butanyl, substituted or unsubstituted *tert*-amyl, or substituted or unsubstituted *n*-hexyl. In certain embodiments, A² is phenyl substituted with –O(substituted or unsubstituted alkyl). In certain embodiments, A² is phenyl substituted with –O(substituted or unsubstituted C₁₋₁₂ alkyl). In certain embodiments, A² is phenyl substituted with –O(substituted or unsubstituted C₁₋₆ alkyl). In certain embodiments, A² is phenyl substituted with –O(unsubstituted C₁₋₆ alkyl). In certain embodiments, A² is phenyl substituted with –O(substituted C₁₋₆ alkyl). In certain embodiments, A² is phenyl substituted with –O(substituted or unsubstituted methyl, substituted or unsubstituted ethyl, substituted or unsubstituted *n*-propyl, substituted or unsubstituted isopropyl, substituted or unsubstituted *n*-butyl, substituted or unsubstituted *tert*-butyl, substituted or unsubstituted *sec*-butyl, substituted or unsubstituted isobutyl, substituted or unsubstituted *n*-pentyl, substituted or unsubstituted 3-pentanyl, substituted or unsubstituted amyl, substituted or unsubstituted neopentyl, substituted or unsubstituted 3-methyl-2-butanyl, substituted or unsubstituted *tert*-amyl, or substituted or unsubstituted *n*-hexyl). In certain embodiments, A² is phenyl substituted with



[0142] In certain embodiments, A² is of formula:



wherein:

each occurrence of R⁴ is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroalkenyl, substituted or unsubstituted heteroalkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, –CN, –OR^A, –SCN, –SR^A, –SSR^A, –N₃, –NO, –N(R^A)₂, –NO₂, –C(=O)R^A, –C(=O)OR^A, –C(=O)SR^A, –C(=O)N(R^A)₂, –C(=NR^A)R^A, –C(=NR^A)OR^A, –C(=NR^A)SR^A, –C(=NR^A)N(R^A)₂, –S(=O)R^A, –S(=O)OR^A, –S(=O)SR^A, –S(=O)N(R^A)₂, –S(=O)₂R^A, –S(=O)₂OR^A, –

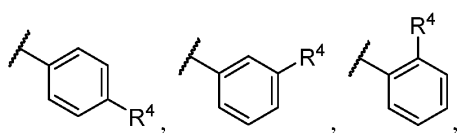
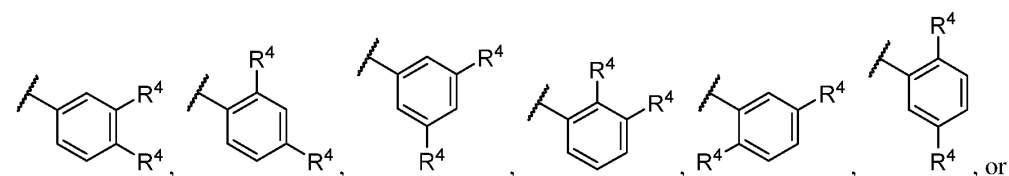
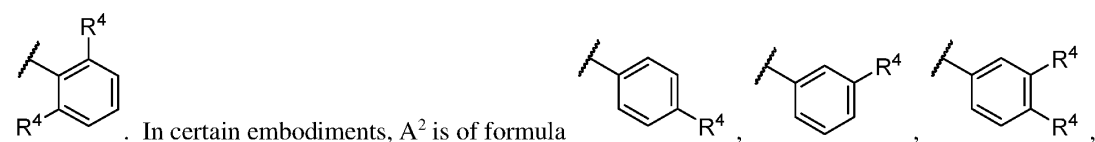
$S(=O)_2SR^A$, $-S(=O)_2N(R^A)_2$, $-OC(=O)R^A$, $-OC(=O)OR^A$, $-OC(=O)SR^A$, $-OC(=O)N(R^A)_2$, $-OC(=NR^A)R^A$, $-OC(=NR^A)OR^A$, $-OC(=NR^A)SR^A$, $-OC(=NR^A)N(R^A)_2$, $-OS(=O)R^A$, $-OS(=O)OR^A$, $-OS(=O)SR^A$, $-OS(=O)N(R^A)_2$, $-OS(=O)_2R^A$, $-OS(=O)_2OR^A$, $-OS(=O)_2SR^A$, $-OS(=O)_2N(R^A)_2$, $-ON(R^A)_2$, $-SC(=O)R^A$, $-SC(=O)OR^A$, $-SC(=O)SR^A$, $-SC(=O)N(R^A)_2$, $-SC(=NR^A)R^A$, $-SC(=NR^A)OR^A$, $-SC(=NR^A)SR^A$, $-SC(=NR^A)N(R^A)_2$, $-NR^AC(=O)R^A$, $-NR^AC(=O)OR^A$, $-NR^AC(=O)SR^A$, $-NR^AC(=O)N(R^A)_2$, $-NR^AC(=NR^A)R^A$, $-NR^AC(=NR^A)OR^A$, $-NR^AC(=NR^A)SR^A$, $-NR^AC(=NR^A)N(R^A)_2$, $-NR^AS(=O)R^A$, $-NR^AS(=O)OR^A$, $-NR^AS(=O)SR^A$, $-NR^AS(=O)N(R^A)_2$, $-NR^AS(=O)_2R^A$, $-NR^AS(=O)_2OR^A$, $-NR^AS(=O)_2SR^A$, $-NR^AS(=O)_2N(R^A)_2$, $-Si(R^A)_3$, $-Si(R^A)_2OR^A$, $-Si(R^A)(OR^A)_2$, $-Si(OR^A)_3$, $-OSi(R^A)_3$, $-OSi(R^A)_2OR^A$, $-OSi(R^A)(OR^A)_2$, $-OSi(OR^A)_3$, or $-B(OR^A)_2$; and

n is 0, 1, 2, 3, 4, or 5.

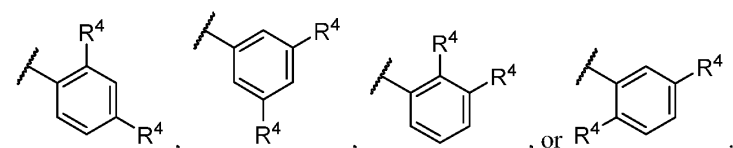
[0143] In certain embodiments, n is 0. In certain embodiments, n is 1. In certain embodiments, n is 2.

In certain embodiments, n is 3. In certain embodiments, n is 4. In certain embodiments, n is 5. In certain embodiments, n is 0, 1, or 2.

[0144] In certain embodiments, A^2 is of formula

. In certain embodiments, A^2 is of formula



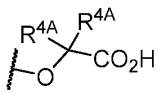
[0145] In certain embodiments, at least one occurrence of R^4 is halogen. In certain embodiments, at least one occurrence of R^4 is substituted or unsubstituted alkyl. In certain embodiments, at least one occurrence of R^4 is substituted or unsubstituted alkenyl. In certain embodiments, at least one occurrence of R^4 is substituted or unsubstituted alkynyl. In certain embodiments, at least one occurrence of R^4 is substituted or unsubstituted heteroalkyl. In certain embodiments, at least one occurrence of R^4 is substituted or unsubstituted heteroalkenyl. In certain embodiments, at least one occurrence of R^4 is substituted or unsubstituted heteroalkynyl. In certain embodiments, at least one occurrence of R^4 is substituted or unsubstituted carbocyclyl. In certain embodiments, at least one occurrence of R^4 is substituted or unsubstituted heterocyclyl. In certain embodiments, at least one occurrence of R^4 is substituted or unsubstituted aryl. In certain embodiments, at least one occurrence of R^4 is substituted or unsubstituted

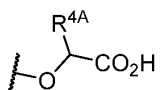
48

embodiments, at least one occurrence of R^4 is $-NR^A C(=O)N(R^A)_2$. In certain embodiments, at least one occurrence of R^4 is $-NR^A C(=NR^A)R^A$. In certain embodiments, at least one occurrence of R^4 is $-NR^A C(=NR^A)OR^A$. In certain embodiments, at least one occurrence of R^4 is $-NR^A C(=NR^A)SR^A$. In certain embodiments, at least one occurrence of R^4 is $-NR^A C(=NR^A)N(R^A)_2$. In certain embodiments, at least one occurrence of R^4 is $-NR^A S(=O)R^A$. In certain embodiments, at least one occurrence of R^4 is $-NR^A S(=O)OR^A$. In certain embodiments, at least one occurrence of R^4 is $-NR^A S(=O)SR^A$. In certain embodiments, at least one occurrence of R^4 is $-NR^A S(=O)N(R^A)_2$. In certain embodiments, at least one occurrence of R^4 is $-NR^A S(=O)_2R^A$. In certain embodiments, at least one occurrence of R^4 is $-NR^A S(=O)_2OR^A$. In certain embodiments, at least one occurrence of R^4 is $-NR^A S(=O)_2SR^A$. In certain embodiments, at least one occurrence of R^4 is $-NR^A S(=O)_2N(R^A)_2$. In certain embodiments, at least one occurrence of R^4 is $-Si(R^A)_3$. In certain embodiments, at least one occurrence of R^4 is $-Si(R^A)_2OR^A$. In certain embodiments, at least one occurrence of R^4 is $-Si(R^A)(OR^A)_2$. In certain embodiments, at least one occurrence of R^4 is $-Si(OR^A)_3$. In certain embodiments, at least one occurrence of R^4 is $-OSi(R^A)_3$. In certain embodiments, at least one occurrence of R^4 is $-OSi(R^A)_2OR^A$. In certain embodiments, at least one occurrence of R^4 is $-OSi(R^A)(OR^A)_2$. In certain embodiments, at least one occurrence of R^4 is $-OSi(OR^A)_3$. In certain embodiments, at least one occurrence of R^4 is $-B(OR^A)_2$.

[0146] In certain embodiments, each occurrence of R^4 is independently halogen, substituted or unsubstituted alkyl, or $-OR^A$. In certain embodiments, at least one occurrence of R^4 is $-F$, $-Cl$, $-Br$, or $-I$. In certain embodiments, at least one occurrence of R^4 is substituted or unsubstituted alkyl. In certain embodiments, at least one occurrence of R^4 is substituted or unsubstituted C_{1-12} alkyl. In certain embodiments, at least one occurrence of R^4 is substituted or unsubstituted C_{1-6} alkyl. In certain embodiments, at least one occurrence of R^4 is unsubstituted C_{1-6} alkyl. In certain embodiments, at least one occurrence of R^4 is substituted C_{1-6} alkyl. In certain embodiments, at least one occurrence of R^4 is substituted or unsubstituted methyl, substituted or unsubstituted ethyl, substituted or unsubstituted *n*-propyl, substituted or unsubstituted isopropyl, substituted or unsubstituted *n*-butyl, substituted or unsubstituted *tert*-butyl, substituted or unsubstituted *sec*-butyl, substituted or unsubstituted isobutyl, substituted or unsubstituted *n*-pentyl, substituted or unsubstituted 3-pentanyl, substituted or unsubstituted amyl, substituted or unsubstituted neopentyl, substituted or unsubstituted 3-methyl-2-butanyl, substituted or unsubstituted *tert*-amyl, or substituted or unsubstituted *n*-hexyl. In certain embodiments, at least one occurrence of R^4 is $-OR^A$. In certain embodiments, at least one occurrence of R^4 is $-O$ (substituted or unsubstituted alkyl). In certain embodiments, at least one occurrence of R^4 is $-O$ (substituted or unsubstituted C_{1-12} alkyl). In certain embodiments, at least one occurrence of R^4 is $-O$ (substituted or unsubstituted C_{1-6} alkyl). In certain embodiments, at least one occurrence of R^4 is $-O$ (unsubstituted C_{1-6} alkyl). In certain embodiments, at least one occurrence of R^4 is $-O$ (substituted C_{1-6} alkyl). In certain embodiments, at least one occurrence of R^4 is $-O$ (substituted or unsubstituted methyl, substituted or unsubstituted ethyl, substituted or unsubstituted *n*-propyl, substituted or unsubstituted isopropyl, substituted or unsubstituted *n*-butyl, substituted or unsubstituted *tert*-butyl, substituted or unsubstituted *sec*-butyl, substituted or unsubstituted isobutyl, substituted or unsubstituted *n*-pentyl, substituted or

unsubstituted 3-pentanyl, substituted or unsubstituted amyl, substituted or unsubstituted neopentyl, substituted or unsubstituted 3-methyl-2-butanyl, substituted or unsubstituted *tert*-amyl, or substituted or unsubstituted *n*-hexyl).

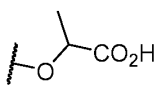
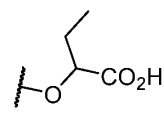
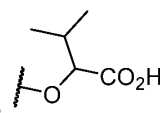
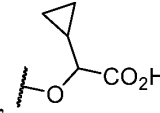
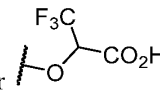
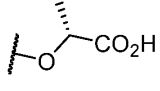
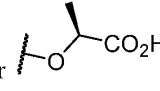
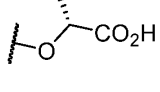
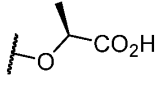
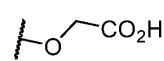
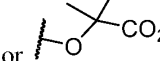
[0147] In certain embodiments, at least one occurrence of R⁴ is of formula , wherein each occurrence of R^{4A} is independently hydrogen, substituted or unsubstituted alkyl, or substituted or unsubstituted cycloalkyl. In certain embodiments, at least one occurrence of R^{4A} is hydrogen. In certain

embodiments, at least one occurrence of R⁴ is of formula . In certain embodiments, each occurrence of R^{4A} is hydrogen.

[0148] In certain embodiments, at least one occurrence of R^{4A} is substituted or unsubstituted alkyl. In certain embodiments, at least one occurrence of R^{4A} is substituted or unsubstituted C₁₋₁₂ alkyl. In certain embodiments, at least one occurrence of R^{4A} is substituted or unsubstituted C₁₋₆ alkyl. In certain embodiments, at least one occurrence of R^{4A} is unsubstituted C₁₋₆ alkyl. In certain embodiments, at least one occurrence of R^{4A} is substituted C₁₋₆ alkyl. In certain embodiments, at least one occurrence of R^{4A} is substituted or unsubstituted methyl, substituted or unsubstituted ethyl, substituted or unsubstituted *n*-propyl, substituted or unsubstituted isopropyl, substituted or unsubstituted *n*-butyl, substituted or unsubstituted *tert*-butyl, substituted or unsubstituted *sec*-butyl, substituted or unsubstituted isobutyl, substituted or unsubstituted *n*-pentyl, substituted or unsubstituted 3-pentanyl, substituted or unsubstituted amyl, substituted or unsubstituted neopentyl, substituted or unsubstituted 3-methyl-2-butanyl, substituted or unsubstituted *tert*-amyl, or substituted or unsubstituted *n*-hexyl. In certain embodiments, at least one occurrence of R^{4A} is substituted or unsubstituted methyl, substituted or unsubstituted ethyl, substituted or unsubstituted isopropyl, or trifluoromethyl. In certain embodiments, at least one occurrence of R^{4A} is unsubstituted methyl, unsubstituted ethyl, or unsubstituted isopropyl. In certain embodiments, at least one occurrence of R^{4A} is substituted methyl, substituted ethyl, or substituted isopropyl.

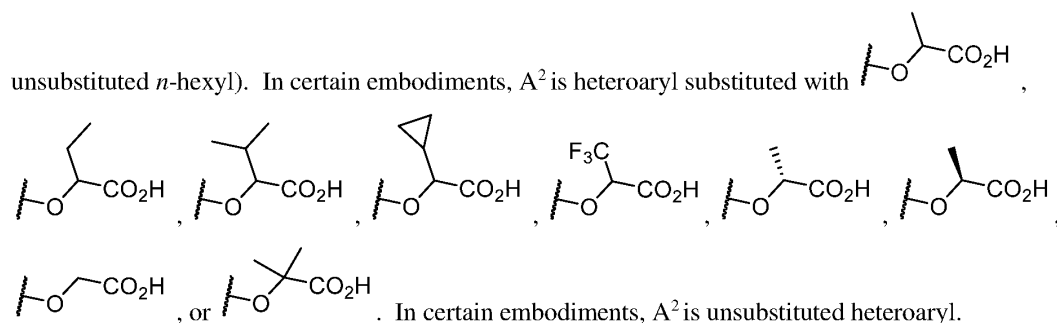
[0149] In certain embodiments, at least one occurrence of R^{4A} is substituted or unsubstituted carbocyclyl. In certain embodiments, at least one occurrence of R^{4A} is substituted or unsubstituted C₁₋₆ cycloalkyl. In certain embodiments, at least one occurrence of R^{4A} is substituted or unsubstituted, monocyclic carbocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 3- to 10-membered carbocyclyl). In certain embodiments, at least one occurrence of R^{4A} is substituted or unsubstituted, polycyclic carbocyclyl (*e.g.*, substituted or unsubstituted, bicyclic or tricyclic, 3- to 14-membered carbocyclyl). In certain embodiments, at least one occurrence of R^{4A} is substituted or unsubstituted saturated carbocyclyl. In certain embodiments, at least one occurrence of R^{4A} is substituted or unsubstituted cyclopropyl, substituted or unsubstituted cyclobutyl, substituted or unsubstituted cyclopentyl, substituted or unsubstituted cyclohexyl, substituted or unsubstituted cycloheptyl, substituted or unsubstituted cyclooctyl, substituted or unsubstituted cyclononyl, or substituted or unsubstituted cyclodecyl. In certain

embodiments, at least one occurrence of R^{4A} is substituted or unsubstituted cyclopropyl. In certain embodiments, at least one occurrence of R^{4A} is substituted cyclopropyl. In certain embodiments, at least one occurrence of R^{4A} is unsubstituted cyclopropyl.

[0150] In certain embodiments, at least one occurrence of R^4 is of formula ,
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or . In certain embodiments, at least one occurrence of R^4 is of formula  or . In certain embodiments, at least one occurrence of R^4 is of formula . In certain embodiments, at least one occurrence of R^4 is of formula . In certain embodiments, at least one occurrence of R^4 is of formula  or .

[0151] In certain embodiments, A^2 is substituted or unsubstituted heteroaryl. In certain embodiments, A^2 is substituted or unsubstituted 5–14 membered heteroaryl. In certain embodiments, A^2 is substituted or unsubstituted monocyclic heteroaryl. In certain embodiments, A^2 is substituted or unsubstituted 5- to 6-membered, monocyclic heteroaryl. In certain embodiments, A^2 is substituted or unsubstituted pyrrolyl, substituted or unsubstituted furanyl, substituted or unsubstituted thiophenyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted triazolyl, substituted or unsubstituted oxadiazolyl, substituted or unsubstituted thiadiazolyl, or substituted or unsubstituted tetrazolyl. In certain embodiments, A^2 is substituted or unsubstituted pyridinyl, substituted or unsubstituted pyridazinyl, substituted or unsubstituted pyrimidinyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted triazinyl, substituted or unsubstituted tetrazinyl, substituted or unsubstituted oxepinyl, or substituted or unsubstituted thiepinyl. In certain embodiments, A^2 is substituted or unsubstituted bicyclic heteroaryl (*e.g.* substituted or unsubstituted bicyclic, 9- or 10-membered heteroaryl, wherein 1, 2, 3, or 4 atoms in the heteroaryl ring system are independently oxygen, nitrogen, or sulfur). In certain embodiments, A^2 is substituted or unsubstituted indolyl, substituted or unsubstituted isoindolyl, substituted or unsubstituted indazolyl, substituted or unsubstituted benzotriazolyl, substituted or unsubstituted benzothiophenyl, substituted or unsubstituted isobenzothiophenyl, substituted or unsubstituted benzofuranyl, substituted or unsubstituted benzoisofuranyl, substituted or unsubstituted benzimidazolyl, substituted or unsubstituted benzoxazolyl, substituted or unsubstituted benzisoxazolyl, substituted or unsubstituted benzoxadiazolyl, substituted or

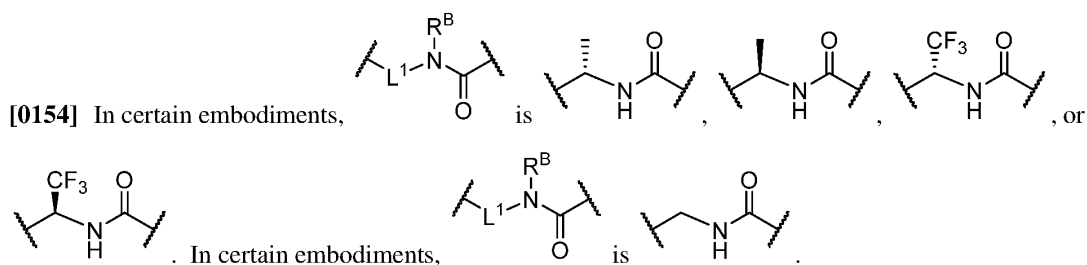
unsubstituted benzthiazolyl, substituted or unsubstituted benzisothiazolyl, substituted or unsubstituted benzthiadiazolyl, substituted or unsubstituted indoliziny, substituted or unsubstituted purinyl. In certain embodiments, A² is substituted or unsubstituted naphthyridinyl, substituted or unsubstituted pteridinyl, substituted or unsubstituted quinolinyl, substituted or unsubstituted isoquinolinyl, substituted or unsubstituted cinnolinyl, substituted or unsubstituted quinoxalinyl, substituted or unsubstituted phthalazinyl, or substituted or unsubstituted quinazolinyl. In certain embodiments, A² is heteroaryl substituted with halogen, substituted or unsubstituted alkyl, and/or -OR^A. In certain embodiments, A² is heteroaryl substituted with -F, -Cl, -Br, and/or -I. In certain embodiments, A² is heteroaryl substituted with substituted or unsubstituted alkyl. In certain embodiments, A² is heteroaryl substituted with substituted or unsubstituted C₁₋₁₂ alkyl. In certain embodiments, A² is heteroaryl substituted with substituted or unsubstituted C₁₋₆ alkyl. In certain embodiments, A² is heteroaryl substituted with unsubstituted C₁₋₆ alkyl. In certain embodiments, A² is heteroaryl substituted with substituted C₁₋₆ alkyl. In certain embodiments, A² is heteroaryl substituted with substituted or unsubstituted methyl, substituted or unsubstituted ethyl, substituted or unsubstituted *n*-propyl, substituted or unsubstituted isopropyl, substituted or unsubstituted *n*-butyl, substituted or unsubstituted *tert*-butyl, substituted or unsubstituted *sec*-butyl, substituted or unsubstituted isobutyl, substituted or unsubstituted *n*-pentyl, substituted or unsubstituted 3-pentanyl, substituted or unsubstituted amyl, substituted or unsubstituted neopentyl, substituted or unsubstituted 3-methyl-2-butanyl, substituted or unsubstituted *tert*-amyl, or substituted or unsubstituted *n*-hexyl. In certain embodiments, A² is heteroaryl substituted with -O(substituted or unsubstituted alkyl). In certain embodiments, A² is heteroaryl substituted with -O(substituted or unsubstituted C₁₋₁₂ alkyl). In certain embodiments, A² is heteroaryl substituted with -O(substituted or unsubstituted C₁₋₆ alkyl). In certain embodiments, A² is heteroaryl substituted with -O(unsubstituted C₁₋₆ alkyl). In certain embodiments, A² is heteroaryl substituted with -O(substituted C₁₋₆ alkyl). In certain embodiments, A² is heteroaryl substituted with -O(substituted or unsubstituted methyl, substituted or unsubstituted ethyl, substituted or unsubstituted *n*-propyl, substituted or unsubstituted isopropyl, substituted or unsubstituted *n*-butyl, substituted or unsubstituted *tert*-butyl, substituted or unsubstituted *sec*-butyl, substituted or unsubstituted isobutyl, substituted or unsubstituted *n*-pentyl, substituted or unsubstituted 3-pentanyl, substituted or unsubstituted amyl, substituted or unsubstituted neopentyl, substituted or unsubstituted 3-methyl-2-butanyl, substituted or unsubstituted *tert*-amyl, or substituted or



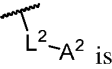
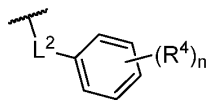
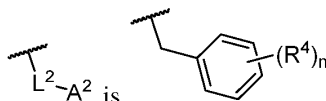
L¹, L², and L³

[0152] In certain embodiments, each of L¹, L², and L³ is independently a bond or substituted or unsubstituted alkylene.

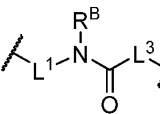
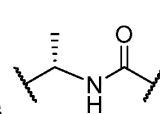
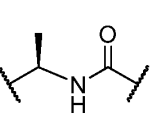
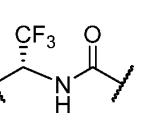
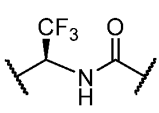
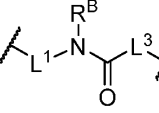
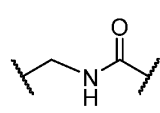
[0153] In certain embodiments, L¹ is a bond or substituted or unsubstituted alkylene. In certain embodiments, L¹ is a bond. In certain embodiments, L¹ is substituted or unsubstituted alkylene. In certain embodiments, L¹ is substituted or unsubstituted C₁₋₁₂ alkylene. In certain embodiments, L¹ is substituted or unsubstituted C₁₋₆ alkylene. In certain embodiments, L¹ is unsubstituted C₁₋₆ alkylene. In certain embodiments, L¹ is substituted C₁₋₆ alkylene. In certain embodiments, L¹ is substituted or unsubstituted methylene, substituted or unsubstituted ethylene, substituted or unsubstituted *n*-propylene, substituted or unsubstituted isopropylene, substituted or unsubstituted *n*-butylene, substituted or unsubstituted *tert*-butylene, substituted or unsubstituted *sec*-butylene, substituted or unsubstituted isobutylene, substituted or unsubstituted *n*-pentylene, substituted or unsubstituted 3-pentylene, substituted or unsubstituted amylene, substituted or unsubstituted neopentylene, substituted or unsubstituted 3-methylene-2-butylene, substituted or unsubstituted *tert*-amylene, or substituted or unsubstituted *n*-hexylene. In certain embodiments, L¹ is substituted or unsubstituted methylene. In certain embodiments, L¹ is substituted methylene. In certain embodiments, L¹ is methylene substituted with at least one substituted or unsubstituted alkyl. In certain embodiments, L¹ is methylene substituted with at least one substituted or unsubstituted C₁₋₆ alkyl. In certain embodiments, L¹ is methylene substituted with at least one unsubstituted C₁₋₆ alkyl. In certain embodiments, L¹ is methylene substituted with at least one substituted C₁₋₆ alkyl. In certain embodiments, L¹ is methylene substituted with at least one substituted or unsubstituted methyl, substituted or unsubstituted ethyl, substituted or unsubstituted *n*-propyl, substituted or unsubstituted isopropyl, substituted or unsubstituted *n*-butyl, substituted or unsubstituted *tert*-butyl, substituted or unsubstituted *sec*-butyl, substituted or unsubstituted isobutyl, substituted or unsubstituted *n*-pentyl, substituted or unsubstituted 3-pentyl, substituted or unsubstituted amyl, substituted or unsubstituted neopentyl, substituted or unsubstituted 3-methyl-2-butyl, substituted or unsubstituted *tert*-amyl, or substituted or unsubstituted *n*-hexyl. In certain embodiments, L¹ is methylene substituted with at least one substituted or unsubstituted methyl. In certain embodiments, L¹ is methylene substituted with at least one substituted methyl. In certain embodiments, L¹ is methylene substituted with at least one unsubstituted methyl. In certain embodiments, L¹ is $-\text{CH}(\text{CH}_3)-$ or $-\text{CH}(\text{CF}_3)-$. In certain embodiments, L¹ is unsubstituted methylene.

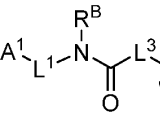
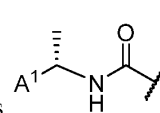
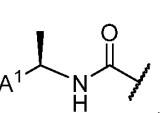
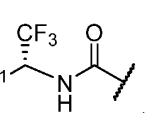
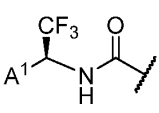
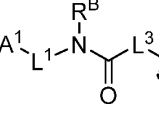
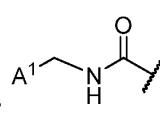
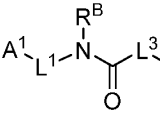
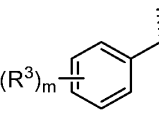
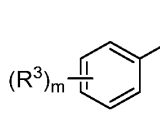
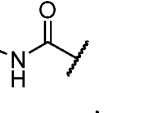


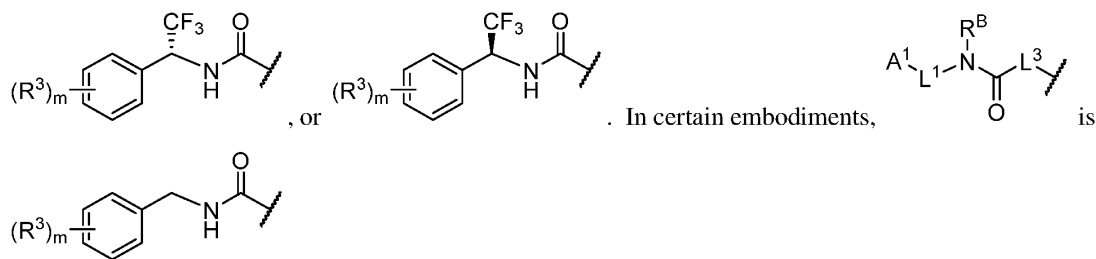
least one substituted methyl. In certain embodiments, L^2 is methylene substituted with at least one unsubstituted methyl. In certain embodiments, L^2 is unsubstituted methylene.

[0157] In certain embodiments, L^2-A^2 is . In certain embodiments, L^2-A^2 is . In certain embodiments, L^2-A^2 is .

[0158] In certain embodiments, L^3 is a bond or substituted or unsubstituted alkylene. In certain embodiments, L^3 is a bond. In certain embodiments, L^3 is substituted or unsubstituted alkylene. In certain embodiments, L^3 is substituted or unsubstituted C_{1-12} alkylene. In certain embodiments, L^3 is substituted or unsubstituted C_{1-6} alkylene. In certain embodiments, L^3 is unsubstituted C_{1-6} alkylene. In certain embodiments, L^3 is substituted C_{1-6} alkylene. In certain embodiments, L^3 is substituted or unsubstituted methylene, substituted or unsubstituted ethylene, substituted or unsubstituted *n*-propylene, substituted or unsubstituted isopropylene, substituted or unsubstituted *n*-butylene, substituted or unsubstituted *tert*-butylene, substituted or unsubstituted *sec*-butylene, substituted or unsubstituted isobutylene, substituted or unsubstituted *n*-pentylene, substituted or unsubstituted 3-pentylene, substituted or unsubstituted amylene, substituted or unsubstituted neopentylene, substituted or unsubstituted 3-methylene-2-butanylene, substituted or unsubstituted *tert*-amylene, or substituted or unsubstituted *n*-hexylene. In certain embodiments, L^3 is substituted or unsubstituted methylene. In certain embodiments, L^3 is substituted methylene. In certain embodiments, L^3 is unsubstituted methylene.

[0159] In certain embodiments,  is , , , or . In certain embodiments,  is .

[0160] In certain embodiments,  is , , , or . In certain embodiments,  is . In certain embodiments,  is , , , or .



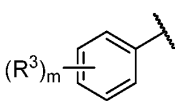
Y, R¹, and p

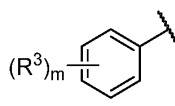
[0161] In certain embodiments, Y is C or N.

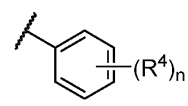
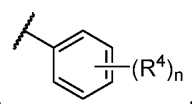
[0162] In certain embodiments, each occurrence of R¹ is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroalkenyl, substituted or unsubstituted heteroalkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -CN, -OR^A, -SCN, -SR^A, -SSR^A, -N₃, -NO, -N(R^A)₂, -NO₂, -C(=O)R^A, -C(=O)OR^A, -C(=O)SR^A, -C(=O)N(R^A)₂, -C(=NR^A)R^A, -C(=NR^A)OR^A, -C(=NR^A)SR^A, -C(=NR^A)N(R^A)₂, -S(=O)R^A, -S(=O)OR^A, -S(=O)SR^A, -S(=O)N(R^A)₂, -S(=O)₂R^A, -S(=O)₂OR^A, -S(=O)₂SR^A, -S(=O)₂N(R^A)₂, -OC(=O)R^A, -OC(=O)OR^A, -OC(=O)SR^A, -OC(=O)N(R^A)₂, -OC(=NR^A)R^A, -OC(=NR^A)OR^A, -OC(=NR^A)SR^A, -OC(=NR^A)N(R^A)₂, -OS(=O)R^A, -OS(=O)OR^A, -OS(=O)SR^A, -OS(=O)N(R^A)₂, -OS(=O)₂R^A, -OS(=O)₂OR^A, -OS(=O)₂SR^A, -OS(=O)₂N(R^A)₂, -ON(R^A)₂, -SC(=O)R^A, -SC(=O)OR^A, -SC(=O)SR^A, -SC(=O)N(R^A)₂, -SC(=NR^A)R^A, -SC(=NR^A)OR^A, -SC(=NR^A)SR^A, -SC(=NR^A)N(R^A)₂, -NR^AC(=O)R^A, -NR^AC(=O)OR^A, -NR^AC(=O)SR^A, -NR^AC(=O)N(R^A)₂, -NR^AC(=NR^A)R^A, -NR^AC(=NR^A)OR^A, -NR^AC(=NR^A)SR^A, -NR^AC(=NR^A)N(R^A)₂, -NR^AS(=O)R^A, -NR^AS(=O)OR^A, -NR^AS(=O)SR^A, -NR^AS(=O)N(R^A)₂, -NR^AS(=O)₂R^A, -NR^AS(=O)₂OR^A, -NR^AS(=O)₂SR^A, -NR^AS(=O)₂N(R^A)₂, -Si(R^A)₃, -Si(R^A)₂OR^A, -Si(R^A)(OR^A)₂, -Si(OR^A)₃, -OSi(R^A)₃, -OSi(R^A)₂OR^A, -OSi(R^A)(OR^A)₂, -OSi(OR^A)₃, or -B(OR^A)₂.

[0163] In certain embodiments, p is 0, 1, 2, or 3. In certain embodiments, p is 0. In certain embodiments, p is 1. In certain embodiments, p is 2. In certain embodiments, p is 3.

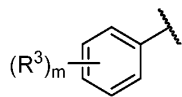
[0164] In certain embodiments, Y is C. In certain embodiments, Y is C, and L³ is a bond. In certain

embodiments, Y is C, and A¹ is of formula . In certain embodiments, Y is C, A¹ is of

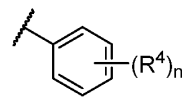
formula , and L³ is a bond. In certain embodiments, Y is C, and A² is of formula

. In certain embodiments, Y is C, A² is of formula , and L³ is a bond.

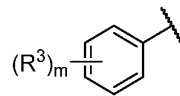
In certain embodiments, Y is C, A¹ is of formula



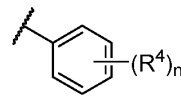
, and A² is of formula



. In certain embodiments, Y is C, A¹ is of formula

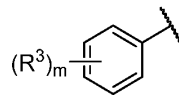


, A² is of formula



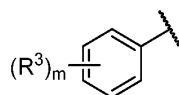
and L³ is a bond. In certain embodiments, Y is C, and p is 0. In certain embodiments, Y is C, p is 0, and

L³ is a bond. In certain embodiments, Y is C, p is 0, and A¹ is of formula



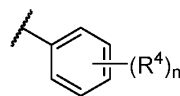
. In certain

embodiments, Y is C, p is 0, A¹ is of formula



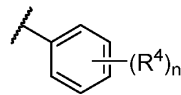
, and L³ is a bond. In certain

embodiments, Y is C, p is 0, and A² is of formula



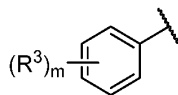
. In certain embodiments, Y is C, p is

0, A² is of formula

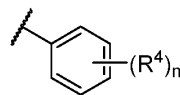


, and L³ is a bond. In certain embodiments, Y is C, p is 0, A¹ is of

formula

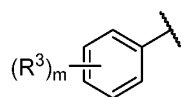


, and A² is of formula

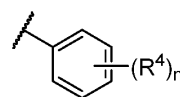


. In certain embodiments, Y is C, p is 0,

A¹ is of formula



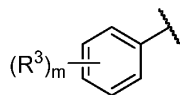
, A² is of formula



, and L³ is a bond. In certain

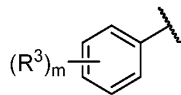
embodiments, Y is C, and p is 1. In certain embodiments, Y is C, p is 1, and L³ is a bond. In certain

embodiments, Y is C, p is 1, and A¹ is of formula



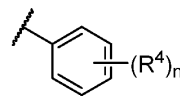
. In certain embodiments, Y is C, p is

1, A¹ is of formula

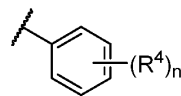


, and L³ is a bond. In certain embodiments, Y is C, p is 1, and A² is

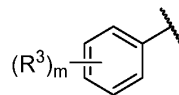
of formula



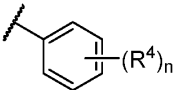
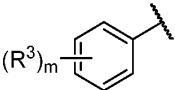
. In certain embodiments, Y is C, p is 1, A² is of formula

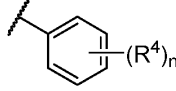


and L³ is a bond. In certain embodiments, Y is C, p is 1, A¹ is of formula

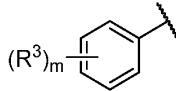


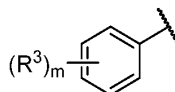
, and A² is of

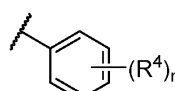
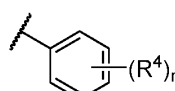
formula . In certain embodiments, Y is C, p is 1, A¹ is of formula , A²

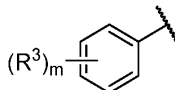
is of formula , and L³ is a bond.

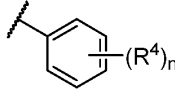
[0165] In certain embodiments, Y is N. In certain embodiments, Y is N, and R^{2A} is absent. In certain embodiments, Y is N, R^{2A} is absent, and L³ is a bond. In certain embodiments, Y is N, R^{2A} is absent, and

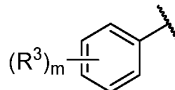
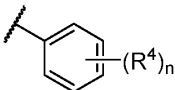
A¹ is of formula . In certain embodiments, Y is N, R^{2A} is absent, A¹ is of formula

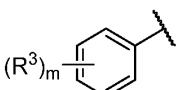
, and L³ is a bond. In certain embodiments, Y is N, R^{2A} is absent, and A² is of formula

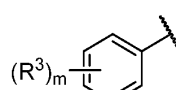
. In certain embodiments, Y is N, R^{2A} is absent, A² is of formula , and

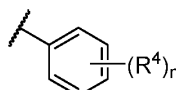
L³ is a bond. In certain embodiments, Y is N, R^{2A} is absent, A¹ is of formula , and A² is

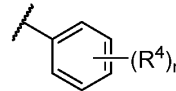
of formula . In certain embodiments, Y is N, R^{2A} is absent, A¹ is of formula

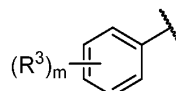
, A² is of formula , and L³ is a bond. In certain embodiments, Y is N, R^{2A} is absent, and p is 0. In certain embodiments, Y is N, R^{2A} is absent, p is 0, and L³ is a bond. In

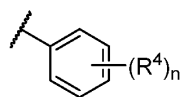
certain embodiments, Y is N, R^{2A} is absent, p is 0, and A¹ is of formula . In certain

embodiments, Y is N, R^{2A} is absent, p is 0, A¹ is of formula , and L³ is a bond. In certain

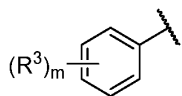
embodiments, Y is N, R^{2A} is absent, p is 0, and A² is of formula . In certain

embodiments, Y is N, R^{2A} is absent, p is 0, A² is of formula , and L³ is a bond. In certain

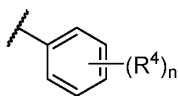
embodiments, Y is N, R^{2A} is absent, p is 0, A¹ is of formula , and A² is of formula



. In certain embodiments, Y is N, R^{2A} is absent, p is 0, A¹ is of formula



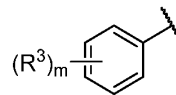
, A² is of formula



, and L³ is a bond. In certain embodiments, Y is N,

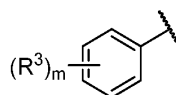
R^{2A} is absent, and p is 1. In certain embodiments, Y is N, R^{2A} is absent, p is 1, and L³ is a bond. In

certain embodiments, Y is N, R^{2A} is absent, p is 1, and A¹ is of formula



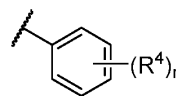
. In certain

embodiments, Y is N, R^{2A} is absent, p is 1, A¹ is of formula



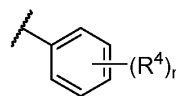
, and L³ is a bond. In certain

embodiments, Y is N, R^{2A} is absent, p is 1, and A² is of formula



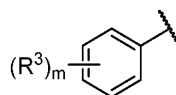
. In certain

embodiments, Y is N, R^{2A} is absent, p is 1, A² is of formula

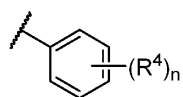


, and L³ is a bond. In certain

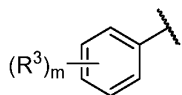
embodiments, Y is N, R^{2A} is absent, p is 1, A¹ is of formula



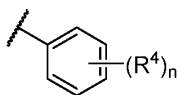
, and A² is of formula



. In certain embodiments, Y is N, R^{2A} is absent, p is 1, A¹ is of formula



, A² is of formula



, and L³ is a bond.

[0166] In certain embodiments, at least one occurrence of R¹ is halogen. In certain embodiments, at least one occurrence of R¹ is -F, -Cl, -Br, or -I. In certain embodiments, at least one occurrence of R¹ is -F. In certain embodiments, at least one occurrence of R¹ is substituted or unsubstituted alkyl. In certain embodiments, at least one occurrence of R¹ is substituted or unsubstituted alkenyl. In certain embodiments, at least one occurrence of R¹ is substituted or unsubstituted alkynyl. In certain embodiments, at least one occurrence of R¹ is substituted or unsubstituted heteroalkyl. In certain embodiments, at least one occurrence of R¹ is substituted or unsubstituted heteroalkenyl. In certain embodiments, at least one occurrence of R¹ is substituted or unsubstituted heteroalkynyl. In certain embodiments, at least one occurrence of R¹ is substituted or unsubstituted carbocyclyl. In certain embodiments, at least one occurrence of R¹ is substituted or unsubstituted heterocyclyl. In certain embodiments, at least one occurrence of R¹ is substituted or unsubstituted aryl. In certain embodiments, at least one occurrence of R¹ is substituted or unsubstituted heteroaryl. In certain embodiments, at least one occurrence of R¹ is -CN. In certain embodiments, at least one occurrence of R¹ is -OR^A. In certain

60

$\text{NR}^{\text{A}}\text{C}(=\text{NR}^{\text{A}})\text{OR}^{\text{A}}$. In certain embodiments, at least one occurrence of R^1 is $-\text{NR}^{\text{A}}\text{C}(=\text{NR}^{\text{A}})\text{SR}^{\text{A}}$. In certain embodiments, at least one occurrence of R^1 is $-\text{NR}^{\text{A}}\text{C}(=\text{NR}^{\text{A}})\text{N}(\text{R}^{\text{A}})_2$. In certain embodiments, at least one occurrence of R^1 is $-\text{NR}^{\text{A}}\text{S}(=\text{O})\text{R}^{\text{A}}$. In certain embodiments, at least one occurrence of R^1 is $-\text{NR}^{\text{A}}\text{S}(=\text{O})\text{OR}^{\text{A}}$. In certain embodiments, at least one occurrence of R^1 is $-\text{NR}^{\text{A}}\text{S}(=\text{O})\text{SR}^{\text{A}}$. In certain embodiments, at least one occurrence of R^1 is $-\text{NR}^{\text{A}}\text{S}(=\text{O})\text{N}(\text{R}^{\text{A}})_2$. In certain embodiments, at least one occurrence of R^1 is $-\text{NR}^{\text{A}}\text{S}(=\text{O})_2\text{R}^{\text{A}}$. In certain embodiments, at least one occurrence of R^1 is $-\text{NR}^{\text{A}}\text{S}(=\text{O})_2\text{OR}^{\text{A}}$. In certain embodiments, at least one occurrence of R^1 is $-\text{NR}^{\text{A}}\text{S}(=\text{O})_2\text{SR}^{\text{A}}$. In certain embodiments, at least one occurrence of R^1 is $-\text{NR}^{\text{A}}\text{S}(=\text{O})_2\text{N}(\text{R}^{\text{A}})_2$. In certain embodiments, at least one occurrence of R^1 is $-\text{Si}(\text{R}^{\text{A}})_3$. In certain embodiments, at least one occurrence of R^1 is $-\text{Si}(\text{R}^{\text{A}})_2\text{OR}^{\text{A}}$. In certain embodiments, at least one occurrence of R^1 is $-\text{Si}(\text{R}^{\text{A}})(\text{OR}^{\text{A}})_2$. In certain embodiments, at least one occurrence of R^1 is $-\text{Si}(\text{OR}^{\text{A}})_3$. In certain embodiments, at least one occurrence of R^1 is $-\text{OSi}(\text{R}^{\text{A}})_3$. In certain embodiments, at least one occurrence of R^1 is $-\text{OSi}(\text{R}^{\text{A}})_2\text{OR}^{\text{A}}$. In certain embodiments, at least one occurrence of R^1 is $-\text{OSi}(\text{R}^{\text{A}})(\text{OR}^{\text{A}})_2$. In certain embodiments, at least one occurrence of R^1 is $-\text{OSi}(\text{OR}^{\text{A}})_3$. In certain embodiments, at least one occurrence of R^1 is $-\text{B}(\text{OR}^{\text{A}})_2$.

R^{2A} and R^{2B}

[0167] In certain embodiments, $\text{R}^{2\text{A}}$ is absent, hydrogen, substituted or unsubstituted alkyl, or a nitrogen protecting group, provided that when Y is N, $\text{R}^{2\text{A}}$ is absent. In certain embodiments, $\text{R}^{2\text{A}}$ is absent. In certain embodiments, Y is N, and $\text{R}^{2\text{A}}$ is absent. In certain embodiments, $\text{R}^{2\text{A}}$ is substituted or unsubstituted alkyl. In certain embodiments, $\text{R}^{2\text{A}}$ is substituted or unsubstituted C_{1-12} alkyl. In certain embodiments, $\text{R}^{2\text{A}}$ is substituted or unsubstituted C_{1-6} alkyl. In certain embodiments, $\text{R}^{2\text{A}}$ is unsubstituted C_{1-6} alkyl. In certain embodiments, $\text{R}^{2\text{A}}$ is substituted C_{1-6} alkyl. In certain embodiments, $\text{R}^{2\text{A}}$ is substituted or unsubstituted methyl, substituted or unsubstituted ethyl, substituted or unsubstituted *n*-propyl, substituted or unsubstituted isopropyl, substituted or unsubstituted *n*-butyl, substituted or unsubstituted *tert*-butyl, substituted or unsubstituted *sec*-butyl, substituted or unsubstituted isobutyl, substituted or unsubstituted *n*-pentyl, substituted or unsubstituted 3-pentanyl, substituted or unsubstituted amyl, substituted or unsubstituted neopentyl, substituted or unsubstituted 3-methyl-2-butanyl, substituted or unsubstituted *tert*-amyl, or substituted or unsubstituted *n*-hexyl. In certain embodiments, $\text{R}^{2\text{A}}$ is substituted or unsubstituted methyl, substituted or unsubstituted ethyl, substituted or unsubstituted isopropyl, substituted or unsubstituted 2-methylpropyl, substituted or unsubstituted 2,2-dimethylpropyl, substituted or unsubstituted cyclopropylmethyl, or substituted or unsubstituted cyclobutylmethyl. In certain embodiments, $\text{R}^{2\text{A}}$ is substituted methyl, substituted ethyl, substituted isopropyl, substituted 2-methylpropyl, substituted 2,2-dimethylpropyl, substituted cyclopropylmethyl, or substituted cyclobutylmethyl. In certain embodiments, $\text{R}^{2\text{A}}$ is unsubstituted methyl, unsubstituted ethyl, unsubstituted isopropyl, unsubstituted 2-methylpropyl, unsubstituted 2,2-dimethylpropyl, unsubstituted cyclopropylmethyl, or unsubstituted cyclobutylmethyl. In certain embodiments, $\text{R}^{2\text{A}}$ is a nitrogen protecting group.

[0168] In certain embodiments, R^{2B} is hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroalkenyl, substituted or unsubstituted heteroalkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-\text{CN}$, $-\text{OR}^A$, $-\text{SCN}$, $-\text{SR}^A$, $-\text{SSR}^A$, $-\text{N}_3$, $-\text{NO}$, $-\text{N}(\text{R}^A)_2$, $-\text{NO}_2$, $-\text{C}(=\text{O})\text{R}^A$, $-\text{C}(=\text{O})\text{OR}^A$, $-\text{C}(=\text{O})\text{SR}^A$, $-\text{C}(=\text{O})\text{N}(\text{R}^A)_2$, $-\text{C}(=\text{NR}^A)\text{R}^A$, $-\text{C}(=\text{NR}^A)\text{OR}^A$, $-\text{C}(=\text{NR}^A)\text{SR}^A$, $-\text{C}(=\text{NR}^A)\text{N}(\text{R}^A)_2$, $-\text{S}(=\text{O})\text{R}^A$, $-\text{S}(=\text{O})\text{OR}^A$, $-\text{S}(=\text{O})\text{SR}^A$, $-\text{S}(=\text{O})\text{N}(\text{R}^A)_2$, $-\text{S}(=\text{O})_2\text{R}^A$, $-\text{S}(=\text{O})_2\text{OR}^A$, $-\text{S}(=\text{O})_2\text{SR}^A$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^A)_2$, $-\text{OC}(=\text{O})\text{R}^A$, $-\text{OC}(=\text{O})\text{OR}^A$, $-\text{OC}(=\text{O})\text{SR}^A$, $-\text{OC}(=\text{O})\text{N}(\text{R}^A)_2$, $-\text{OC}(=\text{NR}^A)\text{R}^A$, $-\text{OC}(=\text{NR}^A)\text{OR}^A$, $-\text{OC}(=\text{NR}^A)\text{SR}^A$, $-\text{OC}(=\text{NR}^A)\text{N}(\text{R}^A)_2$, $-\text{OS}(=\text{O})\text{R}^A$, $-\text{OS}(=\text{O})\text{OR}^A$, $-\text{OS}(=\text{O})\text{SR}^A$, $-\text{OS}(=\text{O})\text{N}(\text{R}^A)_2$, $-\text{OS}(=\text{O})_2\text{R}^A$, $-\text{OS}(=\text{O})_2\text{OR}^A$, $-\text{OS}(=\text{O})_2\text{SR}^A$, $-\text{OS}(=\text{O})_2\text{N}(\text{R}^A)_2$, $-\text{ON}(\text{R}^A)_2$, $-\text{SC}(=\text{O})\text{R}^A$, $-\text{SC}(=\text{O})\text{OR}^A$, $-\text{SC}(=\text{O})\text{SR}^A$, $-\text{SC}(=\text{O})\text{N}(\text{R}^A)_2$, $-\text{SC}(=\text{NR}^A)\text{R}^A$, $-\text{SC}(=\text{NR}^A)\text{OR}^A$, $-\text{SC}(=\text{NR}^A)\text{SR}^A$, $-\text{SC}(=\text{NR}^A)\text{N}(\text{R}^A)_2$, $-\text{NR}^A\text{C}(=\text{O})\text{R}^A$, $-\text{NR}^A\text{C}(=\text{O})\text{OR}^A$, $-\text{NR}^A\text{C}(=\text{O})\text{SR}^A$, $-\text{NR}^A\text{C}(=\text{O})\text{N}(\text{R}^A)_2$, $-\text{NR}^A\text{C}(=\text{NR}^A)\text{R}^A$, $-\text{NR}^A\text{C}(=\text{NR}^A)\text{OR}^A$, $-\text{NR}^A\text{C}(=\text{NR}^A)\text{SR}^A$, $-\text{NR}^A\text{C}(=\text{NR}^A)\text{N}(\text{R}^A)_2$, $-\text{NR}^A\text{S}(=\text{O})\text{R}^A$, $-\text{NR}^A\text{S}(=\text{O})\text{OR}^A$, $-\text{NR}^A\text{S}(=\text{O})\text{SR}^A$, $-\text{NR}^A\text{S}(=\text{O})\text{N}(\text{R}^A)_2$, $-\text{NR}^A\text{S}(=\text{O})_2\text{R}^A$, $-\text{NR}^A\text{S}(=\text{O})_2\text{OR}^A$, $-\text{NR}^A\text{S}(=\text{O})_2\text{SR}^A$, $-\text{NR}^A\text{S}(=\text{O})_2\text{N}(\text{R}^A)_2$, $-\text{Si}(\text{R}^A)_3$, $-\text{Si}(\text{R}^A)_2\text{OR}^A$, $-\text{Si}(\text{R}^A)(\text{OR}^A)_2$, $-\text{Si}(\text{OR}^A)_3$, $-\text{OSi}(\text{R}^A)_3$, $-\text{OSi}(\text{R}^A)_2\text{OR}^A$, $-\text{OSi}(\text{R}^A)(\text{OR}^A)_2$, $-\text{OSi}(\text{OR}^A)_3$, or $-\text{B}(\text{OR}^A)_2$.

[0169] In certain embodiments, R^{2B} is hydrogen. In certain embodiments, R^{2B} is substituted or unsubstituted alkyl. In certain embodiments, R^{2B} is substituted or unsubstituted C_{1-12} alkyl. In certain embodiments, R^{2B} is substituted or unsubstituted C_{1-6} alkyl. In certain embodiments, R^{2B} is unsubstituted C_{1-6} alkyl. In certain embodiments, R^{2B} is substituted C_{1-6} alkyl. In certain embodiments, R^{2B} is substituted or unsubstituted methyl, substituted or unsubstituted ethyl, substituted or unsubstituted *n*-propyl, substituted or unsubstituted isopropyl, substituted or unsubstituted *n*-butyl, substituted or unsubstituted *tert*-butyl, substituted or unsubstituted *sec*-butyl, substituted or unsubstituted isobutyl, substituted or unsubstituted *n*-pentyl, substituted or unsubstituted 3-pentanyl, substituted or unsubstituted amyl, substituted or unsubstituted neopentyl, substituted or unsubstituted 3-methyl-2-butanyl, substituted or unsubstituted *tert*-amyl, or substituted or unsubstituted *n*-hexyl. In certain embodiments, R^{2B} is substituted or unsubstituted methyl. In certain embodiments, R^{2B} is substituted methyl. In certain embodiments, R^{2B} is unsubstituted methyl.

R^A and R^B

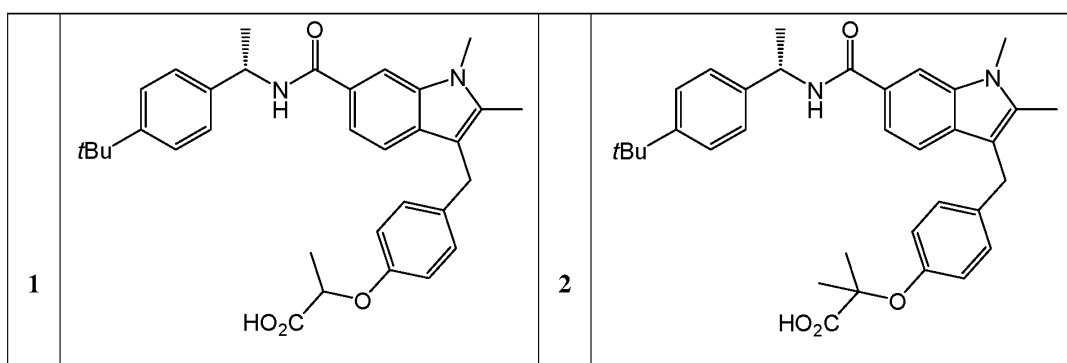
[0170] In certain embodiments, each occurrence of R^A is independently hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroalkenyl, substituted or unsubstituted heteroalkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, a nitrogen protecting group when attached to a nitrogen atom, an oxygen protecting group when attached to an oxygen atom, or a sulfur protecting group when attached to a sulfur atom, or two occurrences of R^A are joined together with their intervening atom to form an substituted or unsubstituted heterocyclic ring or

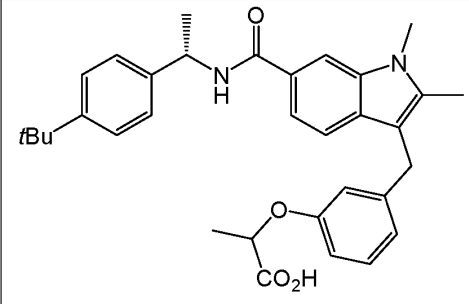
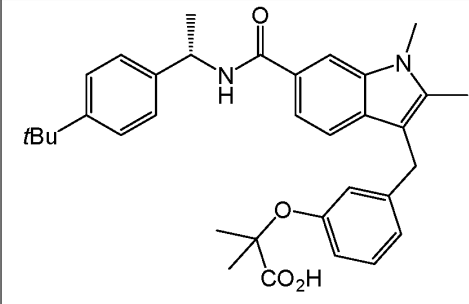
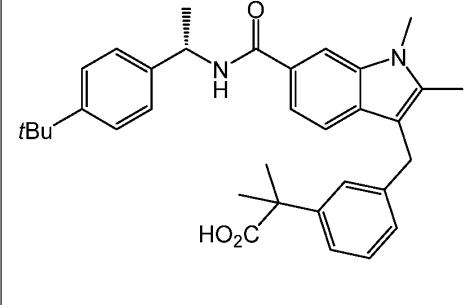
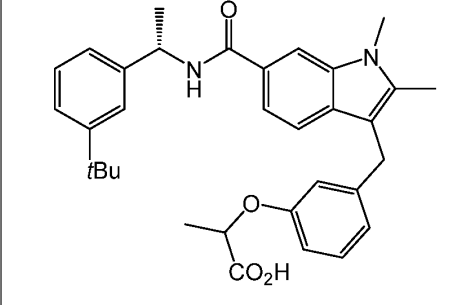
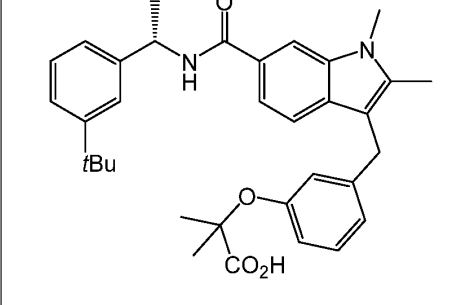
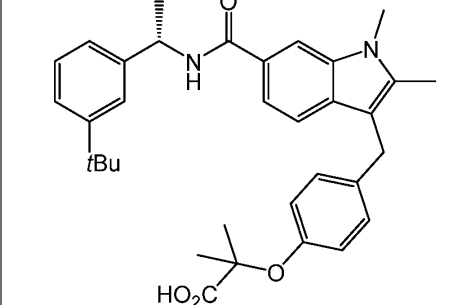
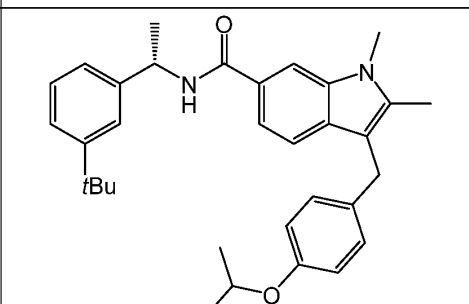
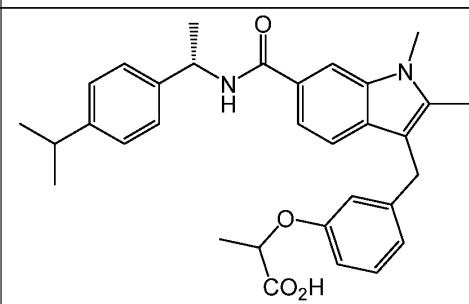
substituted or unsubstituted heteroaryl ring. In certain embodiments, at least one occurrence of R^A is independently hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroalkenyl, substituted or unsubstituted heteroalkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, a nitrogen protecting group when attached to a nitrogen atom, an oxygen protecting group when attached to an oxygen atom, or a sulfur protecting group when attached to a sulfur atom, or two occurrences of R^A are joined together with their intervening atom to form an substituted or unsubstituted heterocyclic ring or substituted or unsubstituted heteroaryl ring. In certain embodiments, at least one occurrence of R^A is hydrogen. In certain embodiments, at least one occurrence of R^A is substituted or unsubstituted acyl. In certain embodiments, at least one occurrence of R^A is substituted or unsubstituted C_{1-12} alkyl. In certain embodiments, at least one occurrence of R^A is substituted or unsubstituted C_{1-6} alkyl. In certain embodiments, at least one occurrence of R^A is unsubstituted C_{1-6} alkyl. In certain embodiments, at least one occurrence of R^A is substituted C_{1-6} alkyl. In certain embodiments, at least one occurrence of R^A is substituted or unsubstituted methyl, substituted or unsubstituted ethyl, substituted or unsubstituted *n*-propyl, substituted or unsubstituted isopropyl, substituted or unsubstituted *n*-butyl, substituted or unsubstituted *tert*-butyl, substituted or unsubstituted *sec*-butyl, substituted or unsubstituted isobutyl, substituted or unsubstituted *n*-pentyl, substituted or unsubstituted 3-pentanyl, substituted or unsubstituted amyl, substituted or unsubstituted neopentyl, substituted or unsubstituted 3-methyl-2-butanyl, substituted or unsubstituted *tert*-amyl, or substituted or unsubstituted *n*-hexyl. In certain embodiments, at least one occurrence of R^A is substituted or unsubstituted C_{2-12} alkenyl. In certain embodiments, at least one occurrence of R^A is substituted or unsubstituted C_{2-6} alkenyl. In certain embodiments, at least one occurrence of R^A is substituted or unsubstituted ethenyl, substituted or unsubstituted 1-propenyl, substituted or unsubstituted 2-propenyl, substituted or unsubstituted 1-butenyl, substituted or unsubstituted 2-butenyl, substituted or unsubstituted butadienyl, substituted or unsubstituted pentenyl, substituted or unsubstituted pentadienyl, or substituted or unsubstituted hexenyl. In certain embodiments, at least one occurrence of R^A is substituted or unsubstituted C_{2-12} alkynyl. In certain embodiments, at least one occurrence of R^A is substituted or unsubstituted C_{2-6} alkynyl. In certain embodiments, at least one occurrence of R^A is substituted or unsubstituted ethynyl, substituted or unsubstituted 1-propynyl, substituted or unsubstituted 2-propynyl, substituted or unsubstituted 1-butyne, substituted or unsubstituted 2-butyne, substituted or unsubstituted pentynyl, or substituted or unsubstituted hexynyl. In certain embodiments, at least one occurrence of R^A is substituted or unsubstituted hetero C_{1-12} alkyl. In certain embodiments, at least one occurrence of R^A is substituted or unsubstituted hetero C_{1-6} alkyl. In certain embodiments, at least one occurrence of R^A is substituted or unsubstituted hetero C_{1-12} alkenyl. In certain embodiments, at least one occurrence of R^A is substituted or unsubstituted hetero C_{1-6} alkenyl. In certain embodiments, at least one occurrence of R^A is substituted or unsubstituted hetero C_{1-12} alkynyl. In certain embodiments, at least one occurrence of R^A is substituted or unsubstituted hetero C_{1-6} alkynyl. In certain embodiments, at least one occurrence of R^A is

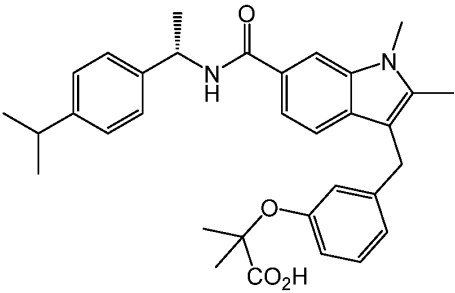
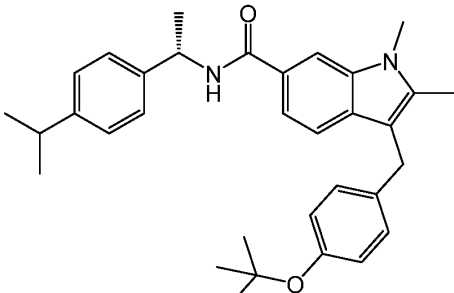
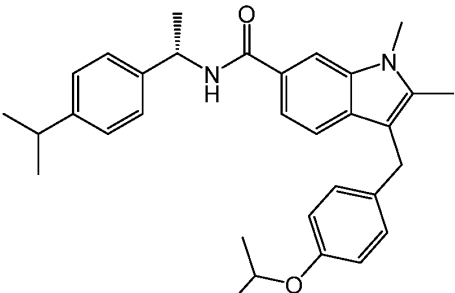
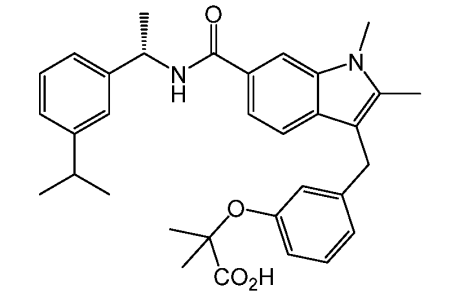
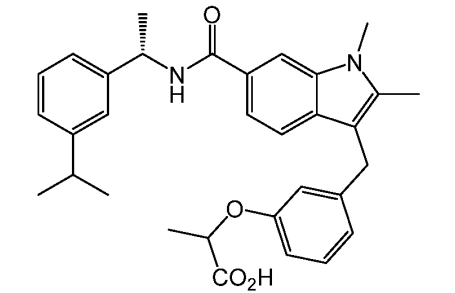
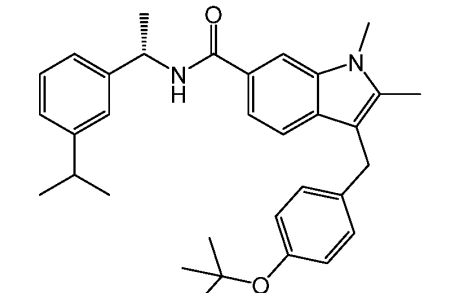
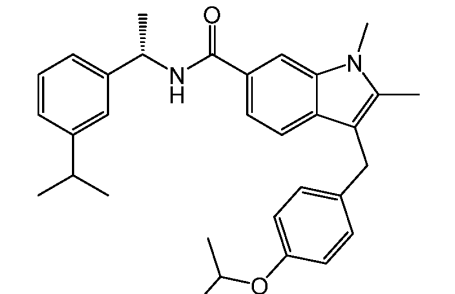
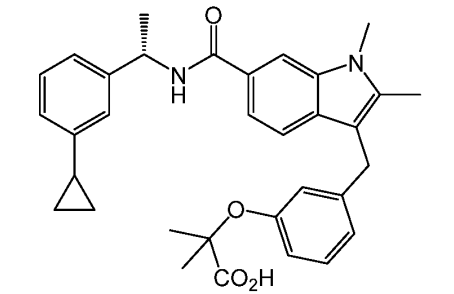
substituted or unsubstituted C₃₋₁₄ cycloalkyl. In certain embodiments, at least one occurrence of R^A is substituted or unsubstituted 5–10 membered heterocyclyl. In certain embodiments, at least one occurrence of R^A is substituted or unsubstituted 6–14 membered aryl. In certain embodiments, at least one occurrence of R^A is substituted or unsubstituted 5–14 membered heteroaryl. In certain embodiments, at least one occurrence of R^A is a nitrogen protecting group when attached to a nitrogen atom. In certain embodiments, at least one occurrence of R^A is an oxygen protecting group when attached to an oxygen atom. In certain embodiments, at least one occurrence of R^A is a sulfur protecting group when attached to a sulfur atom. In certain embodiments, at least two occurrences of R^A are joined together with their intervening atom to form an substituted or unsubstituted 5–10 membered heterocyclic ring. In certain embodiments, at least two occurrences of R^A are joined together with their intervening atom to form an substituted or unsubstituted 5–14 membered heteroaryl ring.

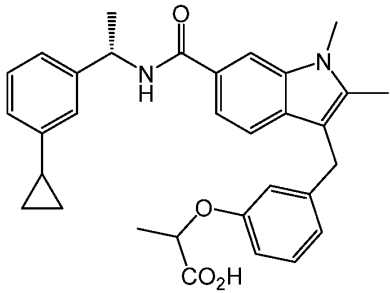
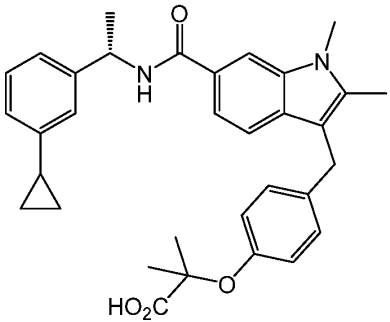
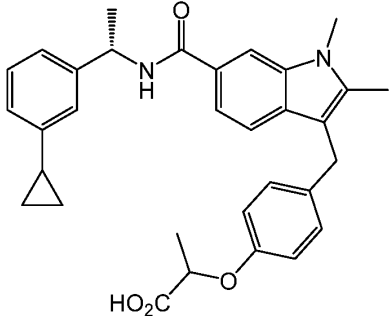
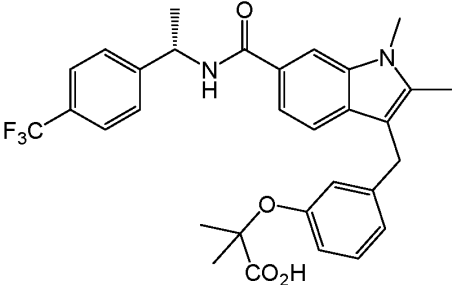
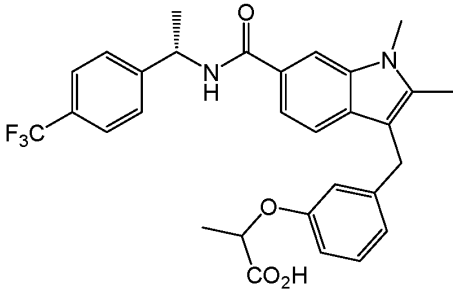
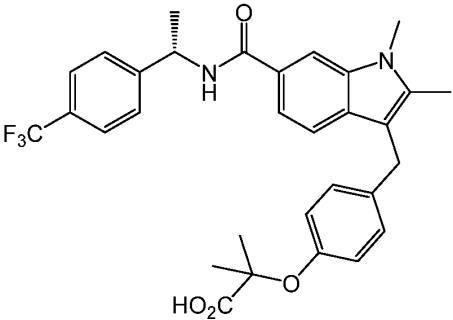
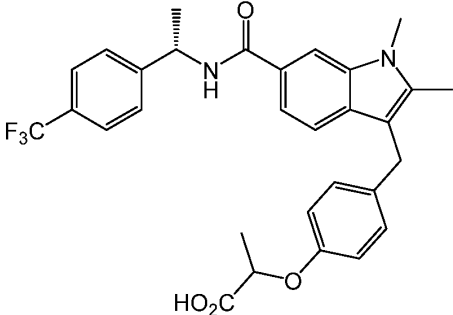
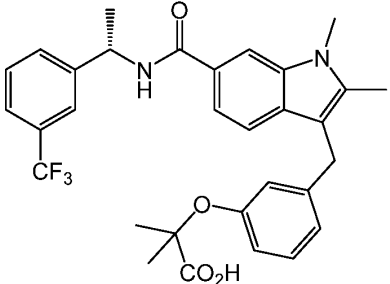
[0171] In certain embodiments, each occurrence of R^B is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted acyl, or a nitrogen protecting group. In certain embodiments, at least one occurrence of R^B is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted acyl, or a nitrogen protecting group. In certain embodiments, at least one occurrence of R^B is hydrogen. In certain embodiments, at least one occurrence of R^B is substituted or unsubstituted alkyl. In certain embodiments, at least one occurrence of R^B is substituted or unsubstituted C₁₋₁₀ alkyl. In certain embodiments, at least one occurrence of R^B is substituted or unsubstituted C₁₋₆ alkyl. In certain embodiments, at least one occurrence of R^B is substituted or unsubstituted C₁₋₃ alkyl. In certain embodiments, at least one occurrence of R^B is substituted or unsubstituted C₁₋₃ alkyl. In certain embodiments, R^B is substituted or unsubstituted methyl, substituted or unsubstituted ethyl, substituted or unsubstituted n-propyl, or substituted or unsubstituted isopropyl. In certain embodiments, at least one occurrence of R^B is substituted or unsubstituted acyl. In certain embodiments, at least one occurrence of R^B is a nitrogen protecting group.

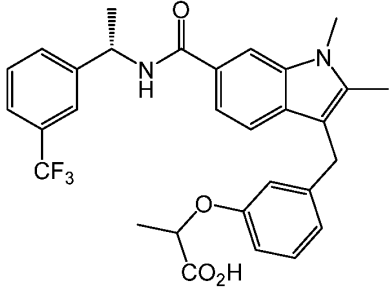
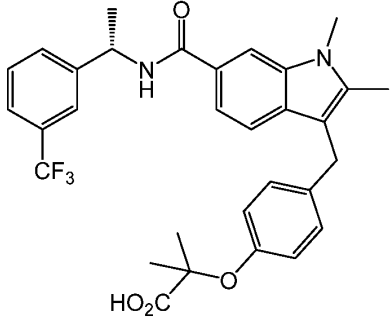
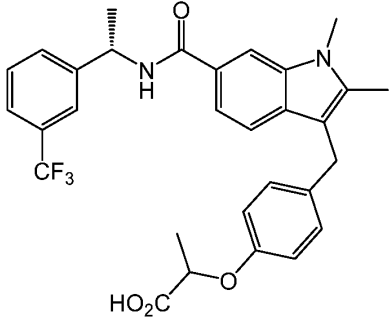
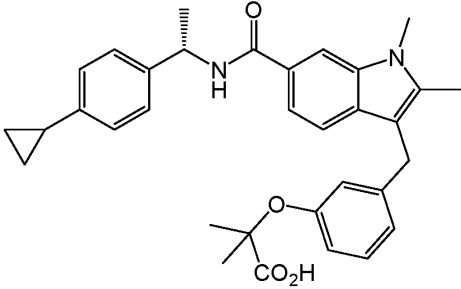
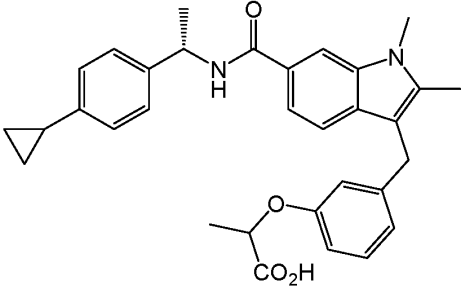
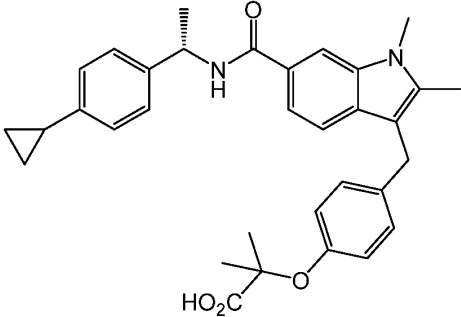
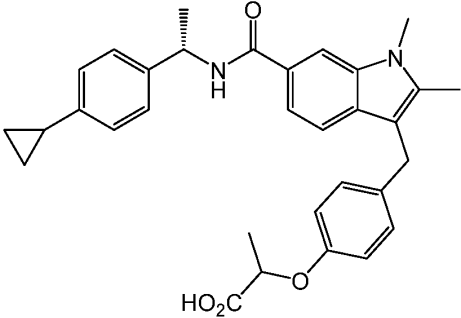
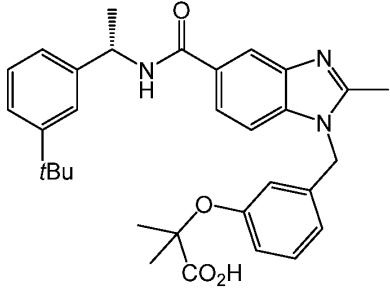
[0172] In certain embodiments, the compound of Formula (I) is of formula:



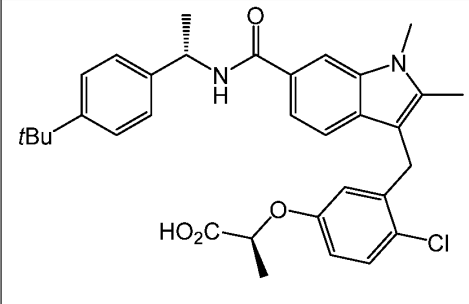
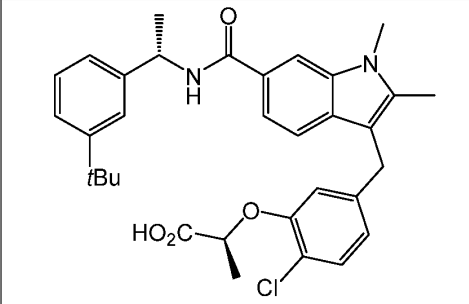
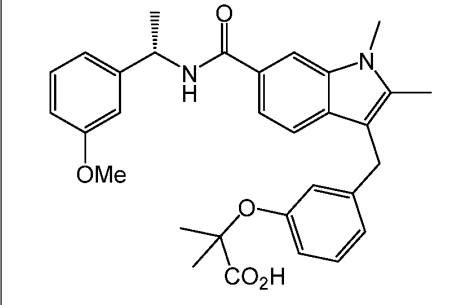
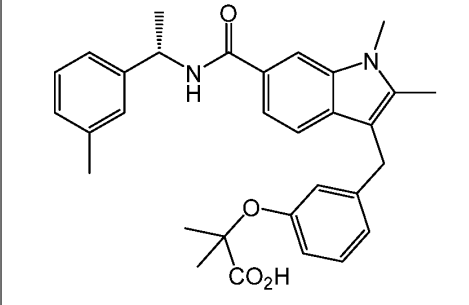
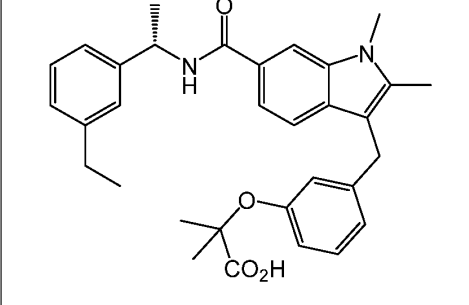
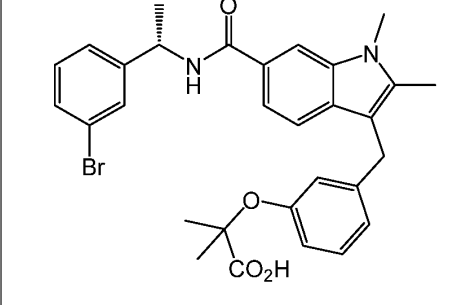
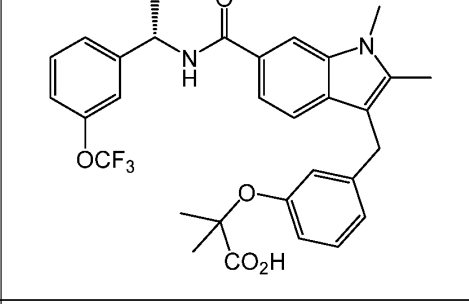
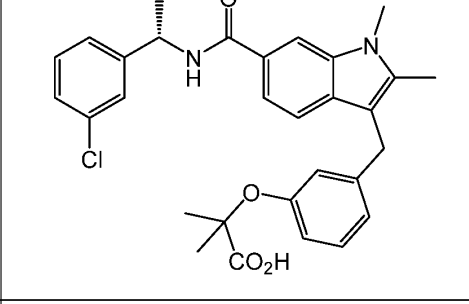
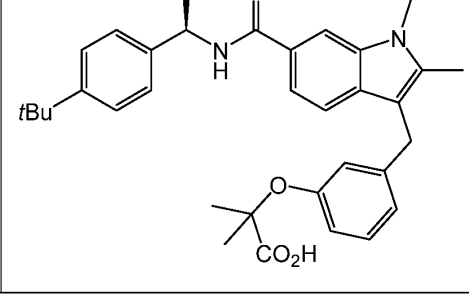
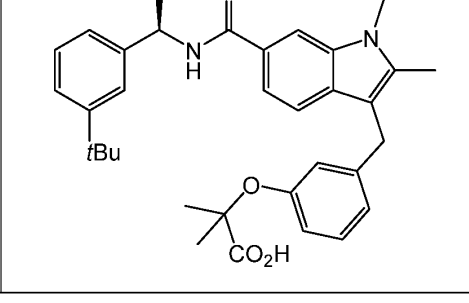
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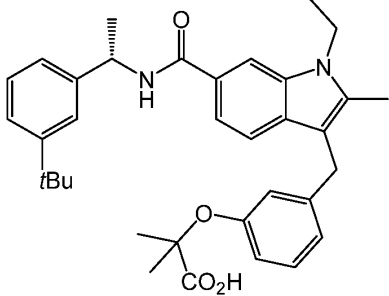
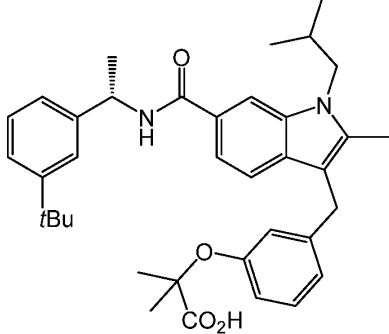
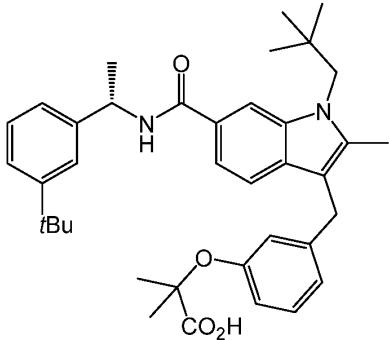
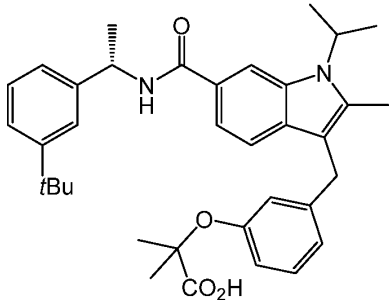
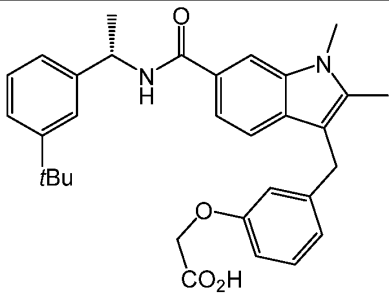
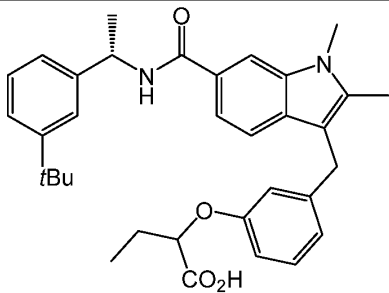
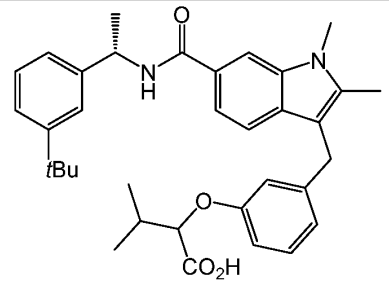
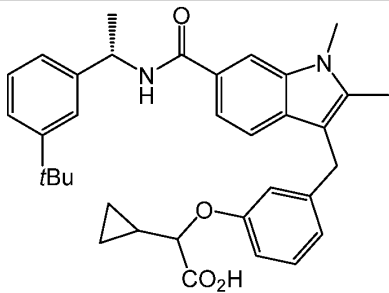
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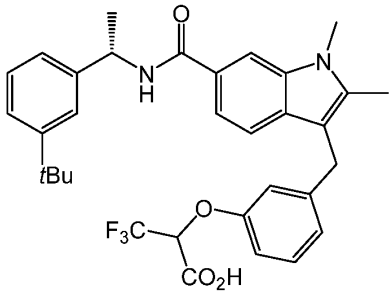
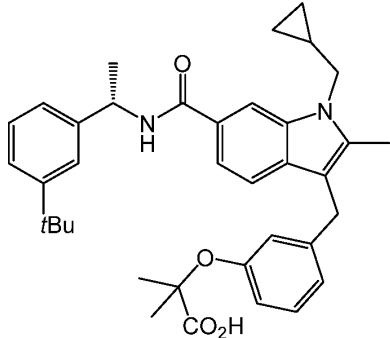
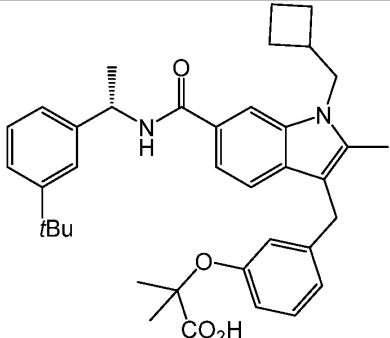
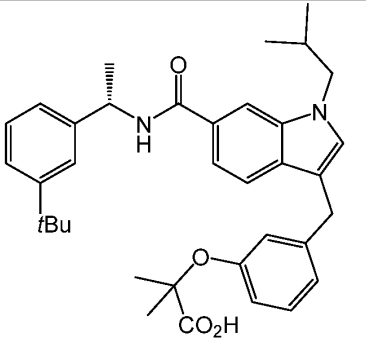
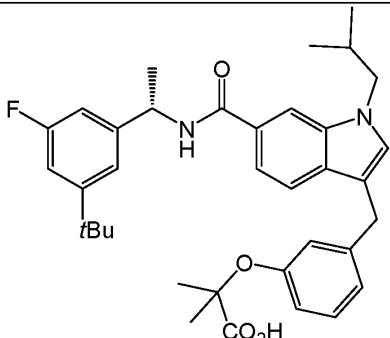
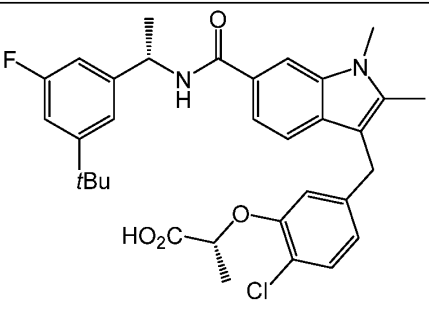
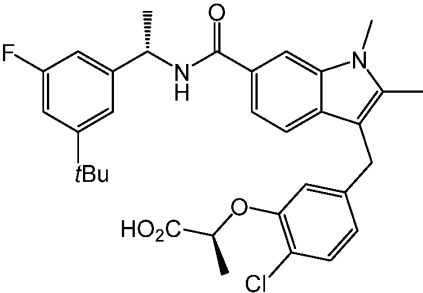
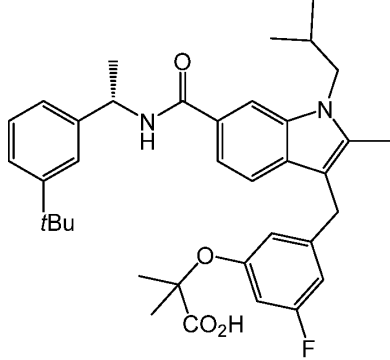
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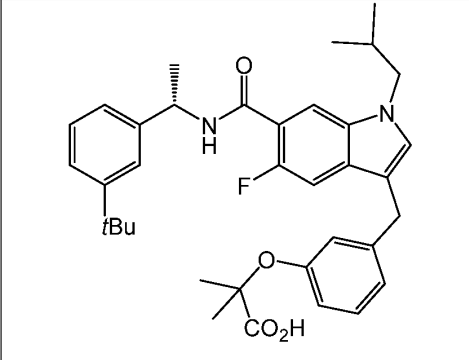
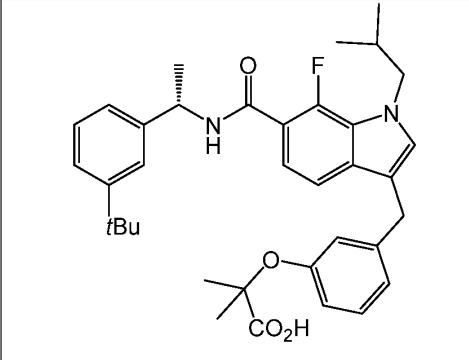
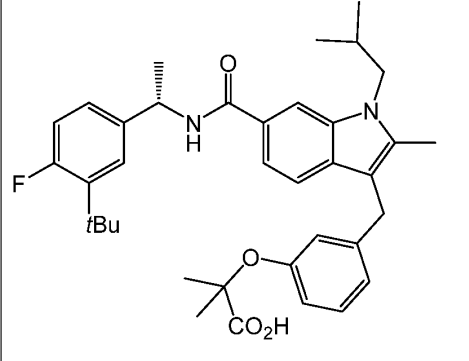
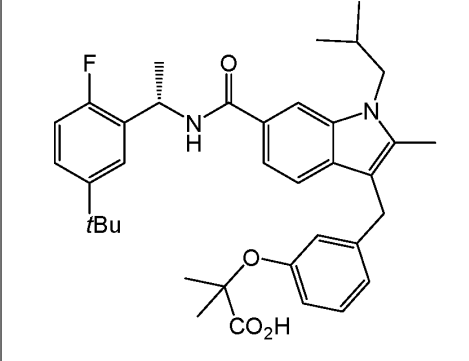
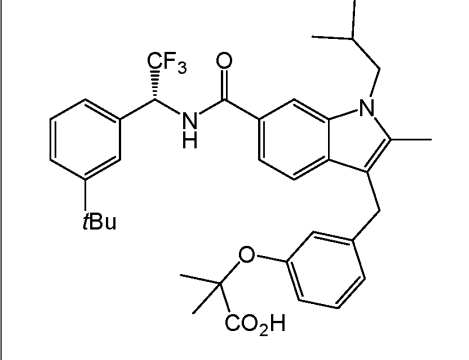
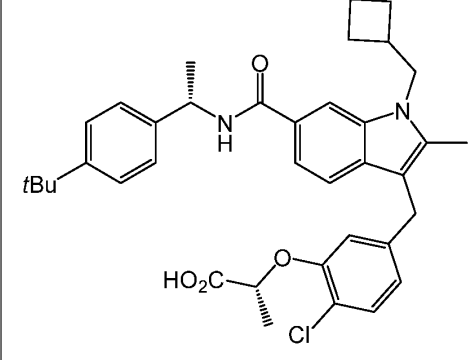
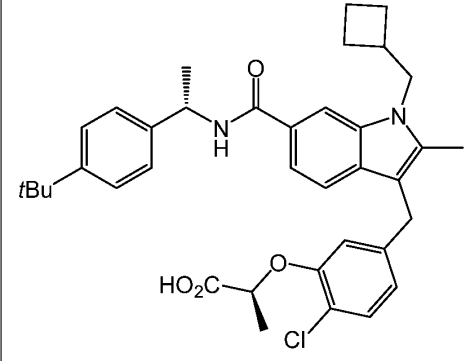
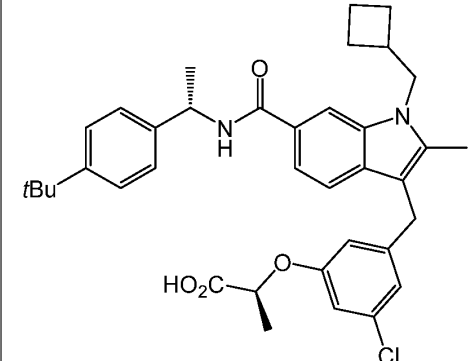
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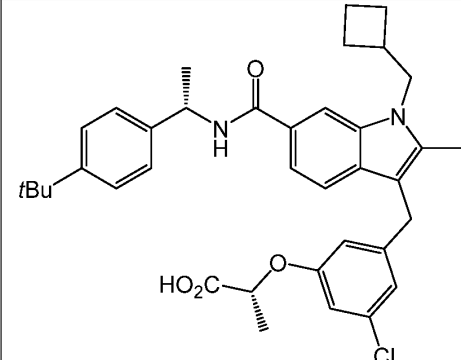
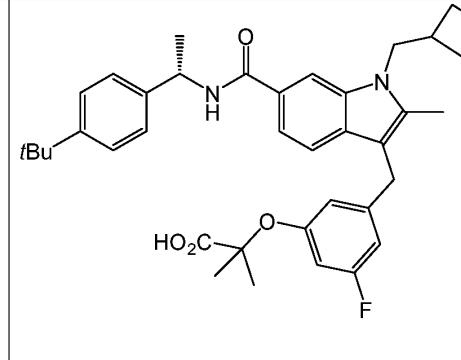
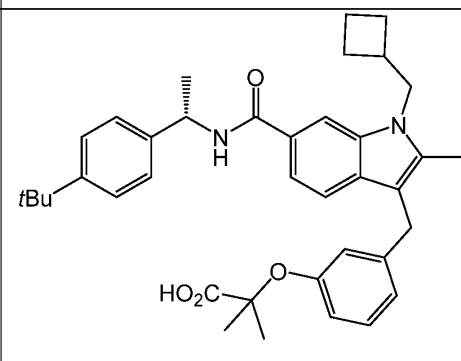
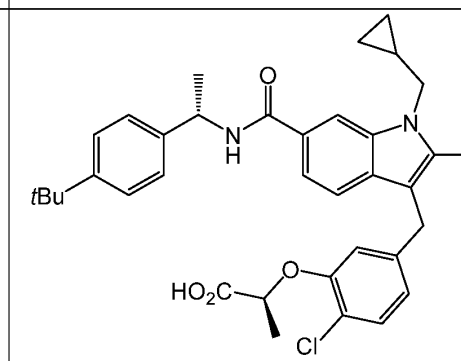
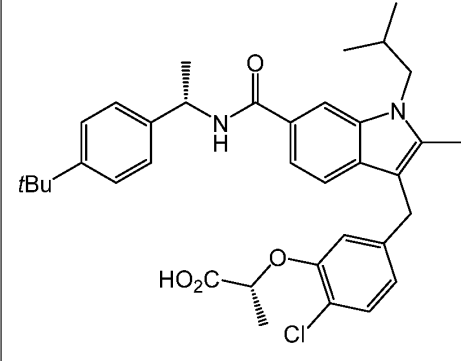
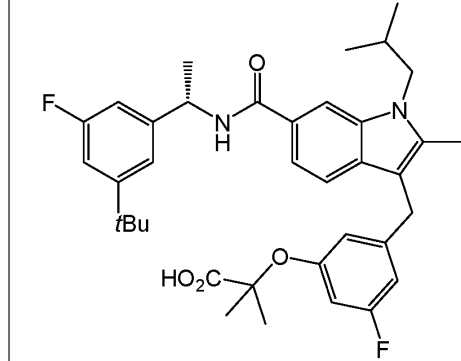
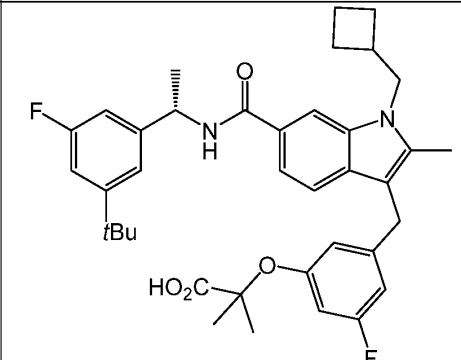
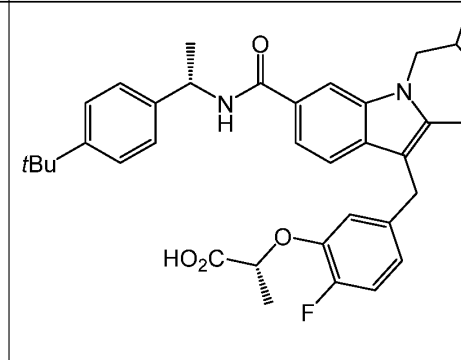
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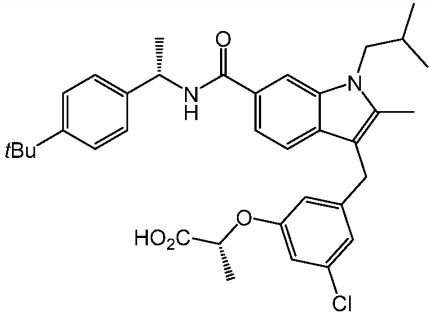
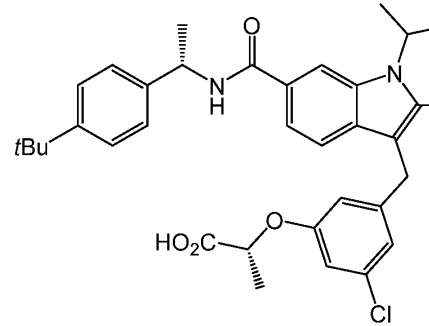
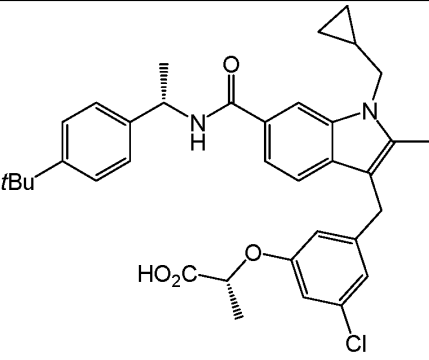
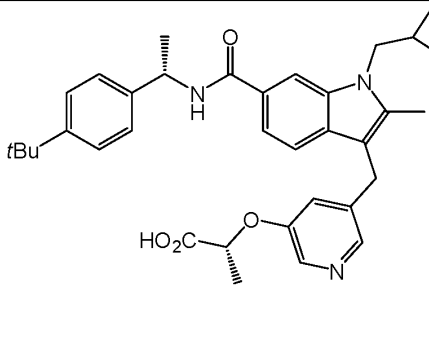
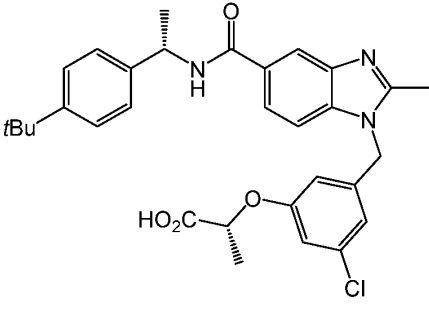
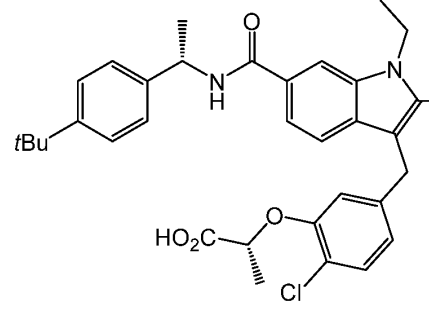
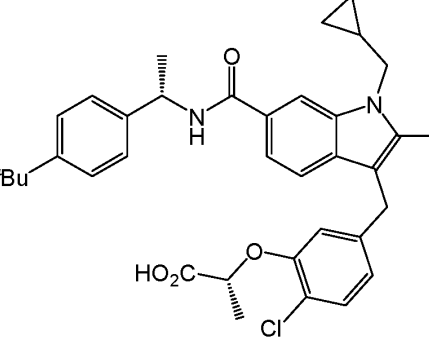
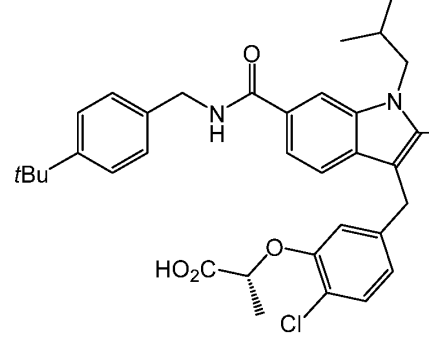
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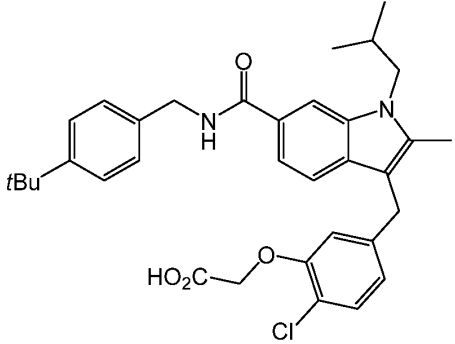
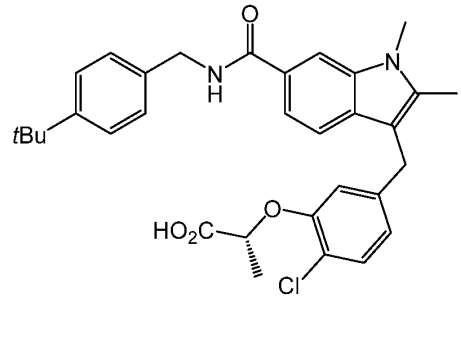
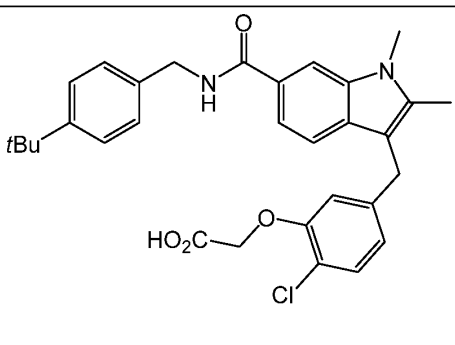
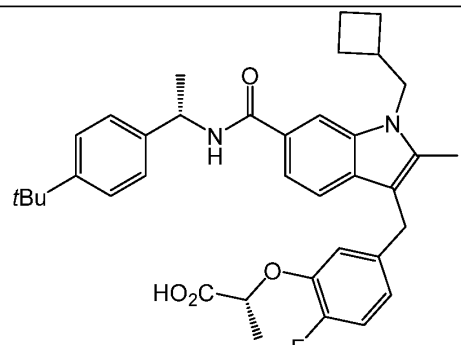
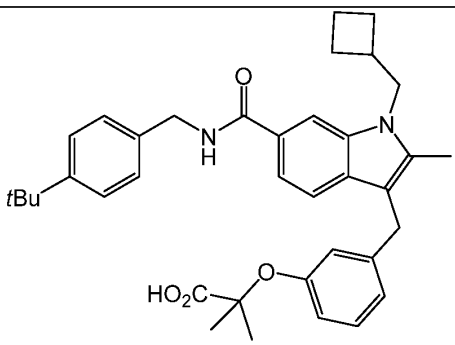
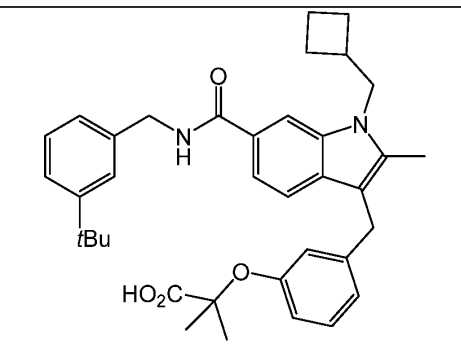
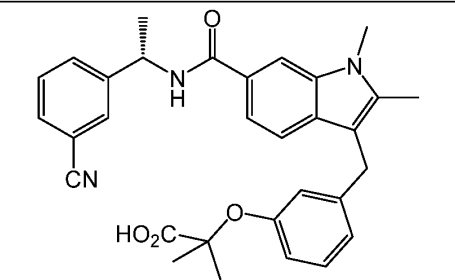
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or a pharmaceutically acceptable salt or prodrug thereof.

[0173] In certain embodiments, the compound is not a peroxisome proliferator-activated receptor γ (PPAR γ) agonist. In certain embodiments, the compound is a PPAR γ antagonist. In certain embodiments, the compound is a PPAR γ inverse agonist.

[0174] In certain embodiments, a "provided compound (a compound described herein, a compound of the present disclosure) is a compound of any of the formulae herein (*e.g.*, Formula (I)), or pharmaceutically acceptable salt or prodrug thereof. In certain embodiments, a provided compound is a compound of any of the formulae herein (*e.g.*, Formula (I)), or a pharmaceutically acceptable salt thereof. In certain embodiments, a provided compound is a compound of any of the formulae herein (*e.g.*, Formula (I)), or a salt thereof.

[0175] In certain embodiments, a provided compound is not a compound of any formulae described in International PCT Application Publication No. WO 2012/170554. In certain embodiments, a provided compound is not a compound of any formulae described in International PCT Application Publication No. WO 2012/170561. In certain embodiments, a provided compound is not a compound of any formulae described in International PCT Application Publication No. WO 2013/078233. In certain embodiments, a provided compound is not a compound of any formulae described in International PCT Application Publication No. WO 2013/078237. In certain embodiments, a provided compound is not a compound of any formulae described in International PCT Application Publication No. WO 2013/078240. In certain embodiments, a provided compound is not a compound of any formulae described in International PCT Application Publication No. WO 2015/161108.

Pharmaceutical Compositions and Kits

[0176] In one aspect, the present disclosure provides pharmaceutical compositions comprising a provided compound. In some embodiments, the pharmaceutical composition comprises one or more excipients. In certain embodiments, the pharmaceutical compositions described herein comprise a provided compound and an excipient.

[0177] In certain embodiments, the pharmaceutical composition comprises an effective amount of the provided compound. In certain embodiments, the effective amount is a therapeutically effective amount. In certain embodiments, the effective amount is a prophylactically effective amount. In certain embodiments, the effective amount is an amount effective for treating a disease or disorder associated with associated with peroxisome proliferator-activated receptor γ (PPAR γ) (*e.g.*, progressive bone disease, proliferative disease, metabolic disease) in a subject in need thereof. In certain embodiments, the effective amount is an amount effective for preventing a disease or disorder associated with peroxisome proliferator-activated receptor γ (PPAR γ) (*e.g.*, progressive bone disease, proliferative disease, metabolic disease) in a subject in need thereof. In certain embodiments, the effective amount is an amount effective for reducing the risk of developing a disease or disorder associated with peroxisome proliferator-activated receptor γ (PPAR γ) (*e.g.*, progressive bone disease, proliferative disease, metabolic disease) in a subject in need thereof. In certain embodiments, the effective amount is an amount effective for treating, preventing, or reducing the risk of developing a disease or disorder associated with peroxisome proliferator-activated receptor γ (PPAR γ) (*e.g.*, progressive bone disease, proliferative disease, metabolic disease) in a subject in need thereof, wherein side effects (*e.g.*, weight gain, edema, impairment of bone growth or formation, cardiac hypertrophy, congestive heart failure, vascular leak syndrome, hepatotoxicity) experienced by the

subject are reduced compared with administration of a PPAR γ agonist. In certain embodiments, the effective amount is an amount effective for modulating (*e.g.*, upregulating, downregulating, increasing, decreasing) PPAR γ in a subject in need thereof or in a cell, tissue, or biological sample. In certain embodiments, the effective amount is an amount not effective for activating PPAR γ . In certain embodiments, the effective amount is an amount effective for reducing phosphorylation of PPAR γ at serine 273. In certain embodiments, the effective amount is an amount effective for normalizing the functional remodeling activities of osteocytes, osteoblasts, and/or osteoclasts to result in healthy bone structure and/or strength. In certain embodiments, the functional remodeling activities are measured by increased bone cortical area, lower bone marrow adiposity, increased bone material strength, and/or increased bone turnover markers and circulating osteoprogenitors. *See, e.g.*, L. A. Stechschulte *et al.*, *EBioMedicine* **2016**, 10, 174-184. In certain embodiments, the effective amount is an amount effective for decreasing marrow adiposity. In certain embodiments, the effective amount is an amount effective for increasing trabecular and/or cortical bone. In certain embodiments, the effective amount is an amount effective for improving metabolic parameters by reducing fasting plasma glucose into a normal range less than 100 mg/dl and HbA1c less than 6%.

[0178] In certain embodiments, the subject is an animal. In certain embodiments, the subject is a human. In certain embodiments, the subject is a human aged 18 years or older. In certain embodiments, the subject is a human aged 12-18 years, exclusive. In certain embodiments, the subject is a human aged 2-12 years, inclusive. In certain embodiments, the subject is a human younger than 2 years. In certain embodiments, the subject is a non-human animal. In certain embodiments, the subject is a mammal. In certain embodiments, the subject is a non-human mammal. In certain embodiments, the subject is a domesticated animal, such as a dog, cat, cow, pig, horse, sheep, or goat. In certain embodiments, the subject is a companion animal, such as a dog or cat. In certain embodiments, the subject is a livestock animal, such as a cow, pig, horse, sheep, or goat. In certain embodiments, the subject is a zoo animal. In another embodiment, the subject is a research animal, such as a rodent (*e.g.*, mouse, rat), dog, pig, or non-human primate. In certain embodiments, the animal is a genetically engineered animal. In certain embodiments, the animal is a transgenic animal (*e.g.*, transgenic mice and transgenic pigs). In certain embodiments, the subject is a fish or reptile.

[0179] In certain embodiments, the effective amount is an amount effective for modulating (*e.g.*, upregulating, downregulating, increasing, decreasing) activity of PPAR γ by at least about 10%, at least about 20%, at least about 30%, at least about 40%, 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 98%, at least about 99%, or at least about 100%. In certain embodiments, the effective amount is an amount effective for modulating (*e.g.*, upregulating, downregulating, increasing, decreasing) activity of PPAR γ by a range between a percentage described in this paragraph and another percentage described in this paragraph, inclusive.

[0180] In certain embodiments, the effective amount is an amount effective for reducing phosphorylation of PPAR γ at serine 273 by at least about 10%, at least about 20%, at least about 30%, at least about 40%, 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 98%, at least about 99%, or at least about 100%. In certain embodiments, the effective amount is an amount effective for reducing phosphorylation of PPAR γ at serine 273 by a range between a percentage described in this paragraph and another percentage described in this paragraph, inclusive.

[0181] In certain embodiments, the pharmaceutical composition is for use in treating a disease or disorder associated with peroxisome proliferator-activated receptor γ (PPAR γ) (*e.g.*, progressive bone disease, proliferative disease, metabolic disease) in a subject in need thereof. In certain embodiments, the pharmaceutical composition is for use in preventing a disease or disorder associated with peroxisome proliferator-activated receptor γ (PPAR γ) (*e.g.*, progressive bone disease, proliferative disease, metabolic disease) in a subject in need thereof. In certain embodiments, the pharmaceutical composition is for use in modulating (*e.g.*, upregulating, downregulating, increasing, decreasing) PPAR γ in a subject in need thereof or in a cell, tissue, or biological sample.

[0182] A provided compound or pharmaceutical composition, as described herein, can be administered in combination with one or more additional pharmaceutical agents (*e.g.*, therapeutically and/or prophylactically active agents). The provided compounds or pharmaceutical compositions can be administered in combination with additional pharmaceutical agents that improve their activity (*e.g.*, activity (*e.g.*, potency and/or efficacy) in treating a disease or disorder associated with peroxisome proliferator-activated receptor γ (PPAR γ) in a subject in need thereof, in preventing a disease or disorder associated with PPAR γ in a subject in need thereof, and/or in reducing the risk of developing a disease or disorder associated with PPAR γ in a subject in need thereof), improve bioavailability, improve safety, reduce drug resistance, reduce and/or modify metabolism, inhibit excretion, and/or modify distribution in a subject or cell. It will also be appreciated that the additional pharmaceutical agents employed may achieve a desired effect for the same disorder, and/or it may achieve different effects. In certain embodiments, a pharmaceutical composition described herein including a provided compound described herein and an additional pharmaceutical agent exhibit a synergistic effect that is absent in a pharmaceutical composition including one of the provided compounds and the additional pharmaceutical agent, but not both. In some embodiments, the additional pharmaceutical agent achieves a desired effect for the same disorder. In some embodiments, the additional pharmaceutical agent achieves different effects.

[0183] The provided compound or pharmaceutical composition can be administered concurrently with, prior to, or subsequent to one or more additional pharmaceutical agents, which are different from the compound or pharmaceutical composition and may be useful as, *e.g.*, combination therapies. Pharmaceutical agents include therapeutically active agents. Pharmaceutical agents also include prophylactically active agents. Pharmaceutical agents include small organic molecules such as drug compounds (*e.g.*, compounds approved for human or veterinary use by the U.S. Food and Drug Administration as provided in the Code of Federal Regulations (CFR)), peptides, proteins, carbohydrates, monosaccharides, oligosaccharides, polysaccharides, nucleoproteins, mucoproteins, lipoproteins, synthetic polypeptides, synthetic proteins, small molecules linked to proteins, glycoproteins, steroids, nucleic acids,

DNAs, RNAs, nucleotides, nucleosides, oligonucleotides, antisense oligonucleotides, lipids, hormones, vitamins, and cells. In certain embodiments, the additional pharmaceutical agent is a pharmaceutical agent useful for treating and/or preventing a disease or disorder associated with peroxisome proliferator-activated receptor γ (PPAR γ).

[0184] Each additional pharmaceutical agent may be administered at a dose and/or on a time schedule determined for that pharmaceutical agent. The additional pharmaceutical agents may also be administered together with each other and/or with the compound or pharmaceutical composition described herein in a single dose or administered separately in different doses. The particular combination to employ in a regimen will take into account compatibility of the compound described herein with the additional pharmaceutical agent(s) and/or the desired therapeutic and/or prophylactic effect to be achieved. In general, it is expected that the additional pharmaceutical agent(s) in combination be utilized at levels that do not exceed the levels at which they are utilized individually. In some embodiments, the levels utilized in combination will be lower than those utilized individually.

[0185] The additional pharmaceutical agents include, but are not limited to, anti-proliferative agents, anti-cancer agents, anti-angiogenesis agents, steroidal or non-steroidal anti-inflammatory agents, immunosuppressants, anti-bacterial agents, anti-viral agents, cardiovascular agents, cholesterol-lowering agents, anti-diabetic agents, anti-allergic agents, contraceptive agents, pain-relieving agents, anesthetics, anti-coagulants, inhibitors of an enzyme, steroidal agents, steroidal or antihistamine, antigens, vaccines, antibodies, decongestant, sedatives, opioids, analgesics, anti-pyretics, hormones, and prostaglandins. In certain embodiments, the additional pharmaceutical agents include, but are not limited to, cardiovascular agents, cholesterol-lowering agents, anti-diabetic agents, anti-coagulants, steroidal agents, hormones, and prostaglandins. In certain embodiments, the additional pharmaceutical agent is a cardiovascular agent. In certain embodiments, the additional pharmaceutical agent is a cholesterol-lowering agent. In certain embodiments, the additional pharmaceutical agent is an anti-diabetic agent. In certain embodiments, the additional pharmaceutical agent is an anti-coagulant. In certain embodiments, the additional pharmaceutical agent is a steroidal agent. In certain embodiments, the additional pharmaceutical agent is a hormone. In certain embodiments, the additional pharmaceutical agent is a prostaglandin.

[0186] In certain embodiments, the provided compound or pharmaceutical composition is a solid. In certain embodiments, the provided compound or pharmaceutical composition is a powder. In certain embodiments, the provided compound or pharmaceutical composition can be dissolved in a liquid to make a solution. In certain embodiments, the provided compound or pharmaceutical composition is dissolved in water to make an aqueous solution. In certain embodiments, the pharmaceutical composition is a liquid for parental injection. In certain embodiments, the pharmaceutical composition is a liquid for oral administration (*e.g.*, ingestion). In certain embodiments, the pharmaceutical composition is a liquid (*e.g.*, aqueous solution) for intravenous injection. In certain embodiments, the pharmaceutical composition is a liquid (*e.g.*, aqueous solution) for subcutaneous injection.

[0187] Pharmaceutical compositions described herein can be prepared by any method known in the art of pharmacology. In general, such preparatory methods include the steps of bringing the composition

comprising a provided compound (*i.e.*, the “active ingredient”) into association with a carrier and/or one or more other accessory ingredients, and then, if necessary and/or desirable, shaping and/or packaging the product into a desired single- or multi-dose unit.

[0188] Pharmaceutical compositions can be prepared, packaged, and/or sold in bulk, as a single unit dose, and/or as a plurality of single unit doses. A “unit dose” is a discrete amount of the pharmaceutical composition comprising a predetermined amount of the active ingredient. The amount of the active ingredient is generally equal to the dosage of the active ingredient which would be administered to a subject and/or a convenient fraction of such a dosage, such as one-half or one-third of such a dosage.

[0189] Relative amounts of the provided compound, pharmaceutically acceptable excipient, agent, and/or any additional ingredients in a pharmaceutical composition described herein will vary, depending upon the identity, size, and/or condition of the subject treated and further depending upon the route by which the pharmaceutical composition is to be administered. The pharmaceutical composition may comprise between 0.1% and 100% (w/w) agent, inclusive.

[0190] Pharmaceutically acceptable excipients used in manufacture of provided pharmaceutical compositions include inert diluents, dispersing and/or granulating agents, surface active agents and/or emulsifiers, disintegrating agents, binding agents, preservatives, buffering agents, lubricating agents, and/or oils. Excipients and accessory ingredients, such as cocoa butter and suppository waxes, coloring agents, coating agents, sweetening, flavoring, and perfuming agents, may also be present in the pharmaceutical composition.

[0191] Exemplary diluents include calcium carbonate, sodium carbonate, calcium phosphate, dicalcium phosphate, calcium sulfate, calcium hydrogen phosphate, sodium phosphate lactose, sucrose, cellulose, microcrystalline cellulose, kaolin, mannitol, sorbitol, inositol, sodium chloride, dry starch, cornstarch, powdered sugar, and mixtures thereof.

[0192] Exemplary granulating and/or dispersing agents include potato starch, corn starch, tapioca starch, sodium starch glycolate, clays, alginic acid, guar gum, citrus pulp, agar, bentonite, cellulose, and wood products, natural sponge, cation-exchange resins, calcium carbonate, silicates, sodium carbonate, cross-linked poly(vinyl-pyrrolidone) (crospovidone), sodium carboxymethyl starch (sodium starch glycolate), carboxymethyl cellulose, cross-linked sodium carboxymethyl cellulose (croscarmellose), methylcellulose, pregelatinized starch (starch 1500), microcrystalline starch, water insoluble starch, calcium carboxymethyl cellulose, magnesium aluminum silicate (Veegum), sodium lauryl sulfate, quaternary ammonium compounds, and mixtures thereof.

[0193] Exemplary surface active agents and/or emulsifiers include natural emulsifiers (*e.g.*, acacia, agar, alginic acid, sodium alginate, tragacanth, chondrux, cholesterol, xanthan, pectin, gelatin, egg yolk, casein, wool fat, cholesterol, wax, and lecithin), colloidal clays (*e.g.*, bentonite (aluminum silicate) and Veegum (magnesium aluminum silicate)), long chain amino acid derivatives, high molecular weight alcohols (*e.g.*, stearyl alcohol, cetyl alcohol, oleyl alcohol, triacetin monostearate, ethylene glycol distearate, glyceryl monostearate, and propylene glycol monostearate, polyvinyl alcohol), carbomers (*e.g.*, carboxy polymethylene, polyacrylic acid, acrylic acid polymer, and carboxyvinyl polymer), carrageenan, cellulosic

derivatives (*e.g.*, carboxymethylcellulose sodium, powdered cellulose, hydroxymethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose), sorbitan fatty acid esters (*e.g.*, polyoxyethylene sorbitan monolaurate (Tween® 20), polyoxyethylene sorbitan monostearate (Tween® 60), polyoxyethylene sorbitan monooleate (Tween® 80), sorbitan monopalmitate (Span® 40), sorbitan monostearate (Span® 60), sorbitan tristearate (Span® 65), glyceryl monooleate, sorbitan monooleate (Span® 80), polyoxyethylene esters (*e.g.*, polyoxyethylene monostearate (Myrj® 45), polyoxyethylene hydrogenated castor oil, polyethoxylated castor oil, polyoxymethylene stearate, and Solutol®), sucrose fatty acid esters, polyethylene glycol fatty acid esters (*e.g.*, Cremophor®), polyoxyethylene ethers, (*e.g.*, polyoxyethylene lauryl ether (Brij® 30)), poly(vinyl-pyrrolidone), diethylene glycol monolaurate, triethanolamine oleate, sodium oleate, potassium oleate, ethyl oleate, oleic acid, ethyl laurate, sodium lauryl sulfate, Pluronic® F-68, poloxamer P-188, cetrimonium bromide, cetylpyridinium chloride, benzalkonium chloride, docusate sodium, and/or mixtures thereof.

[0194] Exemplary binding agents include starch (*e.g.*, cornstarch and starch paste), gelatin, sugars (*e.g.*, sucrose, glucose, dextrose, dextrin, molasses, lactose, lactitol, mannitol, *etc.*), natural and synthetic gums (*e.g.*, acacia, sodium alginate, extract of Irish moss, panwar gum, ghatti gum, mucilage of isapol husks, carboxymethylcellulose, methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, microcrystalline cellulose, cellulose acetate, poly(vinyl-pyrrolidone), magnesium aluminum silicate (Veegum®), and larch arabogalactan), alginates, polyethylene oxide, polyethylene glycol, inorganic calcium salts, silicic acid, polymethacrylates, waxes, water, alcohol, and/or mixtures thereof.

[0195] Exemplary preservatives include antioxidants, chelating agents, antimicrobial preservatives, antifungal preservatives, antiprotozoan preservatives, alcohol preservatives, acidic preservatives, and other preservatives. In certain embodiments, the preservative is an antioxidant. In other embodiments, the preservative is a chelating agent.

[0196] Exemplary antioxidants include alpha tocopherol, ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, monothioglycerol, potassium metabisulfite, propionic acid, propyl gallate, sodium ascorbate, sodium bisulfite, sodium metabisulfite, and sodium sulfite.

[0197] Exemplary chelating agents include ethylenediaminetetraacetic acid (EDTA) and salts and hydrates thereof (*e.g.*, sodium edetate, disodium edetate, trisodium edetate, calcium disodium edetate, dipotassium edetate, and the like), citric acid and salts and hydrates thereof (*e.g.*, citric acid monohydrate), fumaric acid and salts and hydrates thereof, malic acid and salts and hydrates thereof, phosphoric acid and salts and hydrates thereof, and tartaric acid and salts and hydrates thereof. Exemplary antimicrobial preservatives include benzalkonium chloride, benzethonium chloride, benzyl alcohol, bronopol, cetrimide, cetylpyridinium chloride, chlorhexidine, chlorobutanol, chlorocresol, chloroxylenol, cresol, ethyl alcohol, glycerin, hexetidine, imidurea, phenol, phenoxyethanol, phenylethyl alcohol, phenylmercuric nitrate, propylene glycol, and thimerosal.

[0198] Exemplary antifungal preservatives include butyl paraben, methyl paraben, ethyl paraben, propyl paraben, benzoic acid, hydroxybenzoic acid, potassium benzoate, potassium sorbate, sodium benzoate, sodium propionate, and sorbic acid.

[0199] Exemplary alcohol preservatives include ethanol, polyethylene glycol, phenol, phenolic compounds, bisphenol, chlorobutanol, hydroxybenzoate, and phenylethyl alcohol.

[0200] Exemplary acidic preservatives include vitamin A, vitamin C, vitamin E, beta-carotene, citric acid, acetic acid, dehydroacetic acid, ascorbic acid, sorbic acid, and phytic acid.

[0201] Other preservatives include tocopherol, tocopherol acetate, deteroxime mesylate, cetrimide, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), ethylenediamine, sodium lauryl sulfate (SLS), sodium lauryl ether sulfate (SLES), sodium bisulfite, sodium metabisulfite, potassium sulfite, potassium metabisulfite, Glydant® Plus, Phenonip®, methylparaben, Germall® 115, Germaben® II, Neolone®, Kathon®, and Euxyl®.

[0202] Exemplary buffering agents include citrate buffer solutions, acetate buffer solutions, phosphate buffer solutions, ammonium chloride, calcium carbonate, calcium chloride, calcium citrate, calcium glutubionate, calcium gluceptate, calcium gluconate, D-gluconic acid, calcium glycerophosphate, calcium lactate, propanoic acid, calcium levulinate, pentanoic acid, dibasic calcium phosphate, phosphoric acid, tribasic calcium phosphate, calcium hydroxide phosphate, potassium acetate, potassium chloride, potassium gluconate, potassium mixtures, dibasic potassium phosphate, monobasic potassium phosphate, potassium phosphate mixtures, sodium acetate, sodium bicarbonate, sodium chloride, sodium citrate, sodium lactate, dibasic sodium phosphate, monobasic sodium phosphate, sodium phosphate mixtures, tromethamine, magnesium hydroxide, aluminum hydroxide, alginic acid, pyrogen-free water, isotonic saline, Ringer's solution, ethyl alcohol, and mixtures thereof.

[0203] Exemplary lubricating agents include magnesium stearate, calcium stearate, stearic acid, silica, talc, malt, glyceryl behenate, hydrogenated vegetable oils, polyethylene glycol, sodium benzoate, sodium acetate, sodium chloride, leucine, magnesium lauryl sulfate, sodium lauryl sulfate, and mixtures thereof.

[0204] Exemplary natural oils include almond, apricot kernel, avocado, babassu, bergamot, black current seed, borage, cade, camomile, canola, caraway, carnauba, castor, cinnamon, cocoa butter, coconut, cod liver, coffee, corn, cotton seed, emu, eucalyptus, evening primrose, fish, flaxseed, geraniol, gourd, grape seed, hazel nut, hyssop, isopropyl myristate, jojoba, kukui nut, lavandin, lavender, lemon, litsea cubeba, macademia nut, mallow, mango seed, meadowfoam seed, mink, nutmeg, olive, orange, orange roughy, palm, palm kernel, peach kernel, peanut, poppy seed, pumpkin seed, rapeseed, rice bran, rosemary, safflower, sandalwood, sasquana, savoury, sea buckthorn, sesame, shea butter, silicone, soybean, sunflower, tea tree, thistle, tsubaki, vetiver, walnut, and wheat germ oils. Exemplary synthetic oils include, but are not limited to, butyl stearate, caprylic triglyceride, capric triglyceride, cyclomethicone, diethyl sebacate, dimethicone 360, isopropyl myristate, mineral oil, octyldodecanol, oleyl alcohol, silicone oil, and mixtures thereof.

[0205] Liquid dosage forms for oral and parenteral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active

ingredients, the liquid dosage forms may comprise 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 (*e.g.*, 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 pharmaceutical compositions can include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents. In certain embodiments for parenteral administration, the conjugates described herein are mixed with solubilizing agents such as Cremophor®, alcohols, oils, modified oils, glycols, polysorbates, cyclodextrins, polymers, and mixtures thereof.

[0206] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions can be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation can be a sterile injectable solution, suspension, or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that can 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 di-glycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

[0207] The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid pharmaceutical compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[0208] 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 can be accomplished by the use of 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 may be accomplished by dissolving or suspending the drug in an oil vehicle.

[0209] Pharmaceutical compositions for rectal or vaginal administration are typically suppositories which can be prepared by mixing the conjugates described herein with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol, or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active ingredient.

[0210] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active ingredient is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or (a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, (b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose, and acacia, (c)

humectants such as glycerol, (d) disintegrating agents such as agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, (e) solution retarding agents such as paraffin, (f) absorption accelerators such as quaternary ammonium compounds, (g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, (h) absorbents such as kaolin and bentonite clay, and (i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets, and pills, the dosage form may include a buffering agent.

[0211] Solid compositions of a similar type can 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 solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the art of pharmacology. They may optionally comprise opacifying agents and can be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of encapsulating compositions which can be used include polymeric substances and waxes.

[0212] The active ingredient can be in a 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 ingredient can be admixed with at least one inert diluent such as sucrose, lactose, or starch. Such dosage forms may comprise, as is normal practice, additional substances other than inert diluents, *e.g.*, tableting lubricants and other tableting aids such as a magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may comprise buffering agents. They may optionally comprise opacifying agents and can be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of encapsulating agents which can be used include polymeric substances and waxes.

[0213] Dosage forms for topical and/or transdermal administration of a compound described herein may include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants, and/or patches. Generally, the active ingredient is admixed under sterile conditions with a pharmaceutically acceptable carrier or excipient and/or any needed preservatives and/or buffers as can be required. Additionally, the present disclosure contemplates the use of transdermal patches, which often have the added advantage of providing controlled delivery of an active ingredient to the body. Such dosage forms can be prepared, for example, by dissolving and/or dispensing the active ingredient in the proper medium. Alternatively or additionally, the rate can be controlled by either providing a rate controlling membrane and/or by dispersing the active ingredient in a polymer matrix and/or gel.

[0214] Formulations suitable for topical administration include, but are not limited to, liquid and/or semi-liquid preparations such as liniments, lotions, oil-in-water and/or water-in-oil emulsions such as creams, ointments, and/or pastes, and/or solutions and/or suspensions. Topically administrable formulations may,

for example, comprise from about 1% to about 10% (w/w) active ingredient, although the concentration of the active ingredient can be as high as the solubility limit of the active ingredient in the solvent.

Formulations for topical administration may further comprise one or more of the additional ingredients described herein.

[0215] Suitable devices for use in delivering injectable pharmaceutical compositions described herein include short needle devices. Injectable pharmaceutical compositions can be administered by devices which limit the effective penetration length of a needle into the skin. Alternatively or additionally, conventional syringes can be used in the classical mantoux method of administration. Jet injection devices which deliver liquid formulations via a liquid jet injector and/or via a needle. Ballistic powder/particle delivery devices which use compressed gas to accelerate the compound in powder form are suitable.

[0216] A pharmaceutical composition described herein can be prepared, packaged, and/or sold in a formulation suitable for pulmonary administration via the buccal cavity. Such a formulation may comprise dry particles which comprise the active ingredient and which have a diameter in the range from about 0.5 to about 7 nanometers, or from about 1 to about 6 nanometers. Such pharmaceutical compositions are conveniently in the form of dry powders for administration using a device comprising a dry powder reservoir to which a stream of propellant can be directed to disperse the powder and/or using a self-propelling solvent/powder dispensing container such as a device comprising the active ingredient dissolved and/or suspended in a low-boiling propellant in a sealed container. Such powders comprise particles wherein at least 98% of the particles by weight have a diameter greater than 0.5 nanometers and at least 95% of the particles by number have a diameter less than 7 nanometers. Alternatively, at least 95% of the particles by weight have a diameter greater than 1 nanometer and at least 90% of the particles by number have a diameter less than 6 nanometers. Dry powder pharmaceutical compositions may include a solid fine powder diluent such as sugar and are conveniently provided in a unit dose form.

[0217] Low boiling propellants generally include liquid propellants having a boiling point of below 65 °F at atmospheric pressure. Generally, the propellant may constitute 50 to 99.9% (w/w) of the pharmaceutical composition, and the active ingredient may constitute 0.1 to 20% (w/w) of the pharmaceutical composition. The propellant may further comprise additional ingredients such as a liquid non-ionic and/or solid anionic surfactant and/or a solid diluent (which may have a particle size of the same order as particles comprising the active ingredient).

[0218] Pharmaceutical compositions described herein formulated for pulmonary delivery may provide the active ingredient in the form of droplets of a solution and/or suspension. Such formulations can be prepared, packaged, and/or sold as aqueous and/or dilute alcoholic solutions and/or suspensions, optionally sterile, comprising the active ingredient, and may conveniently be administered using any nebulization and/or atomization device. Such formulations may further comprise one or more additional ingredients including a flavoring agent such as saccharin sodium, a volatile oil, a buffering agent, a surface active agent, and/or a preservative such as methylhydroxybenzoate. The droplets provided by this route of administration may have an average diameter in the range from about 0.1 to about 200 nanometers.

[0219] Formulations described herein as being useful for pulmonary delivery are useful for intranasal delivery of a pharmaceutical composition described herein. Another formulation suitable for intranasal administration is a coarse powder comprising the active ingredient and having an average particle from about 0.2 to 500 micrometers. Such a formulation is administered by rapid inhalation through the nasal passage from a container of the powder held close to the nares.

[0220] Formulations for nasal administration may, for example, comprise from about as little as 0.1% (w/w) to as much as 100% (w/w) of the active ingredient, and may comprise one or more of the additional ingredients described herein. A pharmaceutical composition described herein can be prepared, packaged, and/or sold in a formulation for buccal administration. Such formulations may, for example, be in the form of tablets and/or lozenges made using conventional methods, and may contain, for example, 0.1 to 20% (w/w) active ingredient, the balance comprising an orally dissolvable and/or degradable composition and, optionally, one or more of the additional ingredients described herein. Alternately, formulations for buccal administration may comprise a powder and/or an aerosolized and/or atomized solution and/or suspension comprising the active ingredient. Such powdered, aerosolized, and/or aerosolized formulations, when dispersed, may have an average particle and/or droplet size in the range from about 0.1 to about 200 nanometers, and may further comprise one or more of the additional ingredients described herein.

[0221] A pharmaceutical composition described herein can be prepared, packaged, and/or sold in a formulation for ophthalmic administration. Such formulations may, for example, be in the form of eye drops including, for example, a 0.1-1.0% (w/w) solution and/or suspension of the active ingredient in an aqueous or oily liquid carrier or excipient. Such drops may further comprise buffering agents, salts, and/or one or more other of the additional ingredients described herein. Other ophthalmically-administrable formulations which are useful include those which comprise the active ingredient in microcrystalline form and/or in a liposomal preparation. Ear drops and/or eye drops are also contemplated as being within the scope of this disclosure.

[0222] Although the descriptions of pharmaceutical compositions provided herein are principally directed to pharmaceutical compositions which are suitable for administration to humans, it will be understood by the skilled artisan that such pharmaceutical compositions are generally suitable for administration to animals of all sorts. Modification of pharmaceutical compositions suitable for administration to humans in order to render the pharmaceutical compositions suitable for administration to various animals is well understood, and the ordinarily skilled veterinary pharmacologist can design and/or perform such modification with ordinary experimentation.

[0223] Provided compounds are typically formulated in dosage unit form for ease of administration and uniformity of dosage. It will be understood, however, that the total daily usage of the pharmaceutical compositions described herein will be decided by a physician within the scope of sound medical judgment. The specific therapeutically effective dose level for any particular subject or organism will depend upon a variety of factors including the disease being treated and the severity of the disorder; the activity of the specific active ingredient employed; the specific composition employed; the age, body

weight, general health, sex, and diet of the subject; the time of administration, route of administration, and rate of excretion of the specific active ingredient employed; the duration of the treatment; drugs used in combination or coincidental with the specific active ingredient employed; and like factors well known in the medical arts.

[0224] The provided compounds and pharmaceutical compositions provided herein can be administered by any route, including enteral (*e.g.*, oral), parenteral, intravenous, intramuscular, intraarticular, intra-arterial, intramedullary, intrathecal, subcutaneous, intraventricular, transdermal, interdermal, rectal, intravaginal, intraperitoneal, topical (as by powders, ointments, creams, and/or drops), mucosal, nasal, buccal, sublingual; by intratracheal instillation, bronchial instillation, and/or inhalation; and/or as an oral spray, nasal spray, and/or aerosol. Specifically, contemplated routes are intraarticular administration, oral administration, intravenous administration (*e.g.*, systemic intravenous injection), regional administration *via* blood and/or lymph supply, and/or direct administration to an affected site. In general, the most appropriate route of administration will depend upon a variety of factors including the nature of the agent (*e.g.*, its stability in the environment of the gastrointestinal tract), and/or the condition of the subject (*e.g.*, whether the subject is able to tolerate oral administration).

[0225] The exact amount of a provided compound required to achieve an effective amount will vary from subject to subject, depending, for example, on species, age, and general condition of a subject, severity of the side effects or disorder, identity of the particular compound of the disclosure, mode of administration, and the like. An effective amount may be included in a single dose (*e.g.*, single oral dose) or multiple doses (*e.g.*, multiple oral doses). In certain embodiments, when multiple doses are administered to a subject or applied to a biological sample, tissue, or cell, any two doses of the multiple doses include different or substantially the same amounts of an agent described herein.

[0226] In certain embodiments, a pharmaceutical composition comprising a provided compound is administered, orally or parenterally, at dosage levels of each pharmaceutical composition sufficient to deliver from about 0.001 mg/kg to about 200 mg/kg in one or more dose administrations for one or several days (depending on the mode of administration). In certain embodiments, the effective amount per dose varies from about 0.001 mg/kg to about 200 mg/kg, about 0.001 mg/kg to about 100 mg/kg, about 0.01 mg/kg to about 100 mg/kg, from about 0.01 mg/kg to about 50 mg/kg, preferably from about 0.1 mg/kg to about 40 mg/kg, preferably from about 0.5 mg/kg to about 30 mg/kg, from about 0.01 mg/kg to about 10 mg/kg, from about 0.1 mg/kg to about 10 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic and/or prophylactic effect. In certain embodiments, the compounds described herein may be at dosage levels sufficient to deliver from about 0.001 mg/kg to about 200 mg/kg, from about 0.001 mg/kg to about 100 mg/kg, from about 0.01 mg/kg to about 100 mg/kg, from about 0.01 mg/kg to about 50 mg/kg, preferably from about 0.1 mg/kg to about 40 mg/kg, preferably from about 0.5 mg/kg to about 30 mg/kg, from about 0.01 mg/kg to about 10 mg/kg, from about 0.1 mg/kg to about 10 mg/kg, and more preferably from about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic and/or prophylactic effect. The desired dosage may be delivered three times a day, two times a day, once a day,

every other day, every third day, every week, every two weeks, every three weeks, or every four weeks. In certain embodiments, the desired dosage may be delivered using multiple administrations (*e.g.*, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or more administrations). In certain embodiments, the pharmaceutical composition described herein is administered at a dose that is below the dose at which the agent causes non-specific effects.

[0227] In certain embodiments, the pharmaceutical composition is administered at a dose of about 0.001 mg to about 1000 mg per unit dose. In certain embodiments, the pharmaceutical composition is administered at a dose of about 0.01 mg to about 200 mg per unit dose. In certain embodiments, the pharmaceutical composition is administered at a dose of about 0.01 mg to about 100 mg per unit dose. In certain embodiments, pharmaceutical composition is administered at a dose of about 0.01 mg to about 50 mg per unit dose. In certain embodiments, the pharmaceutical composition is administered at a dose of about 0.01 mg to about 10 mg per unit dose. In certain embodiments, the pharmaceutical composition is administered at a dose of about 0.1 mg to about 10 mg per unit dose.

[0228] Dose ranges as described herein provide guidance for the administration of provided compounds or pharmaceutical compositions to an adult. The amount to be administered to, for example, a child or an adolescent can be determined by a medical practitioner or person skilled in the art and can be lower or the same as that administered to an adult. In certain embodiments, a dose described herein is a dose to an adult human whose body weight is 70 kg.

[0229] In certain embodiments, when multiple doses are administered to a subject or applied to a tissue or cell, the frequency of administering the multiple doses to the subject or applying the multiple doses to the tissue or cell may be, in non-limiting examples, three doses a day, two doses a day, one dose a day, one dose every other day, one dose every third day, one dose every week, one dose every two weeks, one dose every three weeks, or one dose every four weeks, or even slow dose controlled delivery over a selected period of time using a drug delivery device. In certain embodiments, when multiple doses are administered to a subject or applied to a biological sample, tissue, or cell, the duration between the first dose and last dose of the multiple doses is one day, two days, four days, one week, two weeks, three weeks, one month, two months, three months, four months, six months, nine months, one year, two years, three years, four years, five years, seven years, ten years, fifteen years, twenty years, or the lifetime of the subject, tissue, or cell. In certain embodiments, the duration between the first dose and last dose of the multiple doses is three months, six months, or one year. In certain embodiments, the duration between the first dose and last dose of the multiple doses is the lifetime of the subject, tissue, or cell.

[0230] Also encompassed by the present disclosure are kits (*e.g.*, pharmaceutical packs). In certain embodiments, the kit comprises a provided compound or pharmaceutical composition described herein, and instructions for using the compound or pharmaceutical composition. In certain embodiments, the kit comprises a first container, wherein the first container includes the compound or pharmaceutical composition. In some embodiments, the kit further comprises a second container. In certain embodiments, the second container includes an excipient (*e.g.*, an excipient for dilution or suspension of the compound or pharmaceutical composition). In certain embodiments, the second container includes an additional

pharmaceutical agent. In some embodiments, the kit further comprises a third container. In certain embodiments, the third container includes an additional pharmaceutical agent. In some embodiments, the provided compound or pharmaceutical composition included in the first container and the excipient or additional pharmaceutical agent included in the second container are combined to form one unit dosage form. In some embodiments, the provided compound or pharmaceutical composition included in the first container, the excipient included in the second container, and the additional pharmaceutical agent included in the third container are combined to form one unit dosage form. In certain embodiments, each of the first, second, and third containers is independently a vial, ampule, bottle, syringe, dispenser package, tube, or inhaler.

[0231] In certain embodiments, the instructions are for administering the provided compound or pharmaceutical composition to a subject (*e.g.*, a subject in need of treatment or prevention of a disease or disorder described herein). In certain embodiments, the instructions are for contacting a biological sample or cell with the provided compound or pharmaceutical composition. In certain embodiments, the instructions comprise information required by a regulatory agency, such as the U.S. Food and Drug Administration (FDA) or the European Agency for the Evaluation of Medicinal Products (EMA). In certain embodiments, the instructions comprise prescribing information.

[0232] In certain embodiments, the kits and instructions provide for treating a disease or disorder associated with peroxisome proliferator-activated receptor γ (PPAR γ) in a subject in need thereof. In certain embodiments, the kits and instructions provide for preventing a disease or disorder associated with PPAR γ in a subject in need thereof. In certain embodiments, the kits and instructions provide for reducing the risk of developing a disease or disorder associated with PPAR γ in a subject in need thereof. In certain embodiments, the kits and instructions provide for modulating (*e.g.*, upregulating, downregulating, increasing, decreasing) PPAR γ in a subject in need thereof or in a cell, tissue, or biological sample.

[0233] A kit described herein may include one or more additional pharmaceutical agents described herein as a separate pharmaceutical composition.

[0234] Another object of the present disclosure is the use of a compound as described herein in the manufacture of a medicament for use in the treatment of a disorder or disease described herein. Another object of the present disclosure is the use of a compound as described herein for use in the treatment of a disorder or disease described herein.

Methods of Treatment and Prevention

[0235] In another aspect, the present disclosure provides methods of treating or preventing a disease or disorder in a subject in need thereof, comprising administering to the subject in need thereof a provided compound or pharmaceutical composition. In certain embodiments, the present disclosure provides methods of treating a disease or disorder in a subject in need thereof, comprising administering to the subject in need thereof a provided compound or pharmaceutical composition. In certain embodiments, the present disclosure provides methods of preventing a disease or disorder in a subject in need thereof, comprising administering to the subject in need thereof a provided compound or pharmaceutical

composition. In certain embodiments, the disease or disorder is associated with peroxisome proliferator-activated receptor γ (PPAR γ) (*e.g.*, progressive bone disease, proliferative disease, metabolic disease).

[0236] In another aspect, the present disclosure provides a provided compound or pharmaceutical composition for use in treating or preventing a disease or disorder in a subject in need thereof. In another aspect, the present disclosure provides a provided compound or pharmaceutical composition for use in treating a disease or disorder in a subject in need thereof. In another aspect, the present disclosure provides a provided compound or pharmaceutical composition for use in preventing a disease or disorder in a subject in need thereof. In certain embodiments, the disease or disorder is associated with peroxisome proliferator-activated receptor γ (PPAR γ) (*e.g.*, progressive bone disease, proliferative disease, metabolic disease).

[0237] In another aspect, the present disclosure provides a provided compound or pharmaceutical composition for use in the manufacture of a medicament for treatment or prevention of a disease or disorder in a subject in need thereof. In another aspect, the present disclosure provides a provided compound or pharmaceutical composition for use in the manufacture of a medicament for treatment of a disease or disorder in a subject in need thereof. In another aspect, the present disclosure provides a provided compound or pharmaceutical composition for use in the manufacture of a medicament for prevention of a disease or disorder in a subject in need thereof. In certain embodiments, the disease or disorder is associated with peroxisome proliferator-activated receptor γ (PPAR γ) (*e.g.*, progressive bone disease, proliferative disease, metabolic disease).

[0238] In certain embodiments, the disease or disorder is associated with peroxisome proliferator-activated receptor γ (PPAR γ) (*e.g.*, progressive bone disease, proliferative disease, metabolic disease). In certain embodiments, the disease or disorder is a progressive bone disease (*e.g.*, osteoporosis, Paget's Disease). In certain embodiments, the progressive bone disease is osteoporosis. In certain embodiments, the progressive bone disease is Paget's Disease. In certain embodiments, the disease or disorder is a proliferative disease (*e.g.*, cancer). In certain embodiments, the proliferative disease is cancer (*e.g.*, colorectal cancer, pancreatic cancer, bladder cancer, esophageal cancer, breast cancer, prostate cancer, blood cancer, bone cancer). In certain embodiments, the proliferative disease is colorectal cancer. In certain embodiments, the proliferative disease is pancreatic cancer. In certain embodiments, the proliferative disease is bladder cancer. In certain embodiments, the proliferative disease is esophageal cancer. In certain embodiments, the proliferative disease is breast cancer. In certain embodiments, the proliferative disease is prostate cancer. In certain embodiments, the proliferative disease is blood cancer (*e.g.*, multiple myeloma). In certain embodiments, the cancer is multiple myeloma. In certain embodiments, the proliferative disease is bone cancer. In certain embodiments, the disease or disorder is a metabolic disease (*e.g.*, diabetes, obesity, metabolic syndrome, atherosclerotic vascular disease, non-alcoholic steatohepatitis (NASH), fatty liver disease, weight loss, adipose tissue remodeling, metabolic bone disease, or hyperparathyroidism). In certain embodiments, the metabolic disease is diabetes. In certain embodiments, the metabolic disease is obesity. In certain embodiments, the metabolic disease is metabolic syndrome. In certain embodiments, the metabolic disease is atherosclerotic vascular disease.

In certain embodiments, the metabolic disease is non-alcoholic steatohepatitis (NASH). In certain embodiments, the metabolic disease is fatty liver disease. In certain embodiments, the metabolic disease is weight loss. In certain embodiments, the metabolic disease is adipose tissue remodeling. In certain embodiments, the metabolic disease is metabolic bone disease. In certain embodiments, the metabolic disease is hyperparathyroidism.

[0239] In another aspect, the present disclosure provides a method of treating a condition associated with peroxisome proliferator-activated receptor γ (PPAR γ). In certain specific embodiments, the condition is metabolic syndrome.

[0240] In certain embodiments, side effects experienced by the subject (*e.g.*, weight gain, edema, impairment of bone growth or formation, cardiac hypertrophy, congestive heart failure, vascular leak syndrome, hepatotoxicity) are reduced compared with administration of a PPAR γ agonist. In certain embodiments, weight gain experienced by the subject is reduced compared with administration of a PPAR γ agonist. In certain embodiments, edema experienced by the subject is reduced compared with administration of a PPAR γ agonist. In certain embodiments, impairment of bone growth or formation experienced by the subject is reduced compared with administration of a PPAR γ agonist. In certain embodiments, cardiac hypertrophy experienced by the subject is reduced compared with administration of a PPAR γ agonist. In certain embodiments, congestive heart failure experienced by the subject is reduced compared with administration of a PPAR γ agonist. In certain embodiments, vascular leak syndrome experienced by the subject is reduced compared with administration of a PPAR γ agonist. In certain embodiments, hepatotoxicity experienced by the subject is reduced compared with administration of a PPAR γ agonist.

[0241] In certain embodiments, the method comprises improving osteocyte, osteoblast, and/or osteoclast activities. In certain embodiments, the method comprises improving osteocyte activity. In certain embodiments, the method comprises improving osteoblast activity. In certain embodiments, the method comprises normalizing the functional remodeling activities of osteocytes, osteoblasts, and/or osteoclasts to result in healthy bone structure and/or strength. In certain embodiments, the functional remodeling activities are measured by increased bone cortical area, lower bone marrow adiposity, increased bone material strength, and/or increased bone turnover markers and circulating osteoprogenitors. *See, e.g.*, L. A. Stechschulte *et al.*, *EBioMedicine* **2016**, 10, 174-184. In certain embodiments, the method comprises increasing trabecular and cortical bone and/or improving metabolic parameters. In certain embodiments, the method comprises increasing trabecular and cortical bone (*e.g.*, by at least about 10%, at least about 20%, at least about 30%, at least about 40%, 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 98%, at least about 99%, or at least about 100%). In certain embodiments, the method comprises increasing trabecular bone (*e.g.*, by at least about 10%, at least about 20%, at least about 30%, at least about 40%, 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 98%, at least about 99%, or at least about 100%). In certain embodiments, the method comprises increasing cortical bone (*e.g.*, by at least about 10%, at least about 20%, at least about 30%, at least about 40%, 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 98%, at least about 99%, or at least about 100%). In certain embodiments, the method comprises improving metabolic parameters by reducing fasting plasma glucose into a normal range less than 100 mg/dl and HbA1c less than 6%. In certain embodiments, the method comprises decreasing marrow adiposity (*e.g.*, by at least about 10%, at least about 20%, at least about 30%, at least about 40%, 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 98%, at least about 99%, or at least about 100%).

Methods of Modulating Peroxisome Proliferator-Activated Receptor γ (PPAR γ), and Inhibiting Cell Proliferation or Promoting Apoptosis

[0242] In another aspect, the present disclosure provides methods of modulating (*e.g.*, upregulating, downregulating, increasing, decreasing) peroxisome proliferator-activated receptor γ (PPAR γ) in a subject in need thereof or in a cell, tissue, or biological sample, comprising administering to the subject in need thereof or contacting the cell, tissue, or biological sample with an effective amount of a provided compound or pharmaceutical composition. In certain embodiments, the present disclosure provides methods of modulating PPAR γ in a subject in need thereof, comprising administering to the subject in need thereof an effective amount of a provided compound or pharmaceutical composition. In certain embodiments, the present disclosure provides methods of modulating PPAR γ in a cell, tissue, or biological sample, comprising contacting the cell, tissue, or biological sample with an effective amount of a provided compound or pharmaceutical composition.

[0243] In another aspect, the present disclosure provides methods of inhibiting cell proliferation in a subject in need thereof or in a cell, tissue, or biological sample, comprising administering to the subject in need thereof or contacting the cell, tissue, or biological sample with an effective amount of a provided compound or pharmaceutical composition. In certain embodiments, the present disclosure provides methods of inhibiting cell proliferation in a subject in need thereof comprising administering to the subject in need thereof an effective amount of a provided compound or pharmaceutical composition. In certain embodiments, the present disclosure provides methods of inhibiting cell proliferation in a cell, tissue, or biological sample, comprising contacting the cell, tissue, or biological sample with an effective amount of a provided compound or pharmaceutical composition. In certain embodiments, the method comprises inhibiting cell proliferation (*e.g.*, by at least about 10%, at least about 20%, at least about 30%, at least about 40%, 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 98%, at least about 99%, or at least about 100%).

[0244] In certain embodiments, the method comprises antagonism of PPAR γ . In certain embodiments, the antagonism comprises maintaining the receptor at basal activity (*e.g.*, neutral activity). In certain embodiments, the antagonism comprises outcompeting and/or blocking agonists from binding, preventing activation of the receptor. In certain embodiments, the method comprises inverse agonism of PPAR γ . In certain embodiments, the inverse agonism comprises binding to the receptor and/or increasing interactions with co-depressors. In certain embodiments, the inverse agonism comprises reducing the receptor activity

below basal level (*e.g.*, neutral level). In certain embodiments, the method does not comprise agonism of PPAR γ . In certain embodiments, the method comprises reducing phosphorylation of PPAR γ at serine 273 (*e.g.*, by at least about 10%, at least about 20%, at least about 30%, at least about 40%, 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 98%, at least about 99%, or at least about 100%).

[0245] In certain embodiments, the method comprises improving osteocyte, osteoblast, and/or osteoclast activities. In certain embodiments, the method comprises improving osteocyte activity. In certain embodiments, the method comprises improving osteoblast activity. In certain embodiments, the method comprises normalizing the functional remodeling activities of osteocytes, osteoblasts, and/or osteoclasts to result in healthy bone structure and/or strength. In certain embodiments, the functional remodeling activities are measured by increased bone cortical area, lower bone marrow adiposity, increased bone material strength, and/or increased bone turnover markers and circulating osteoprogenitors. *See, e.g.*, L. A. Stechschulte *et al.*, *EBioMedicine* **2016**, 10, 174-184.

[0246] In certain embodiments, the method comprises increasing trabecular and cortical bone and/or improving metabolic parameters. In certain embodiments, the method comprises increasing trabecular and cortical bone (*e.g.*, by at least about 10%, at least about 20%, at least about 30%, at least about 40%, 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 98%, at least about 99%, or at least about 100%). In certain embodiments, the method comprises increasing trabecular bone (*e.g.*, by at least about 10%, at least about 20%, at least about 30%, at least about 40%, 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 98%, at least about 99%, or at least about 100%). In certain embodiments, the method comprises increasing cortical bone (*e.g.*, by at least about 10%, at least about 20%, at least about 30%, at least about 40%, 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 98%, at least about 99%, or at least about 100%). In certain embodiments, the method comprises improving metabolic parameters by reducing fasting plasma glucose into a normal range less than 100 mg/dl and HbA1c less than 6%. In certain embodiments, the method comprises decreasing marrow adiposity (*e.g.*, by at least about 10%, at least about 20%, at least about 30%, at least about 40%, 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 98%, at least about 99%, or at least about 100%).

[0247] In certain embodiments, the cell, tissue, or biological sample is *in vivo*. In certain embodiments, the cell, tissue, or biological sample is *in vitro*.

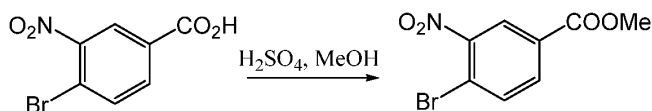
EXAMPLES

[0248] In order that the present disclosure may be more fully understood, the following examples are set forth. The synthetic and biological examples described in this application are offered to illustrate the

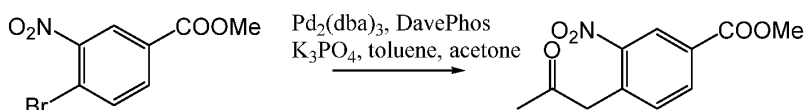
compounds, pharmaceutical compositions, and methods provided herein and are not to be construed in any way as limiting in their scope.

Example 1: Compound Synthesis.

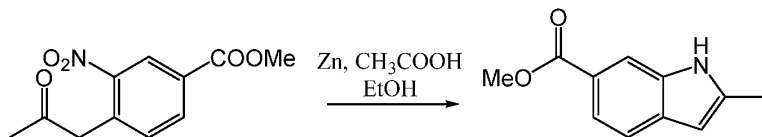
[0249] Compound 1: 2-(4-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy) propanoic acid.



[0250] Step 1: methyl 4-bromo-3-nitrobenzoate. A solution of 4-bromo-3-nitrobenzoic acid (10 g, 0.04 mol) in methanol (50 mL) was treated with 5 mL conc. sulfuric acid and refluxed for 4 hours. After cooling, the solvent was removed under vacuum and the residue was diluted with 100 mL of cold saturated solution of sodium bicarbonate and extracted twice with ethyl acetate (100 mL x2). The combined organic layer was washed with water and brine, dried over sodium sulfate and concentrated under vacuum to afford the title compound as white powder (10.1 g, Yield 97%). The crude product was used for the next step without any further purification. ¹H NMR (400 MHz, CDCl₃) δ 8.57 (s, 1H), 8.13 (d, J = 8Hz, 1H), 7.42 (d, J = 8Hz, 1H), 3.95 (s, 3H), 2.65 (s, 3H).



[0251] Step 2: methyl 3-nitro-4-(2-oxopropyl) benzoate. Methyl 4-bromo-3-nitrobenzoate (10 g, 0.038 mol) in toluene (100 mL) and acetone (12.75 g, 0.22 mol), 4-methoxyphenol (0.94 g, 7.58 mmol), potassium phosphate (17.74 g, 0.083 mol), 2-dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl (0.6 g, 1.5 mmol), tris(dibenzylideneacetone) dipalladium (0) (0.34 g, 0.4 mmol) were added sequentially and stirred at 50°C overnight. After cooling to room temperature, water and ethyl acetate were added to the reaction mixture. The organic layer was separated and washed with brine, dried over sodium sulfate, filtrated and dried under vacuum. The residue was purified by chromatography on silica gel (EtOAc/hexane) to afford the title compound as red oil (6.5 g, Yield 72%). ¹H NMR (400 MHz, CDCl₃) δ 8.65 (s, 1H), 8.15 (dd, J = 8, 1 Hz, 1H), 7.20 (d, J = 8Hz, 1H), 4.12 (s, 2H), 3.89 (s, 3H), 2.26 (s, 3H).

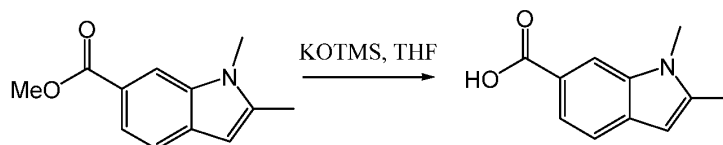


[0252] Step 3: methyl 2-methyl-1H-indole-6-carboxylate. Zinc dust (3.7 g, 0.056 mmol) and glacial acetic acid (2.01 g, 0.168 mmol) were added to a round bottomed flask. EtOH (20 mL) and methyl 3-nitro-4-(2-oxopropyl) benzoate (6.5 g, 0.019 mmol) were sequentially added by syringe at ambient temperature. The mixture was stirred at rt for 90 min. Water (200 mL) was then added to the reaction mixture and then it was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were then

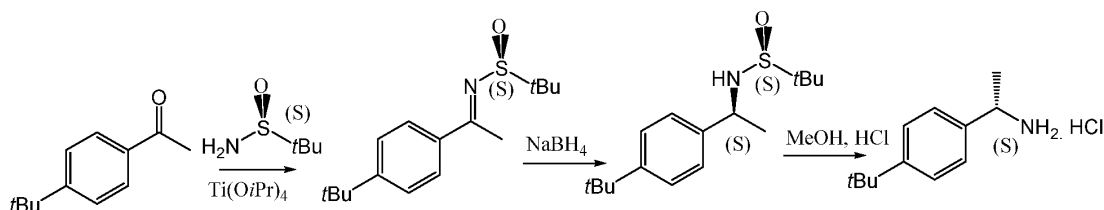
washed with brine, dried over sodium sulfate, and concentrated in vacuum. The residue was purified by column chromatography on silica gel (hexane/EtOAc, 10:1 (v/v)). The product was isolated as light brown (2.5 g, Yield 71%). ¹H NMR (400 MHz, CDCl₃): δ 8.23 (s, 1H), 8.05 (d, J = 1.7 Hz, 1H), 7.78 (dd, J = 8.3, 1.5 Hz, 1H), 7.53 (d, J = 8.3 Hz, 1H), 6.30 (dd, J = 2.1, 1 Hz, 1H), 3.95 (s, 3H), 2.51 (s, 3H). ESI-MS (m/z): 189. 62 [M]⁺.



[0253] Step 4: methyl 1,2-dimethyl-1H-indole-6-carboxylate. To a stirred solution of methyl 2-methyl-1H-indole-6-carboxylate (0.5 g, 2.64 mmol) in dry DMF (10 mL) was added NaH (60% dispersion in oil, 0.129 g, 3.17 mmol) in portions. The mixture was stirred for 30 min, then iodomethane (246 μL, 3.96 mmol) was added in one portion. The reaction became exothermic and was cooled in an ice bath. After 16 hours at 90°C, the reaction mixture was cooled down, quenched with water (100 mL) and extracted with diethyl ether (100 mL ×2). The combined organic layers were dried over sodium sulfate and concentrated under vacuum. The residue was purified on silica gel (hexanes/EtOAc, 10:1 (v/v)) gave the title compound (0.52 g, 97%) as light-yellow solid. ¹H NMR (400 MHz, CDCl₃): δ 8.01 (s, 1H), 7.75 (dd, J = 8.28, 1.4 Hz, 1H), 7.51 (d, J = 8.28 Hz, 1H), 6.28 (s, 1H), 3.93 (s, 3H), 3.70 (s, 3H), 2.44 (d, J = 0.53 Hz, 3H). ESI-MS (m/z): 203. 62 [M]⁺.



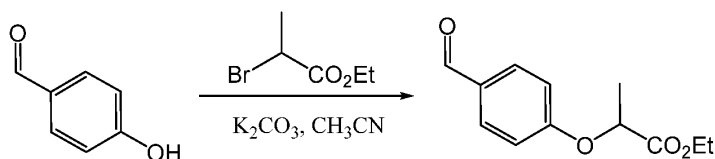
[0254] Step 5: 1,2-dimethyl-1H-indole-6-carboxylic acid. To a stirred solution of potassium trimethylsilonate in THF (2.56 mL, 2M in THF, 5.12 mmol) was added methyl 1,2-dimethyl-1H-indole-6-carboxylate (0.52 g, 2.56 mmol) in one portion and the reaction mixture was heated at 60°C for 10 minutes. The mixture was allowed to cool down and quenched with 5 N HCl aqueous solution (20 mL) and extracted with ethyl acetate (50 mL ×2). The combined organic layers were washed with a saturated sodium bicarbonate and brine, dried over sodium sulfate and concentrated in vacuo. The obtained yellow solid was used in the next step without further purification (0.48 g, Yield >99%). ESI-MS (m/z): 189.51 [M]⁺.



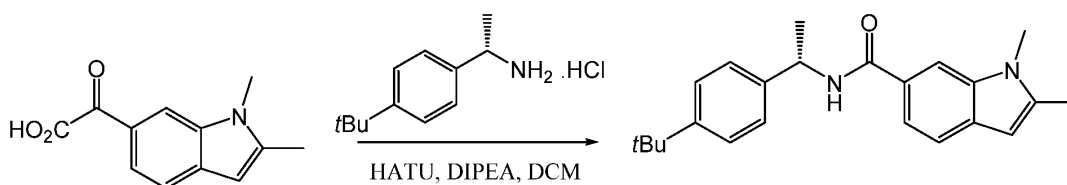
[0255] Step 6: (S)-1-(4-(tert-butyl)phenyl)ethanamine hydrochloride. 1-(4-tert-butylphenyl)ethanone (1 g, 5.7 mmol) and (S)-2-methylpropane-2-sulfonamide (1 g, 8.5 mmol) were added to Ti(OiPr)₄ (5.2 mL,

17.11 mmol) under argon. The resultant deep yellow solution was heated at 80°C overnight. The mixture was quenched with saturated NH₄Cl solution and diluted with ethyl acetate. The mixture was filtered through a pad of Celite and washed with ethyl acetate. The layers were separated and the organic layer was washed with brine, dried over sodium sulfate, and concentrated to give (S,E)-N-(1-(4-*tert*-butylphenyl)ethylidene)-2-methylpropane-2-sulfonamide as yellow syrup (1.5 g, yield 94%) which was used for the next step without further purification. ESI-MS (m/z): 279.51 [M]⁺. To a cooled solution of the crude imine (1.5 g, 5.35 mmol) in THF/H₂O (10 mL, 50:1 (v/v)) at -50°C was added NaBH₄ (0.78 g, 16.07 mmol) in one portion. The resulting mixture was warmed to rt and stirred for 3 hours. The mixture was then portioned between ethyl acetate (100 mL) and water (200 mL). The organic layer was separated, washed with brine, dried over sodium sulfate and concentrated. The analysis of the residue by ¹H-NMR and analytical HPLC showed a complete consumption of the imine and the detection of mixture of diastereomers. The major diastereoisomer was isolated by chromatography on silica gel as white solid (1.1 g, yield 71%). ¹H NMR (400 MHz, CDCl₃): δ 7.22 (dd, J = 8.4 Hz, 2H), 7.14 (d, J = 8.4 Hz, 2H), 4.42 (qd, J = 6.6, 4.1 Hz, 1H), 1.42 (d, J = 6.7 Hz, 3H), 1.19(s, 9H), 1.08 (s, 9H).

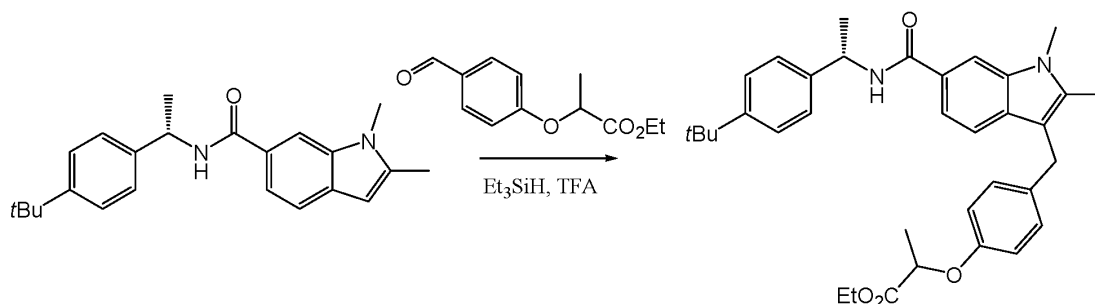
[0256] The corresponding sulfonamide was dissolved in methanol (10 mL) and Conc. HCl (1 mL) was added dropwise to the solution. The reaction was monitored by analytical reverse-phase HPLC until the disappearance of the starting material. The reaction mixture was concentrated in vacuo and the crude residue was suspended in ethanol (1 mL) and crashed out of solution by addition of diethyl ether and the chiral salt was isolated by filtration as white solid (0.8 g, yield 95%). ¹H NMR (400 MHz, DMSO-d₆) δ 8.34 (s, 3H), 7.43- 7.37 (m, 4H), 4.35 (q, J = 5.9 Hz, 1H), 1.49 (d, J = 6.8 Hz, 3H), 1.25 (s, 9H).



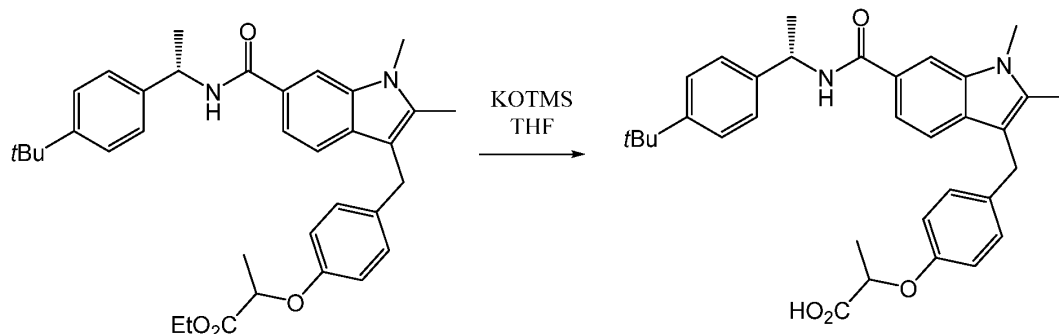
[0257] Step 7: ethyl 2-(4-formylphenoxy)propanoate. To a mixture of 4-hydroxybenzaldehyde (3 g, 24.6 mmol), ethyl bromopropionate (3.2 mL, 24.6 mmol) and K₂CO₃ (6 g, 49.2 mmol) was added acetonitrile (50 mL). The reaction mixture was refluxed for 3 hours. After completion of the reaction, K₂CO₃ was removed by filtration and the filtrate was concentrated under vacuum and subjected to column chromatography (hexane/EtOAc) to give the final product as transparent liquid (5.2 g, yield 94%). ¹H NMR (600 MHz, CDCl₃): δ 9.88 (s, 1H), 7.83 (d, J = 8.82 Hz, 2H), 6.97(d, J = 8.82 Hz, 2H), 4.87 (q, J = 6.84 Hz, 1H), 4.24 (q, J = 7.20 Hz, 2H), 1.66 (d, J = 6.84 Hz, 3H), 1.25 (t, J = 7.20 Hz, 3H). ESI-MS (m/z): 222. 63 [M]⁺.



[0258] Step 8: (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide. To a mixture of 1,2-dimethyl-1H-indole-6-carboxylic acid (0.385 g, 2.03 mmol) in DCM (10 mL) was added DIEA (1.12 mL, 6.09 mmol) and HATU (1.16 g, 1.9 mmol). The mixture was stirred for 5 min, and then (S)-1-(4-(tert-butyl)phenyl)ethanamine hydrochloride (0.403 g, 1.9 mmol) was added. The reaction mixture was stirred at rt for 30 min. The completion of the reaction was monitored by anal. HPLC. The solvent was removed in vacuo to obtain the crude which was purified by flash chromatography (hexane/EtOAc, 10:1 (v/v)) to obtain the title compound (0.7 g, yield 97%). ¹H NMR (400 MHz, CDCl₃): δ 7.83 (s, 1H), 7.41 (d, J = 8.82 Hz, 1H), 7.33(m, 5H), 6.34 (d, J = 8.81 Hz, 1H), 6.19 (s, 1H), 5.32 (q, J = 4.1 Hz, 1H), 3.63 (s, 3H), 2.37 (s, 3H), 1.55 (d, J = 4.1 Hz, 3H), 1.24 (s, 9H). ESI-MS (m/z): 348.84 [M]⁺.

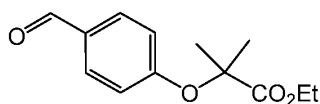


[0259] Step 9: ethyl 2-(4-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy propanoate. Triethylsilane (11 μL, 0.67 mmol) and trifluoroacetic acid (31 μL, 0.41 mmol) were sequentially added dropwise over 1 min to a stirred solution of (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide (45 mg, 0.13 mmol) and ethyl 2-(4-formylphenoxy)propanoate (29 mg, 0.13 mmol) in DCM (1 mL) at 0° C. The mixture was then warmed to rt and stirred for 2 hours. The reaction was monitored by analytical-HPLC until the complete consumption of the starting materials. The resulting mixture was quenched by a saturated solution of sodium bicarbonate (20 mL) and diluted with ethyl acetate (50 mL). The organic layer was separated, dried and concentrated in vacuo. The crude product was used for the next step without any further purification (72 mg, yield > 99%). ¹H NMR (400 MHz, CDCl₃): δ 7.81 (s, 1H), 7.25 (m, 6H), 6.96 (d, J = 8.4 Hz, 1H), 6.65 (m, 2H), 6.51 (d, J = 8.0 Hz, 1H), 5.31 (q, J = 6.8 Hz, 1H), 4.58 (q, J = 7.1 Hz, 1H), 4.10 (q, J = 7.2 Hz, 2H), 3.90 (s, 2H), 3.55 (s, 3H), 2.24 (s, 3H), 1.51 (d, J = 7.2 Hz, 3H), 1.48 (d, J = 6.8 Hz, 3H), 1.21 (s, 9H), 1.13 (t, J = 7.2 Hz, 3H).

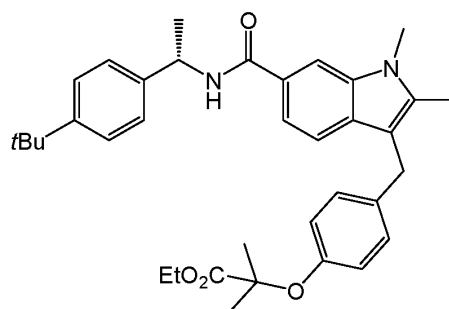


[0260] Step 10: 2-(4-((6-((*S*)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy) propanoic acid. To a stirred solution of potassium trimethylsilonate in THF (128 μ L, 2M in THF, 0.26 mmol) was added a solution of ethyl 2-(4-((6-((*S*)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy) propanoate (72 mg, 0.13 mmol) in THF (1 mL) in one portion and the reaction mixture was heated at 60°C for 10 minutes. The mixture was allowed to cool down and quenched with 5 N HCl aqueous solution (5 mL) and extracted with ethyl acetate (30 mL $\times$ 2). The combined organic layers were washed with a saturated sodium bicarbonate and brine, dried over sodium sulfate and concentrated in vacuo. The crude product was purified by prep-HPLC to yield the title compound (**1**) as yellowish solid. ^1H NMR (400 MHz, CDCl_3): δ 7.83 (s, 1H), 7.22 (m, 6H), 6.96 (d, J = 8.0 Hz, 2H), 6.69 (d, J = 6.0 Hz, 2H), 5.31 (q, J = 6.7 Hz, 1H), 4.63 (q, J = 6.8 Hz, 1H), 3.92 (s, 2H), 3.57 (s, 3H), 2.26 (s, 3H), 1.51 (d, J = 6.8 Hz, 6H), 1.21 (s, 9H).

[0261] Compound 2: (*S*)-2-(4-((6-((1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoic acid.

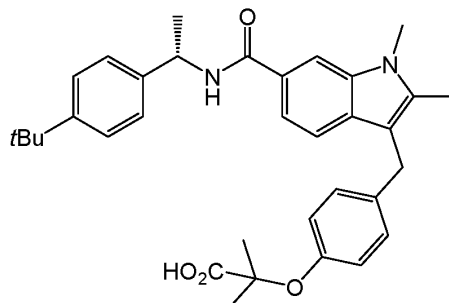


[0262] Step 1: ethyl 2-(4-formylphenoxy)-2-methylpropanoate. The title compound was prepared following the same general protocol as described in Step 7, Compound 1, using 3-hydroxybenzaldehyde instead 4-hydroxybenzaldehyde. A transparent oil was obtained (1 g, yield 88%). ^1H NMR (400 MHz, CDCl_3) δ 9.79 (s, 1H), 7.71 (d, J = 8.3 Hz, 2H), 6.82 (d, J = 8.3 Hz, 2H), 4.14 (q, J = 8.1 Hz, 2H), 1.58 (s, 6H), 1.14 (t, J = 8.1 Hz, 3H).

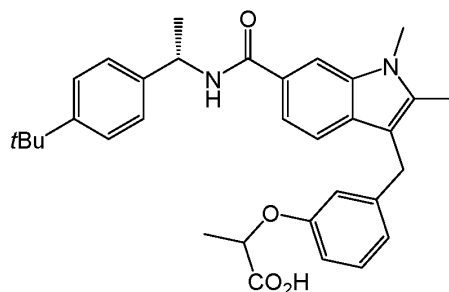


[0263] Step 2: ethyl (*S*)-2-(4-((6-((1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoate. The title compound was prepared following the same general

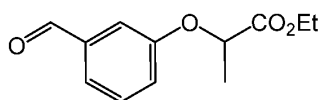
protocol as described in Step 9, Compound 1, using ethyl 2-(4-formylphenoxy)-2-methylpropanoate instead of the ethyl 2-(4-formylphenoxy)propanoate. A light-yellow solid was obtained (75 mg, yield 77%). ¹H NMR (400 MHz, CDCl₃): δ 7.82 (s, 1H), 7.29 (m, 6H), 6.97 (d, J = 8.4 Hz, 1H), 6.64 (d, 8.4 Hz, 2H), 6.45 (d, J = 8.0 Hz, 1H), 5.30 (q, J = 6.9 Hz, 1H), 4.13 (q, J = 7.3 Hz, 2H), 3.89 (s, 2H), 3.57 (s, 3H), 2.25 (s, 3H), 1.48 (d, J = 6.8 Hz, 3H), 1.45 (s, 6H), 1.22 (s, 9H), 1.18 (t, J = 7.2 Hz, 3H).



[0264] Step 3: (S)-2-(4-((6-((1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-2-methyl propanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the (ethyl (S)-2-(4-((6-((1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoate instead of the ethyl 2-(4-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy) propanoate. A yellow solid was obtained (50 mg, yield 71%). ¹H NMR (400 MHz, CDCl₃) δ 7.84 (d, J = 1.3 Hz, 1H), 7.40 – 7.24 (m, 3H), 7.24 – 7.18 (m, 2H), 6.96 (d, J = 8.6 Hz, 2H), 6.71 (d, J = 8.6 Hz, 2H), 6.35 (d, J = 7.9 Hz, 1H), 5.30 (p, J = 7.0 Hz, 1H), 3.94 (s, 2H), 3.61 (s, 3H), 2.28 (s, 3H), 1.53 (d, J = 6.9 Hz, 3H), 1.46 (s, 6H), 1.24 (s, 9H).

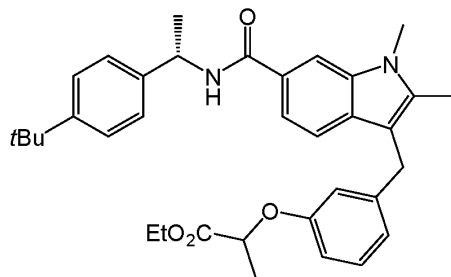


[0265] Compound 3: 2-(3-((6-(((S)-1-(4-(tert-butyl) phenyl) ethyl) carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl) phenoxy) propanoic acid.

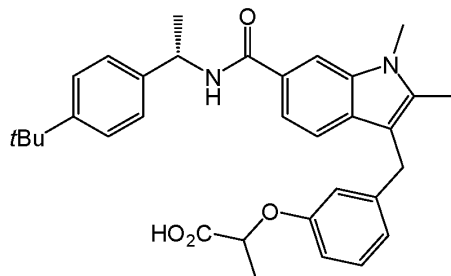


[0266] Step 1: ethyl 2-(3-formylphenoxy)propanoate. The title compound was prepared following the same general protocol as described in Step 7, Compound 1, using ethyl α-bromoisobutyrate instead of the ethyl bromopropionate. A transparent oil was obtained (0.95 g, yield 34%). ¹H NMR (400 MHz, CDCl₃) δ 9.72 (t, J = 1.2 Hz, 1H), 7.35 – 7.17 (m, 2H), 7.14 (dt, J = 3.1, 1.6 Hz, 1H), 6.97 (ddd, J = 7.9, 2.6, 1.3 Hz,

1H), 4.80 – 4.46 (m, 1H), 4.01 (dddd, J = 8.0, 7.1, 6.1, 1.7 Hz, 2H), 1.43 (dt, J = 6.8, 1.2 Hz, 3H), 1.03 (t, J = 7.1 Hz, 3H).

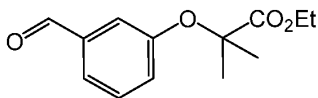


[0267] Step 2: ethyl 2-(3-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy) propanoate. The title compound was prepared following the same general protocol as described in Step 9, Compound 1, using ethyl 2-(3-formylphenoxy)propanoate instead of the ethyl 2-(4-formylphenoxy)propanoate. A yellow solid was obtained (48 mg, yield 88%).



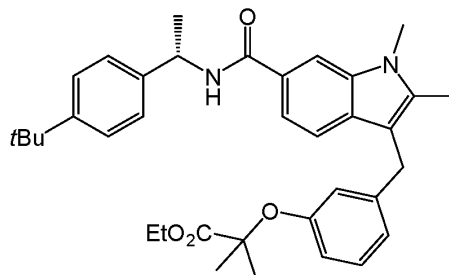
[0268] Step 3: 2-(3-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy) propanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the (ethyl 2-(3-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy) propanoate instead of the ethyl 2-(4-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy) propanoate. A yellow solid was obtained (40 mg, yield 87%). ¹H NMR (400 MHz, CDCl₃) δ 7.79 (d, J = 4.7 Hz, 1H), 7.47 – 7.21 (m, 5H), 7.21 – 7.06 (m, 1H), 6.98 (td, J = 7.9, 3.9 Hz, 1H), 6.71 (dd, J = 7.6, 3.1 Hz, 1H), 6.63 – 6.51 (m, 2H), 6.43 (dd, J = 8.0, 4.3 Hz, 1H), 5.27 (t, J = 6.7 Hz, 1H), 4.55 (q, J = 6.8 Hz, 1H), 4.02 – 3.72 (m, 2H), 3.46 (d, J = 2.4 Hz, 3H), 2.19 (d, J = 2.3 Hz, 3H), 1.51 (dd, J = 6.9, 1.4 Hz, 3H), 1.48 (dd, J = 6.9, 2.3 Hz, 3H), 1.23 (s, 9H).

[0269] Compound 4: (S)-2-(3-((6-((1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoic acid.

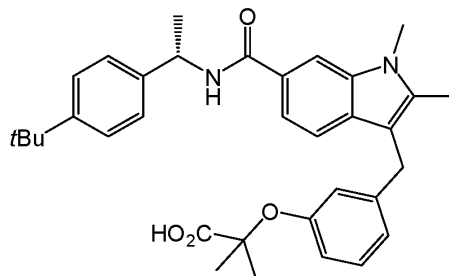


[0270] Step 1: ethyl 2-(3-formylphenoxy)-2-methylpropanoate. The title compound was prepared following the same general protocol as described in Step 7, Compound 1, using ethyl α-bromoisobutyrate instead of the ethyl bromopropionate and the 3-hydroxybenzaldehyde instead of the 4-benzaldehyde. A transparent oil was obtained (1.1 g, yield 90%). ¹H NMR (400 MHz, CDCl₃) δ 9.85 (d, J = 0.8 Hz, 1H),

7.41 (dq, $J = 7.5, 1.1$ Hz, 1H), 7.32 (t, $J = 7.8$ Hz, 1H), 7.23 (tt, $J = 3.0, 1.6$ Hz, 1H), 7.04 (ddt, $J = 8.1, 2.0, 0.9$ Hz, 1H), 4.16 (td, $J = 7.1, 0.8$ Hz, 2H), 1.54 (d, $J = 0.9$ Hz, 6H), 0.83 – 0.73 (m, 3H).

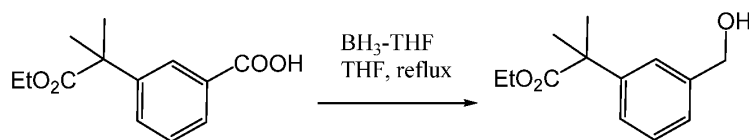


[0271] Step 2: ethyl (S)-2-(3-((6-((1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoate. The title compound was prepared following the same general protocol as described in Step 9, Compound 1, using ethyl 2-(3-formylphenoxy)-2-methylpropanoate instead of the ethyl 2-(4-formylphenoxy)propanoate. A yellow solid was obtained (30 mg, yield 96%).



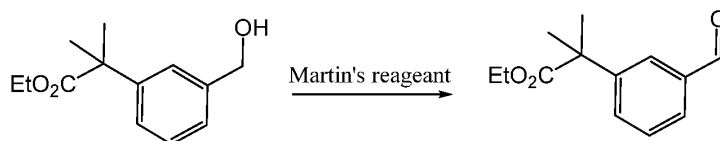
[0272] Step 3: (S)-2-(3-((6-((1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the ethyl (S)-2-(3-((6-((1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoate instead of the ethyl 2-(4-((6-((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)propanoate. A yellow solid was obtained (25 mg, yield 84%). ¹H NMR (400 MHz, CDCl₃) δ 7.82 (s, 1H), 7.43 – 7.20 (m, 5H), 6.98 (t, $J = 7.9$ Hz, 1H), 6.78 (d, $J = 7.6$ Hz, 1H), 6.64 (d, $J = 1.9$ Hz, 1H), 6.60 (dd, $J = 8.1, 2.6$ Hz, 1H), 6.35 (d, $J = 7.9$ Hz, 1H), 5.29 (p, $J = 7.2$ Hz, 1H), 3.93 (s, 2H), 3.58 (s, 3H), 2.26 (s, 3H), 1.54 (d, $J = 6.9$ Hz, 3H), 1.44 (s, 6H), 1.24 (s, 9H).

[0273] Compound 5: (S)-2-(3-((6-((1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoic acid.

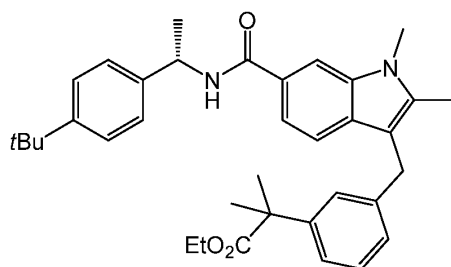


[0274] Step 1: ethyl 2-(3-(hydroxymethyl)phenyl)-2-methylpropanoate. To a solution of 3-(1-ethoxy-2-methyl-1-oxopropan-2-yl)benzoic acid (100 mg, 0.24 mmol) in THF (10 mL) was added BH₃-THF (0.25 mL). The mixture was stirred at 65°C for 7 hr. Then the reaction mixture was cooled to rt and quenched with H₂O. After removal of solvent, the crude product was used for the next step without any further

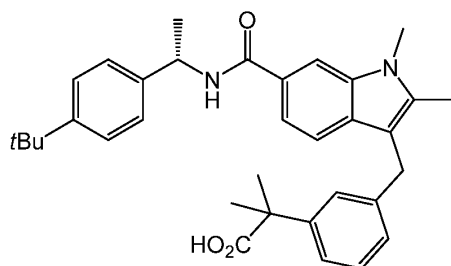
purification. ^1H NMR (400 MHz, CDCl_3) δ 7.92 (dd, J = 7.4, 1.3 Hz, 1H), 7.81 (d, J = 8.2 Hz, 1H), 7.49 – 7.26 (m, 2H), 4.53 (s, 2H), 4.29 (br, 1H), 4.00 (q, J = 7.1 Hz, 2H), 1.46 (d, J = 0.9 Hz, 6H), 1.07 (t, J = 7.6 Hz, 3H).



[0275] Step 2: ethyl 2-(3-formylphenyl)-2-methylpropanoate. To a solution of ethyl 2-(3-(hydroxymethyl)phenyl)-2-methylpropanoate (90 mg, 0.4 mmol) in dichloromethane (10 mL) was added Dess-Martin reagent (203 mg, 0.48 mmol). The mixture was stirred at rt for 4 hours. The mixture was filtered, solvent was evaporated under vacuum. The crude product was used for the next step without any further purification.



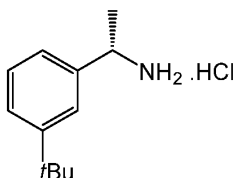
[0276] Step 3: ethyl (S)-2-(3-((6-((1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenyl)-2-methylpropanoate. The title compound was prepared following the same general protocol as described in Step 9, Compound 1, using the ethyl 2-(3-formylphenyl)-2-methylpropanoate instead of the ethyl 2-(4-formylphenoxy)propanoate. A light-yellow solid was obtained (20 mg, yield 73%). ^1H NMR (400 MHz, CDCl_3) δ 7.35 (m, 1H), 7.30 – 7.19 (m, 6H), 7.14 – 7.07 (m, 1H), 7.07 – 6.90 (m, 1H), 6.35 (d, J = 7.9 Hz, 1H), 5.40 – 5.22 (m, 1H), 4.03 (q, J = 7.1 Hz, 2H), 3.99 – 3.92 (m, 2H), 3.62 (d, J = 1.3 Hz, 3H), 2.30 (s, 3H), 1.53 (d, J = 6.9 Hz, 3H), 1.49 (s, 6H), 1.23 (d, J = 0.5 Hz, 9H), 1.09 (d, J = 7.1 Hz, 3H).



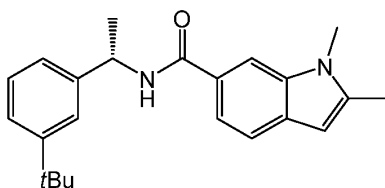
[0277] Step 4: (S)-2-(3-((6-((1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenyl)-2-methylpropanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the ethyl (S)-2-(3-((6-((1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenyl)-2-methylpropanoate instead of the (ethyl 2-(4-((6-((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-

yl)methyl)phenoxy)propanoate. A brown solid was obtained (10 mg, yield 53%). ¹H NMR (400 MHz, CDCl₃) δ 7.84 (s, 1H), 7.36 – 7.20 (m, 6H), 7.18 – 6.99 (m, 4H), 6.33 (d, J = 7.9 Hz, 1H), 5.30 (t, J = 7.3 Hz, 1H), 3.98 (s, 2H), 3.64 (s, 3H), 2.30 (s, 3H), 1.54 (dd, J = 6.9, 2.2 Hz, 3H), 1.47 (d, J = 2.1 Hz, 6H), 1.24 (s, 9H).

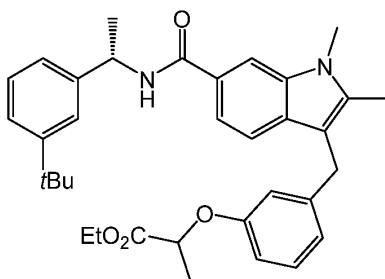
[0278] Compound 6: 2-(3-((6-(((S)-1-(3-(tert-butyl)phenyl) ethyl) carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl) phenoxy)propanoic acid.



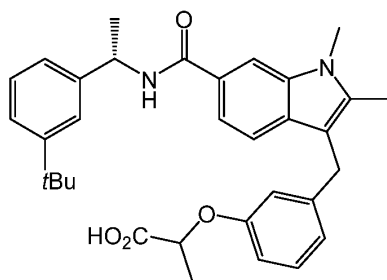
[0279] Step 1: (S)-1-(3-(tert-butyl)phenyl)ethanamine hydrochloride. The title compound was prepared following the same general protocol as described in Step 6, Compound 1, using the 1-(3-*tert*-butylphenyl)ethenone instead of the 1-(4-*tert*-butylphenyl)ethenone. A white solid was obtained (0.87 g, yield 71%). ¹H NMR (600 MHz, DMSO-d₆) δ 8.35 (s, 3H), 7.50 (t, J = 1.68 Hz, 1H), 7.39 (dd, J = 7.72, 1.74 Hz, 1H), 7.35 (t, J = 7.68 Hz, 1H), 7.26–7.17 (m, 1H), 4.37 (q, J = 6.8 Hz, 1H), 1.49 (d, J = 6.8 Hz, 3H), 1.27 (s, 9H).



[0280] Step 2: (S)-N-(1-(3-(tert-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide. The title compound was prepared following the same general protocol as described in Step 8, Compound 1, using the (S)-1-(3-(tert-butyl)phenyl)ethan-1-amine hydrochloride instead of (S)-1-(4-(tert-butyl)phenyl)ethan-1-amine hydrochloride. A yellow solid was obtained (0.14 g, yield 99%).

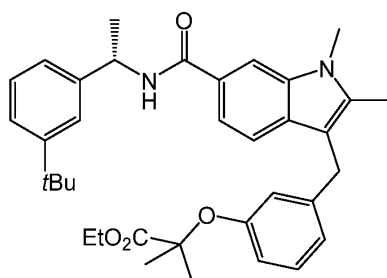


[0281] Step 3: ethyl 2-(3-((6-(((S)-1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy) propanoate. The title compound was prepared following the same general protocol as described in Step 9, Compound 1, using the (S)-N-(1-(3-(tert-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide and the ethyl 2-(3-formylphenoxy)propanoate instead of the ethyl 2-(4-formylphenoxy)propanoate. A yellow solid was obtained (65 mg, yield 90%).

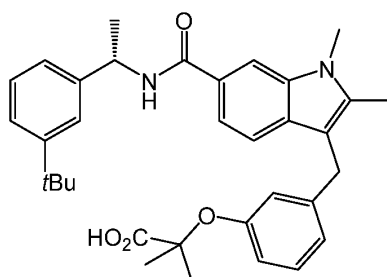


[0282] Step 4: 2-(3-((6-(((S)-1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy) propanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the ethyl 2-(3-((6-(((S)-1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy) propanoate instead of the (ethyl 2-(4-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)propanoate. A yellow solid was obtained (50 mg, yield 81%). ¹H NMR (400 MHz, MeOD) δ 8.52 (d, J = 7.8 Hz, 1H), 7.78 (s, 1H), 7.38 (t, J = 3.6 Hz, 2H), 7.25 (d, J = 8.0 Hz, 1H), 7.21 – 6.99 (m, 3H), 6.95 (d, J = 6.4 Hz, 2H), 6.64 (s, 2H), 5.29 – 5.03 (m, 1H), 3.89 (s, 2H), 3.63 (s, 3H), 2.29 (s, 3H), 1.48 (d, J = 6.9 Hz, 6H), 1.21 (s, 9H).

[0283] Compound 7: (S)-2-(3-((6-((1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl) phenoxy)-2-methylpropanoic acid.

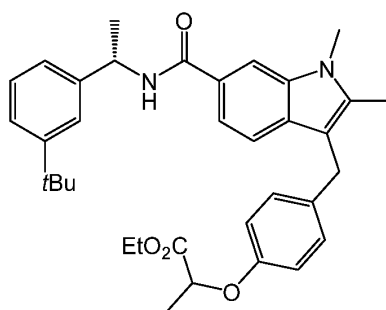


[0284] Step 1: ethyl (S)-2-(3-((6-((1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoate. The title compound was prepared following the same general protocol as described in Step 9, Compound 1, using the (S)-N-(1-(3-(tert-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide and the ethyl 2-(3-formylphenoxy)-2-methylpropanoate instead of the ethyl 2-(4-formylphenoxy)propanoate. A yellow solid was obtained (82 mg, yield 84%).

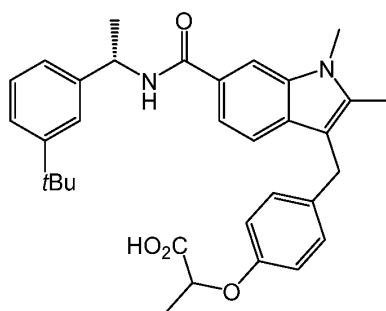


[0285] Step 2: (S)-2-(3-((6-((1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-2-methyl propanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the ethyl (S)-2-(3-((6-((1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoate instead of the (ethyl 2-(4-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy) propanoate. A yellow solid was obtained (71 mg, yield 90%). ¹H NMR (400 MHz, CDCl₃) δ 7.82 (s, 1H), 7.35 (d, J = 2.1 Hz, 1H), 7.23 (td, J = 7.7, 4.0 Hz, 4H), 7.15 (dt, J = 6.8, 1.9 Hz, 1H), 6.92 (t, J = 7.8 Hz, 1H), 6.81 – 6.70 (m, 1H), 6.64 (s, 1H), 6.57 (d, J = 8.3 Hz, 1H), 6.39 (d, J = 8.0 Hz, 1H), 5.30 (p, J = 7.0 Hz, 1H), 3.89 (s, 2H), 3.54 (s, 3H), 2.22 (s, 3H), 1.54 (d, J = 6.8 Hz, 3H), 1.42 (s, 6H), 1.24 (s, 9H).

[0286] Compound 8: 2-(4-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy) propanoic acid.



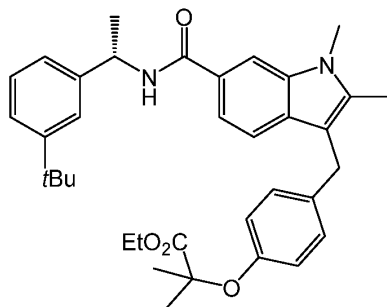
[0287] Step 1: ethyl 2-(4-((6-(((S)-1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy) propanoate. The title compound was prepared following the same general protocol as described in Step 9, Compound 1, using (S)-N-(1-(3-(tert-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide. A yellow solid was obtained (49 mg, yield 96 %).



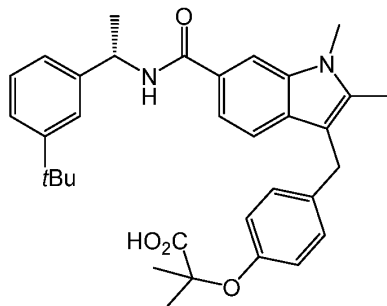
[0288] Step 2: 2-(4-((6-(((S)-1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy) propanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the ethyl 2-(4-((6-(((S)-1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy) propanoate instead of the (ethyl 2-(4-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy) propanoate. A yellow solid was obtained (32 mg, yield 69%). ¹H NMR (400 MHz,

CDCl₃) δ 7.84 (s, 1H), 7.34 – 7.19 (m, 6H), 7.04 – 6.85 (m, 2H), 6.67 (d, J = 8.4 Hz, 2H), 6.36 (d, J = 8.0 Hz, 1H), 5.29 (p, J = 7.0 Hz, 1H), 4.61 (qd, J = 6.9, 1.4 Hz, 1H), 3.92 (s, 2H), 3.58 (s, 3H), 2.27 (s, 3H), 1.52 (d, J = 6.9 Hz, 6H), 1.23 (s, 9H).

[0289] Compound 9: (S)-2-(4-((6-((1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoic acid.

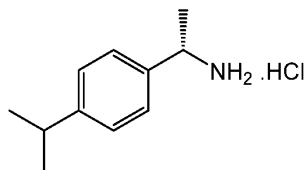


[0290] Step 1: ethyl (S)-2-(4-((6-((1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoate. The title compound was prepared following the same general protocol as described in Step 9, Compound 1, using the (S)-N-(1-(3-(tert-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide and the ethyl 2-(4-formylphenoxy)-2-methylpropanoate instead of the ethyl 2-(4-formylphenoxy)propanoate. A yellow solid was obtained (59 mg, yield 86 %).

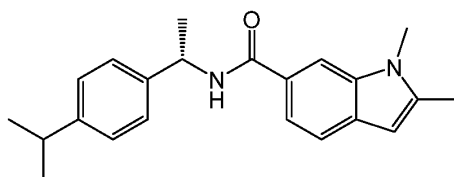


[0291] Step 2: (S)-2-(4-((6-((1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the ethyl (S)-2-(4-((6-((1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoate instead of the (ethyl 2-(4-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy) propanoate. A yellow solid was obtained (39 mg, yield 85%). ¹H NMR (400 MHz, CDCl₃) δ 7.90 – 7.73 (m, 1H), 7.35 (q, J = 1.6 Hz, 1H), 7.30 – 7.20 (m, 4H), 7.16 (dt, J = 6.6, 2.1 Hz, 1H), 6.94 (d, J = 8.6 Hz, 2H), 6.63 (d, J = 8.6 Hz, 2H), 5.31 (q, J = 7.1 Hz, 1H), 3.93 (s, 2H), 3.61 (s, 3H), 2.28 (s, 3H), 1.97 (s, 6H), 1.55 (d, J = 6.9 Hz, 3H), 1.46 (s, 6H), 1.25 (s, 9H).

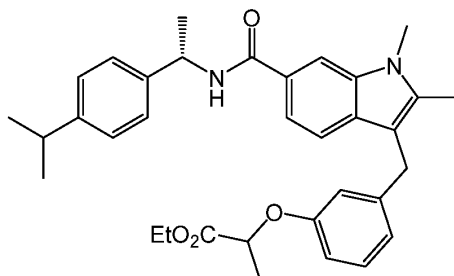
[0292] Compound 10: 2-(3-((6-(((S)-1-(4-isopropylphenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)propanoic acid.



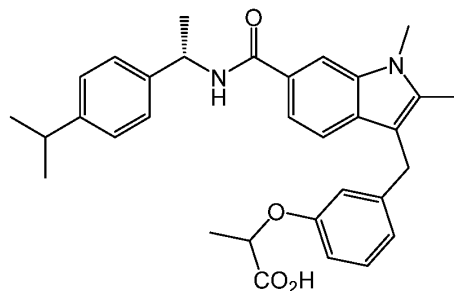
[0293] Step 1: (S)-1-(4-isopropylphenyl)ethanamine hydrochloride. The title compound was prepared following the same general protocol as described in Step 6, Compound 1, using the 1-(4-isopropylphenyl)ethenone instead of the 1-(4-*tert*-butylphenyl)ethenone. A white solid was obtained (0.5 g, yield 41%). ¹H NMR (600 MHz, DMSO-*d*₆) δ 8.57 (s, 3H), 7.44 (d, *J* = 8.08 Hz, 2H), 7.29 (d, *J* = 8.08 Hz, 2H), 4.34 (q, *J* = 6.72 Hz, 1H), 2.92 (p, *J* = 6.88 Hz, 1H), 1.52 (d, *J* = 6.76 Hz, 3H), 1.20 (d, *J* = 6.8 Hz, 6H).



[0294] Step 2: (S)-N-(1-(4-isopropylphenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide. The title compound was prepared following the same general protocol as described in Step 8, Compound 1, using the (S)- (S)-1-(4-isopropylphenyl)ethanamine hydrochloride instead of (S)-1-(4-(*tert*-butyl)phenyl)ethanamine hydrochloride. A yellow solid was obtained (0.17 g, yield 98%).

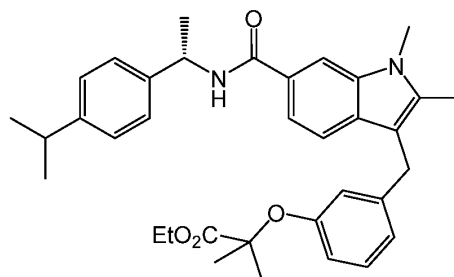


[0295] Step 3: ethyl 2-(3-((6-(((S)-1-(4-isopropylphenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy) propanoate. The title compound was prepared following the same general protocol as described in Step 9, Compound 1, using the (S)-N-(1-(4-isopropylphenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(*tert*-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide and the ethyl 2-(3-formylphenoxy)propanoate instead of the ethyl 2-(4-formylphenoxy)propanoate. A yellow solid was obtained (15 mg, yield 84%).

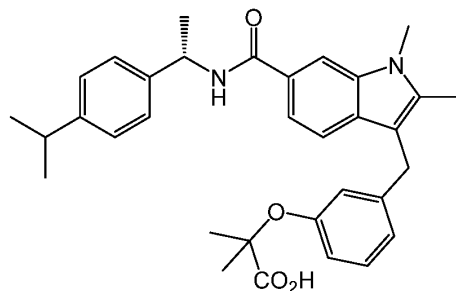


[0296] Step 4: 2-(3-((6-(((S)-1-(4-isopropylphenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy) propanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the ethyl 2-(3-((6-(((S)-1-(4-isopropylphenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy) propanoate instead of the (ethyl 2-(4-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy) propanoate. A yellow solid was obtained (12 mg, yield 84%). ¹H NMR (400 MHz, MeOD) δ 7.78 (s, 1H), 7.38 (dd, J = 8.3, 1.6 Hz, 1H), 7.28 (d, J = 8.3 Hz, 1H), 7.23 (d, J = 8.3 Hz, 2H), 7.15 – 7.06 (m, 2H), 6.99 (t, J = 7.9 Hz, 1H), 6.68 (d, J = 7.6 Hz, 1H), 6.59 (s, 1H), 6.57 – 6.50 (m, 1H), 5.16 (t, J = 6.5 Hz, 1H), 4.48 (q, J = 6.8 Hz, 1H), 3.94 (s, 2H), 3.65 (s, 3H), 2.77 (p, J = 6.9 Hz, 1H), 2.31 (s, 3H), 1.47 (d, J = 6.9 Hz, 3H), 1.39 (d, J = 6.8 Hz, 3H), 1.14 (td, J = 7.1, 2.6 Hz, 6H).

[0297] Compound 11: (S)-2-(3-((6-((1-(4-isopropylphenyl) ethyl) carbamoyl)-1,2-dimethyl-1H-indol-3-yl) methyl) phenoxy)-2- methylpropanoic acid.

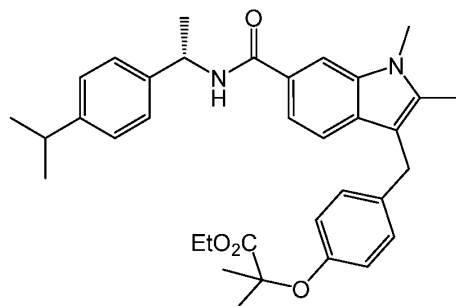


[0298] Step 1: ethyl (S)-2-(3-((6-((1-(4-isopropylphenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-2-methyl propanoate. The title compound was prepared following the same general protocol as described in Step 9, Compound 1, using the (S)-N-(1-(4-isopropylphenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide and the ethyl 2-(3-formylphenoxy)-2-methylpropanoate instead of the ethyl 2-(4-formylphenoxy)propanoate. A yellow solid was obtained (14 mg, yield 93%).

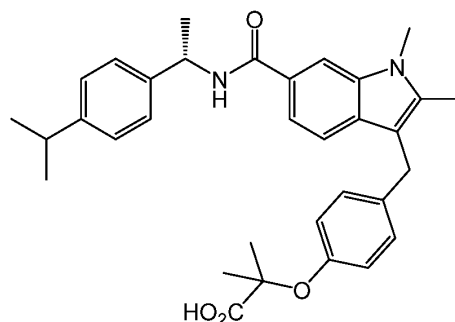


[0299] Step 2: (S)-2-(3-((6-((1-(4-isopropylphenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-2-methyl propanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the ethyl (S)-2-(3-((6-((1-(4-isopropylphenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-2-methyl propanoate instead of the (ethyl 2-(4-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy) propanoate. A yellow solid was obtained (12 mg, yield 90%). ¹H NMR (400 MHz, CDCl₃) δ 7.82 (s, 1H), 7.25 (dd, J = 13.9, 7.2 Hz, 4H), 7.14 (d, J = 8.0 Hz, 2H), 7.02 (t, J = 7.8 Hz, 1H), 6.82 (d, J = 7.6 Hz, 1H), 6.63 (d, J = 12.8 Hz, 2H), 6.30 (d, J = 7.9 Hz, 1H), 5.29 (t, J = 7.1 Hz, 1H), 3.95 (s, 2H), 3.62 (s, 3H), 2.83 (p, J = 7.0 Hz, 1H), 2.28 (s, 3H), 1.53 (s, 3H), 1.44 (s, 6H), 1.19 (t, J = 7.1 Hz, 6H).

[0300] Compound 12: (S)-2-(4-((6-((1-(4-isopropylphenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoic acid.

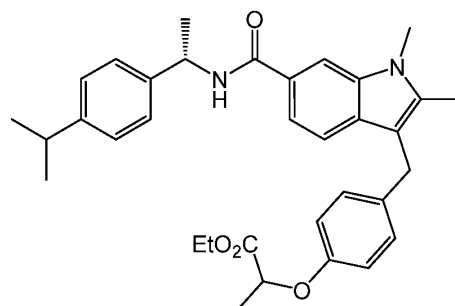


[0301] Step 1: ethyl (S)-2-(4-((6-((1-(4-isopropylphenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-2-methyl propanoate. The title compound was prepared following the same general protocol as described in Step 9, Compound 1, using the (S)-N-(1-(4-isopropylphenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide and the ethyl 2-(4-formylphenoxy)-2-methylpropanoate instead of the ethyl 2-(4-formylphenoxy)propanoate. A yellow solid was obtained (12 mg, yield 80%).

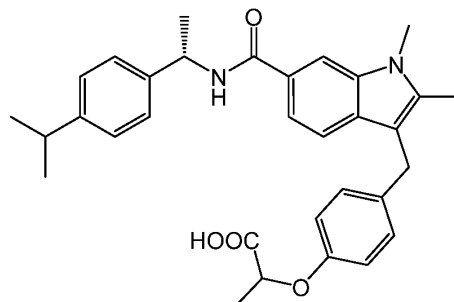


[0302] Step 2: (S)-2-(4-((6-((1-(4-isopropylphenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-2-methyl propanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the ethyl (S)-2-(3-((6-((1-(4-isopropylphenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-2-methyl propanoate instead of the (ethyl 2-(4-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy) propanoate. A yellow solid was obtained (10 mg, yield 87%). ¹H NMR (400 MHz, CDCl₃) δ 7.83 (s, 1H), 7.48 – 7.22 (m, 4H), 7.14 (d, J = 7.9 Hz, 2H), 6.99 (d, J = 8.0 Hz, 2H), 6.73 (d, J = 8.0 Hz, 2H), 6.29 (s, 1H), 5.33 – 5.25 (m, 1H), 3.95 (s, 2H), 3.64 (s, 3H), 2.82 (p, J = 6.9 Hz, 1H), 2.30 (s, 3H), 1.54 (d, J = 6.5 Hz, 3H), 1.44 (s, 6H), 1.17 (d, J = 6.9 Hz, 6H).

[0303] Compound 13: 2-(4-((6-(((S)-1-(4-isopropylphenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy) propanoic acid.

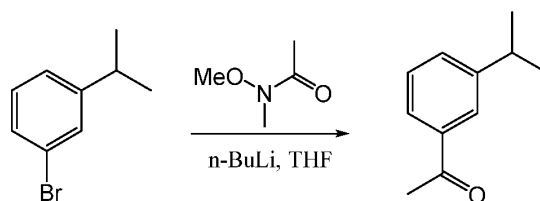


[0304] Step 1: ethyl 2-(4-((6-(((S)-1-(4-isopropylphenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy) propanoate. The title compound was prepared following the same general protocol as described in Step 9, Compound 1, using the (S)-N-(1-(4-isopropylphenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide. A yellow solid was obtained (14 mg, yield 95%).

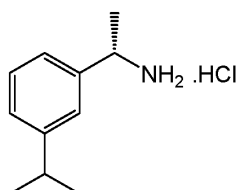


[0305] Step 2: 2-(4-((6-(((*S*)-1-(4-isopropylphenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy) propanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the ethyl 2-(4-((6-(((*S*)-1-(4-isopropylphenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy) propanoate instead of the (ethyl 2-(4-((6-(((*S*)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy) propanoate. A yellow solid was obtained (11 mg, yield 82%). ¹H NMR (400 MHz, CDCl₃) δ 7.84 (s, 1H), 7.34 – 7.23 (m, 3H), 7.21 (s, 1H), 7.14 (d, J = 8.0 Hz, 2H), 7.00 (d, J = 8.5 Hz, 2H), 6.69 (d, J = 8.6 Hz, 2H), 6.33 (d, J = 7.9 Hz, 1H), 5.33 – 5.25 (m, 1H), 3.95 (s, 2H), 3.63 (s, 3H), 2.83 (p, J = 6.9 Hz, 1H), 2.30 (s, 3H), 1.54 (d, J = 6.8 Hz, 6H), 1.17 (d, J = 6.9 Hz, 6H).

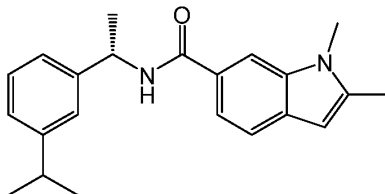
[0306] Compound 14: (*S*)-2-(3-((6-((1-(3-isopropylphenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoic acid.



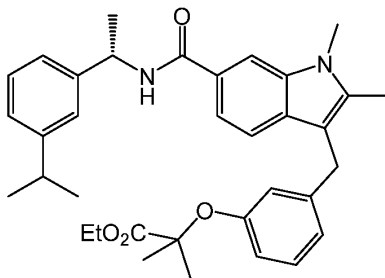
[0307] Step 1: 1-(3-isopropylphenyl)ethanone. To a solution of 1-bromo-3-isopropylbenzene (3 g, 16.6 mmol) in THF was added dropwise with n-BuLi (9 mL, 24.9 mol) at -60°C. After stirred 30 minutes, N-methoxy-N-methylacetamide (2 g, 20 mmol) was added. The mixture was stirred at -30°C for 3 hours. Then the mixture was quenched with H₂O, the mixture was partitioned between ethyl acetate and water. The layer was separated and washed with water, brine, dried over sodium sulfate, and concentrated. The residue was purified on silica gel (hexanes/EtOAc, 20:1 (v/v)) to afford the titled compound. 1-(3-isopropylphenyl)ethanone as transparent oil (2.2 g, yield 81%). ¹H NMR (400 MHz, CDCl₃) δ 7.83 (s, 1H), 7.8 (dt, J = 7.6, 1.4 Hz, 1H), 7.53-7.33 (m, 2H), 3.00 (dt, J = 13.8, 6.9 Hz, 1H), 1.30 (d, J = 6.7 Hz, 6H).



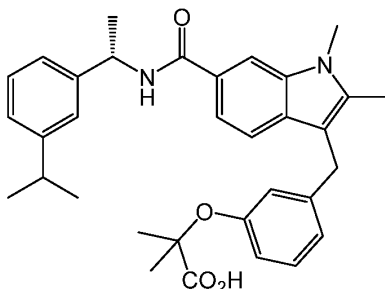
[0308] Step 2: (S)-1-(3-isopropylphenyl)ethanamine hydrochloride. The title compound was prepared following the same general protocol as described in Step 6, Compound 1, using the 1-(3-isopropylphenyl)ethanone instead of the 1-(4-*tert*-butylphenyl)ethenone. A white solid was obtained (1.5 g, yield 61%). ¹H NMR (600 MHz, DMSO-*d*₆) δ 8.75 (s, 3H), 7.53 (s, 1H), 7.41-7.37 (m, 2H), 7.30 (t, *J* = 1.32 Hz, 1H), 4.4 (t, *J* = 5.04 Hz, 1H), 2.97 (p, *J* = 6.9 Hz, 1H), 1.52 (d, *J* = 6.84 Hz, 3H), 1.28 (d, *J* = 6.96 Hz, 6H).



[0309] Step 3: (S)-N-(1-(3-isopropylphenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide. The title compound was prepared following the same general protocol as described in Step 8, Compound 1, using the (S)- (S)-1-(3-isopropylphenyl)ethanamine hydrochloride instead of (S)-1-(4-(*tert*-butyl)phenyl)ethanamine hydrochloride. A yellow solid was obtained (0.32 g, yield 95%).



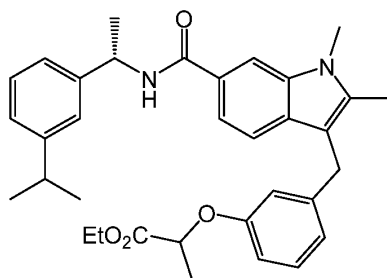
[0310] Step 4: ethyl (S)-2-(3-((6-((1-(3-isopropylphenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-2-methyl propanoate. The title compound was prepared following the same general protocol as described in Step 9, Compound 1, using the (S)-N-(1-(3-isopropylphenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(*tert*-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide and the ethyl 2-(4-formylphenoxy)-2-methylpropanoate instead of the ethyl 2-(4-formylphenoxy)propanoate. A yellow solid was obtained (52 mg, yield 94%).



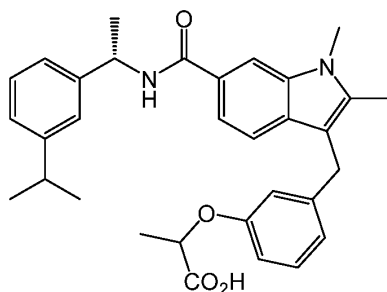
[0311] Step 5: (S)-2-(3-((6-((1-(3-isopropylphenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-2-methyl propanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the ethyl (S)-2-(3-((6-((1-(3-

isopropylphenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-2-methyl propanoate instead of the (ethyl 2-(4-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy) propanoate. A yellow solid was obtained (45 mg, yield 91%). ¹H NMR (400 MHz, CDCl₃) δ 7.82 (d, J = 1.5 Hz, 1H), 7.28 – 7.11 (m, 5H), 7.07 (dt, J = 7.6, 1.6 Hz, 1H), 6.93 (t, J = 7.8 Hz, 1H), 6.74 (dt, J = 7.8, 1.1 Hz, 1H), 6.64 (t, J = 2.0 Hz, 1H), 6.58 (ddd, J = 8.1, 2.6, 0.9 Hz, 1H), 6.39 (d, J = 7.9 Hz, 1H), 5.30 (p, J = 7.0 Hz, 1H), 3.90 (s, 2H), 3.53 (s, 3H), 2.83 (p, J = 6.9 Hz, 1H), 2.23 (s, 3H), 1.53 (d, J = 6.9 Hz, 3H), 1.45 (s, 6H), 1.17 (d, J = 6.9 Hz, 6H).

[0312] Compound 15: 2-(3-(((S)-1-(3-isopropylphenyl) ethyl) carbamoyl)-1,2-dimethyl-1H-indol-3-yl) methyl) phenoxy) propanoic acid.



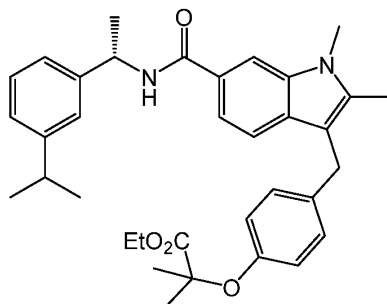
[0313] Step 1: ethyl 2-(3-(((S)-1-(3-isopropylphenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy) propanoate. The title compound was prepared following the same general protocol as described in Step 9, Compound 1, using the (S)-N-(1-(3-isopropylphenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide and the ethyl 2-(3-formylphenoxy)propanoate instead of the ethyl 2-(4-formylphenoxy)propanoate. A yellow solid was obtained (92 mg, yield 95%).



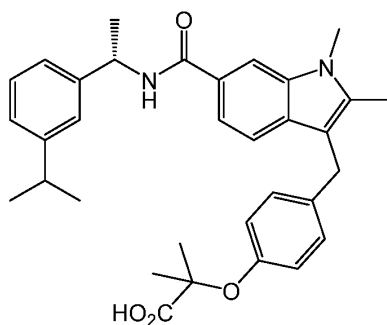
[0314] Step 2: 2-(3-(((S)-1-(3-isopropylphenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy) propanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the ethyl 2-(3-(((S)-1-(3-isopropylphenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy) propanoate instead of the (ethyl 2-(4-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy) propanoate. A yellow solid was obtained (80 mg, yield 94%). ¹H NMR (400 MHz, CDCl₃) δ 7.82 (q, J = 1.5 Hz, 1H), 7.35 – 7.22 (m, 3H), 7.22 – 7.11 (m, 2H), 7.11 – 6.95 (m, 2H), 6.76 – 6.68 (m, 1H), 6.63 – 6.52 (m, 2H), 6.43 (q, J = 9.1 Hz, 1H), 6.20 (br, 1H), 5.33 – 5.25 (m, 1H), 4.59 –

4.55 (m, 1H), 3.95 – 3.85 (m, 3H), 3.49 (d, $J = 2.7$ Hz, 2H), 2.25 (dd, $J = 32.7, 1.7$ Hz, 3H), 1.69 – 1.37 (m, 6H), 1.17 (d, $J = 7.0$ Hz, 6H).

[0315] Compound 16: (S)-2-(4-((6-((1-(3-isopropylphenyl)ethyl) carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoic acid.

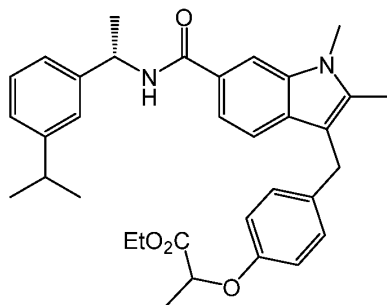


[0316] Step 1: ethyl (S)-2-(4-((6-((1-(3-isopropylphenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoate. The title compound was prepared following the same general protocol as described in Step 9, Compound 1, using the (S)-N-(1-(3-isopropylphenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide and the ethyl 2-(3-formylphenoxy)-2-methylpropanoate instead of the ethyl 2-(4-formylphenoxy)propanoate. A yellow solid was obtained (49 mg, yield 89%).

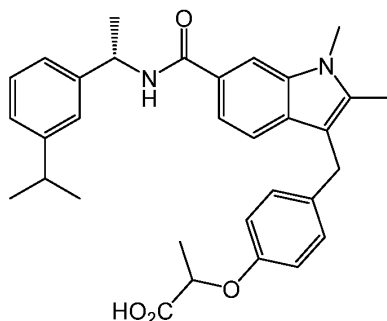


[0317] Step 2: (S)-2-(4-((6-((1-(3-isopropylphenyl)ethyl) carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the ethyl (S)-2-(4-((6-((1-(3-isopropylphenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoate instead of the (ethyl 2-(4-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy) propanoate. A yellow solid was obtained (31 mg, yield 67%). ^1H NMR (400 MHz, CDCl_3) δ 7.95 (s, 1H), 7.33 (dd, $J = 16.5, 8.0$ Hz, 3H), 7.29 – 7.22 (m, 2H), 7.17 (d, $J = 7.3$ Hz, 1H), 7.04 (d, $J = 7.9$ Hz, 2H), 6.92 – 6.77 (m, 2H), 6.56 (d, $J = 7.8$ Hz, 1H), 5.40 (s, 1H), 4.03 (s, 2H), 3.69 (s, 3H), 2.92 (p, $J = 6.9$ Hz, 1H), 2.37 (s, 3H), 1.63 (d, $J = 6.9$ Hz, 3H), 1.56 (s, 6H), 1.26 (d, $J = 6.9$ Hz, 6H).

[0318] Compound 17: 2-(4-((6-(((S)-1-(3-isopropylphenyl) ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl) phenoxy) propanoic acid.

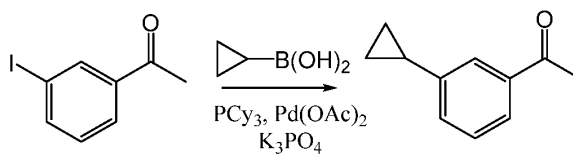


[0319] Step 1: ethyl 2-(4-((6-(((S)-1-(3-isopropylphenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy) propanoate. The title compound was prepared following the same general protocol as described in Step 9, Compound 1, using the (S)-N-(1-(3-isopropylphenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide. A yellow solid was obtained (59 mg, yield 88%).



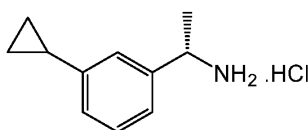
[0320] Step 2: 2-(4-((6-(((S)-1-(3-isopropylphenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy) propanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the ethyl 2-(4-((6-(((S)-1-(3-isopropylphenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy) propanoate instead of the (ethyl 2-(4-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy) propanoate. A yellow solid was obtained (25 mg, yield 85%). ¹H NMR (400 MHz, CDCl₃) δ 7.84 (s, 1H), 7.34 – 7.10 (m, 5H), 7.07 (d, J = 7.5 Hz, 1H), 6.96 (d, J = 8.0 Hz, 2H), 6.72 – 6.64 (m, 2H), 6.41 (d, J = 8.0 Hz, 1H), 5.29 (t, J = 7.2 Hz, 1H), 4.61 (ddd, J = 6.9, 4.9, 1.8 Hz, 1H), 3.92 (s, 2H), 3.58 (s, 3H), 2.83 (q, J = 6.9 Hz, 1H), 2.26 (s, 3H), 1.52 (dd, J = 7.0, 1.8 Hz, 6H), 1.22 – 1.13 (m, 6H).

[0321] Compound 18: (S)-2-(3-((6-((1-(3-cyclopropylphenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoic acid.

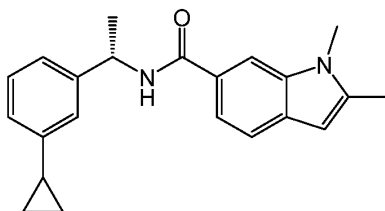


[0322] Step 1: 1-(3-cyclopropylphenyl)ethanone. Tricyclohexylphosphine (0.085 g, 0.3mmol), palladium(II) acetate (0.136 g, 0.61mmol), cyclopropylboronic acid (0.68 g, 7.93 mmol) and K₃PO₄ (4.51

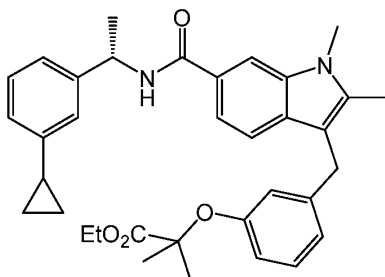
g, 21.3 mmol) were added to a flame-dried three-neck flask equipped with a stir bar and a reflux condenser under N₂. Toluene (20 mL) and H₂O (5 mL) were added to the reaction flask, and the mixture was stirred. 1-(3-iodophenyl)ethanone (1.5 g, 6.1 mmol) in toluene (5 mL) was then added via syringe. The reaction mixture was placed into an oil bath and stirred at 110 °C and left to stir for 24 hours. Upon completion, the reaction mixture was diluted with ethyl acetate (100 mL) and washed with water twice. The organic layer was dried with sodium sulfate, concentrated in vacuo and purified by column chromatography (hexanes/EtOAc, 20:1 (v/v)) to afford the titled compound a brownish oil (0.9 g, yield 92%). ¹H NMR (400 MHz, CDCl₃) δ 7.88 (ddd, J = 7.6, 1.8, 1.2 Hz, 1H), 7.85 – 7.79 (m, 1H), 7.50 (td, J = 7.6, 0.6 Hz, 1H), 7.46 – 7.36 (m, 1H), 2.75 (s, 3H), 2.12 (ddd, J = 8.4, 5.1, 3.3 Hz, 1H), 1.29 – 1.05 (m, 2H), 1.04 – 0.84 (m, 2H).



[0323] Step 2: (S)-1-(3-cyclopropylphenyl)ethanamine hydrochloride. The title compound was prepared following the same general protocol as described in Step 6, Compound 1, using the 1-(3-cyclopropylphenyl)ethanone instead of the 1-(4-*tert*-butylphenyl)ethenone. A white solid was obtained (1.3 g, yield 76%). ¹H NMR (600 MHz, DMSO-d₆) δ 7.81 (s, 1H), 7.27 – 7.19 (m, 2H), 7.17 – 7.03 (m, 3H), 6.99 – 6.91 (m, 1H), 6.86 (d, J = 7.5 Hz, 1H), 6.75 (d, J = 7.7 Hz, 1H), 6.65 (s, 1H), 6.59 (d, J = 8.1 Hz, 1H), 6.36 (d, J = 7.8 Hz, 1H), 5.26 (t, J = 7.2 Hz, 1H), 3.91 (s, 3H), 3.56 (s, 3H), 1.81 (s, 1H), 1.52 (d, J = 6.8 Hz, 3H), 1.42 (s, 6H), 0.91 – 0.82 (m, 2H), 0.61 (dt, J = 6.4, 4.5 Hz, 2H).

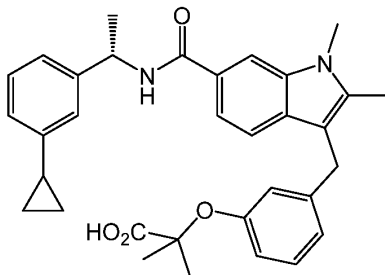


[0324] Step 3: (S)-N-(1-(3-cyclopropylphenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide. The title compound was prepared following the same general protocol as described in Step 8, Compound 1, using the (S)- (S)-1-(3-cyclopropylphenyl)ethanamine hydrochloride instead of (S)-1-(4-(*tert*-butyl)phenyl)ethanamine hydrochloride. A yellow solid was obtained (0.12 g, yield 98%).



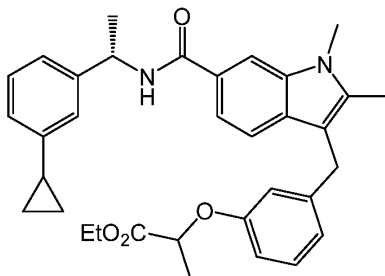
[0325] Step 4: ethyl (S)-2-(3-((6-((1-(3-cyclopropylphenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoate. The title compound was prepared following the same general

protocol as described in Step 9, Compound 1, using the (S)-N-(1-(3-cyclopropylphenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide and the ethyl 2-(3-formylphenoxy)-2-methylpropanoate instead of the ethyl 2-(4-formylphenoxy)propanoate. A yellow solid was obtained (27 mg, yield 96%).

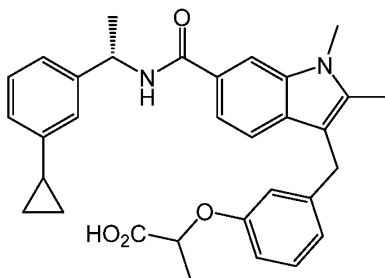


[0326] Step 5: (S)-2-(3-((6-((1-(3-cyclopropylphenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-2-methyl propanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the ethyl (S)-2-(3-((6-((1-(3-cyclopropylphenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoate instead of the (ethyl 2-(4-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy) propanoate. A yellow solid was obtained (18 mg, yield 85%). ¹H NMR (400 MHz, CDCl₃) δ 7.81 (s, 1H), 7.27 – 7.19 (m, 2H), 7.17 – 7.03 (m, 3H), 6.99 – 6.91 (m, 1H), 6.86 (d, J = 7.5 Hz, 1H), 6.75 (d, J = 7.7 Hz, 1H), 6.65 (s, 1H), 6.59 (d, J = 8.1 Hz, 1H), 6.36 (d, J = 7.8 Hz, 1H), 5.26 (t, J = 7.2 Hz, 1H), 3.91 (s, 3H), 3.56 (s, 3H), 1.81 (s, 1H), 1.52 (d, J = 6.8 Hz, 3H), 1.42 (s, 6H), 0.91 – 0.82 (m, 2H), 0.61 (dt, J = 6.4, 4.5 Hz, 2H).

[0327] Compound 19: 2-(3-((6-(((S)-1-(3-cyclopropylphenyl) ethyl) carbamoyl)-1,2-dimethyl-1H-indol-3-yl) methyl) phenoxy)propanoic acid.

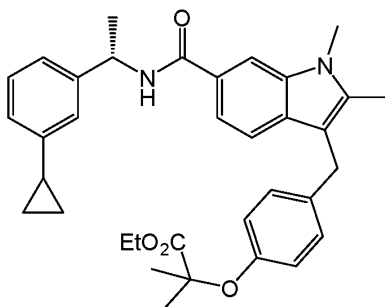


[0328] Step 1: ethyl 2-(3-((6-(((S)-1-(3-cyclopropylphenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy) propanoate. The title compound was prepared following the same general protocol as described in Step 9, Compound 1, using the (S)-N-(1-(3-cyclopropylphenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide and the ethyl 2-(3-formylphenoxy)propanoate instead of the ethyl 2-(4-formylphenoxy)propanoate. A yellow solid was obtained (25 mg, yield 90%).

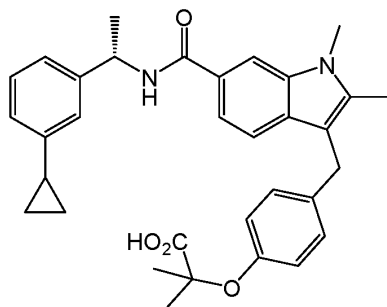


[0329] Step 2: 2-(3-((6-(((S)-1-(3-cyclopropylphenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy) propanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the ethyl 2-(3-((6-(((S)-1-(3-cyclopropylphenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy) propanoate instead of the (ethyl 2-(4-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy) propanoate. A yellow solid was obtained (20 mg, yield 84%). ¹H NMR (400 MHz, CDCl₃) δ 7.79 (s, 1H), 7.26 (d, J = 8.1 Hz, 1H), 7.21 – 7.17 (m, 1H), 7.14 (d, J = 7.6 Hz, 1H), 7.12 – 7.04 (m, 2H), 7.00 (td, J = 7.8, 3.6 Hz, 1H), 6.90 – 6.83 (m, 1H), 6.73 (d, J = 7.7 Hz, 1H), 6.66 – 6.52 (m, 2H), 6.40 (d, J = 7.2 Hz, 1H), 5.29 – 5.24 (m, 1H), 4.69 – 4.45 (m, 1H), 4.06 – 3.81 (m, 2H), 3.50 (d, J = 2.4 Hz, 3H), 2.21 (d, J = 2.3 Hz, 3H), 1.98 – 1.71 (m, 1H), 1.50 (td, J = 6.9, 2.5 Hz, 6H), 1.04 – 0.82 (m, 2H), 0.71 – 0.50 (m, 2H).

[0330] Compound 20: (S)-2-(4-((6-((1-(3-cyclopropylphenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoic acid.

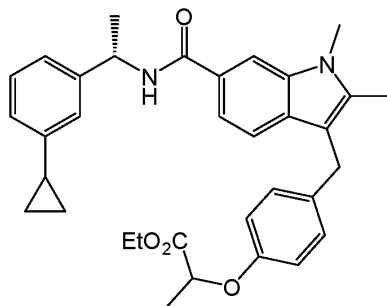


[0331] Step 1: ethyl (S)-2-(4-((6-((1-(3-cyclopropylphenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoate. The title compound was prepared following the same general protocol as described in Step 9, Compound 1, using the (S)-N-(1-(3-cyclopropylphenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide and the ethyl 2-(4-formylphenoxy)-2-methylpropanoate instead of ethyl 2-(4-formylphenoxy)propanoate. A yellow solid was obtained (22 mg, yield 81%).

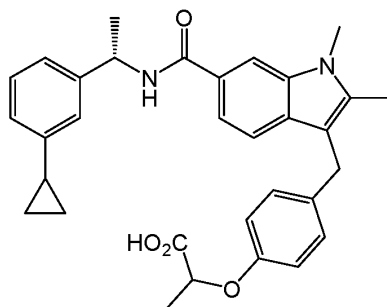


[0332] Step 2: 2-(4-((6-(((S)-1-(3-cyclopropylphenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy) propanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the ethyl (S)-2-(4-((6-((1-(3-cyclopropylphenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoate instead of the (ethyl 2-(4-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy) propanoate. A yellow solid was obtained (18 mg, yield 90%). ¹H NMR (400 MHz, CD₂Cl₂) δ 7.72 (s, 1H), 7.22 (d, J = 7.9 Hz, 2H), 7.12 – 7.01 (m, 4H), 6.96 – 6.88 (m, 2H), 6.82 (d, J = 7.6 Hz, 1H), 6.64 (d, J = 16.2 Hz, 2H), 6.48 (s, 1H), 5.13 (s, 1H), 3.90 (s, 2H), 3.54 (s, 3H), 2.25 (d, J = 4.2 Hz, 3H), 1.77 (s, 1H), 1.45 (d, J = 7.0 Hz, 3H), 1.35 (s, 6H), 0.83 (d, J = 8.6 Hz, 2H), 0.58 (s, 2H).

[0333] Compound 21: 2-(4-((6-(((S)-1-(3-cyclopropylphenyl) ethyl) carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl) phenoxy)propanoic acid.

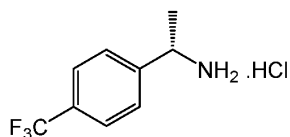


[0334] Step 1: ethyl 2-(4-((6-(((S)-1-(3-cyclopropylphenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy) propanoate. The title compound was prepared following the same general protocol as described in Step 9, Compound 1, using the (S)-N-(1-(3-cyclopropylphenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide. A yellow solid was obtained (35 mg, yield 89%).

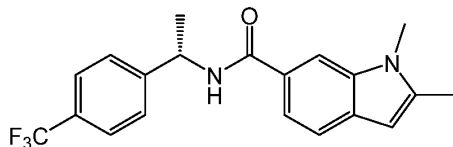


[0335] Step 2: 2-(4-((6-(((S)-1-(3-cyclopropylphenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy) propanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using ethyl 2-(4-((6-(((S)-1-(3-cyclopropylphenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy) propanoate instead of the (ethyl 2-(4-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy) propanoate. A yellow solid was obtained (24 mg, yield 72%). ¹H NMR (400 MHz, MeOD) δ 7.78 (d, J = 1.5 Hz, 1H), 7.37 (dd, J = 8.3, 1.6 Hz, 1H), 7.25 (d, J = 8.3 Hz, 1H), 7.17 – 7.03 (m, 3H), 6.93 (d, J = 8.3 Hz, 2H), 6.83 (t, J = 4.3 Hz, 1H), 6.64 (d, J = 8.4 Hz, 2H), 5.13 (t, J = 7.4 Hz, 1H), 3.89 (s, 2H), 3.64 (s, 3H), 2.29 (s, 3H), 1.79 (ddd, J = 13.4, 8.5, 5.0 Hz, 1H), 1.46 (d, J = 7.1 Hz, 3H), 1.39 (d, J = 6.6 Hz, 3H), 1.01 – 0.73 (m, 2H), 0.56 (ddd, J = 7.2, 4.5, 1.9 Hz, 2H).

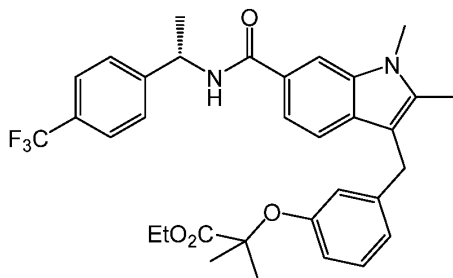
[0336] **Compound 22: (S)-2-(3-((1,2-dimethyl-6-((1-(4-(trifluoromethyl)phenyl)ethyl)carbamoyl)-1H-indol-3-yl)methyl) phenoxy)-2-methylpropanoic acid.**



[0337] Step 1: (S)-1-(4-(trifluoromethyl)phenyl)ethanamine hydrochloride. The title compound was prepared following the same general protocol as described in Step 6, Compound 1, using the 1-(4-(trifluoromethyl)phenyl)ethanone instead of the 1-(4-tert-butylphenyl)ethenone. A white solid was obtained (1.1 g, yield 48%). ¹H NMR (400 MHz, DMSO-d₆) δ 8.57 (s, 3H), 7.79 (d, J = 8.28 Hz, 2H), 7.72 (d, J = 8.28 Hz, 2H), 4.50 (p, d, J = 5.12 Hz, 1H), 1.53 (d, J = 6.84 Hz, 3H).

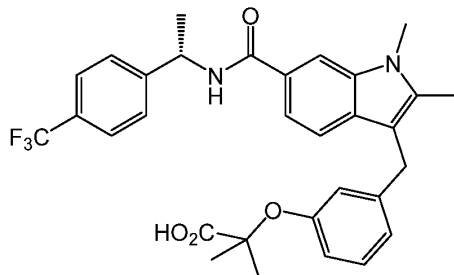


[0338] Step 2: (S)-1,2-dimethyl-N-(1-(4-(trifluoromethyl)phenyl)ethyl)-1H-indole-6-carboxamide. The title compound was prepared following the same general protocol as described in Step 8, Compound 1, using the (S)-1-(4-(trifluoromethyl)phenyl)ethanamine hydrochloride instead of (S)-1-(4-(tert-butyl)phenyl)ethanamine hydrochloride. A yellow solid was obtained (0.14 g, yield 99%).



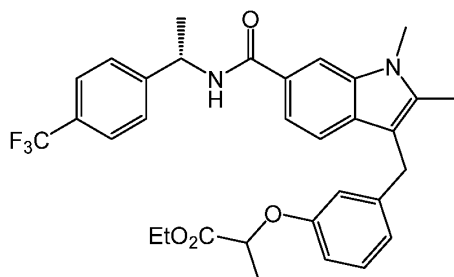
[0339] Step 3: ethyl (S)-2-(3-((1,2-dimethyl-6-((1-(4-(trifluoromethyl)phenyl)ethyl)carbamoyl)-1H-indol-3-yl)methyl) phenoxy)-2-methylpropanoate. The title compound was prepared following the same general protocol as described in Step 9, Compound 1, using the (S)-1,2-dimethyl-N-(1-(4-

(trifluoromethyl)phenyl)ethyl)-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide and the ethyl 2-(3-formylphenoxy)-2-methylpropanoate instead of the ethyl 2-(4-formylphenoxy)propanoate. A yellow solid was obtained (14 mg, yield 56%).

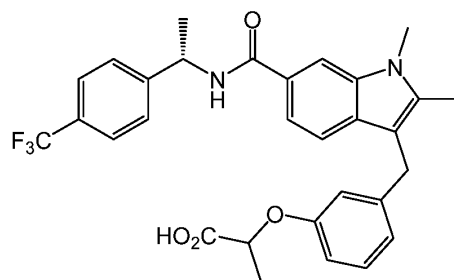


[0340] Step 4: (S)-2-(3-((1,2-dimethyl-6-((1-(4-(trifluoromethyl)phenyl)ethyl)carbamoyl)-1H-indol-3-yl)methyl) phenoxy)-2-methylpropanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the ethyl (S)-2-(3-((1,2-dimethyl-6-((1-(4-(trifluoromethyl)phenyl)ethyl)carbamoyl)-1H-indol-3-yl)methyl)phenoxy)-2-methyl propanoate instead of the (ethyl 2-(4-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy) propanoate. A yellow solid was obtained (10 mg, yield 75%). ¹H NMR (400 MHz, CDCl₃) δ 7.90 – 7.66 (m, 1H), 7.50 (d, J = 8.2 Hz, 2H), 7.41 (d, J = 8.1 Hz, 2H), 7.35 – 7.20 (m, 2H), 7.00 (t, J = 7.9 Hz, 1H), 6.85 – 6.71 (m, 1H), 6.74 – 6.55 (m, 2H), 6.49 (d, J = 7.6 Hz, 1H), 5.30 (p, J = 7.0 Hz, 1H), 3.93 (s, 2H), 3.56 (s, 3H), 2.26 (s, 3H), 1.52 (d, J = 1.1 Hz, 3H), 1.45 (s, 6H).

[0341] Compound 23: 2-(3-((1,2-dimethyl-6-(((S)-1-(4-(trifluoromethyl)phenyl)ethyl)carbamoyl)-1H-indol-3-yl)methyl) phenoxy)propanoic acid.

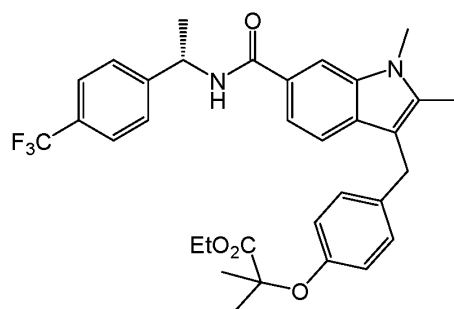


[0342] Step 1: ethyl 2-(3-((1,2-dimethyl-6-(((S)-1-(4-(trifluoromethyl)phenyl)ethyl)carbamoyl)-1H-indol-3-yl)methyl) phenoxy)propanoate. The title compound was prepared following the same general protocol as described in Step 9, Compound 1, using the (S)-1,2-dimethyl-N-(1-(4-(trifluoromethyl)phenyl)ethyl)-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide and the 2-(3-formylphenoxy)propanoate instead of the ethyl 2-(4-formylphenoxy)propanoate. A yellow solid was obtained (37 mg, yield 92%).

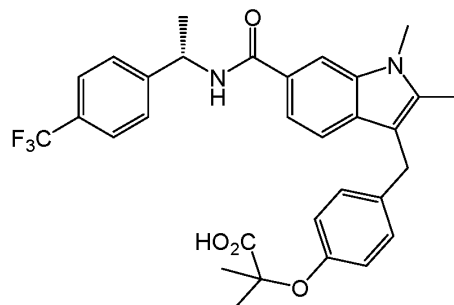


[0343] Step 2: 2-(3-((1,2-dimethyl-6-(((S)-1-(4-(trifluoromethyl)phenyl)ethyl)carbamoyl)-1H-indol-3-yl)methyl)phenoxy) propanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the ethyl 2-(3-((1,2-dimethyl-6-(((S)-1-(4-(trifluoromethyl)phenyl)ethyl)carbamoyl)-1H-indol-3-yl)methyl) phenoxy) propanoate instead of the (ethyl 2-(4-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy) propanoate. A yellow solid was obtained (29 mg, yield 82%). ¹H NMR (400 MHz, CDCl₃) δ 7.79 (s, 1H), 7.47 (dd, J = 8.3, 3.6 Hz, 2H), 7.44 – 7.35 (m, 2H), 7.31 – 7.19 (m, 2H), 7.02 (td, J = 7.9, 4.7 Hz, 1H), 6.86 – 6.68 (m, 1H), 6.68 – 6.50 (m, 3H), 5.28 (q, J = 7.0 Hz, 1H), 4.57 (qd, J = 6.8, 3.3 Hz, 1H), 4.05 – 3.86 (s, 2H), 3.49 (s, 3H), 2.27 – 2.01 (s, 3H), 1.48 (dd, J = 7.0, 1.9 Hz, 6H).

[0344] Compound 24: (S)-2-(4-((1,2-dimethyl-6-((1-(4-(trifluoromethyl)phenyl)ethyl)carbamoyl)-1H-indol-3-yl)methyl) phenoxy)-2-methylpropanoic acid.

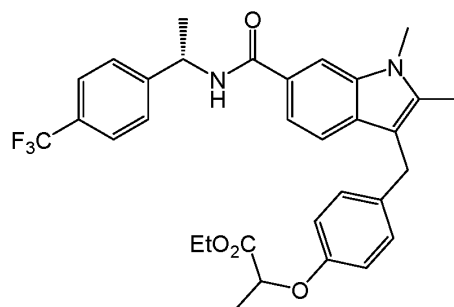


[0345] Step 1: ethyl (S)-2-(4-((1,2-dimethyl-6-((1-(4-(trifluoromethyl)phenyl)ethyl)carbamoyl)-1H-indol-3-yl)methyl) phenoxy)-2-methylpropanoate. The title compound was prepared following the same general protocol as described in Step 9, Compound 1, using the (S)-1,2-dimethyl-N-(1-(4-(trifluoromethyl)phenyl)ethyl)-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide and the ethyl 2-(4-formylphenoxy)-2-methylpropanoate instead of the ethyl 2-(4-formylphenoxy)propanoate. A yellow solid was obtained (35 mg, yield 92%).

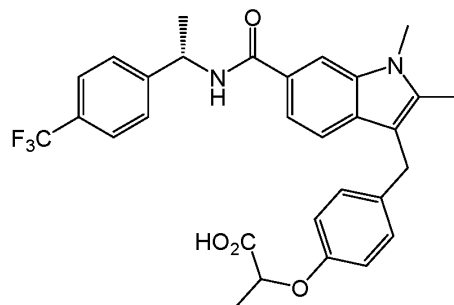


[0346] Step 2: (S)-2-(4-((1,2-dimethyl-6-((1-(4-(trifluoromethyl)phenyl)ethyl)carbamoyl)-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the ethyl (S)-2-(4-((1,2-dimethyl-6-((1-(4-(trifluoromethyl)phenyl)ethyl)carbamoyl)-1H-indol-3-yl)methyl) phenoxy)-2-methylpropanoate instead of the (ethyl 2-(4-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy) propanoate. A yellow solid was obtained (25 mg, yield 75%). ¹H NMR (400 MHz, CDCl₃) δ 7.84 (d, J = 1.4 Hz, 1H), 7.51 (d, J = 8.2 Hz, 2H), 7.43 (d, J = 8.1 Hz, 2H), 7.32 – 7.20 (m, 2H), 7.01 – 6.95 (m, 2H), 6.78 – 6.68 (m, 2H), 6.39 (d, J = 7.5 Hz, 1H), 5.32 (q, J = 7.1 Hz, 1H), 3.96 (s, 2H), 3.63 (s, 3H), 2.30 (s, 3H), 1.54 (d, J = 6.9 Hz, 6H), 1.47 (s, 6H).

[0347] Compound 25: 2-(4-((1,2-dimethyl-6-(((S)-1-(4-(trifluoromethyl)phenyl)ethyl)carbamoyl)-1H-indol-3-yl) methyl) phenoxy)propanoic acid.

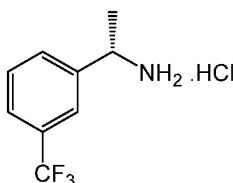


[0348] Step 1: ethyl 2-(4-((1,2-dimethyl-6-(((S)-1-(4-(trifluoromethyl)phenyl)ethyl)carbamoyl)-1H-indol-3-yl)methyl) phenoxy)propanoate. The title compound was prepared following the same general protocol as described in Step 9, Compound 1, using the (S)-1,2-dimethyl-N-(1-(4-(trifluoromethyl)phenyl)ethyl)-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide. A yellow solid was obtained (24 mg, yield 84%).

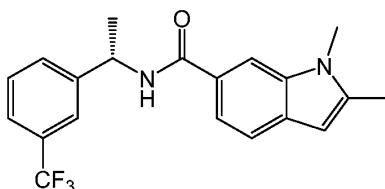


[0349] Step 2: 2-(4-((1,2-dimethyl-6-(((S)-1-(4-(trifluoromethyl)phenyl)ethyl)carbamoyl)-1H-indol-3-yl)methyl)phenoxy) propanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the ethyl 2-(4-((1,2-dimethyl-6-(((S)-1-(4-(trifluoromethyl)phenyl)ethyl)carbamoyl)-1H-indol-3-yl)methyl) phenoxy) propanoate instead of the (ethyl 2-(4-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy) propanoate. A yellow solid was obtained (19 mg, yield 83%). ¹H NMR (400 MHz, MeOD) δ 8.61 (d, J = 7.6 Hz, 1H), 7.80 (d, J = 1.5 Hz, 1H), 7.59 – 7.46 (m, 4H), 7.39 (dd, J = 8.3, 1.6 Hz, 1H), 7.26 (d, J = 8.3 Hz, 1H), 6.93 (dd, J = 8.6, 2.3 Hz, 2H), 6.75 – 6.52 (m, 2H), 5.22 (t, J = 7.1 Hz, 1H), 4.44 (dd, J = 13.7, 6.8 Hz, 1H), 3.88 (s, 2H), 3.63 (s, 3H), 2.29 (s, 3H), 1.50 (d, J = 7.1 Hz, 3H), 1.39 (dd, J = 11.7, 5.0 Hz, 3H).

[0350] Compound 26: (S)-2-(3-((1,2-dimethyl-6-((1-(3-(trifluoromethyl)phenyl)ethyl)carbamoyl)-1H-indol-3-yl)methyl) phenoxy)-2-methylpropanoic acid.

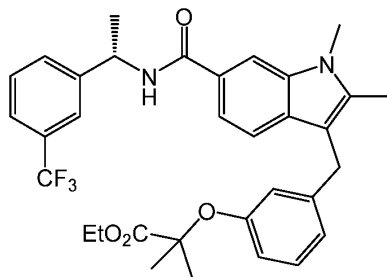


[0351] Step 1: (S)-1-(3-(trifluoromethyl)phenyl)ethanamine hydrochloride. The title compound was prepared following the same general protocol as described in Step 6, Compound 1, using the 1-(3-(trifluoromethyl)phenyl)ethanone instead of the 1-(4-tert-butylphenyl)ethenone. A white solid was obtained (1.47 g, yield 81%). ¹H NMR (400 MHz, DMSO-d₆) δ 8.57 (s, 3H), 7.88 (s, 1H), 7.82 (d, J = 7.52 Hz, 1H), 7.82 (d, J = 7.59 Hz, 1H), 7.82 (t, J = 7.68 Hz, 1H), 4.52 (p, d, J = 5.09 Hz, 1H), 1.54 (d, J = 6.84 Hz, 3H).

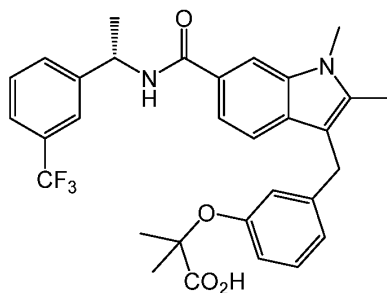


[0352] Step 2: (S)-1,2-dimethyl-N-(1-(3-(trifluoromethyl)phenyl)ethyl)-1H-indole-6-carboxamide. The title compound was prepared following the same general protocol as described in Step 8, Compound 1,

using the (S)-1-(3-(trifluoromethyl)phenyl)ethanamine hydrochloride instead of (S)-1-(4-(tert-butyl)phenyl)ethanamine hydrochloride. A yellow solid was obtained (0.17 g, yield 94%).

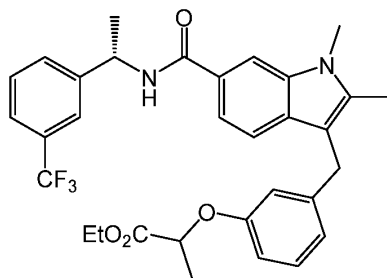


[0353] Step 3: ethyl (S)-2-(3-((1,2-dimethyl-6-((1-(3-(trifluoromethyl)phenyl)ethyl)carbamoyl)-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoate. The title compound was prepared following the same general protocol as described in Step 9, Compound 1, using the (S)-1,2-dimethyl-N-(1-(4-(trifluoromethyl)phenyl)ethyl)-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide and the ethyl 2-(3-formylphenoxy)-2-methylpropanoate instead of the ethyl 2-(4-formylphenoxy)propanoate. A yellow solid was obtained (45 mg, yield 90%).

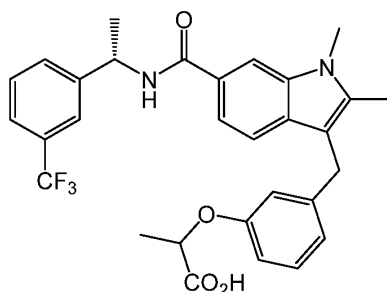


[0354] Step 4: (S)-2-(3-((1,2-dimethyl-6-((1-(3-(trifluoromethyl)phenyl)ethyl)carbamoyl)-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the ethyl (S)-2-(3-((1,2-dimethyl-6-((1-(3-(trifluoromethyl)phenyl)ethyl)carbamoyl)-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoate instead of the (ethyl 2-(4-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)propanoate. A yellow solid was obtained (33 mg, yield 78%). ¹H NMR (400 MHz, CDCl₃) δ 7.80 (s, 1H), 7.56 (s, 1H), 7.51 (d, J = 7.8 Hz, 1H), 7.43 (d, J = 7.8 Hz, 1H), 7.36 (t, J = 7.8 Hz, 1H), 7.29 – 7.14 (m, 2H), 6.98 (t, J = 7.9 Hz, 1H), 6.76 (d, J = 7.6 Hz, 1H), 6.64 (s, 1H), 6.60 (d, J = 7.7 Hz, 1H), 6.52 (d, J = 7.4 Hz, 1H), 5.32 (q, J = 7.1 Hz, 1H), 3.92 (s, 2H), 3.54 (s, 3H), 1.52 (d, J = 7.1 Hz, 3H), 1.44 (s, 6H).

[0355] Compound 27: 2-(3-((1,2-dimethyl-6-(((S)-1-(3-(trifluoromethyl)phenyl)ethyl)carbamoyl)-1H-indol-3-yl)methyl)phenoxy)propanoic acid.

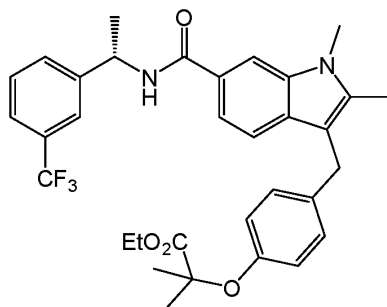


[0356] Step 1: ethyl 2-(3-((1,2-dimethyl-6-(((S)-1-(3-(trifluoromethyl)phenyl)ethyl)carbamoyl)-1H-indol-3-yl)methyl)phenoxy)propanoate. The title compound was prepared following the same general protocol as described in Step 9, Compound 1, using the (S)-1,2-dimethyl-N-(1-(3-(trifluoromethyl)phenyl)ethyl)-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide and the ethyl 2-(3-formylphenoxy)propanoate instead of the ethyl 2-(4-formylphenoxy)propanoate. A yellow solid was obtained (27 mg, yield 86 %).

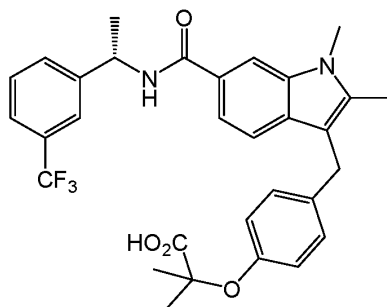


[0357] Step 2: 2-(3-((1,2-dimethyl-6-(((S)-1-(3-(trifluoromethyl)phenyl)ethyl)carbamoyl)-1H-indol-3-yl)methyl)phenoxy)propanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the ethyl 2-(3-((1,2-dimethyl-6-(((S)-1-(3-(trifluoromethyl)phenyl)ethyl)carbamoyl)-1H-indol-3-yl)methyl)phenoxy)propanoate instead of the (ethyl 2-(4-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)propanoate. A yellow solid was obtained (20 mg, yield 80%). ¹H NMR (400 MHz, CDCl₃) δ 7.83 – 7.76 (m, 1H), 7.55 (s, 1H), 7.48 (d, J = 7.8 Hz, 1H), 7.42 (d, J = 8.1 Hz, 1H), 7.33 (t, J = 7.7 Hz, 1H), 7.28 – 7.19 (m, 2H), 7.02 (dt, J = 10.5, 7.8 Hz, 1H), 6.80 – 6.71 (m, 1H), 6.67 – 6.48 (m, 3H), 5.30 (h, J = 7.3 Hz, 1H), 4.56 (dq, J = 9.5, 6.7 Hz, 1H), 3.92 (d, J = 4.8 Hz, 2H), 3.46 (d, J = 1.8 Hz, 3H), 2.21 (d, J = 1.4 Hz, 3H), 1.58 – 1.44 (m, 5H).

[0358] Compound 28: (S)-2-(4-((1,2-dimethyl-6-((1-(3-(trifluoromethyl)phenyl)ethyl)carbamoyl)-1H-indol-3-yl)methyl)phenoxy)-2-methyl propanoic acid.

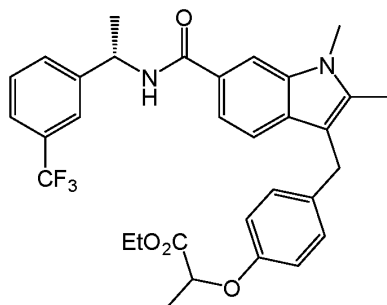


[0359] Step 1: ethyl (S)-2-(4-((1,2-dimethyl-6-((1-(3-(trifluoromethyl)phenyl)ethyl)carbamoyl)-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoate. The title compound was prepared following the same general protocol as described in Step 9, Compound 1, using the (S)-1,2-dimethyl-N-(1-(3-(trifluoromethyl)phenyl)ethyl)-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide and the ethyl 2-(4-formylphenoxy)-2-methylpropanoate instead of the ethyl 2-(4-formylphenoxy)propanoate. A yellow solid was obtained (38 mg, yield 93%).

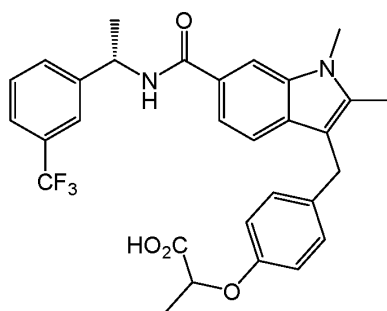


[0360] Step 2: (S)-2-(4-((1,2-dimethyl-6-((1-(3-(trifluoromethyl)phenyl)ethyl)carbamoyl)-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the ethyl (S)-2-(4-((1,2-dimethyl-6-((1-(3-(trifluoromethyl)phenyl)ethyl)carbamoyl)-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoate instead of the (ethyl 2-(4-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)propanoate. A yellow solid was obtained (28 mg, yield 79%). ¹H NMR (400 MHz, MeOD) δ 7.80 (d, J = 1.5 Hz, 1H), 7.63 (s, 1H), 7.59 (d, J = 6.8 Hz, 2H), 7.49 – 7.41 (m, 3H), 7.39 (dd, J = 8.3, 1.6 Hz, 1H), 7.28 (d, J = 8.3 Hz, 1H), 6.96 (d, J = 8.5 Hz, 2H), 6.66 (d, J = 8.6 Hz, 2H), 5.23 (q, J = 6.9 Hz, 1H), 3.93 (s, 2H), 3.66 (s, 3H), 2.31 (s, 3H), 1.51 (d, J = 7.1 Hz, 3H), 1.40 (s, 6H).

[0361] Compound 29: 2-(4-((1,2-dimethyl-6-(((S)-1-(3-(trifluoromethyl)phenyl)ethyl)carbamoyl)-1H-indol-3-yl)methyl)phenoxy)propanoic acid.

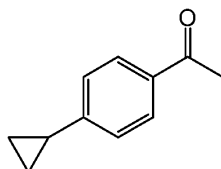


[0362] Step 1: ethyl 2-(4-((1,2-dimethyl-6-(((S)-1-(3-(trifluoromethyl)phenyl)ethyl)carbamoyl)-1H-indol-3-yl)methyl)phenoxy)propanoate. The title compound was prepared following the same general protocol as described in Step 9, Compound 1, using the (S)-1,2-dimethyl-N-(1-(3-(trifluoromethyl)phenyl)ethyl)-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide. A yellow solid was obtained (43 mg, yield 91%).

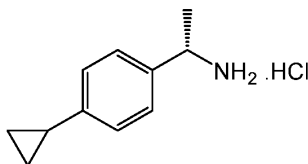


[0363] Step 2: 2-(4-((1,2-dimethyl-6-(((S)-1-(3-(trifluoromethyl)phenyl)ethyl)carbamoyl)-1H-indol-3-yl)methyl)phenoxy)propanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the ethyl 2-(4-((1,2-dimethyl-6-(((S)-1-(3-(trifluoromethyl)phenyl)ethyl)carbamoyl)-1H-indol-3-yl)methyl)phenoxy)propanoate instead of the (ethyl 2-(4-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)propanoate. A yellow solid was obtained (35 mg, yield 85%). ¹H NMR (400 MHz, CDCl₃) δ 8.54 (br, 1H), 7.81 (s, 1H), 7.54 (s, 1H), 7.48 (d, J = 7.9 Hz, 1H), 7.40 (dd, J = 8.0, 2.8 Hz, 1H), 7.35 – 7.29 (m, 1H), 7.26 – 7.19 (m, 2H), 7.02 – 6.89 (m, 2H), 6.77 – 6.62 (m, 2H), 6.60 (d, J = 7.7 Hz, 1H), 5.30 (q, J = 7.2 Hz, 1H), 4.60 (q, J = 6.8 Hz, 1H), 3.91 (s, 2H), 3.54 (d, J = 1.2 Hz, 3H), 2.25 (s, 3H), 1.50 (dd, J = 6.9, 3.5 Hz, 6H).

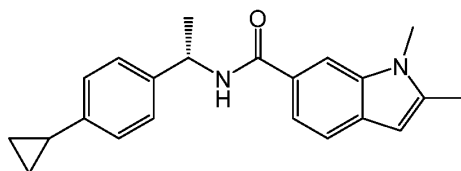
[0364] Compound 30: (S)-2-(3-((6-(((1-(4-cyclopropylphenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoic acid.



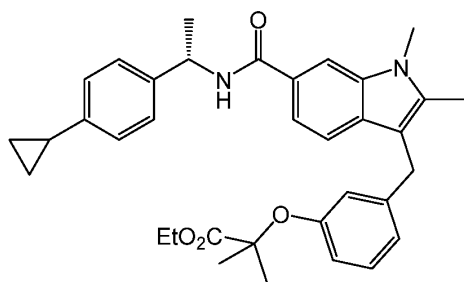
[0365] Step 1: (S)-1-(4-cyclopropylphenyl)ethanamine hydrochloride. The title compound was prepared following the same general protocol as described in Step 1, Compound 18, using the 1-(4-bromophenyl)ethanone instead of the 1-(3-iodophenyl)ethanone. A brownish oil was obtained (1.1 g, yield 92%). ¹H NMR (400 MHz, CDCl₃) δ 7.76 (d, J = 8.4 Hz, 2H), 7.03 (d, J = 8.3 Hz, 2H), 2.48 (s, 3H), 1.85 (tt, J = 8.4, 5.0 Hz, 1H), 1.07 – 0.82 (m, 2H), 0.81 – 0.55 (m, 2H).



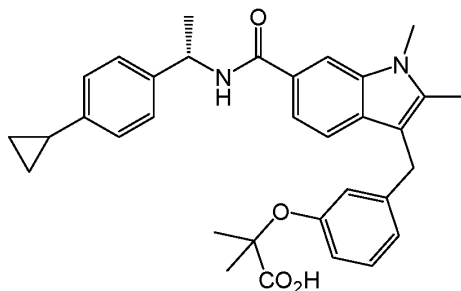
[0366] Step 2: (S)-1-(4-cyclopropylphenyl)ethanamine hydrochloride. The title compound was prepared following the same general protocol as described in Step 6, Compound 1, using the 1-(4-cyclopropylphenyl)ethanone instead of the 1-(4-*tert*-butylphenyl)ethanone. A white solid was obtained (1.2 g, yield 81%). ¹H NMR (600 MHz, DMSO-d₆) δ 8.56 (s, 3H), 7.45 (d, J = 8.22 Hz, 2H), 7.17 (d, J = 8.22 Hz, 2H), 4.38 (p, d, J = 5.76 Hz, 1H), 2.00 (tt, J = 8.4, 5.0 Hz, 1H), 1.55 (d, J = 6.84 Hz, 3H), 1.02 – 0.99 (m, 2H), 0.73 – 0.71 (m, 2H).



[0367] Step 3: (S)-N-(1-(4-cyclopropylphenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide. The title compound was prepared following the same general protocol as described in Step 8, Compound 1, using the (S)-1-(4-cyclopropylphenyl)ethanamine hydrochloride instead of (S)-1-(4-(*tert*-butyl)phenyl)ethanamine hydrochloride. A yellow solid was obtained (0.155 g, yield 97%).

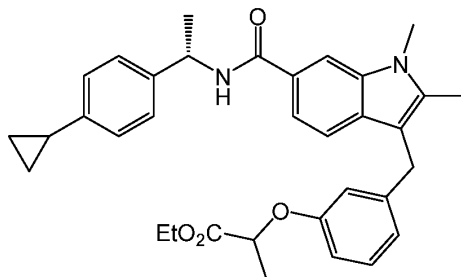


[0368] Step 4: ethyl (S)-2-(3-((6-((1-(4-cyclopropylphenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoate. The title compound was prepared following the same general protocol as described in Step 9, Compound 1, using the (S)-N-(1-(4-cyclopropylphenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(*tert*-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide and the ethyl 2-(4-formylphenoxy)-2-methylpropanoate instead of the ethyl 2-(4-formylphenoxy)propanoate. A yellow solid was obtained (39 mg, yield 95%).

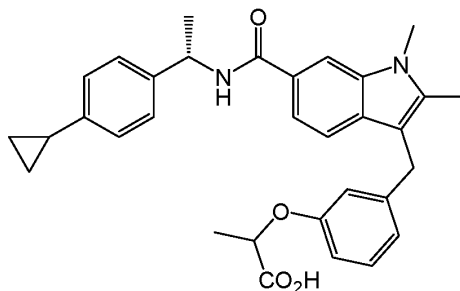


[0369] Step 5: (S)-2-(3-((6-((1-(4-cyclopropylphenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-2-methyl propanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the ethyl (S)-2-(3-((6-((1-(4-cyclopropylphenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoate instead of the (ethyl 2-(4-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy) propanoate. A yellow solid was obtained (27 mg, yield 73%). ¹H NMR (400 MHz, CDCl₃) δ 7.81 (s, 1H), 7.45 (s, 1H), 7.23 (d, J = 8.7 Hz, 2H), 7.14 – 7.01 (m, 2H), 6.99 (d, J = 8.1 Hz, 3H), 6.86 (d, J = 7.6 Hz, 1H), 6.65 (d, J = 6.3 Hz, 2H), 6.28 (d, J = 7.7 Hz, 1H), 5.31 – 5.23 (m, 1H), 3.98 (s, 2H), 3.65 (s, 3H), 2.31 (s, 3H), 1.86 – 1.77 (m, 1H), 1.53 (d, J = 6.8 Hz, 3H), 1.43 (s, 6H), 0.97 – 0.77 (m, 2H), 0.61 (dt, J = 6.5, 4.6 Hz, 2H).

[0370] Compound 31: 2-(3-((6-(((S)-1-(4-cyclopropylphenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)propanoic acid.

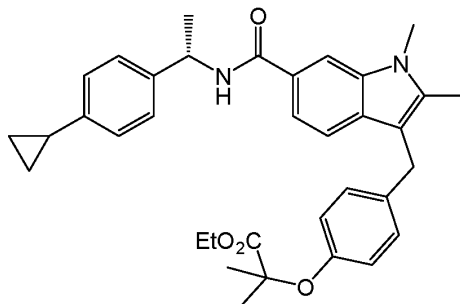


[0371] Step 1: ethyl 2-(3-((6-(((S)-1-(4-cyclopropylphenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy) propanoate. The title compound was prepared following the same general protocol as described in Step 9, Compound 1, using the (S)-N-(1-(4-cyclopropylphenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide and the ethyl 2-(3-formylphenoxy)propanoate instead of the ethyl 2-(4-formylphenoxy)propanoate. A yellow solid was obtained (31 mg, yield 91%).

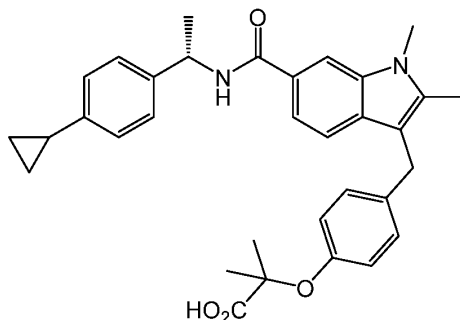


[0372] Step 2: 2-(3-((6-(((S)-1-(4-cyclopropylphenyl)ethyl) carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy) propanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the ethyl 2-(3-((6-(((S)-1-(4-cyclopropylphenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy) propanoate instead of the (ethyl 2-(4-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy) propanoate. A yellow solid was obtained (19 mg, yield 64%). ¹H NMR (400 MHz, MeOD) δ 7.78 (d, J = 1.5 Hz, 1H), 7.43 – 7.35 (m, 2H), 7.30 – 7.25 (m, 1H), 7.19 (d, J = 8.2 Hz, 2H), 7.12 (dt, J = 6.9, 2.5 Hz, 1H), 6.99 (t, J = 7.9 Hz, 1H), 6.94 (d, J = 8.3 Hz, 2H), 6.68 (d, J = 7.7 Hz, 1H), 6.60 (s, 1H), 6.54 (d, J = 8.1 Hz, 1H), 5.14 (t, J = 7.2 Hz, 1H), 4.46 (q, J = 6.7 Hz, 1H), 3.93 (s, 2H), 3.66 (s, 3H), 2.31 (s, 3H), 1.83 – 1.72 (m, 1H), 1.46 (d, J = 7.1 Hz, 3H), 1.39 (d, J = 6.7 Hz, 3H), 0.87 – 0.76 (m, 2H), 0.58 – 0.49 (m, 2H).

[0373] Compound 32 (S)-2-(4-((6-((1-(4-cyclopropylphenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoic acid.

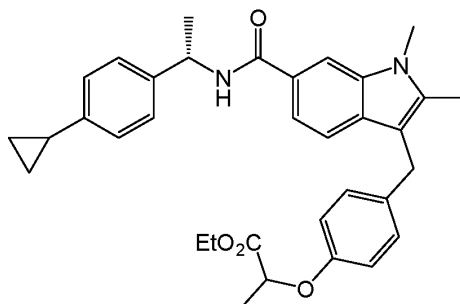


[0374] Step 1: ethyl (S)-2-(4-((6-((1-(4-cyclopropylphenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoate. The title compound was prepared following the same general protocol as described in Step 9, Compound 1, using the (S)-N-(1-(4-cyclopropylphenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide and the ethyl 2-(4-formylphenoxy)-2-methylpropanoate instead of the ethyl 2-(4-formylphenoxy)propanoate. A yellow solid was obtained (18 mg, yield 87%).

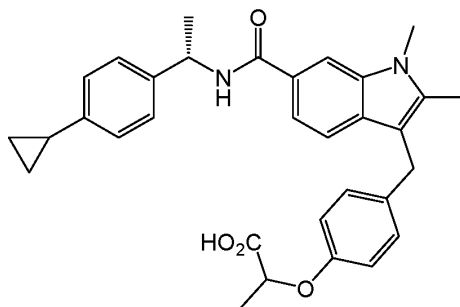


[0375] Step 2: (S)-2-(4-((6-((1-(4-cyclopropylphenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-2-methyl propanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the ethyl (S)-2-(4-((6-((1-(4-cyclopropylphenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoate instead of the (ethyl 2-(4-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy) propanoate. A yellow solid was obtained (10 mg, yield 58%). ¹H NMR (400 MHz, CDCl₃) δ 7.83 (d, J = 1.5 Hz, 1H), 7.37 – 7.16 (m, 4H), 7.01 – 6.92 (m, 4H), 6.72 (d, J = 8.6 Hz, 2H), 6.32 (d, J = 7.9 Hz, 1H), 5.27 (p, J = 7.0 Hz, 1H), 3.94 (s, 2H), 3.61 (s, 3H), 2.28 (s, 3H), 1.80 (tt, J = 8.4, 5.1 Hz, 1H), 1.51 (d, J = 6.9 Hz, 3H), 1.47 (s, 6H), 0.92 – 0.77 (m, 2H), 0.64 – 0.55 (m, 2H).

[0376] Compound 33: 2-(4-((6-(((S)-1-(4-cyclopropylphenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl) phenoxy)propanoic acid.

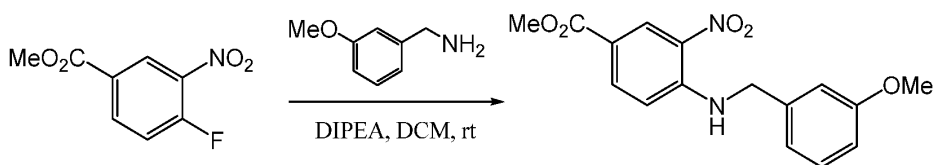


[0377] Step 1: ethyl 2-(4-((6-(((S)-1-(4-cyclopropylphenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy) propanoate. The title compound was prepared following the same general protocol as described in Step 9, Compound 1, using the (S)-N-(1-(4-cyclopropylphenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide. A yellow solid was obtained (40 mg, yield 94%).

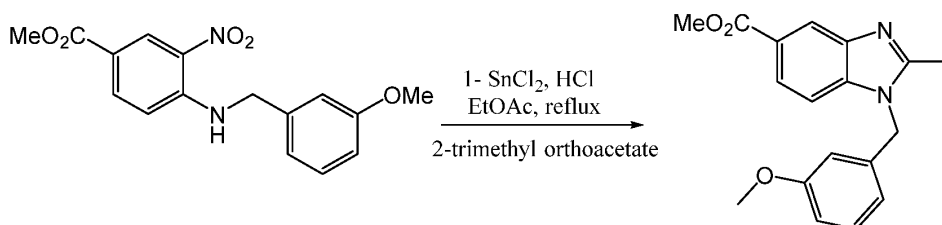


[0378] Step 2: 2-(4-((6-(((S)-1-(4-cyclopropylphenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy) propanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using ethyl 2-(4-((6-(((S)-1-(4-cyclopropylphenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy) propanoate instead of the (ethyl 2-(4-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)propanoate. A yellow solid was obtained (32 mg, yield 84%). ¹H NMR (400 MHz, CDCl₃) δ 7.82 (s, 1H), 7.24 (dd, J = 11.0, 8.3 Hz, 4H), 7.00 (t, J = 8.4 Hz, 4H), 6.70 (d, J = 8.7 Hz, 2H), 6.27 (d, J = 7.8 Hz, 1H), 5.27 (t, J = 7.1 Hz, 1H), 4.66 (q, J = 6.8 Hz, 1H), 3.95 (s, 2H), 3.64 (s, 3H), 2.30 (s, 3H), 1.86 – 1.76 (m, 1H), 1.53 (dd, J = 6.9, 5.5 Hz, 6H), 0.92 – 0.82 (m, 2H), 0.60 (dt, J = 6.5, 4.5 Hz, 2H).

[0379] Compound 34: (S)-2-(3-((5-((1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-2-methyl-1H-benzo[d]imidazol-1-yl)methyl) phenoxy)-2-methylpropanoic acid.

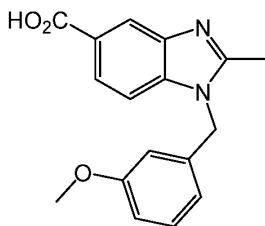


[0380] Step 1: methyl 4-((3-methoxybenzyl)amino)-3-nitrobenzoate. Methyl 4-fluoro-3-nitrobenzoate (3 g, 15 mmol), (3-methoxyphenyl)methanamine (2.08 g, 15 mmol) and N,N-diisopropylethylamine (5.5 mL, 30 mmol) were stirred in CH₂Cl₂ (25 mL) at rt for 2 hours. The solvent was evaporated. The crude mixture was dissolved in dichloromethane and washed with water. The organic phase was evaporated in vacuo to collect the title compound as orange powder (4.1 g, yield 86%). ¹H NMR (400 MHz, CDCl₃) δ 8.83 (d, J = 2.1 Hz, 1H), 8.64 (s, 1H), 7.93 (ddd, J = 9.0, 2.1, 0.7 Hz, 1H), 7.29 – 7.17 (m, 1H), 6.89 – 6.82 (m, 1H), 6.80 – 6.74 (m, 3H), 4.50 (d, J = 5.6 Hz, 2H), 3.82 (s, 3H), 3.73 (s, 3H).

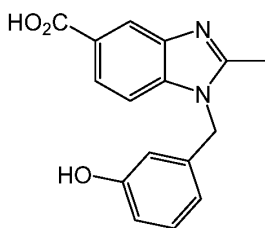


[0381] Step 2: methyl 1-(3-methoxybenzyl)-2-methyl-1H-benzo[d]imidazole-5-carboxylate. methyl 4-((3-methoxybenzyl)amino)-3-nitrobenzoate (1 g, 3.15 mmol) was suspended in ethyl acetate (50ml) and

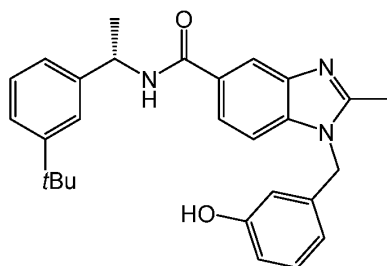
$\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (2.98 g, 15.8 mmol) and concentrated HCl (5 mL) were added. It was heated to reflux for 2 hours then cooled to room temperature. The progress of the reaction was monitored by analytical-HPLC until the total consumption of the starting material. The reaction mixture was then poured onto cold water (200 mL) and cooled in an ice bath. It was basified with careful addition of saturated sodium bicarbonate solution (50 mL). The precipitate was removed by filtration through celite, washed with EtOAc (200 mL). The filtrate was transferred to separating funnel and aqueous phase separated and extracted with EtOAc (100 mL). The combined organics were dried over anhydrous sodium sulfate and evaporated to dryness. The crude product was used for the next step without any further purification. Subsequently, the methyl 3-amino-4-((3-methoxybenzyl)amino)benzoate was suspended in 20 mL of trimethyl orthoacetate. A concentrated HCl (5 mL) was added to the reaction mixture and stirred for 1h at rt. The reaction was quenched with a saturated solution of sodium bicarbonate (100 mL). The aqueous solution was extracted with EtOAc (50 mL) and organic phase was dried over anhydrous sodium sulfate and evaporated to dryness. The residue was purified by flash chromatography and the desired product was isolated as brown solid (0.5 g, yield 53%). ^1H NMR (400 MHz, CDCl_3) δ 8.47 (dd, $J = 1.6, 0.7$ Hz, 1H), 7.93 (dd, $J = 8.6, 1.5$ Hz, 1H), 7.26 (dd, $J = 8.6, 0.7$ Hz, 1H), 7.20 (t, $J = 7.9$ Hz, 1H), 6.79 (ddd, $J = 8.3, 2.6, 0.9$ Hz, 1H), 6.69 (ddd, $J = 7.5, 1.7, 0.9$ Hz, 1H), 6.63 (t, $J = 2.1$ Hz, 1H), 5.29 (s, 2H), 3.87 (s, 3H), 3.68 (s, 3H), 2.65 (s, 3H).



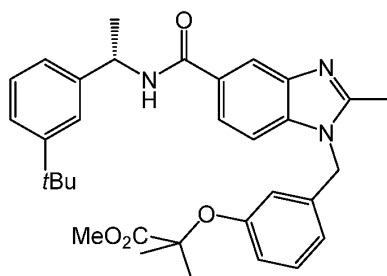
[0382] Step 3: 1-(3-methoxybenzyl)-2-methyl-1H-benzo[d]imidazole-5-carboxylic acid. The title compound was prepared following the same general protocol as described in Step 5, Compound 1, using the methyl 1-(3-methoxybenzyl)-2-methyl-1H-benzo[d]imidazole-5-carboxylate instead of the methyl 1,2-dimethyl-1H-indole-6-carboxylate. A yellow sticky oil was obtained (55 mg, yield 91%).



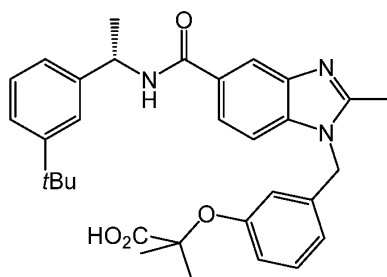
[0383] Step 4: 1-(3-hydroxybenzyl)-2-methyl-1H-benzo[d]imidazole-5-carboxylic acid. The title compound was prepared following the same general protocol as described in Step 3, Compound 90, using the 1-(3-methoxybenzyl)-2-methyl-1H-benzo[d]imidazole-5-carboxylic acid instead of the 1-(cyclobutylmethyl)-3-((2-methoxypyridin-4-yl)methyl)-2-methyl-1H-indole-6-carboxylic acid. A grey solid was obtained (49 mg, yield 94%).



[0384] Step 5: (S)-N-(1-(3-(tert-butyl)phenyl)ethyl)-1-(3-hydroxybenzyl)-2-methyl-1H-benzo[d]imidazole-5-carboxamide. The title compound was prepared following the same general protocol as described in Step 8, Compound 1, using the 1-(3-hydroxybenzyl)-2-methyl-1H-benzo[d]imidazole-5-carboxylic acid instead of 1,2-dimethyl-1H-indole-6-carboxylic acid and the (3-(tert-butyl)phenyl)methanamine hydrochloride instead of the (S)-1-(4-(tert-butyl)phenyl)ethanamine hydrochloride. A brown solid was obtained (70 mg, yield 90%).



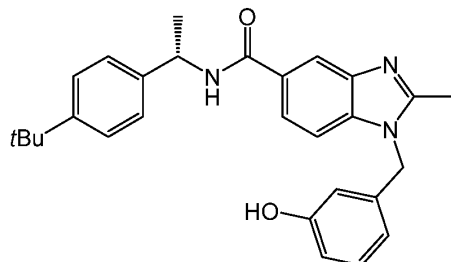
[0385] Step 6: methyl (S)-2-(3-((5-((1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-2-methyl-1H-benzo[d]imidazol-1-yl)methyl)phenoxy)-2-methylpropanoate. The title compound was prepared following the same general protocol as described in Step 2, Compound 42, using the (S)-N-(1-(3-(tert-butyl)phenyl)ethyl)-1-(3-hydroxybenzyl)-2-methyl-1H-benzo[d]imidazole-5-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-3-(2-chloro-3-hydroxybenzyl)-1,2-dimethyl-1H-indole-6-carboxamide and the methyl 2-bromo-2-methylpropanoate instead of the (R)-2-bromopropanoate. A yellow solid was obtained (41 mg, yield 48%).



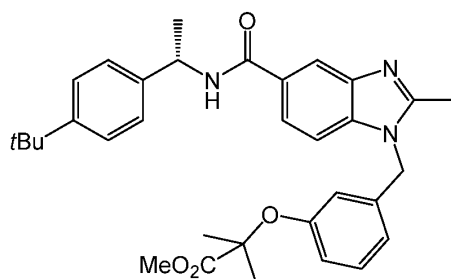
[0386] Step 7: (S)-2-(3-((5-((1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-2-methyl-1H-benzo[d]imidazol-1-yl)methyl)phenoxy)-2-methylpropanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the methyl (S)-2-(3-((5-((1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-2-methyl-1H-benzo[d]imidazol-1-yl)methyl)phenoxy)-2-methylpropanoate instead of the (ethyl 2-(4-((6-((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-

dimethyl-1H-indol-3-yl)methyl)phenoxy)propanoate. A yellow solid was obtained (35 mg, yield 89%). ¹H NMR (400 MHz, CDCl₃) δ 7.95 (s, 1H), 7.78 (d, J = 8.7 Hz, 1H), 7.35 (d, J = 1.9 Hz, 1H), 7.32 – 7.16 (m, 3H), 7.13 (t, J = 8.1 Hz, 1H), 7.07 (d, J = 7.7 Hz, 1H), 6.75 (dd, J = 8.1, 2.1 Hz, 2H), 5.95 (s, 1H), 5.21 (t, J = 7.1 Hz, 1H), 2.65 (s, 3H), 1.54 (d, J = 6.9 Hz, 3H), 1.30 (s, 4H), 1.23 (s, 8H).

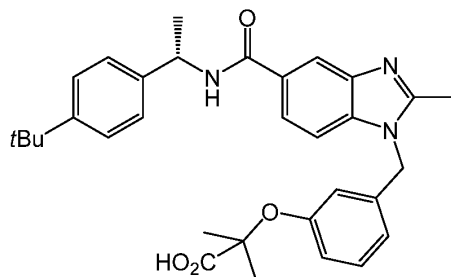
[0387] Compound 35: (S)-2-(3-((5-((1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-2-methyl-1H-benzo[d]imidazol-1-yl)methyl)phenoxy)-2-methylpropanoic acid.



[0388] Step 1: (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1-(3-(hydroxybenzyl)-2-methyl-1H-benzo[d]imidazole-5-carboxamide. The title compound was prepared following the same general protocol as described in Step 8, Compound 1, using the 1-(3-(hydroxybenzyl)-2-methyl-1H-benzo[d]imidazole-5-carboxylic acid instead of 1,2-dimethyl-1H-indole-6-carboxylic acid. A brown solid was obtained (65mg, yield 88%).

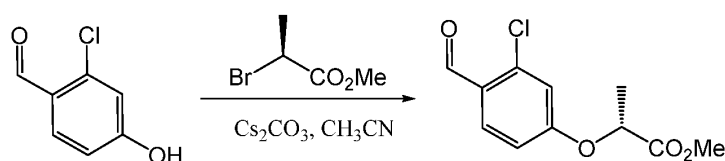


[0389] Step 2: methyl (S)-2-(3-((5-((1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-2-methyl-1H-benzo[d]imidazol-1-yl)methyl)phenoxy)-2-methylpropanoate. The title compound was prepared following the same general protocol as described in Step 2, Compound 42, using the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1-(3-(hydroxybenzyl)-2-methyl-1H-benzo[d]imidazole-5-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-3-(2-chloro-3-(hydroxybenzyl)-1,2-dimethyl-1H-indole-6-carboxamide and the methyl 2-bromo-2-methylpropanoate instead of the (R)-2-bromopropanoate. A yellow solid was obtained (55 mg, yield 69%).

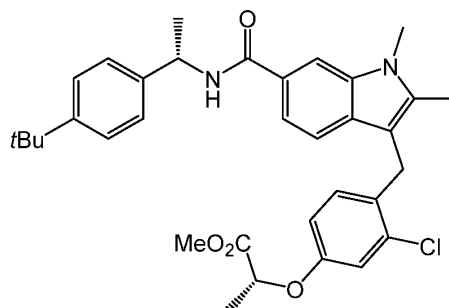


[0390] Step 3: (S)-2-(3-((5-((1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-2-methyl-1H-benzo[d]imidazol-1-yl)methyl)phenoxy)-2-methylpropanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the methyl (S)-2-(3-((5-((1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-2-methyl-1H-benzo[d]imidazol-1-yl)methyl)phenoxy)-2-methylpropanoate instead of the ethyl 2-(4-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)propanoate. A yellow solid was obtained (40 mg, yield 75%). ¹H NMR (400 MHz, CDCl₃) δ 8.18 (s, 1H), 7.84 (s, 1H), 7.42 (d, J = 8.1 Hz, 1H), 7.35 (s, 1H), 7.32 – 7.21 (m, 4H), 7.16 (d, J = 6.3 Hz, 1H), 6.33 (d, J = 7.7 Hz, 1H), 6.18 (s, 1H), 5.30 (t, J = 7.2 Hz, 1H), 5.23 (d, J = 0.6 Hz, 2H), 2.40 (s, 3H), 1.56 (d, J = 6.9 Hz, 3H), 1.26 (s, 9H), 1.19 (d, J = 4.2 Hz, 6H).

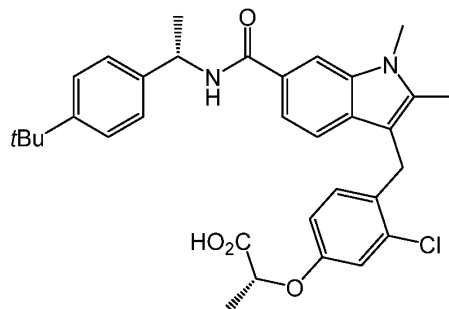
[0391] Compound 36: (R)-2-(4-((c-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)-3-chlorophenoxy)propanoic acid.



[0392] Step 1: methyl (R)-2-(3-chloro-4-formylphenoxy)propanoate. The title compound was prepared following the same general protocol as described in Step 7, Compound 1, using the 2-chloro-4-hydroxybenzaldehyde instead of the 4-hydroxybenzaldehyde and the methyl (S)-2-bromopropanoate instead of the ethyl bromopropionate. A light-yellow solid was obtained (0.259 g, yield 71%). ¹H NMR (600 MHz, CDCl₃) δ 10.32 (s, 1H), 7.89 (d, J = 8.7 Hz, 1H), 6.91 (d, J = 2.4 Hz, 1H), 6.85 (dd, J = 8.7, 2.04 Hz, 1H), 4.87 (q, J = 7.14 Hz, 1H), 3.78 (s, 3H), 1.66 (d, J = 6.78 Hz, 3H).

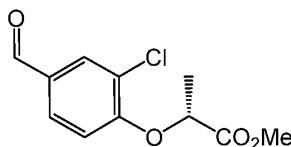


[0393] Step 2: methyl (R)-2-(4-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)-3-chlorophenoxy)propanoate. The title compound was prepared following the same general protocol as described in Step 7, Compound 1, using the methyl methyl (R)-2-(3-chloro-4-formylphenoxy)propanoate instead of the ethyl 2-(4-formylphenoxy)propanoate. A white solid was obtained (15 mg, yield 93%). ESI-MS (m/z): 574.73 [M]⁺.

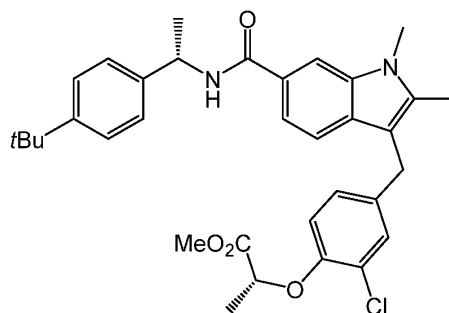


[0394] Step 3: (R)-2-(4-((c-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)-3-chloro phenoxy)propanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the methyl (R)-2-(3-(((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)-4-chlorophenoxy)propanoate instead of the (ethyl 2-(4-(((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)propanoate. A white solid was obtained (9 mg, yield 61%). ¹H NMR (400 MHz, CDCl₃) δ 7.84 (s, 1H), 7.28 (s, 4H), 6.88 (s, 2H), 6.74 – 6.59 (m, 2H), 6.48 (s, 1H), 6.35 (s, 1H), 5.26 (d, J = 22.3 Hz, 1H), 4.58 (s, 1H), 3.98 (s, 2H), 3.62 (s, 3H), 2.26 (s, 3H), 1.79 – 1.38 (m, 6H), 1.23 (s, 9H). ESI-MS (m/z): 560.81 [M]⁺.

[0395] Compound 37: (R)-2-(4-(((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)-2-chloro phenoxy)propanoic acid.

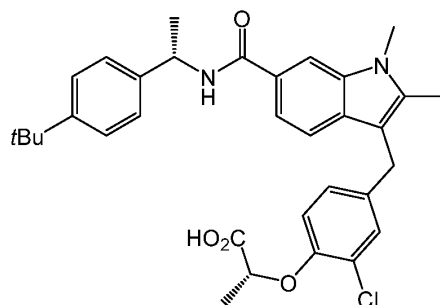


[0396] Step 1: methyl (R)-2-(2-chloro-4-formylphenoxy)propanoate. The title compound was prepared following the same general protocol as described in Step 7, Compound 1, using the 3-chloro-4-hydroxybenzaldehyde instead of the 4-hydroxybenzaldehyde and the methyl (S)-2-bromopropanoate instead of the ethyl bromopropionate. A white solid was obtained (0.24 g, yield 65%). ¹H NMR (400 MHz, CDCl₃) δ 9.85 (s, 1H), 7.93 (d, J = 2.04 Hz, 1H), 6.91 (dd, J = 8.48, 2.4 Hz, 1H), 6.89 (d, J = 8.48 Hz, 1H), 4.92 (q, J = 6.44 Hz, 1H), 3.78 (s, 3H), 1.74 (d, J = 6.8 Hz, 3H).



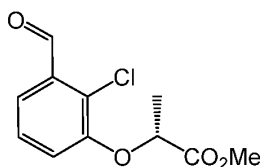
[0397] Step 2: methyl (R)-2-(4-(((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)-2-chlorophenoxy)propanoate. The title compound was prepared following the same

general protocol as described in Step 7, Compound 1, using the methyl (R)-2-(3-chloro-4-formylphenoxy)propanoate instead of the ethyl 2-(4-formylphenoxy)propanoate. A white solid was obtained (14 mg, yield 87%). ESI-MS (m/z): 574.73 [M]⁺.

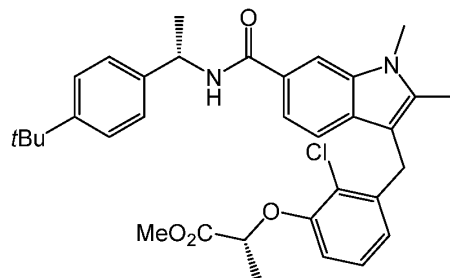


[0398] Step 3: (R)-2-(4-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)-2-chlorophenoxy)propanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the methyl (R)-2-(4-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)-2-chlorophenoxy)propanoate instead of the (ethyl 2-(4-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)propanoate. A white solid was obtained (10 mg, yield 68%). ¹H NMR (400 MHz, CDCl₃) δ 7.85 (d, J = 1.1 Hz, 1H), 7.34 – 7.25 (m, 4H), 7.22 (d, J = 1.1 Hz, 2H), 7.09 (d, J = 2.1 Hz, 1H), 6.87 (dd, J = 8.5, 2.2 Hz, 1H), 6.69 (d, J = 8.4 Hz, 1H), 6.34 (d, J = 7.9 Hz, 1H), 5.30 (t, J = 7.2 Hz, 1H), 4.63 (q, J = 6.9 Hz, 1H), 3.92 (s, 2H), 3.63 (s, 3H), 2.29 (s, 3H), 1.58 (d, J = 6.9 Hz, 3H), 1.54 (d, J = 6.9 Hz, 3H), 1.24 (s, 9H). ESI-MS (m/z): 560.81 [M]⁺.

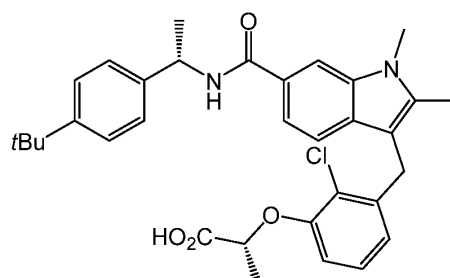
[0399] Compound 38: (R)-2-(3-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)-2-chlorophenoxy)propanoic acid.



[0400] Step 1: methyl (R)-2-(2-chloro-3-formylphenoxy)propanoate. The title compound was prepared following the same general protocol as described in Step 7, Compound 1, using the 2-chloro-3-hydroxybenzaldehyde instead of the 4-hydroxybenzaldehyde and the methyl (S)-2-bromopropanoate instead of the ethyl bromopropionate. A white solid was obtained (0.32 g, yield 88%). ¹H NMR (600 MHz, CDCl₃) δ 10.52 (d, J = 0.78 Hz, 1H), 7.58 (dd, J = 7.8, 1.44 Hz, 1H), 7.30 - 7.28 (m, 1H), 7.07 (dd, J = 6.78, 1.38 Hz, 1H), 4.83 (q, J = 6.84 Hz, 1H), 3.77 (s, 3H), 1.73 (d, J = 6.8 Hz, 3H).

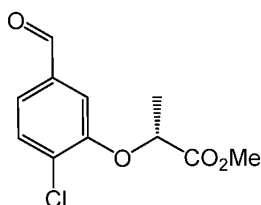


[0401] Step 2: methyl (R)-2-(3-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)-2-chlorophenoxy)propanoate. The title compound was prepared following the same general protocol as described in Step 7, Compound 1, using the methyl (R)-2-(2-chloro-3-formylphenoxy)propanoate instead of the ethyl 2-(4-formylphenoxy) propanoate. A white solid was obtained (20 mg, yield 92%). ESI-MS (m/z): 574.73 [M]⁺.



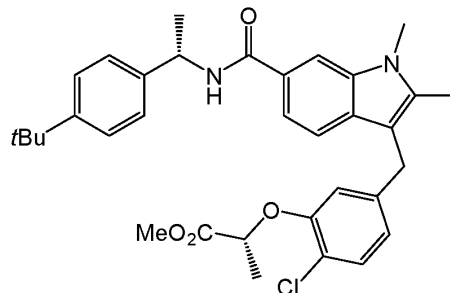
[0402] Step 3: (R)-2-(3-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)-2-chlorophenoxy)propanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the methyl (R)-2-(3-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)-2-chlorophenoxy)propanoate instead of the (ethyl 2-(4-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)propanoate. A white solid was obtained (15 mg, yield 77%). ¹H NMR (400 MHz, CDCl₃) δ 7.88 (s, 1H), 7.41 – 7.25 (m, 4H), 7.24 – 7.20 (m, 2H), 6.80 (t, J = 8.0 Hz, 1H), 6.63 (d, J = 8.1 Hz, 1H), 6.48 (d, J = 7.7 Hz, 1H), 6.32 (d, J = 7.8 Hz, 1H), 5.30 (t, J = 7.1 Hz, 1H), 4.93 – 4.60 (m, 1H), 4.08 (s, 2H), 3.66 (s, 2H), 2.27 (s, 3H), 1.66 (d, J = 6.8 Hz, 3H), 1.55 (d, J = 6.8 Hz, 3H), 1.24 (s, 9H). ESI-MS (m/z): 560.81 [M]⁺.

[0403] Compound 39: (R)-2-(5-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)-2-chlorophenoxy)propanoic acid.

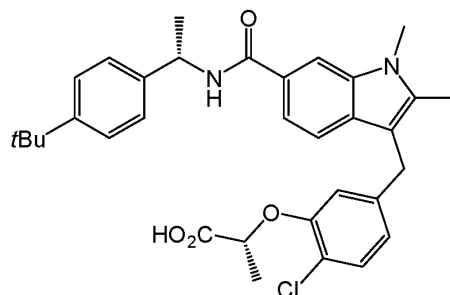


[0404] Step 1: methyl (R)-2-(2-chloro-5-formylphenoxy)propanoate. The title compound was prepared following the same general protocol as described in Step 7, Compound 1, using the 4-chloro-3-

hydroxybenzaldehyde instead of the 4-hydroxybenzaldehyde and the methyl (S)-2-bromopropionate instead of the ethyl bromopropionate. A white solid was obtained (0.29 g, yield 79%). ¹H NMR (400 MHz, CDCl₃) δ 9.90 (s, 1H), 7.58 (d, J = 8.0, 1H), 7.45 (dd, J = 8.12, 1.64 Hz, 1H), 7.31 (d, J = 1.64 Hz, 1H), 4.92 (q, J = 6.8 Hz, 1H), 3.78 (s, 3H), 1.73 (d, J = 6.8 Hz, 3H).

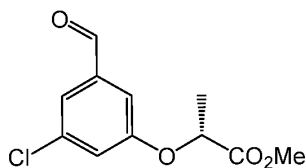


[0405] Step 2: methyl (R)-2-(5-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)-2-chlorophenoxy)propanoate. The title compound was prepared following the same general protocol as described in Step 7, Compound 1, using the methyl (R)-2-(2-chloro-5-formylphenoxy)propanoate instead of the ethyl 2-(4-formylphenoxy)propanoate. A yellow solid was obtained (14 mg, yield 64%). ESI-MS (m/z): 574.73 [M]⁺.

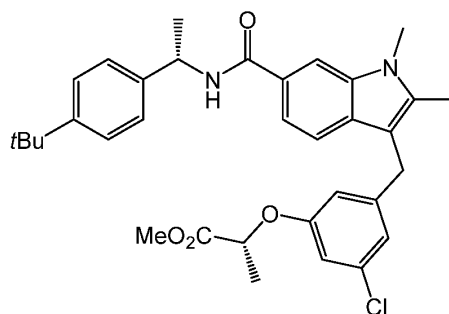


[0406] Step 3: (R)-2-(5-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)-2-chlorophenoxy)propanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the methyl (R)-2-(5-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)-2-chlorophenoxy)propanoate instead of the (ethyl 2-(4-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)propanoate. A white solid was obtained (8 mg, yield 58%). ¹H NMR (400 MHz, CDCl₃) δ 7.77 (s, 1H), 7.45 – 7.23 (m, 4H), 7.23 – 7.19 (m, 1H), 7.13 (s, 2H), 6.71 (dd, J = 8.1, 1.9 Hz, 1H), 6.58 (t, J = 2.5 Hz, 1H), 6.37 (d, J = 7.9 Hz, 1H), 5.28 (p, J = 7.2 Hz, 1H), 4.53 (qd, J = 6.8, 2.3 Hz, 1H), 3.89 (s, 2H), 3.57 (d, J = 1.0 Hz, 3H), 2.26 (s, 3H), 1.64 – 1.47 (m, 6H), 1.24 (s, 9H). ESI-MS (m/z): 560.81 [M]⁺.

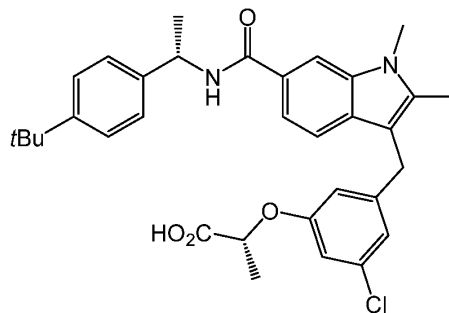
[0407] Compound 40: (R)-2-(3-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)-5-chlorophenoxy)propanoic acid.



[0408] Step 1: methyl (R)-2-(3-chloro-5-formylphenoxy)propanoate. The title compound was prepared following the same general protocol as described in Step 7, Compound 1, using the 5-chloro-3-hydroxybenzaldehyde instead of the 4-hydroxybenzaldehyde and the methyl (S)-2-bromopropanoate instead of the ethyl bromopropionate. A white solid was obtained (0.34 g, yield 92%). ¹H NMR (400 MHz, CDCl₃) δ 9.89 (s, 1H), 7.47 (t, J = 1.36, 1H), 7.22 (dd, J = 2.5, 1.2 Hz, 1H), 7.15 (t, J = 2.28 Hz, 1H), 4.86 (q, J = 6.8 Hz, 1H), 3.78 (s, 3H), 1.66 (d, J = 6.8 Hz, 3H).



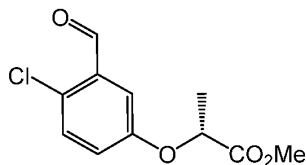
[0409] Step 2: methyl (R)-2-(3-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)-5-chlorophenoxy)propanoate. The title compound was prepared following the same general protocol as described in Step 7, Compound 1, using the methyl (R)-2-(3-chloro-5-formylphenoxy)propanoate instead of the ethyl 2-(4-formylphenoxy)propanoate. A yellow solid was obtained (17 mg, yield 78%). ESI-MS (m/z): 574.73 [M]⁺.



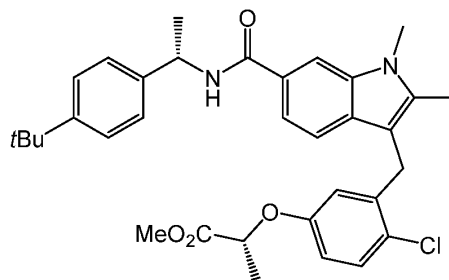
[0410] Step 3: (R)-2-(3-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)-5-chlorophenoxy)propanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the methyl (R)-2-(3-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)-5-chlorophenoxy)propanoate instead of the (ethyl 2-(4-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)propanoate. A white solid was obtained (13 mg, yield 78%). ¹H NMR (400 MHz, CDCl₃) δ 7.78 (s, 1H), 7.42 – 7.21 (m, 6H), 6.72 (s, 1H), 6.60 (s, 1H), 6.47 (s, 1H), 6.34 (s, 1H), 5.44 –

5.14 (m, 1H), 4.54 (d, $J = 6.8$ Hz, 1H), 3.90 (s, 2H), 3.58 (s, 3H), 2.25 (s, 3H), 1.54 (d, $J = 6.8$ Hz, 3H), 1.49 (d, $J = 6.8$ Hz, 3H), 1.24 (s, 9H). ESI-MS (m/z): 560.81 $[M]^+$.

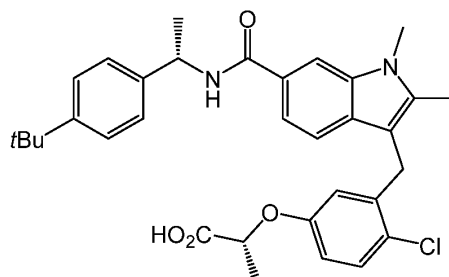
[0411] Compound 41: (*R*)-2-(3-((6-(((*S*)-1-(4-(*tert*-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)-4-chloro phenoxy)propanoic acid.



[0412] Step 1: methyl (*R*)-2-(4-chloro-3-formylphenoxy)propanoate. The title compound was prepared following the same general protocol as described in Step 7, Compound 1, using the 2-chloro-5-hydroxybenzaldehyde instead of the 4-hydroxybenzaldehyde and the methyl (*S*)-2-bromopropanoate instead of the ethyl bromopropionate. A white solid was obtained (0.314 g, yield 75%). ^1H NMR (400 MHz, CDCl_3) δ 10.40 (s, 1H), 7.38 – 7.32 (m, 2H), 7.15 – 7.10 (m, 1H), 4.87 (q, $J = 6.88$ Hz, 1H), 3.77 (s, 3H), 1.69 (dd, $J = 20.88, 6.88$ Hz, 3H).



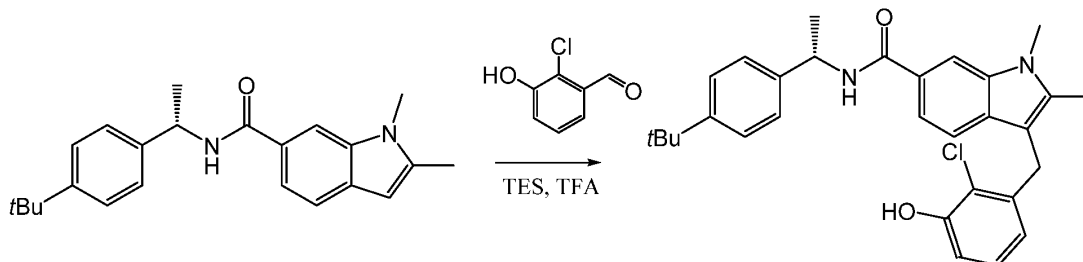
[0413] Step 2: methyl (*R*)-2-(3-((6-(((*S*)-1-(4-(*tert*-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)-4-chlorophenoxy)propanoate. The title compound was prepared following the same general protocol as described in Step 7, Compound 1, using the methyl (*R*)-2-(4-chloro-3-formylphenoxy)propanoate instead of the ethyl 2-(4-formylphenoxy) propanoate. A yellow solid was obtained (15 mg, yield 88%). ESI-MS (m/z): 574.73 $[M]^+$.



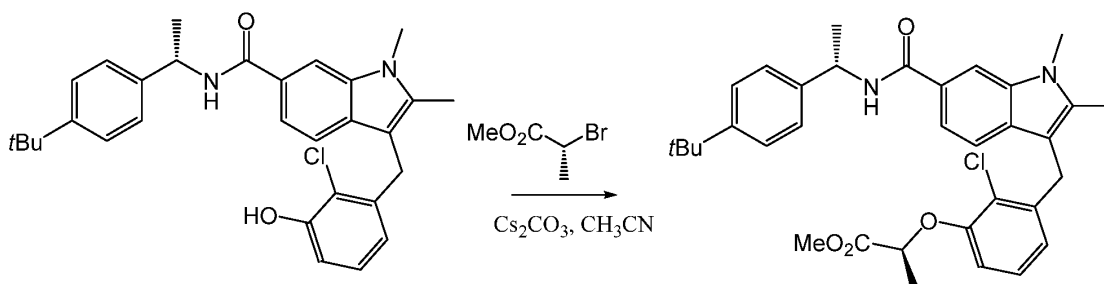
[0414] Step 3: (*R*)-2-(3-((6-(((*S*)-1-(4-(*tert*-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)-4-chloro phenoxy)propanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the methyl (*R*)-2-(3-((6-(((*S*)-1-(4-(*tert*-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)-4-chlorophenoxy)propanoate instead of the (ethyl 2-(4-((6-(((*S*)-1-(4-(*tert*-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-

yl)methyl)phenoxy)propanoate. A white solid was obtained (8 mg, yield 48%). ¹H NMR (400 MHz, CDCl₃) δ 7.77 (s, 1H), 7.46 – 7.09 (m, 6H), 6.56 (d, J = 9.6 Hz, 1H), 6.44 (s, 1H), 6.31 (s, 1H), 5.26 (s, 1H), 4.35 (d, J = 6.3 Hz, 1H), 4.00 (s, 2H), 3.54 (s, 3H), 2.23 (s, 3H), 1.52 (s, 3H), 1.38 (d, J = 6.0 Hz, 3H), 1.23 (s, 9H). ESI-MS (m/z): 560.81 [M]⁺.

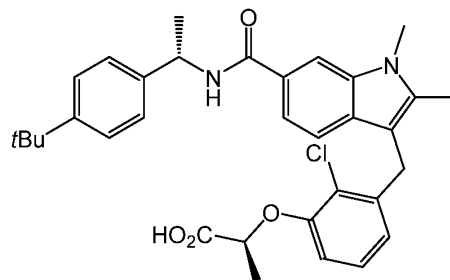
[0415] Compound 42: (S)-2-(3-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)-2-chlorophenoxy)propanoic acid.



[0416] Step 1: (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-3-(2-chloro-3-hydroxybenzyl)-1,2-dimethyl-1H-indole-6-carboxamide. The title compound was prepared following the same general protocol as described in Step 9, Compound 1, using the (2-chloro-3-hydroxybenzaldehyde instead of the ethyl 2-(4-formylphenoxy)propanoate. A light-brown solid was obtained (23 mg, yield 94%). ESI-MS (m/z): 488.75 [M]⁺.

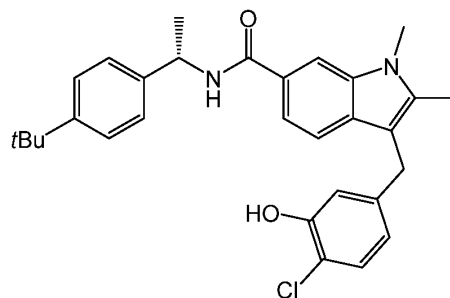


[0417] Step 2: methyl (S)-2-(3-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)-2-chlorophenoxy)propanoate. To a mixture of (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-3-(2-chloro-3-hydroxybenzyl)-1,2-dimethyl-1H-indole-6-carboxamide (23 mg, 0.047 mmol), methyl (R)-2-bromopropanoate (13 μL, 0.075 mmol) and Cs₂CO₃ (32.5 mg, 0.1 mmol) was added DMF (1 mL). The reaction mixture was stirred at 100°C for 3 h. After completion of the reaction, the mixture was diluted with water (100 mL) and extracted with ethyl acetate (50 mL × 2), dried over sodium sulfate and concentrated under vacuum. The residue was subjected to column chromatography (hexane/EtOAc) to give the final product yellow solid (20 g, yield 74%). ESI-MS (m/z): 574.81 [M]⁺.

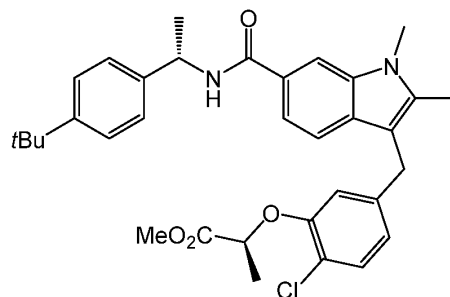


[0418] Step 3: (S)-2-(3-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)-2-chlorophenoxy)propanoic acid. The title compound was prepared following the same general protocol as described in Step 3, Compound 38, using the methyl (S)-2-(3-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)-2-chlorophenoxy)propanoate instead of (R)-2-(3-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)-2-chlorophenoxy)propanoic acid. A yellow solid was obtained (14 mg, yield 72%). ¹H NMR (400 MHz, CDCl₃) δ 7.87 (s, 1H), 7.35 – 7.26 (m, 4H), 7.22 (dd, J = 2.2, 1.1 Hz, 2H), 6.81 (td, J = 8.0, 2.0 Hz, 1H), 6.63 (d, J = 8.3 Hz, 1H), 6.47 (d, J = 7.8 Hz, 1H), 6.35 (d, J = 7.9 Hz, 1H), 5.29 (q, J = 7.0 Hz, 1H), 4.96 (br, 1H), 4.81 – 4.56 (m, 1H), 4.09 (s, 2H), 3.67 (s, 3H), 2.28 (s, 3H), 1.66 (d, J = 6.8 Hz, 3H), 1.55 (d, J = 6.8 Hz, 3H), 1.25 (s, 9H). ESI-MS (m/z): 560.82 [M]⁺.

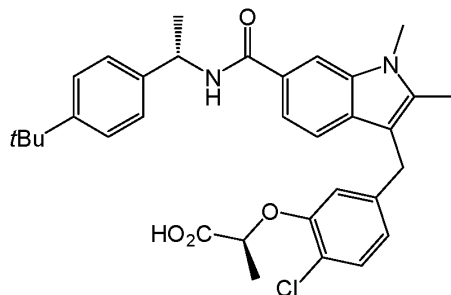
[0419] Compound 43: (S)-2-(5-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)-2-chlorophenoxy)propanoic acid.



[0420] Step 1: (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-3-(4-chloro-3-hydroxybenzyl)-1,2-dimethyl-1H-indole-6-carboxamide. The title compound was prepared following the same general protocol as described in Step 1, Compound 42, using the 4-chloro-3-hydroxybenzaldehyde instead of 2-chloro-3-hydroxybenzaldehyde. A light-brown solid was obtained (24 mg, yield 98%). ESI-MS (m/z): 488.75 [M]⁺.

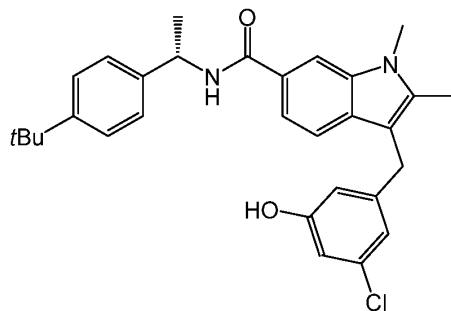


[0421] Step 2: methyl (S)-2-(5-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)-2-chlorophenoxy)propanoate. The title compound was prepared following the same general protocol as described in Step 2, Compound 42, using the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-3-(4-chloro-3-hydroxybenzyl)-1,2-dimethyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-3-(2-chloro-3-hydroxybenzyl)-1,2-dimethyl-1H-indole-6-carboxamide. A yellow solid was obtained (27 mg, yield 95%). ESI-MS (m/z): 574.81 [M]⁺.

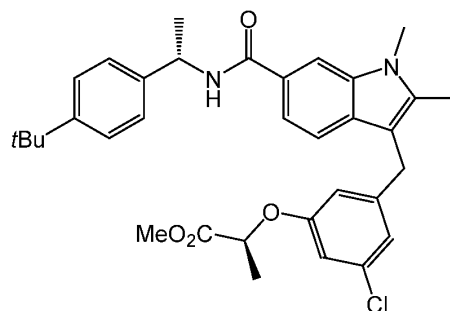


[0422] Step 3: (S)-2-(5-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)-2-chlorophenoxy)propanoic acid. The title compound was prepared following the same general protocol as described in Step 3, Compound 39, using the methyl (S)-2-(5-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)-2-chlorophenoxy)propanoate instead of the methyl (R)-2-(5-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)-2-chlorophenoxy)propanoate. A yellow solid was obtained (19 mg, yield 72%). ¹H NMR (400 MHz, CDCl₃) δ 7.76 (s, 1H), 7.29 (q, J = 8.4 Hz, 4H), 7.22 (d, J = 4.4 Hz, 1H), 7.16 (d, J = 8.1 Hz, 1H), 6.73 (d, J = 8.0 Hz, 1H), 6.57 (s, 1H), 6.38 (d, J = 7.9 Hz, 1H), 5.28 (t, J = 7.1 Hz, 1H), 4.52 (q, J = 6.7 Hz, 1H), 3.93 (s, 2H), 3.61 (d, J = 1.4 Hz, 3H), 2.28 (s, 3H), 1.54 (dd, J = 8.8, 6.9 Hz, 6H), 1.25 (d, J = 0.7 Hz, 9H). ESI-MS (m/z): 560.82 [M]⁺.

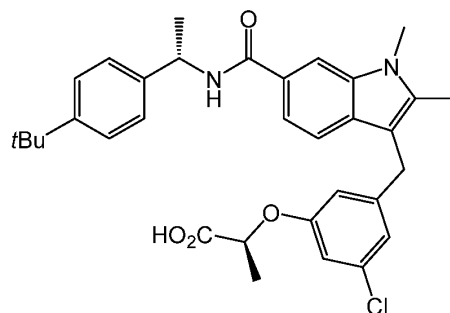
[0423] Compound 44: (S)-2-(3-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)-5-chlorophenoxy)propanoic acid.



[0424] Step 1: (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-3-(3-chloro-5-hydroxybenzyl)-1,2-dimethyl-1H-indole-6-carboxamide. The title compound was prepared following the same general protocol as described in Step 1, Compound 42, using the 3-chloro-5-hydroxybenzaldehyde instead of the 2-chloro-3-hydroxybenzaldehyde. A yellow solid was obtained (17 mg, yield 69%). ESI-MS (m/z): 488.72 [M]⁺.

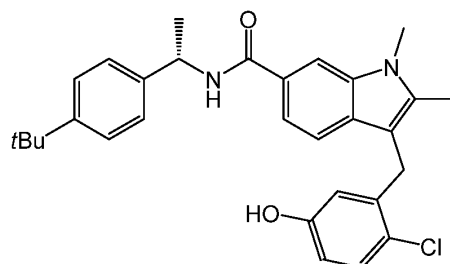


[0425] Step 2: methyl (S)-2-(3-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)-5-chlorophenoxy)propanoate. The title compound was prepared following the same general protocol as described in Step 2, Compound 42, using the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-3-(3-chloro-5-hydroxybenzyl)-1,2-dimethyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-3-(2-chloro-3-hydroxybenzyl)-1,2-dimethyl-1H-indole-6-carboxamide. A yellow solid was obtained (15 mg, yield 75%). ESI-MS (m/z): 574.81 [M]⁺.

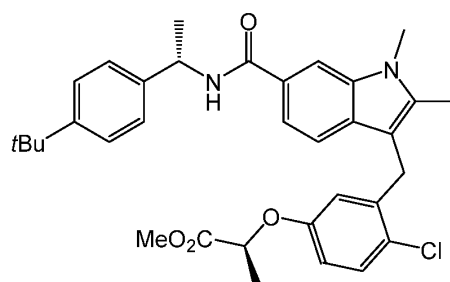


[0426] Step 3: (S)-2-(3-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)-5-chlorophenoxy)propanoic acid. The title compound was prepared following the same general protocol as described in Step 3, Compound 40, using the methyl (S)-2-(5-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)-2-chlorophenoxy)propanoate instead of the methyl (R)-2-(3-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)-5-chlorophenoxy)propanoate. A yellow solid was obtained (12 mg, yield 82%). ¹H NMR (400 MHz, CDCl₃) δ 7.78 (s, 1H), 7.28 (q, J = 8.3 Hz, 4H), 7.22 (s, 2H), 6.71 (s, 1H), 6.60 (s, 1H), 6.46 (d, J = 2.0 Hz, 1H), 6.41 (d, J = 8.0 Hz, 1H), 5.28 (t, J = 7.0 Hz, 1H), 4.54 (q, J = 6.8 Hz, 1H), 3.89 (s, 2H), 3.54 (d, J = 2.1 Hz, 3H), 2.23 (d, J = 1.9 Hz, 3H), 1.54 (d, J = 6.8 Hz, 3H), 1.49 (dd, J = 6.9, 1.2 Hz, 3H), 1.24 (s, 9H). ESI-MS (m/z): 560.82 [M]⁺.

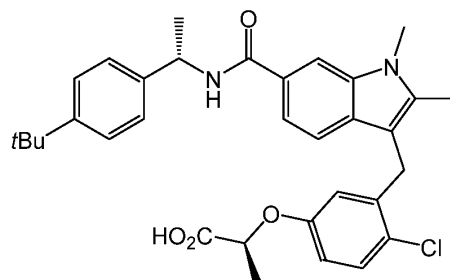
[0427] Compound 45 (S)-2-(3-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)-4-chlorophenoxy) propanoic acid.



[0428] Step 1: (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-3-(2-chloro-5-hydroxybenzyl)-1,2-dimethyl-1H-indole-6-carboxamide. The title compound was prepared following the same general protocol as described in Step 1, Compound 42, using the 2-chloro-5-hydroxybenzaldehyde instead of the 2-chloro-3-hydroxybenzaldehyde. A yellow solid was obtained (20 mg, yield 82%). ESI-MS (m/z): 488.72 $[M]^+$.



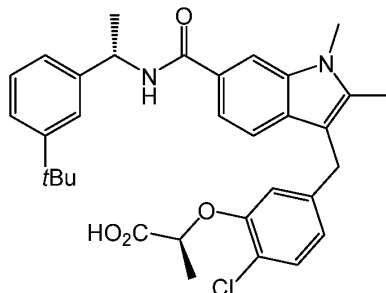
[0429] Step 2: methyl (S)-2-(3-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl-4-chlorophenoxy)propanoate. The title compound was prepared following the same general protocol as described in Step 2, Compound 42, using the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-3-(2-chloro-5-hydroxybenzyl)-1,2-dimethyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-3-(2-chloro-3-hydroxybenzyl)-1,2-dimethyl-1H-indole-6-carboxamide. A yellow solid was obtained (22 mg, yield 95%). ESI-MS (m/z): 574.81 $[M]^+$.



[0430] Step 3: (S)-2-(3-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl-4-chlorophenoxy)propanoic acid. The title compound was prepared following the same general protocol as described in Step 3, Compound 41, using the methyl (S)-2-(3-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl-4-chlorophenoxy)propanoate instead of the methyl (R)-2-(3-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl-5-chlorophenoxy)propanoate. A yellow solid was obtained (17 mg, yield 80%). ^1H NMR (400 MHz, CDCl_3) δ 7.74 (d, J = 2.9 Hz, 1H), 7.34 – 7.21 (m, 4H), 7.19 (s, 1H), 7.16 (dd, J = 8.8, 1.9 Hz, 1H), 6.57 (ddd, J = 8.7, 3.2, 1.3 Hz, 1H), 6.44 (t, J = 8.0 Hz, 1H), 6.29 (d, J = 3.1 Hz, 1H), 5.44 – 5.14 (m, 1H),

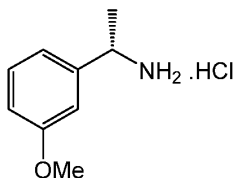
4.34 (q, $J = 6.8$ Hz, 1H), 4.00 (s, 2H), 3.55 (d, $J = 2.4$ Hz, 3H), 2.24 (s, 3H), 1.52 (dd, $J = 6.9, 2.5$ Hz, 3H), 1.38 (dd, $J = 6.8, 1.4$ Hz, 3H), 1.23 (d, $J = 0.9$ Hz, 9H). ESI-MS (m/z): 560.82 $[M]^+$.

[0431] Compound 46: (S)-2-(5-((6-(((S)-1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)-2-chlorophenoxy)propanoic acid.

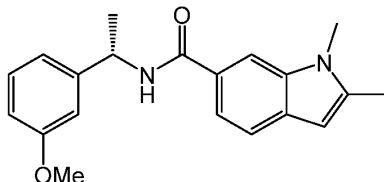


[0432] The title compound was prepared following the same general protocol as described in Step 1, Compound 42, using the (S)-N-(1-(3-(tert-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide. A yellow solid was obtained (20 mg, yield 79%). ^1H NMR (400 MHz, CDCl_3) δ 7.74 (s, 1H), 7.37 – 7.31 (m, 1H), 7.29 – 7.17 (m, 4H), 7.14 (ddd, $J = 8.0, 5.1, 3.1$ Hz, 2H), 6.70 (dd, $J = 8.0, 1.8$ Hz, 1H), 6.55 (t, $J = 2.5$ Hz, 1H), 6.41 (s, 1H), 5.28 (d, $J = 7.6$ Hz, 1H), 4.50 (qd, $J = 6.8, 3.3$ Hz, 1H), 3.88 (d, $J = 1.8$ Hz, 2H), 3.56 (s, 3H), 2.24 (s, 3H), 1.55 (d, $J = 6.7$ Hz, 3H), 1.51 (d, $J = 6.9$ Hz, 3H), 1.25 (s, 9H). ESI-MS (m/z): 560.82 $[M]^+$.

[0433] Compound 47: (S)-2-(3-((6-((1-(3-methoxyphenyl)ethyl) carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoic acid.

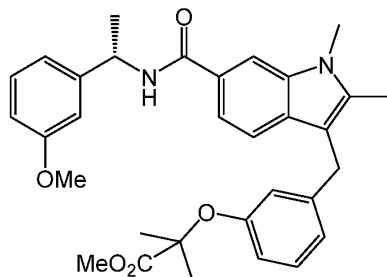


[0434] Step 1: (S)-1-(3-methoxyphenyl)ethanamine hydrochloride. The title compound was prepared following the same general protocol as described in Step 6, Compound 1, using the 1-(3-methoxyphenyl)ethanone instead of the 1-(4-*tert*-butylphenyl)ethenone. A white solid was obtained (0.47 g, yield 73%). ^1H NMR (600 MHz, DMSO-d_6) δ 8.60 (s, 3H), 7.53 (t, $J = 7.96$ Hz, 1H), 7.18 (t, $J = 2$ Hz, 1H), 7.08 (d, $J = 7.76$ Hz, 1H), 6.94 (ddd, $J = 7.56, 2.48, 0.4$, 1H), 4.35 (q, $J = 5.75$ Hz, 1H), 3.77 (s, 3H), 1.51 (d, $J = 7.2$ Hz, 6H).

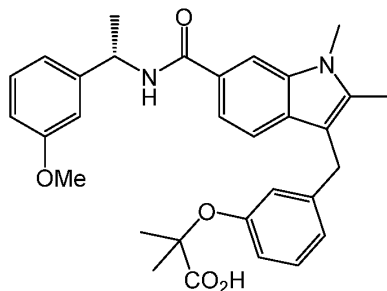


[0435] Step 2: (S)-N-(1-(3-methoxyphenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide. The title compound was prepared following the same general protocol as described in Step 8, Compound 1, using

the (S)-1-(3-methoxyphenyl)ethanamine hydrochloride instead of (S)-1-(4-(tert-butyl)phenyl)ethanamine hydrochloride. A yellow solid was obtained (34 mg, yield 93 %).

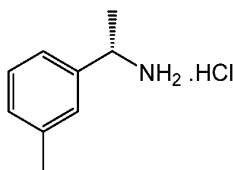


[0436] Step 3: methyl (S)-2-(3-((6-((1-(3-methoxyphenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoate. The title compound was prepared following the same general protocol as described in Step 9, Compound 1, using the (S)-N-(1-(3-methoxyphenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide and the methyl 2-(3-formylphenoxy)-2-methylpropanoate instead of the ethyl 2-(4-formylphenoxy)propanoate. A yellow solid was obtained (50 mg, yield 86 %).

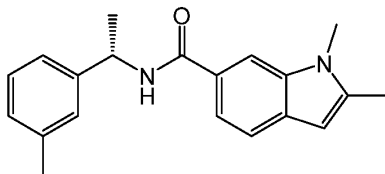


[0437] Step 4: (S)-2-(3-((6-((1-(3-methoxyphenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the methyl (S)-2-(3-((6-((1-(3-methoxyphenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoate instead of the (ethyl 2-(4-((6-((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy) propanoate. A yellow solid was obtained (39 mg, yield 81%). ¹H NMR (400 MHz, CDCl₃) δ 7.80 (d, J = 1.5 Hz, 1H), 7.31 – 7.04 (m, 3H), 6.96 – 6.81 (m, 3H), 6.71 (dtd, J = 7.7, 2.3, 1.0 Hz, 2H), 6.63 (t, J = 2.0 Hz, 1H), 6.56 (ddd, J = 8.2, 2.6, 1.1 Hz, 1H), 6.47 (d, J = 7.8 Hz, 1H), 6.34 (br, 1H), 5.26 (p, J = 7.0 Hz, 1H), 3.87 (s, 2H), 3.70 (d, J = 1.3 Hz, 3H), 3.49 (d, J = 1.2 Hz, 3H), 2.20 (s, 3H), 1.50 (d, J = 6.9 Hz, 3H), 1.44 (d, J = 1.2 Hz, 6H).

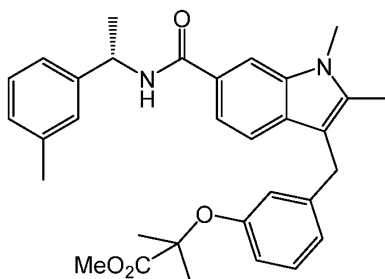
[0438] Compound 48: (S)-2-(3-((1,2-dimethyl-6-((1-(m-tolyl)ethyl)carbamoyl)-1H-indol-3-yl)methyl)phenoxy)-2-methyl propanoic acid.



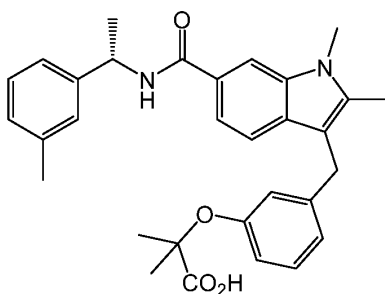
[0439] Step 1: (S)-1-(*m*-tolyl)ethanamine hydrochloride. The title compound was prepared following the same general protocol as described in Step 6, Compound 1, using the 1-(*m*-tolyl)ethanone instead of the 1-(4-*tert*-butylphenyl)ethenone. A white solid was obtained (0.3 g, yield 51%). ¹H NMR (600 MHz, DMSO-*d*₆) δ 8.64 (s, 3H), 7.40- 7.34 (m, 3H), 7.24 (d, *J* = 7.14 Hz, 1H), 4.38 (q, *J* = 6.78 Hz, 1H), 2.37 (s, 3H), 1.57 (d, *J* = 6.84 Hz, 6H).



[0440] Step 2: (S)-1,2-dimethyl-N-(1-(*m*-tolyl)ethyl)-1H-indole-6-carboxamide. The title compound was prepared following the same general protocol as described in Step 8, Compound 1, using the (S)-1-(*m*-tolyl)ethanamine hydrochloride instead of (S)-1-(4-(*tert*-butyl)phenyl)ethanamine hydrochloride. A yellow solid was obtained (15 mg, yield 87 %).



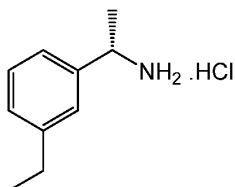
[0441] Step 3: methyl (S)-2-(3-((1,2-dimethyl-6-((1-(*m*-tolyl)ethyl)carbamoyl)-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoate. The title compound was prepared following the same general protocol as described in Step 9, Compound 1, using the (S)-1,2-dimethyl-N-(1-(*m*-tolyl)ethyl)-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(*tert*-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide and the methyl 2-(3-formylphenoxy)-2-methylpropanoate instead of the ethyl 2-(4-formylphenoxy)propanoate. A yellow solid was obtained (20 mg, yield 81 %).



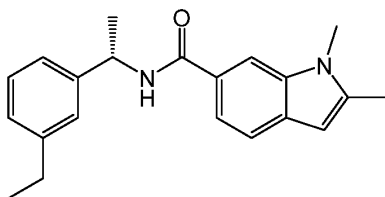
[0442] Step 4: (S)-2-(3-((1,2-dimethyl-6-((1-(*m*-tolyl)ethyl)carbamoyl)-1H-indol-3-yl)methyl)phenoxy)-2-methyl propanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the methyl (S)-2-(3-((1,2-dimethyl-6-((1-(*m*-tolyl)ethyl)carbamoyl)-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoate instead of the (ethyl 2-(4-(((S)-1-(4-(*tert*-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy) propanoate.

A yellow solid was obtained (16 mg, yield 82%). ¹H NMR (400 MHz, CDCl₃) δ 7.82 (d, J = 1.3 Hz, 1H), 7.28 – 7.20 (m, 2H), 7.13 (qd, J = 7.3, 1.3 Hz, 3H), 7.04 – 6.98 (m, 1H), 6.93 (t, J = 7.8 Hz, 1H), 6.74 (d, J = 7.6 Hz, 1H), 6.64 (d, J = 1.9 Hz, 1H), 6.57 (dd, J = 8.0, 2.4 Hz, 1H), 6.40 (d, J = 7.9 Hz, 1H), 5.37 (br, 1H), 5.26 (p, J = 7.1 Hz, 1H), 3.90 (s, 2H), 3.53 (s, 3H), 2.27 (s, 3H), 2.22 (s, 3H), 1.52 (d, J = 6.9 Hz, 3H), 1.44 (s, 6H).

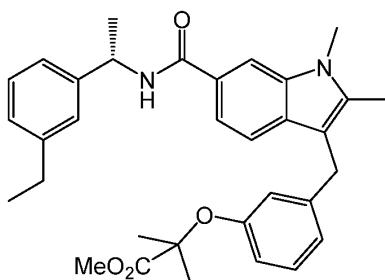
[0443] Compound 49: (S)-2-(3-((6-((1-(3-ethylphenyl)ethyl) carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoic acid.



[0444] Step 1: (S)-1-(3-ethylphenyl)ethanamine hydrochloride. The title compound was prepared following the same general protocol as described in Step 6, Compound 1, using the 1-(3-ethylphenyl)ethanone instead of the 1-(4-*tert*-butylphenyl)ethenone. A white solid was obtained (0.45 g, yield 70%). ¹H NMR (400 MHz, DMSO-d₆) δ 8.09 (br, 3H), 7.38 (s, 1H), 7.33 (dd, J = 6.08, 1.6 Hz, 2H), 7.22– 7.19 (m, 1H), 4.35 (q, J = 6.8 Hz, 1H), 2.64 (q, J = 7.56, 2H), 1.51 (d, J = 6.8 Hz, 6H), 1.21 (t, J = 7.56 Hz, 6H).

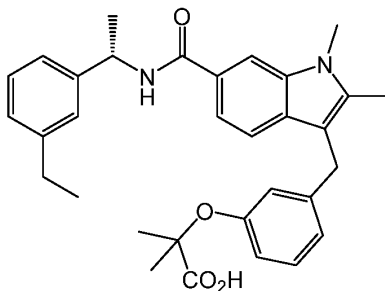


[0445] Step 2: (S)-N-(1-(3-ethylphenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide. The title compound was prepared following the same general protocol as described in Step 8, Compound 1, using the (S)-1-(3-ethylphenyl)ethanamine hydrochloride instead of (S)-1-(4-(*tert*-butyl)phenyl)ethanamine hydrochloride. A yellow solid was obtained (40 mg, yield 94%).



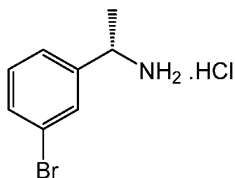
[0446] Step 3: methyl (S)-2-(3-((6-((1-(3-ethylphenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoate. The title compound was prepared following the same general protocol as described in Step 9, Compound 1, using the (S)-N-(1-(3-ethylphenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(*tert*-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-

carboxamide and the methyl 2-(3-formylphenoxy)-2-methylpropanoate instead of the ethyl 2-(4-formylphenoxy)propanoate. A yellow solid was obtained (52 mg, yield 79%).

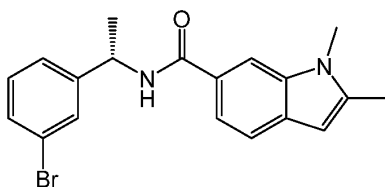


[0447] Step 4: (S)-2-(3-((6-((1-(3-ethylphenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-2-methyl propanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the methyl (S)-2-(3-((6-((1-(3-ethylphenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoate instead of the (ethyl 2-(4-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy) propanoate. A yellow solid was obtained (45 mg, yield 90%). ¹H NMR (400 MHz, CDCl₃) δ 7.93 (d, J = 1.5 Hz, 1H), 7.37 – 7.21 (m, 5H), 7.14 (dt, J = 7.3, 1.6 Hz, 1H), 7.02 (t, J = 7.9 Hz, 1H), 6.87 – 6.80 (m, 1H), 6.75 (t, J = 2.0 Hz, 1H), 6.72 – 6.60 (m, 1H), 6.50 (d, J = 8.0 Hz, 1H), 5.99 (br, 1H), 5.39 (p, J = 7.1 Hz, 1H), 3.99 (s, 2H), 3.63 (s, 3H), 2.67 (q, J = 7.6 Hz, 2H), 2.32 (s, 3H), 1.63 (d, J = 6.9 Hz, 3H), 1.55 (s, 6H), 1.26 (t, J = 7.6 Hz, 3H).

[0448] Compound 50: (S)-2-(3-((6-((1-(3-bromophenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoic acid.

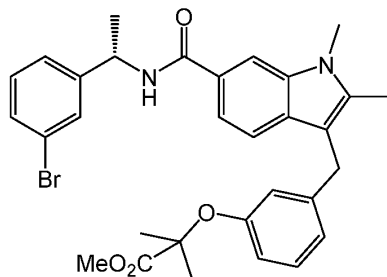


[0449] Step 1: (S)-1-(3-bromophenyl)ethanamine hydrochloride. The title compound was prepared following the same general protocol as described in Step 6, Compound 1, using the 1-(3-bromophenyl)ethanone instead of the 1-(4-tert-butylphenyl)ethenone. A white solid was obtained (0.53 g, yield 66%). ¹H NMR (600 MHz, DMSO-d₆) δ 8.78 (s, 3H), 7.85 (t, J = 1.8, 1H), 7.63 (dd, J = 6.08, 1.6 Hz, 2H), 7.22–7.19 (m, 1H), 4.47 (q, J = 6.66 Hz, 1H), 1.58 (d, J = 6.84 Hz, 6H).

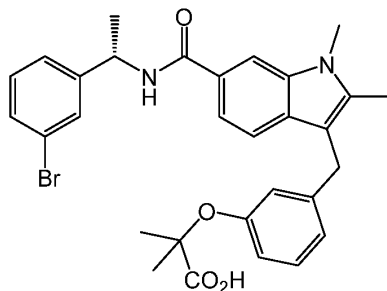


[0450] Step 2: (S)-N-(1-(3-bromophenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide. The title compound was prepared following the same general protocol as described in Step 8, Compound 1, using

the (S)-1-(3-bromophenyl)ethanamine hydrochloride instead of (S)-1-(4-(tert-butyl)phenyl)ethanamine hydrochloride. A yellow solid was obtained (17 mg, yield 82%).

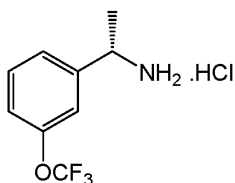


[0451] Step 3: methyl (S)-2-(3-((6-((1-(3-bromophenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoate. The title compound was prepared following the same general protocol as described in Step 9, Compound 1, using the (S)-N-(1-(3-bromophenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide and the methyl 2-(3-formylphenoxy)-2-methylpropanoate instead of the ethyl 2-(4-formylphenoxy)propanoate. A yellow solid was obtained (22 mg, yield 83%).

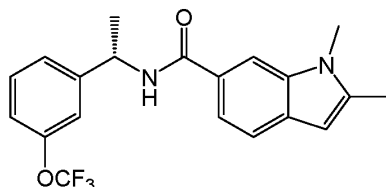


[0452] Step 4: (S)-2-(3-((6-((1-(3-bromophenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the methyl (S)-2-(3-((6-((1-(3-bromophenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoate instead of the (ethyl 2-(4-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy) propanoate. A yellow solid was obtained (19 mg, yield 90%). ¹H NMR (400 MHz, CDCl₃) δ 7.80 (d, J = 1.5 Hz, 1H), 7.45 (t, J = 1.9 Hz, 1H), 7.31 (ddd, J = 7.98, 1.86 Hz, 2H), 7.46 (t, J = 7.86 Hz, 1H), 5.26 (d, J = 7.0 Hz, 1H), 3.93 (s, 2H), 3.57 (s, 3H), 2.26 (s, 3H), 1.50 (d, J = 7.0 Hz, 3H), 1.44 (s, 6H).

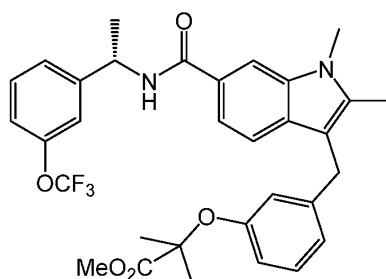
[0453] Compound 51: (S)-2-(3-((1,2-dimethyl-6-((1-(3-(trifluoromethoxy)phenyl)ethyl)carbamoyl)-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoic acid.



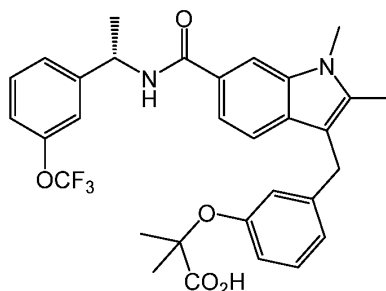
[0454] Step 1: (S)-1-(3-(trifluoromethoxy)phenyl)ethanamine hydrochloride. The title compound was prepared following the same general protocol as described in Step 6, Compound 1, using the 1-(3-(trifluoromethoxy)phenyl)ethanone instead of the 1-(4-*tert*-butylphenyl)ethenone. A white solid was obtained (0.59 g, yield 71%). ¹H NMR (600 MHz, DMSO-*d*₆) δ 8.83 (s, 3H), 7.63-7.58 (m, 3H), 7.37 (s, 1H), 4.49 (q, *J* = 6.60 Hz, 1H), 1.55 (d, *J* = 6.84 Hz, 6H).



[0455] Step 2: (S)-1,2-dimethyl-N-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1H-indole-6-carboxamide. The title compound was prepared following the same general protocol as described in Step 8, Compound 1, using the (S)-1-(3-(trifluoromethoxy)phenyl)ethanamine hydrochloride instead of (S)-1-(4-(*tert*-butyl)phenyl)ethanamine hydrochloride. A light-red solid was obtained (10 mg, yield 75%).



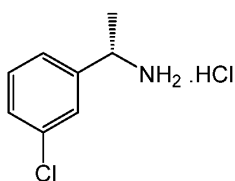
[0456] Step 3: methyl (S)-2-(3-((1,2-dimethyl-6-((1-(3-(trifluoromethoxy)phenyl)ethyl)carbamoyl)-1H-indol-3-yl)methyl) phenoxy)-2-methylpropanoate. The title compound was prepared following the same general protocol as described in Step 9, Compound 1, using the (S)-1,2-dimethyl-N-(1-(3-(trifluoromethoxy)phenyl)ethyl)-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(*tert*-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide and the methyl 2-(3-formylphenoxy)-2-methylpropanoate instead of the ethyl 2-(4-formylphenoxy)propanoate. A yellow solid was obtained (12 mg, yield 77%).



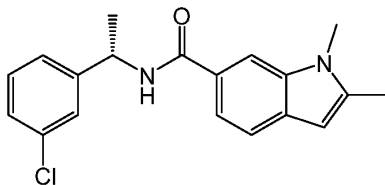
[0457] Step 4: (S)-2-(3-((1,2-dimethyl-6-((1-(3-(trifluoromethoxy)phenyl)ethyl)carbamoyl)-1H-indol-3-yl)methyl) phenoxy)-2-methylpropanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the methyl (S)-2-(3-((1,2-dimethyl-6-((1-(3-(trifluoromethoxy)phenyl)ethyl)carbamoyl)-1H-indol-3-yl)methyl) phenoxy)-2-methylpropanoate instead of the ethyl 2-(4-formylphenoxy)propanoate.

(trifluoromethoxy)phenyl)ethyl)carbamoyl)-1H-indol-3-yl)methyl) phenoxy)-2-methylpropanoate instead of the (ethyl 2-(4-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy) propanoate. A yellow solid was obtained (8 mg, yield 68 %). ¹H NMR (400 MHz, CDCl₃) δ 7.80 (s, 1H), 7.31 – 7.20 (m, 4H), 7.16 (s, 1H), 6.64 (t, J = 2.0 Hz, 1H), 6.60 (dd, J = 8.0, 2.5 Hz, 1H), 6.46 (d, J = 7.8 Hz, 1H), 5.30 (p, J = 7.1 Hz, 1H), 3.92 (s, 2H), 3.56 (d, J = 0.9 Hz, 3H), 2.25 (d, J = 1.0 Hz, 3H), 1.60 – 1.48 (m, 3H), 1.44 (d, J = 0.9 Hz, 6H). ¹³C NMR (101 MHz, CDCl₃) δ 207.23, 176.55, 168.26, 154.57, 149.52, 146.09, 143.12, 137.14, 136.32, 130.49, 130.00, 129.06, 125.90, 124.74, 122.84, 120.06, 119.54, 118.79, 117.78, 117.33, 116.68, 110.06, 109.28, 79.41, 50.82, 48.81, 30.95, 30.14, 29.71, 25.08, 24.98, 21.88, 10.54, 1.91. ¹⁹F NMR (376 MHz, CDCl₃) δ -57.66.

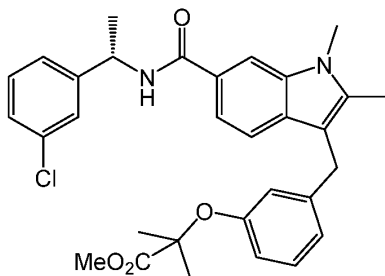
[0458] Compound 52: (S)-2-(3-(((6-((1-(3-chlorophenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoic acid.



[0459] Step 1: (S)-1-(3-chlorophenyl)ethanamine hydrochloride. The title compound was prepared following the same general protocol as described in Step 6, Compound 1, using the 1-(3-chlorophenyl)ethanone instead of the 1-(4-tert-butylphenyl)ethanone. A white solid was obtained (0.50 g, yield 76 %). ¹H NMR (600 MHz, DMSO-d₆) δ 8.70 (s, 3H), 7.53–7.43 (m, 4H), 4.42 (q, J = 6.60 Hz, 1H), 1.52 (d, J = 6.8 Hz, 3H).



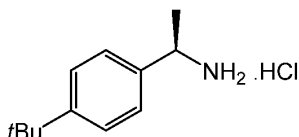
[0460] Step 2: (S)-N-(1-(3-chlorophenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide. The title compound was prepared following the same general protocol as described in Step 8, Compound 1, using the (S)-1-(3-chlorophenyl)ethanamine hydrochloride instead of the (S)-1-(4-(tert-butyl)phenyl)ethanamine hydrochloride. A yellow solid was obtained (20 mg, yield 83%).



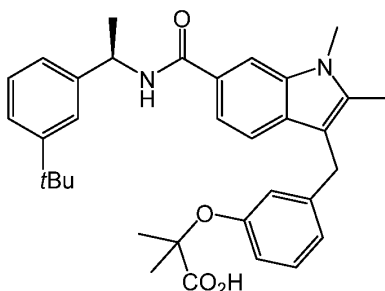
[0461] Step 3: methyl (S)-2-(3-(((6-((1-(3-chlorophenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoate. The title compound was prepared following the same general

CC1=C(C)OC(C1)C2=CC=CC=C2C3=C(C=C2)C(=C4C(=C(C=C3)C(=O)NC[C@H](C4)C5=CC=CC=C5Cl)C6=CC=CC=C6)N(C)C=C6

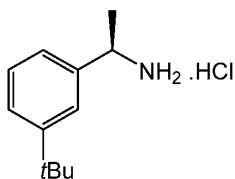
[0463] Compound 53: (R)-2-(3-((6-((1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl) phenoxy)-2-methyl propanoic acid.

CC1=C(C(C(C1)C2=CC=CC=C2C(C)C(C)C)OC3=CC=CC=C3C(=O)O)CC4=CC=CC=C4NC(=O)C5=CC=C6C(=C5)C7=CC=CC=C7C8=C6N(C)C(C)=C8C

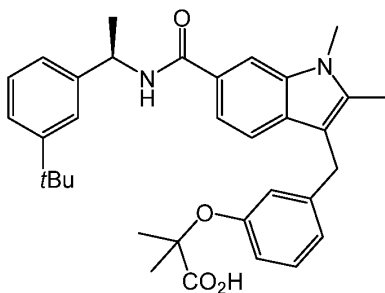
[0465] Step 2: (R)-2-(3-((6-((1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the methyl (R)-2-(3-((6-((1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoate instead of the (ethyl 2-(4-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy) propanoate. A yellow solid was obtained (30 mg, yield 39 %). ¹H NMR (600 MHz, CDCl₃) δ 7.82 (d, J = 1.5 Hz, 1H), 7.31 (dd, J = 8.4, 2.0 Hz, 2H), 7.28 – 7.20 (m, 3H), 6.99 (t, J = 7.8 Hz, 1H), 6.88 – 6.73 (m, 1H), 6.68 – 6.54 (m, 2H), 6.36 (d, J = 7.9 Hz, 1H), 5.37 – 5.20 (m, 1H), 3.93 (s, 2H), 3.59 (s, 3H), 2.26 (s, 3H), 1.54 (d, J = 6.8 Hz, 3H), 1.44 (s, 6H), 1.24 (d, J = 1.0 Hz, 6H).



[0466] Compound 54: (R)-2-(3-((6-((1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-2-methyl propanoic acid.



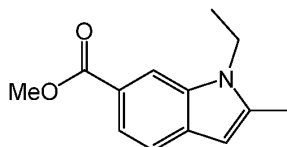
[0467] Step 1: (R)-1-(3-(tert-butyl)phenyl)ethan-1-amine hydrochloride. The title compound was prepared following the same general protocol as described in Step 6, Compound 1, using the (R)-2-methylpropane-2-sulfmamide instead of the (S)-2-methylpropane-2-sulfmamide and the 1-(3-(tert-butyl)phenyl)ethenone instead of the 1-(4-(tert-butyl)phenyl)ethan-1-one. A white solid was obtained (0.4 g, yield 60%).



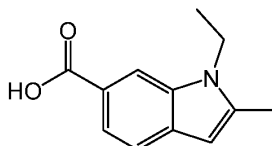
[0468] Step 2: (R)-2-(3-((6-((1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the methyl (R)-2-(3-((6-((1-(3-(tert-

butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoate instead of the (ethyl 2-(4-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy) propanoate. A yellow solid was obtained (41 mg, yield 53 %). ¹H NMR (400 MHz, CDCl₃) δ 7.82 (s, 1H), 7.35 (s, 1H), 7.30 – 7.21 (m, 4H), 7.16 (d, J = 6.2 Hz, 1H), 7.09 – 7.01 (m, 1H), 6.84 (d, J = 7.6 Hz, 1H), 6.71 – 6.56 (m, 2H), 6.35 (d, J = 7.8 Hz, 1H), 5.45 – 5.23 (m, 1H), 3.97 (s, 2H), 3.65 (s, 3H), 2.30 (s, 3H), 1.56 (d, J = 6.8 Hz, 3H), 1.43 (s, 6H), 1.25 (s, 9H).

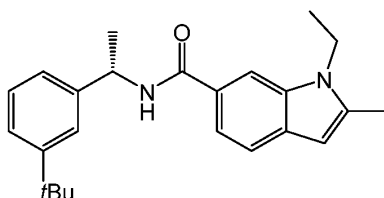
[0469] Compound 55: (S)-2-(3-(((1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-1-ethyl-2-methyl-1H-indol-3-yl)methyl) phenoxy)-2-methylpropanoic acid.



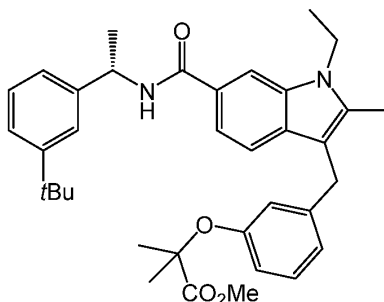
[0470] Step 1: methyl 1-ethyl-2-methyl-1H-indole-6-carboxylate. The title compound was prepared following the same general protocol as described in Step 4, Compound 1, using the iodoethane instead of the methyl iodide. A yellow solid was obtained (95 mg, yield 95%). ESI-MS (m/z): 217.62 [M]⁺.



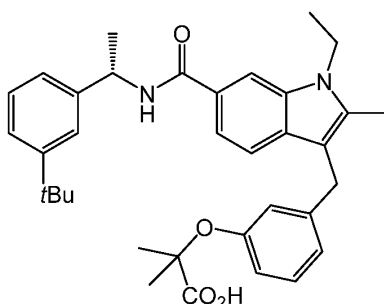
[0471] Step 2: 1-ethyl-2-methyl-1H-indole-6-carboxylic acid. The title compound was prepared following the same general protocol as described in Step 5, Compound 1, using the methyl 1-ethyl-2-methyl-1H-indole-6-carboxylate instead of the methyl 1,2-dimethyl-1H-indole-6-carboxylate. A yellow solid was obtained (87 mg, yield 97%). ESI-MS (m/z): 203.61 [M]⁺.



[0472] Step 3: (S)-N-(1-(3-(tert-butyl)phenyl)ethyl)-1-ethyl-2-methyl-1H-indole-6-carboxamide. The title compound was prepared following the same general protocol as described in Step 8, Compound 1, using the (S)-1-(3-(tert-butyl)phenyl)ethanamine hydrochloride instead of the (S)-1-(4-(tert-butyl)phenyl)ethanamine hydrochloride and the 1-ethyl-2-methyl-1H-indole-6-carboxylic acid instead of the 1-methyl-2-methyl-1H-indole-6-carboxylic acid. A light-yellow solid was obtained (40 mg, yield 75%). ESI-MS (m/z): 362.72 [M]⁺.

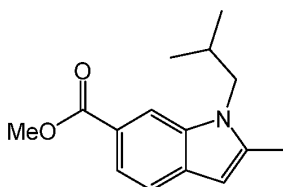


[0473] Step 4: methyl (S)-2-(3-((6-((1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-1-ethyl-2-methyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoate. The title compound was prepared following the same general protocol as described in Step 9, Compound 1, using the (S)-N-(1-(3-(tert-butyl)phenyl)ethyl)-1-ethyl-2-methyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide and the methyl 2-(3-formylphenoxy)-2-methylpropanoate instead of the ethyl 2-(4-formylphenoxy)propanoate. The product was obtained as yellow solid (42 mg, yield 62%).

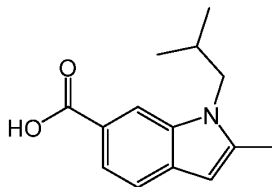


[0474] Step 5: (S)-2-(3-((6-((1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-1-ethyl-2-methyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the methyl (S)-2-(3-((6-((1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-1-ethyl-2-methyl-1H-indol-3-yl)methyl) phenoxy)-2-methylpropanoate instead of the (ethyl 2-(4-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy) propanoate. A white solid was obtained (32 mg, yield 78%). ¹H NMR (400 MHz, CDCl₃) δ 7.93 (d, J = 1.4 Hz, 1H), 7.44 (d, J = 2.1 Hz, 1H), 7.38 – 7.30 (m, 3H), 7.25 (dd, J = 6.7, 2.0 Hz, 1H), 7.14 (t, J = 7.8 Hz, 1H), 6.91 (d, J = 7.6 Hz, 1H), 6.72 (ddd, J = 11.6, 3.3, 1.4 Hz, 2H), 6.49 (d, J = 7.9 Hz, 1H), 5.40 (p, J = 6.8 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 4.05 (s, 2H), 2.39 (s, 3H), 1.66 (d, J = 6.9 Hz, 3H), 1.52 (s, 6H), 1.35 (s, 9H), 1.31 – 1.13 (m, 3H).

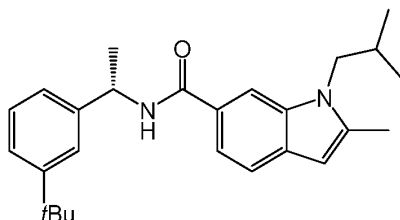
[0475] Compound 56: (S)-2-(3-((6-((1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-1-isobutyl-2-methyl-1H-indol-3-yl)methyl) phenoxy)-2-methylpropanoic acid.



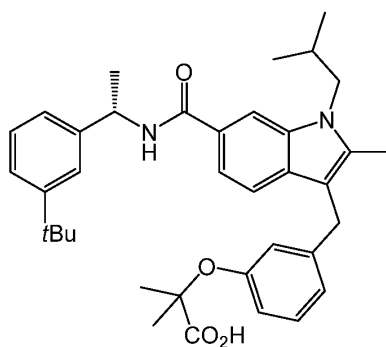
[0476] Step 1: methyl 1-isobutyl-2-methyl-1H-indole-6-carboxylate. The title compound was prepared following the same general protocol as described in Step 4, Compound 1, using the isobutyl bromide instead of the methyl iodide. A yellow solid was obtained (220 mg, yield 94%). ESI-MS (m/z): 245.62 [M]⁺.



[0477] Step 2: 1-isobutyl-2-methyl-1H-indole-6-carboxylic acid. The title compound was prepared following the same general protocol as described in Step 5, Compound 1, using the methyl 1-isobutyl-2-methyl-1H-indole-6-carboxylate instead of the methyl 1,2-dimethyl-1H-indole-6-carboxylate. A brown solid was obtained (200 mg, yield 96%). ESI-MS (m/z): 231.64 [M]⁺.



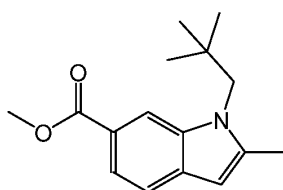
[0478] Step 3: (S)-N-(1-(3-(tert-butyl)phenyl)ethyl)-1-isobutyl-2-methyl-1H-indole-6-carboxamide. The title compound was prepared following the same general protocol as described in Step 8, Compound 1, using the (S)-1-(3-(tert-butyl)phenyl)ethanamine hydrochloride instead of the (S)-1-(4-(tert-butyl)phenyl)ethanamine hydrochloride and the 1-isobutyl-2-methyl-1H-indole-6-carboxylic acid instead of the 1-methyl-2-methyl-1H-indole-6-carboxylic acid. A yellow solid was obtained (310 mg, yield 91%). ESI-MS (m/z): 390.70 [M]⁺.



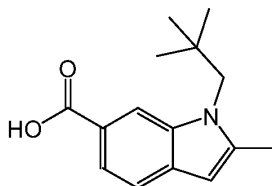
[0479] Step 4: (S)-2-(3-(((6-((1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-1-isobutyl-2-methyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoic acid. The title compound was prepared following the same general protocol as described in Step 9, Compound 1, using the (S)-N-(1-(3-(tert-butyl)phenyl)ethyl)-1-isobutyl-2-methyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide and the methyl 2-(3-formylphenoxy)-2-methylpropanoate instead of the ethyl 2-(4-formylphenoxy)propanoate. The product was obtained as yellow solid (50 mg, yield 70%).

and used for the next step without further purification. The final product was synthesized following the same general protocol as described in Step 10, Compound 1, using the methyl (S)-2-(3-(((1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-1-isobutyl-2-methyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoate instead of the (ethyl 2-(4-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy) propanoate. The product was obtained as brown solid (35 mg, yield 72%). ¹H NMR (400 MHz, CDCl₃) δ 7.93 – 7.76 (m, 1H), 7.35 (d, J = 2.0 Hz, 1H), 7.30 – 7.19 (m, 3H), 7.15 (dt, J = 6.3, 2.0 Hz, 2H), 7.04 (t, J = 8.2 Hz, 1H), 6.81 (d, J = 7.5 Hz, 1H), 6.63 (dd, J = 4.7, 2.5 Hz, 2H), 6.36 (d, J = 7.8 Hz, 1H), 5.31 (q, J = 7.0 Hz, 1H), 3.96 (s, 2H), 3.85 (d, J = 7.7 Hz, 2H), 2.29 (s, 3H), 2.15 (p, J = 6.6 Hz, 1H), 1.55 (d, J = 6.9 Hz, 3H), 1.42 (s, 6H), 1.25 (s, 9H), 0.83 (d, J = 6.6 Hz, 6H).

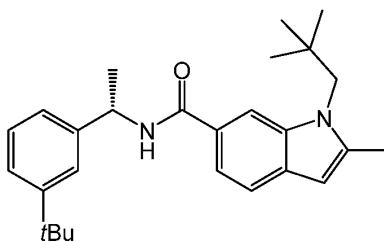
[0480] Compound 57: (S)-2-(3-(((1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-2-methyl-1-neopentyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoic acid.



[0481] Step 1: methyl 2-methyl-1-neopentyl-1H-indole-6-carboxylate. The title compound was prepared following the same general protocol as described in Step 4, Compound 1, using the 1-iodo-2,2-dimethylpropane instead of the methyl iodide. A yellow solid was obtained (12 mg, yield 87%).

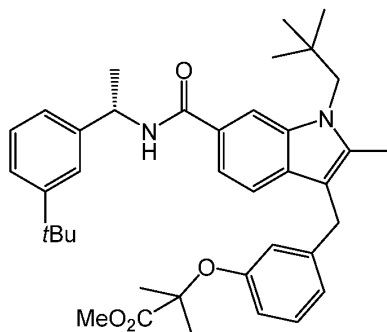


[0482] Step 2: 2-methyl-1-neopentyl-1H-indole-6-carboxylic acid. The title compound was prepared following the same general protocol as described in Step 5, Compound 1, using the methyl 2-methyl-1-neopentyl-1H-indole-6-carboxylate instead of the methyl 1,2-dimethyl-1H-indole-6-carboxylate. A yellow solid was obtained (9mg, yield 80%).

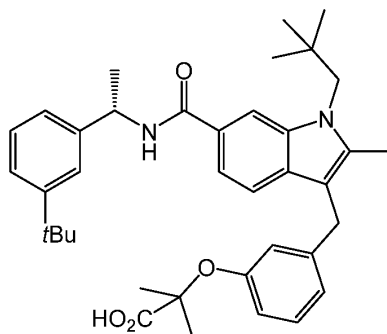


[0483] Step 3: (S)-N-(1-(3-(tert-butyl)phenyl)ethyl)-2-methyl-1-neopentyl-1H-indole-6-carboxamide. The title compound was prepared following the same general protocol as described in Step 8, Compound 1, using the (S)-1-(3-(tert-butyl)phenyl)ethanamine hydrochloride instead of the (S)-1-(4-(tert-butyl)phenyl)ethanamine hydrochloride and the 2-methyl-1-neopentyl-1H-indole-6-carboxylic acid

instead of the 1-methyl-2-methyl-1H-indole-6-carboxylic acid. A brown solid was obtained (14 mg, yield 94%).

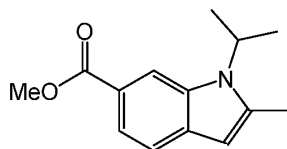


[0484] Step 4: methyl (S)-2-(3-(((6-((1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-2-methyl-1-neopentyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoate. The title compound was prepared following the same general protocol as described in Step 9, Compound 1, using the (S)-N-(1-(3-(tert-butyl)phenyl)ethyl)-2-methyl-1-neopentyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide and the methyl 2-(3-formylphenoxy)-2-methylpropanoate instead of the ethyl 2-(4-formylphenoxy)propanoate. The product was obtained as yellow solid (17 mg, yield 80%).

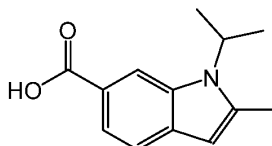


[0485] Step 5: (S)-2-(3-(((6-((1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-2-methyl-1-neopentyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the methyl (S)-2-(3-(((6-((1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-2-methyl-1-neopentyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoate instead of the (ethyl 2-(4-(((S)-1-(4-(tert-butyl)phenyl)ethyl) carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy) propanoate. A light-yellow solid was obtained (10 mg, yield 60 %). ¹H NMR (400 MHz, CDCl₃) δ 7.91 (s, 1H), 7.34 (s, 1H), 7.23 (td, J = 4.1, 2.2 Hz, 3H), 7.18 – 7.09 (m, 2H), 7.04 (t, J = 7.8 Hz, 1H), 6.81 (d, J = 7.6 Hz, 1H), 6.71 – 6.54 (m, 2H), 6.37 (d, J = 7.8 Hz, 1H), 5.28 (t, J = 7.1 Hz, 1H), 3.96 (s, 2H), 3.84 (s, 2H), 2.28 (s, 3H), 1.55 (d, J = 6.9 Hz, 3H), 1.41 (s, 6H), 1.24 (s, 9H), 0.93 (s, 9H).

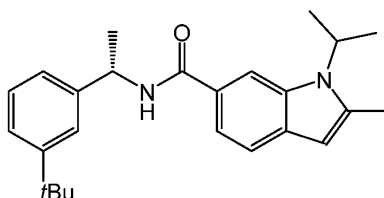
[0486] Compound 58: (S)-2-(3-(((6-((1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-1-isopropyl-2-methyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoic acid.



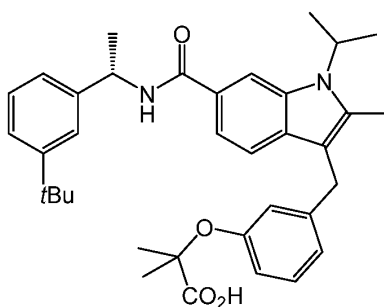
[0487] Step 1: methyl 1-isopropyl-2-methyl-1H-indole-6-carboxylate. The title compound was prepared following the same general protocol as described in Step 4, Compound 1, using the 2-bromopropane instead of the methyl iodide. A yellow solid was obtained (55 mg, yield 90%). ESI-MS (m/z): 232.50 [M+H]⁺.



[0488] Step 2: 1-isopropyl-2-methyl-1H-indole-6-carboxylic acid. The title compound was prepared following the same general protocol as described in Step 5, Compound 1, using the methyl 1-isopropyl-2-methyl-1H-indole-6-carboxylate instead of the methyl 1,2-dimethyl-1H-indole-6-carboxylate. A yellow solid was obtained (50 mg, yield 98%). ESI-MS (m/z): 217.49 [M]⁺.



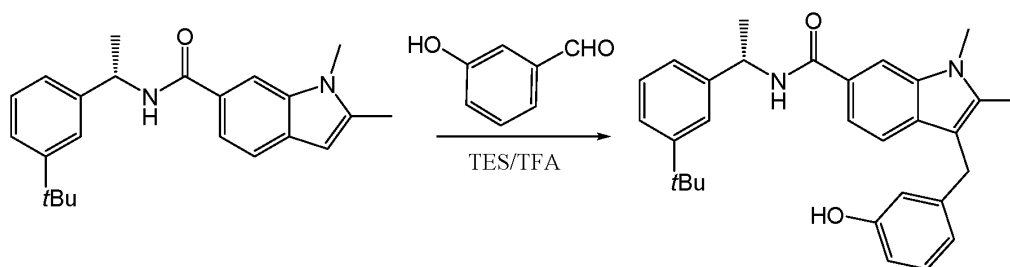
[0489] Step 3: (S)-N-(1-(3-(tert-butyl)phenyl)ethyl)-1-isopropyl-2-methyl-1H-indole-6-carboxamide. The title compound was prepared following the same general protocol as described in Step 8, Compound 1, using the (S)-1-(3-(tert-butyl)phenyl)ethanamine hydrochloride instead of the (S)-1-(4-(tert-butyl)phenyl)ethanamine hydrochloride and the 1-isopropyl-2-methyl-1H-indole-6-carboxylic acid instead of the 1-methyl-2-methyl-1H-indole-6-carboxylic acid. A yellow solid was obtained (25 mg, yield 83%). ESI-MS (m/z): 376.70 [M]⁺.



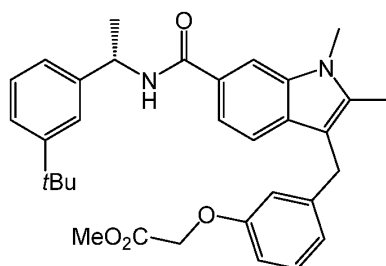
[0490] Step 4: (S)-2-(3-((6-((1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-1-isopropyl-2-methyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoic acid. The title compound was prepared following the same general protocol as described in Step 9, Compound 1, using the (S)-N-(1-(3-(tert-butyl)phenyl)ethyl)-1-isopropyl-2-methyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1,2-

dimethyl-1H-indole-6-carboxamide and the methyl 2-(3-formylphenoxy)-2-methylpropanoate instead of the ethyl 2-(4-formylphenoxy)propanoate. The product was obtained as light-brown solid (22 mg, yield 57%) and used for the next step without further purification. The final product was synthesized following the same general protocol as described in Step 10, Compound 1, using the methyl (S)-2-3-(((6-((1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-1-isopropyl-2-methyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoate instead of the (ethyl 2-(4-(((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy) propanoate. The product was obtained as white powder (12 mg, yield 55%).
¹H NMR (400 MHz, CDCl₃) δ 8.02 (s, 1H), 7.35 (s, 1H), 7.24 (d, J = 6.6 Hz, 3H), 7.16 (d, J = 9.7 Hz, 2H), 7.06 (t, J = 7.9 Hz, 1H), 6.84 (d, J = 7.7 Hz, 1H), 6.64 (d, J = 9.2 Hz, 1H), 6.59 (s, 1H), 6.36 (d, J = 7.6, 1H), 5.42 – 5.24 (m, 1H), 4.68 (dd, J = 14.7, 7.7 Hz, 1H), 4.03 (m, 1H), 3.96 (s, 2H), 2.33 (s, 3H), 1.56 (d, J = 6.9 Hz, 9H), 1.42 (s, 6H), 1.25 (s, 9H).

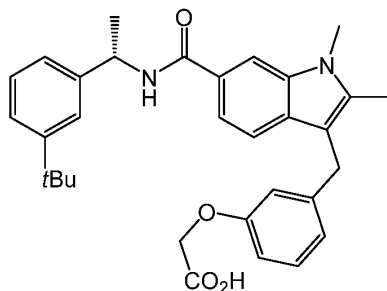
[0491] Compound 59: (S)-2-3-(((6-((1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)acetic acid.



[0492] Step 1: (S)-N-(1-(3-(tert-butyl)phenyl)ethyl)-3-(3-hydroxybenzyl)-1,2-dimethyl-1H-indole-6-carboxamide. The title compound was prepared following the same general protocol as described in Step 1, Compound 42, using the 3-hydroxybenzaldehyde instead of the 2-chloro-3-hydroxybenzaldehyde and the (S)-N-(1-(3-(tert-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide. A yellow solid was obtained (210 mg, yield 85%). ESI-MS (m/z): 454.15 [M]⁺.

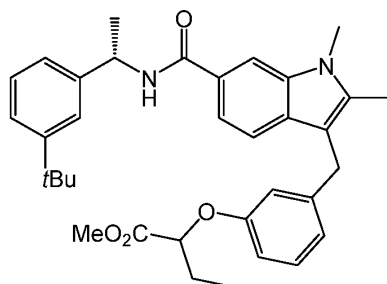


[0493] Step 2: methyl (S)-2-3-(((6-((1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)acetate. The title compound was prepared following the same general protocol as described in Step 2, Compound 42, using the (S)-N-(1-(3-(tert-butyl)phenyl)ethyl)-3-(3-hydroxybenzyl)-1,2-dimethyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-3-(2-chloro-3-hydroxybenzyl)-1,2-dimethyl-1H-indole-6-carboxamide and the methyl 2-bromoacetate instead of the (R)-2-bromopropanoate. A yellow solid was obtained (35mg, yield 81%).

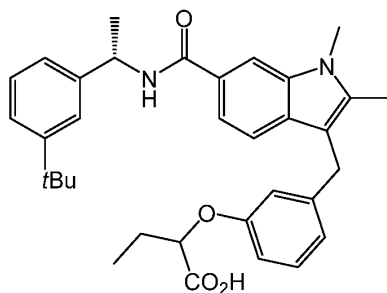


[0494] Step 3: (S)-2-(3-((6-((1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)acetic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the methyl (S)-2-(3-((6-((1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)acetate instead of the (ethyl 2-(4-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)propanoate. A white solid was obtained (20 mg, yield 58%). ¹H NMR (400 MHz, CDCl₃) δ 7.83 (d, J = 1.5 Hz, 1H), 7.39 (d, J = 2.1 Hz, 1H), 7.35 – 7.24 (m, 4H), 7.22 – 7.18 (m, 1H), 7.13 (t, J = 7.8 Hz, 1H), 6.84 (dd, J = 7.6, 1.5 Hz, 1H), 6.72 – 6.56 (m, 2H), 6.41 (d, J = 8.0 Hz, 1H), 5.34 (p, J = 7.0 Hz, 1H), 4.50 (s, 2H), 4.02 (s, 2H), 3.66 (s, 3H), 2.34 (s, 3H), 1.60 (d, J = 6.8 Hz, 3H), 1.29 (s, 9H).

[0495] Compound 60: 2-(3-((6-(((S)-1-(3-(tert-butyl)phenyl)ethyl) carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl) phenoxy)butanoic acid.

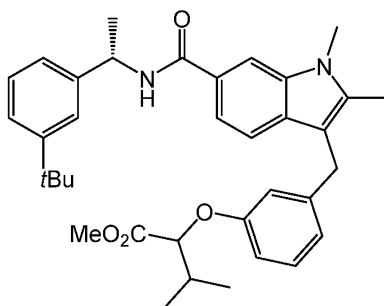


[0496] Step 1: methyl 2-(3-((6-(((S)-1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl) phenoxy)butanoate. The title compound was prepared following the same general protocol as described in Step 2, Compound 42, using the (S)-N-(1-(3-(tert-butyl)phenyl)ethyl)-3-(3-hydroxybenzyl)-1,2-dimethyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-3-(2-chloro-3-hydroxybenzyl)-1,2-dimethyl-1H-indole-6-carboxamide and the methyl 2-bromobutanoate instead of the (R)-2-bromopropanoate. A brown solid was obtained (29mg, yield 73%).

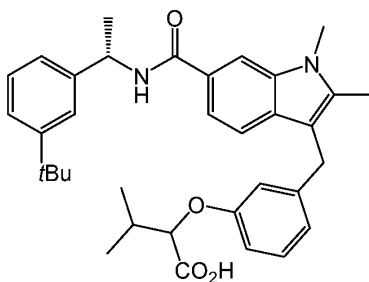


[0497] Step 2: 2-(3-((6-(((S)-1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)butanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the methyl 2-(3-((6-(((S)-1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)butanoate instead of the (ethyl 2-(4-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)propanoate. A brown solid was obtained (19 mg, yield 67%). ¹H NMR (400 MHz, CDCl₃) δ 7.82 (d, J = 1.5 Hz, 1H), 7.39 (d, J = 1.9 Hz, 1H), 7.35 – 7.24 (m, 4H), 7.19 (dt, J = 6.7, 2.0 Hz, 1H), 7.10 – 6.99 (m, 1H), 6.87 – 6.73 (m, 1H), 6.70 – 6.57 (m, 2H), 6.44 (t, J = 7.6 Hz, 1H), 5.34 (p, J = 7.1 Hz, 1H), 4.43 (dd, J = 6.7, 5.5 Hz, 1H), 3.98 (d, J = 2.7 Hz, 2H), 3.57 (d, J = 1.8 Hz, 3H), 2.27 (d, J = 1.7 Hz, 3H), 1.97 – 1.79 (m, 2H), 1.59 (dd, J = 6.9, 1.3 Hz, 3H), 1.29 (d, J = 1.8 Hz, 9H), 1.00 (td, J = 7.4, 1.2 Hz, 3H).

[0498] Compound 61: 2-(3-((6-(((S)-1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-3-methylbutanoic acid.



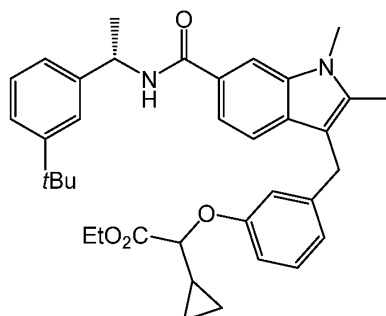
[0499] Step 1: methyl 2-(3-((6-(((S)-1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-3-methylbutanoate. The title compound was prepared following the same general protocol as described in Step 2, Compound 42, using the (S)-N-(1-(3-(tert-butyl)phenyl)ethyl)-3-(3-hydroxybenzyl)-1,2-dimethyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-3-(2-chloro-3-hydroxybenzyl)-1,2-dimethyl-1H-indole-6-carboxamide and the methyl 2-bromo-3-methylbutanoate instead of the (R)-2-bromopropanoate. A yellow solid was obtained (21 mg, yield 82%).



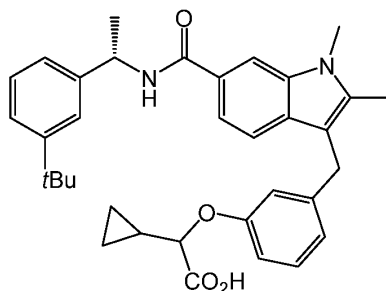
[0500] Step 2: 2-(3-((6-(((S)-1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-3-methylbutanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the methyl 2-(3-((6-(((S)-1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-3-methylbutanoate instead

of the ethyl 2-(4-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)propanoate. A brown solid was obtained (15 mg, yield 53%). ¹H NMR (400 MHz, CDCl₃) δ 7.84 (d, J = 1.5 Hz, 1H), 7.39 (s, 1H), 7.36 – 7.22 (m, 4H), 7.19 (s, 1H), 7.06 (td, J = 7.8, 2.2 Hz, 1H), 6.77 (d, J = 7.6 Hz, 1H), 6.72 – 6.54 (m, 2H), 6.51 – 6.31 (m, 1H), 5.35 (t, J = 7.2 Hz, 1H), 4.29 (d, J = 5.1 Hz, 1H), 3.99 (s, 2H), 3.59 (d, J = 1.2 Hz, 2H), 2.29 (d, J = 1.0 Hz, 2H), 2.21 (dt, J = 12.7, 6.5 Hz, 1H), 1.59 (d, J = 6.9 Hz, 3H), 1.29 (d, J = 1.3 Hz, 9H), 1.07 – 0.98 (m, 6H).

[0501] Compound 62: 2-(3-((6-(((S)-1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-2-cyclopropyl- acetic acid.



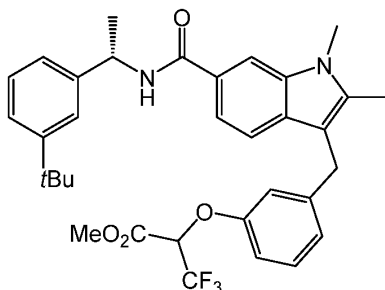
[0502] Step 1: ethyl 2-(3-((6-(((S)-1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-2-cyclopropylacetate. The title compound was prepared following the same general protocol as described in Step 2, Compound 42, using the (S)-N-(1-(3-(tert-butyl)phenyl)ethyl)-3-(3-hydroxybenzyl)-1,2-dimethyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-3-(2-chloro-3-hydroxybenzyl)-1,2-dimethyl-1H-indole-6-carboxamide and the ethyl 2-bromo-2-cyclopropylacetate instead of the (R)-2-bromopropanoate. A yellow solid was obtained (25mg, yield 90%).



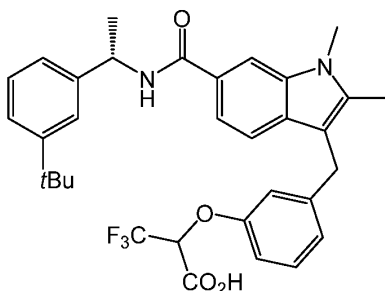
[0503] Step 2: 2-(3-((6-(((S)-1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-2-cyclopropyl- acetic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the ethyl 2-(3-((6-(((S)-1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-2-cyclopropylacetate instead of the ethyl 2-(4-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)propanoate. A light-yellow solid was obtained (19 mg, yield 79%). ¹H NMR (400 MHz, CDCl₃) δ 7.79 (d, J = 1.6 Hz, 1H), 7.34 (d, J = 2.2 Hz, 1H), 7.28 – 7.17 (m, 4H), 7.14 (dt, J = 6.9, 1.9 Hz, 1H), 6.98 (td, J = 7.9, 4.9 Hz, 1H), 6.71 (dd, J = 7.8, 3.9 Hz, 1H), 6.65 – 6.45 (m, 2H), 5.29 (t, J =

6.9 Hz, 1H), 3.91 (d, J = 2.2 Hz, 1H), 3.48 (d, J = 1.1 Hz, 2H), 2.20 (d, J = 1.4 Hz, 3H), 1.53 (dd, J = 6.8, 2.0 Hz, 3H), 1.24 (s, 9H), 0.73 – 0.48 (m, 4H), 0.42 (dddd, J = 7.9, 6.2, 4.4, 2.1 Hz, 1H).

[0504] Compound 63: 2-(3-((6-(((S)-1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl) phenoxy)-3,3,3-trifluoropropanoic acid.

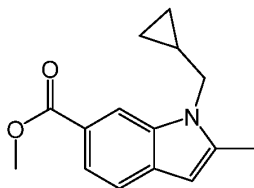


[0505] Step 1: methyl 2-(3-((6-(((S)-1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl) phenoxy)-3,3,3-trifluoropropanoate. The title compound was prepared following the same general protocol as described in Step 2, Compound 42, using the (S)-N-(1-(3-(tert-butyl)phenyl)ethyl)-3-(3-hydroxybenzyl)-1,2-dimethyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-3-(2-chloro-3-hydroxybenzyl)-1,2-dimethyl-1H-indole-6-carboxamide and the methyl 2-bromo-3,3,3-trifluoropropanoate instead of the (R)-2-bromopropanoate. A brown solid was obtained (29mg, yield 89%).

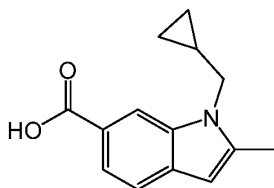


[0506] Step 2: 2-(3-((6-(((S)-1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl) phenoxy)-3,3,3-trifluoropropanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the methyl 2-(3-((6-(((S)-1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl) phenoxy)-3,3,3-trifluoropropanoate instead of the (ethyl 2-(4-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)propanoate. A light-yellow solid was obtained (22 mg, yield 78%). ¹H NMR (600 MHz, CDCl₃) δ 7.70 (s, 1H), 7.36 (d, J = 4.8 Hz, 1H), 7.31 – 7.22 (m, 3H), 7.16 (d, J = 5.8 Hz, 2H), 7.03 (t, J = 8.0 Hz, 1H), 6.72 (d, J = 7.8 Hz, 1H), 6.61 – 6.52 (m, 2H), 6.35 (d, J = 8.2 Hz, 1H), 5.31 (q, J = 7.4 Hz, 1H), 4.04 (dd, J = 13.7, 6.6 Hz, 1H), 3.93 (s, 2H), 3.35 (s, 3H), 2.24 (s, 3H), 1.56 (d, J = 7.0 Hz, 3H), 1.26 (s, 9H).

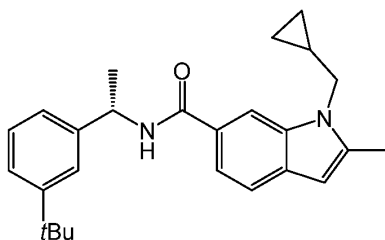
[0507] Compound 64: (S)-2-(3-((6-(((1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-1-(cyclopropylmethyl)-2-methyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoic acid.



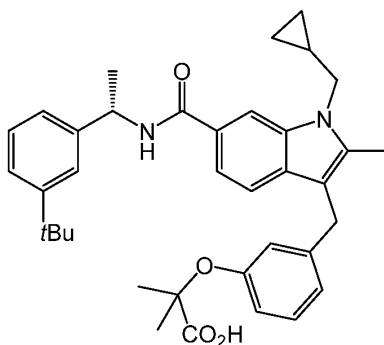
[0508] Step 1: methyl 1-(cyclopropylmethyl)-2-methyl-1H-indole-6-carboxylate. The title compound was prepared following the same general protocol as described in Step 4, Compound 1, using the (iodomethyl)cyclopropane instead of the methyl iodide. A yellow solid was obtained (220 mg, yield 94%). ESI-MS (m/z): 245.62 [M]⁺.



[0509] Step 2: 1-(cyclopropylmethyl)-2-methyl-1H-indole-6-carboxylic acid. The title compound was prepared following the same general protocol as described in Step 5, Compound 1, using the methyl 1-(cyclopropylmethyl)-2-methyl-1H-indole-6-carboxylate instead of the methyl 1,2-dimethyl-1H-indole-6-carboxylate. A brown solid was obtained (190 mg, yield 86%). ¹H NMR (400 MHz, CDCl₃) δ 7.95 (s, 1H), 7.65 (dd, J = 8.2, 1.3 Hz, 1H), 7.35 (d, J = 8.2 Hz, 1H), 6.13 (s, 1H), 5.10 (br, 1H), 3.88 (d, J = 6.4 Hz, 2H), 2.29 (s, 3H), 1.05 (m, 1H), 0.40 (m, 2H), 0.21 (m, 2H). ESI-MS (m/z): 229.56 [M]⁺.

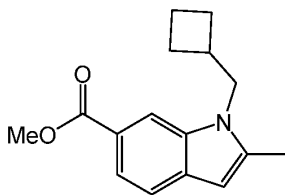


[0510] Step 3: (S)-N-(1-(3-(tert-butyl)phenyl)ethyl)-1-(cyclopropylmethyl)-2-methyl-1H-indole-6-carboxamide. The title compound was prepared following the same general protocol as described in Step 8, Compound 1, using the (S)-1-(3-(tert-butyl)phenyl)ethanamine hydrochloride instead of the (S)-1-(4-(tert-butyl)phenyl)ethanamine hydrochloride and the 1-(cyclopropylmethyl)-2-methyl-1H-indole-6-carboxylic acid instead of the 1-methyl-2-methyl-1H-indole-6-carboxylic acid. A yellow solid was obtained (35 mg, yield 90%). ESI-MS (m/z): 388.74 [M]⁺.

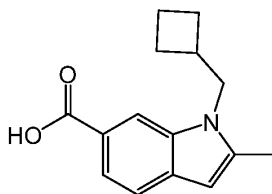


[0511] Step 4: (S)-2-(3-((6-((1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-1-(cyclopropylmethyl)-2-methyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoic acid. Methyl (S)-2-(3-((6-((1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-1-(cyclopropylmethyl)-2-methyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoate was prepared following the same general protocol as described in Step 9, Compound 1, using the (S)-N-(1-(3-(tert-butyl)phenyl)ethyl)-1-(cyclopropylmethyl)-2-methyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide and the methyl 2-(3-formylphenoxy)-2-methylpropanoate instead of the ethyl 2-(4-formylphenoxy)propanoate. The product was obtained as yellow solid (48 mg, yield 90%) and used for the next step without further purification. The final product was synthesized following the same general protocol as described in Step 10, Compound 1, using the (S)-2-(3-((6-((1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-1-(cyclopropylmethyl)-2-methyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoate instead of the (ethyl 2-(4-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)propanoate. The final product was obtained as brown solid (39 mg, yield 84%). ¹H NMR (400 MHz, CDCl₃) δ 7.87 (d, J = 1.5 Hz, 1H), 7.35 (s, 1H), 7.32 – 7.20 (m, 4H), 7.03 (dd, J = 8.8, 7.6 Hz, 1H), 6.82 (d, J = 7.6 Hz, 1H), 6.63 (dd, J = 5.1, 1.5 Hz, 1H), 6.34 (d, J = 7.7 Hz, 1H), 5.31 (q, J = 7.1 Hz, 1H), 3.95 (d, J = 4.0 Hz, 4H), 2.30 (s, 3H), 1.55 (d, J = 6.8 Hz, 3H), 1.43 (s, 6H), 1.25 (d, J = 0.8 Hz, 9H), 1.17 – 1.02 (m, 1H), 0.50 – 0.41 (m, 2H), 0.37 – 0.16 (m, 2H).

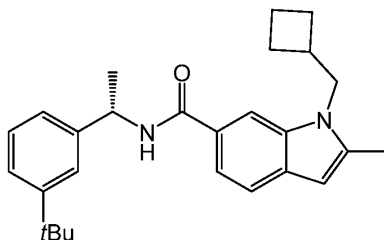
[0512] Compound 65: (S)-2-(3-((6-((1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-1-(cyclobutylmethyl)-2-methyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoic acid.



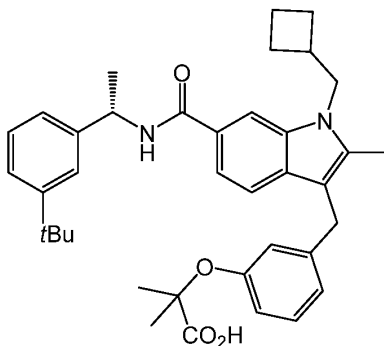
[0513] Step 1: methyl 1-(cyclobutylmethyl)-2-methyl-1H-indole-6-carboxylate. The title compound was prepared following the same general protocol as described in Step 4, Compound 1, using the (bromomethyl)cyclobutane instead of the methyl iodide. A yellow solid was obtained (150 mg, yield 74%). ¹H NMR (600 MHz, CDCl₃) δ 7.96 (d, J = 0.9 Hz, 1H), 7.67 (dd, J = 8.2, 1.4 Hz, 1H), 7.41 (d, J = 8.2, 1H), 6.18 (s, 1H), 4.05 (d, J = 7.0 Hz, 2H), 3.85 (s, 3H), 2.74 (m, 1H), 2.37 (s, 3H), 1.95 (m, 2H), 1.75 (m, 4H). ESI-MS (m/z): 229.56 [M]⁺. ESI-MS (m/z): 257.67 [M]⁺.



[0514] Step 2: 1-(cyclobutylmethyl)-2-methyl-1H-indole-6-carboxylic acid. The title compound was prepared following the same general protocol as described in Step 5, Compound 1, using the methyl 1-(cyclobutylmethyl)-2-methyl-1H-indole-6-carboxylate instead of the methyl 1,2-dimethyl-1H-indole-6-carboxylate. A brown solid was obtained (63 mg, yield 91%). ESI-MS (m/z): 243.69 $[M]^+$.



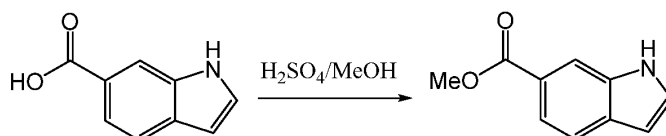
[0515] Step 3: (S)-N-(1-(3-(tert-butyl)phenyl)ethyl)-1-(cyclobutylmethyl)-2-methyl-1H-indole-6-carboxamide. The title compound was prepared following the same general protocol as described in Step 8, Compound 1, using the (S)-1-(3-(tert-butyl)phenyl)ethanamine hydrochloride instead of the (S)-1-(4-(tert-butyl)phenyl)ethanamine hydrochloride and the 1-(cyclobutylmethyl)-2-methyl-1H-indole-6-carboxylic acid instead of the 1-methyl-2-methyl-1H-indole-6-carboxylic acid. A yellow solid was obtained (34 mg, yield 32%). ESI-MS (m/z): 402. 68 $[M]^+$.



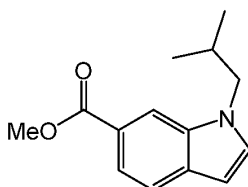
[0516] Step 4: (S)-2-(3-(((6-((1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-1-(cyclobutylmethyl)-2-methyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoic acid. Methyl (S)-2-(3-(((6-((1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-1-(cyclobutylmethyl)-2-methyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoate was prepared following the same general protocol as described in Step 9, Compound 1, using the (S)-N-(1-(3-(tert-butyl)phenyl)ethyl)-1-(cyclobutylmethyl)-2-methyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide and the methyl 2-(3-formylphenoxy)-2-methylpropanoate instead of the ethyl 2-(4-formylphenoxy)propanoate. The product was obtained as yellow solid (50 mg, yield 98%) and used for the next step without further purification. The final product was synthesized following the same general protocol as described in Step

10, Compound 1, using the (S)-2-(3-((6-((1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-1-(cyclobutylmethyl)-2-methyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoate instead of the (ethyl 2-(4-((6-((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)propanoate. The final product was obtained as yellow solid (41 mg, yield 85%). ¹H NMR (400 MHz, CDCl₃) δ 7.98 (s, 1H), 7.45 (s, 1H), 7.33 (q, J = 3.5 Hz, 3H), 7.32 – 7.17 (m, 2H), 7.07 (t, J = 7.7 Hz, 1H), 6.84 (d, J = 7.6 Hz, 1H), 6.70 (d, J = 8.7 Hz, 2H), 6.48 (d, J = 7.7 Hz, 1H), 5.40 (p, J = 7.0 Hz, 1H), 4.91 (br, 3H), 4.12 (d, J = 7.1 Hz, 2H), 4.01 (s, 2H), 2.95 – 2.64 (m, 1H), 2.36 (s, 3H), 2.05 – 1.95 (m, 2H), 1.83 (td, J = 12.6, 6.3 Hz, 4H), 1.64 (d, J = 6.9 Hz, 3H), 1.53 (s, 6H), 1.35 (d, J = 0.9 Hz, 9H).

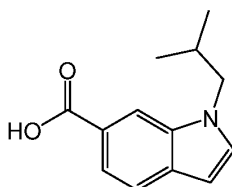
[0517] Compound 66: (S)-2-(3-((6-((1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-1-isobutyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoic acid.



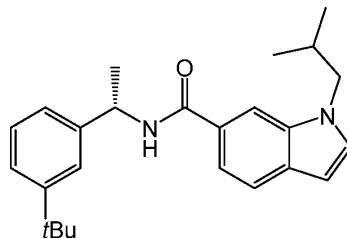
[0518] Step 1: methyl 1H-indole-6-carboxylate. A solution of 1H-indole-6-carboxylic acid (1 g, 6.21 mmol) in methanol (50 ml) was treated with 5 mL conc. sulfuric acid and refluxed for 4 h. After cooling, the solvent was removed under vacuum and the residue was diluted with 100 ml of cold saturated solution of sodium bicarbonate and extracted twice with ethyl acetate (100 mL × 2). The combined organic layer was washed with water and brine, dried over sodium sulfate and concentrated under vacuum to afford the title compound as white powder (1g, Yield 92%). The crude product was used for the next step without any further purification. ¹H NMR (400 MHz, CDCl₃) δ 8.92 (br, 1H), 8.22 (dd, J = 4.6, 0.8 Hz, 1H), 7.87 (dd, J = 8.3, 1.4 Hz, 1H), 7.70 (d, 8.3 Hz, 1H), 7.33 (dd, 3.0, 2.6 Hz, 1H), 6.62 (m, 1H), 3.05 (s, 3H), 2.65 (s, 3H).



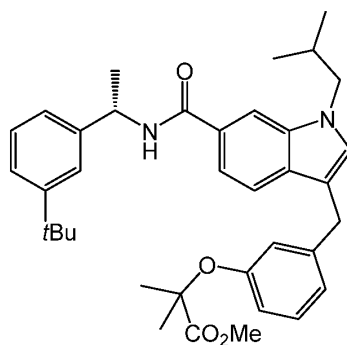
[0519] Step 2: methyl 1-isobutyl-1H-indole-6-carboxylate. The title compound was prepared following the same general protocol as described in Step 4, Compound 1, using the 1-bromo-2-methylpropane instead of the methyl iodide. A white solid was obtained (100 mg, yield 74%). ¹H NMR (400 MHz, CDCl₃) δ 7.99 (d, J = 0.6 Hz, 1H), 7.67 (d, J = 8.2 Hz, 1H), 7.52 (d, J = 8.2, 1H), 7.08 (d, J = 3Hz, 1H), 6.4 (dd, J = 3.0, 0.7 Hz, 1H), 3.82 (s, 3H), 3.80 (d, J = 7.3 Hz, 2H), 2.13 (m, 1H), 0.79 (d, J = 6.6 Hz, 6H).



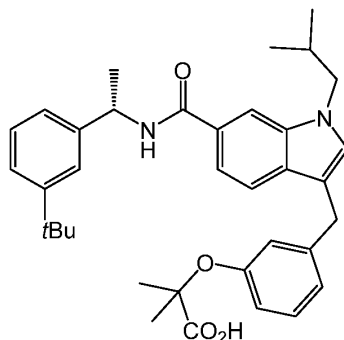
[0520] Step 3: 1-isobutyl-1H-indole-6-carboxylic acid. The title compound was prepared following the same general protocol as described in Step 5, Compound 1, using the methyl 1-isobutyl-1H-indole-6-carboxylate instead of the methyl 1,2-dimethyl-1H-indole-6-carboxylate. A brown solid was obtained (55 mg, yield 91%).



[0521] Step 4: (S)-N-(1-(3-(tert-butyl)phenyl)ethyl)-1-isobutyl-1H-indole-6-carboxamide. The title compound was prepared following the same general protocol as described in Step 8, Compound 1, using the (S)-1-(3-(tert-butyl)phenyl)ethanamine hydrochloride instead of the (S)-1-(4-(tert-butyl)phenyl)ethanamine hydrochloride and the 1-isobutyl-1H-indole-6-carboxylic acid instead of the 1-methyl-2-methyl-1H-indole-6-carboxylic acid. A white solid was obtained (68 mg, yield 71%). ¹H NMR (400 MHz, CDCl₃) δ 7.86 (s, 1H), 7.46 (d, J = 8.2 Hz, 1H), 7.30 (s, 1H), 7.24 (d, J = 1.4 Hz, 1H), 7.17 (m, 3H), 7.03 (d, J = 3.1 Hz, 3H), 6.39 (d, J = 7.6 Hz, 1H), 6.35 (d, J = 3.0 Hz, 1H), 5.28 (q, J = 6.9 Hz, 1H), 3.79 (d, J = 7.44 Hz, 2H), 2.09 (m, 1H), 1.49 (d, J = 6.8 Hz, 3H), 1.18 (s, 9H), 0.75 (d, J = 6.6 Hz, 6H).

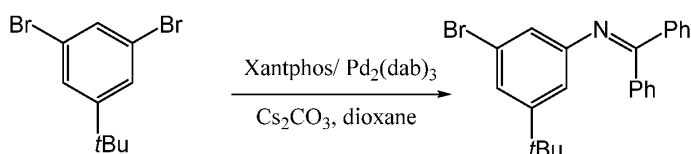


[0522] Step 5: methyl (S)-2-(3-(((6-((1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-1-isobutyl-1H-indol-3-yl)methyl) phenoxy)-2-methylpropanoate. The title compound was prepared following the same general protocol as described in Step 9, Compound 1, using the (S)-N-(1-(3-(tert-butyl)phenyl)ethyl)-1-isobutyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide and the methyl 2-(3-formylphenoxy)-2-methylpropanoate instead of the ethyl 2-(4-formylphenoxy)propanoate. A yellow solid was obtained (80 mg, yield 80%). ¹H NMR (400 MHz, CDCl₃) δ 8.11 – 7.94 (m, 1H), 7.94 – 7.77 (m, 1H), 7.54 (dd, J = 8.4, 1.5 Hz, 1H), 7.30 – 7.15 (m, 4H), 7.06 (t, J = 7.9 Hz, 1H), 6.93 – 6.74 (m, 2H), 6.64 (t, J = 2.0 Hz, 1H), 6.56 (ddd, J = 8.3, 2.6, 1.0 Hz, 1H), 6.35 (d, J = 7.8 Hz, 1H), 5.30 (td, J = 7.2, 2.3 Hz, 1H), 3.98 (s, 2H), 3.82 (d, J = 7.5 Hz, 2H), 3.53 (s, 3H), 2.11 (dt, J = 13.7, 7.1 Hz, 1H), 1.46 (s, 6H), 1.25 (s, 9H), 0.82 (d, J = 6.7 Hz, 6H).

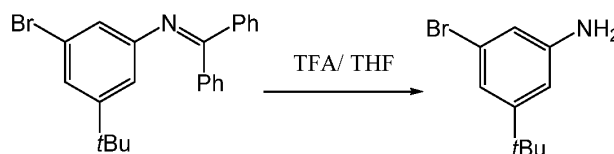


[0523] Step 6: (S)-2-(3-((6-((1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-1-isobutyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the methyl (S)-2-(3-((6-((1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-1-isobutyl-1H-indol-3-yl)methyl) phenoxy)-2-methylpropanoate instead of the (ethyl 2-(4-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)propanoate. A yellow solid was obtained (59 mg, yield 75%). ¹H NMR (400 MHz, CDCl₃) δ 7.87 (d, J = 1.5 Hz, 1H), 7.43 – 7.30 (m, 2H), 7.29 – 7.19 (m, 3H), 7.15 (dt, J = 6.6, 2.1 Hz, 1H), 7.07 (t, J = 7.9 Hz, 1H), 6.88 (dt, J = 7.9, 1.1 Hz, 1H), 6.85 (s, 1H), 6.73 (t, J = 2.0 Hz, 1H), 6.68 (ddd, J = 8.1, 2.6, 1.0 Hz, 1H), 5.30 (t, J = 7.1 Hz, 1H), 3.97 (s, 2H), 3.81 (d, J = 7.4 Hz, 2H), 2.10 (p, J = 6.8 Hz, 1H), 1.55 (d, J = 6.9 Hz, 3H), 1.45 (s, 6H), 1.25 (s, 9H), 0.81 (d, J = 6.7 Hz, 6H).

[0524] Compound 67: (S)-2-(3-((6-((1-(3-(tert-butyl)-5-fluorophenyl)ethyl)carbamoyl)-1-isobutyl-1H-indol-3-yl)methyl) phenoxy)-2-methylpropanoic acid.

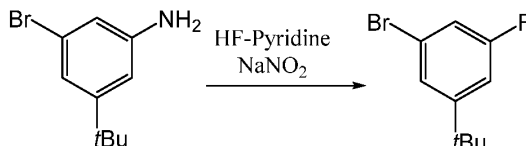


[0525] Step 1: N-(3-bromo-5-(tert-butyl)phenyl)-1,1-diphenylmethanimine. In a Schlenk flask under an argon atmosphere, 1,3-dibromo-5-(tert-butyl)benzene (1 g, 3.42 mmol), benzophenone (0.68 g, 3.76 mmol), Cs₂CO₃ (2.22 g, 6.84 mmol), Pd₂(dba)₃ (0.2 g, 0.228 mmol) and Xantphos (0.4 g, 0.684 mmol) were dissolved in dry dioxane (10 mL). The reaction mixture was stirred at 140°C overnight. The reaction was diluted with water (50 mL) and extracted with ethyl acetate (100 mL). The organic layer was washed with brine, dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography over silica gel (hexane/EtOAc, 20:1 (v/v)) to afford the desired product as yellow oil (1.2 g, yield 89%). ESI-MS (m/z): 391.72 [M]⁺.

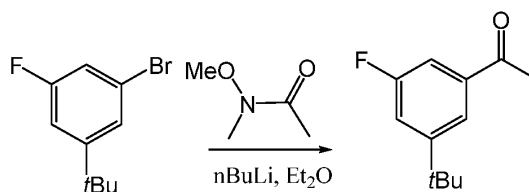


[0526] Step 2: 3-bromo-5-(tert-butyl)aniline. To a solution of N-(3-bromo-5-(tert-butyl)phenyl)-1,1-diphenylmethanimine (1.2g, 3 mmol) in tetrahydrofuran (20 mL) was added trifluoroacetic acid (3 mL).

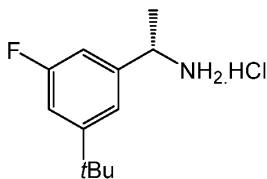
The mixture was stirred for 2 hours at rt. After the reaction was complete, saturated sodium carbonate solution was added to adjust the mixture to pH 9. The mixture was extracted with ethyl acetate (2x 50 mL). The combined organics were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to give 3-bromo-5-(tert-butyl)-1-fluorobenzene. Yellow oil was obtained (0.7 g, yield >99%). ¹H NMR (400 MHz, DMSO) δ 7.37 (t, J = 1.7 Hz, 1H), 7.20 (d, J = 1.7 Hz, 2H), 2.51 (s, 2H), 1.24 (s, 9H). ESI-MS (m/z): 227.85 [M]⁺.



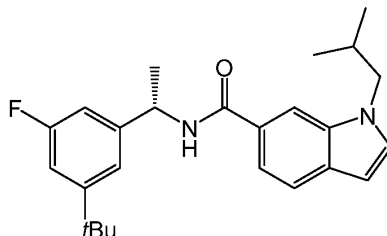
[0527] Step 3: 1-bromo-3-(tert-butyl)-5-fluorobenzene. 3-Bromo-5-(tert-butyl)aniline (0.7 g, 3 mmol) was dissolved in hydrogen fluoride-pyridine (2.6 mL) at 0°C, stirred for 20 min and then NaNO₂ (0.26 g, 3.7 mmol) was added in five batches. The reaction mixture was stirred for 20 min at 0 °C, then heated to 70°C until completion. H₂O and CH₂Cl₂ were added and organic phase was evaporated to dryness under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc, 10:1 (v/v)) to yield the desired product as a transparent oil (0.22 g, yield 31%).



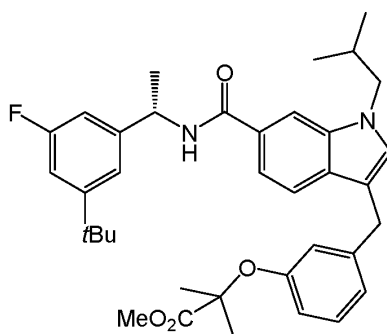
[0528] Step 4: 1-(3-(tert-butyl)-5-fluorophenyl)ethanone. 1-Bromo-3-(tert-butyl)-5-fluorobenzene (220mg, 0.95 mmol) was dissolved in ether (50ml) under nitrogen. The reaction mixture was cooled to -78°C and stirred under nitrogen atmosphere then n-BuLi (2.5 M, 0.4 ml, 0.95 mmol) was added dropwise to the above solution. The reaction mixture was stirred at -78°C for 30 min. After complete addition of n-BuLi, N-methoxy-N-methylacetamide (117 μ L, 1.14 mmol) dropped to the above reaction mixture, while keeping the reaction mixture was below -78°C. After addition, the reaction mixture was warmed slowly to RT for 30 minutes. The reaction mixture was poured into water (100 ml) and the mixture was stirred for 15 minutes. The organic phase was separated and the aqueous phase was extracted with ethyl acetate (100 ml). The combined organic phase was dried over anhydrous sodium sulfate, filtrated, evaporated in vacuum to give the residue and purified by column chromatography on silica gel (hexane/EtOAc, 10:1 (v/v)). The product was isolated as transparent oil (48 mg, yield 21%). ¹H NMR (400 MHz, CDCl₃) δ 7.70 (t, J = 1.6 Hz, 1H), 7.34 (ddd, J = 8.8, 2.4, 1.4 Hz, 1H), 7.20 (ddd, J = 10.3, 2.5, 1.7 Hz, 1H), 2.50 (s, 3H), 1.26 (s, 9H). ESI-MS (m/z): 194.21 [M]⁺.



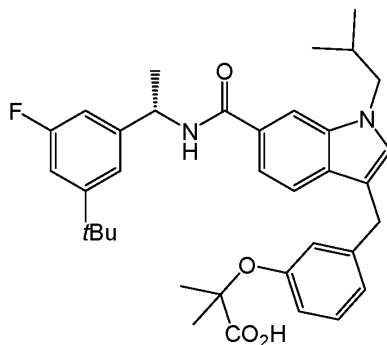
[0529] Step 5: (S)-1-(3-(tert-butyl)-5-fluorophenyl)ethanamine hydrochloride. The title compound was prepared following the same general protocol as described in Step 6, Compound 1, using the 1-(3-(tert-butyl)-5-fluorophenyl)ethanone instead of the 1-(4-*tert*-butylphenyl)ethenone. A brown solid was obtained (50 mg, yield 87%).



[0530] Step 6: (S)-N-(1-(3-(tert-butyl)-5-fluorophenyl)ethyl)-1-isobutyl-1H-indole-6-carboxamide. The title compound was prepared following the same general protocol as described in Step 8, Compound 1, using the (S)-1-(3-(tert-butyl)-5-fluorophenyl)ethanamine hydrochloride instead of the (S)-1-(4-(tert-butyl)phenyl)ethanamine hydrochloride and the 1-isobutyl-1H-indole-6-carboxylic acid instead of the 1-methyl-2-methyl-1H-indole-6-carboxylic acid. A white solid was obtained (27 mg, yield 72%). ESI-MS (*m/z*): 394.94 [*M*]⁺.

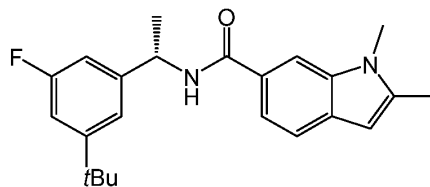


[0531] Step 7: methyl (S)-2-(3-(((1-(3-(tert-butyl)-5-fluorophenyl)ethyl)carbamoyl)-1-isobutyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoate. The title compound was prepared following the same general protocol as described in Step 9, Compound 1, using the (S)-N-(1-(3-(tert-butyl)-5-fluorophenyl)ethyl)-1-isobutyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide and the methyl 2-(3-formylphenoxy)-2-methylpropanoate instead of the ethyl 2-(4-formylphenoxy)propanoate. A yellow solid was obtained (42 mg, yield 97%). ESI-MS (*m/z*): 600.25 [*M*]⁺.

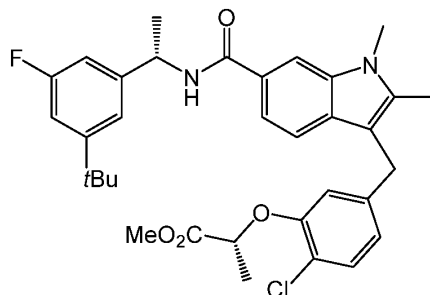


[0532] Step 8: (*S*)-2-(3-((6-((1-(3-(tert-butyl)-5-fluorophenyl)ethyl)carbamoyl)-1-isobutyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the methyl (*S*)-2-(3-((6-((1-(3-(tert-butyl)-5-fluorophenyl)ethyl)carbamoyl)-1-isobutyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoate instead of the (ethyl 2-(4-((6-(((*S*)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)propanoate. A yellow solid was obtained (29 mg, yield 70%). ¹H NMR (400 MHz, CDCl₃) δ 7.88 (d, *J* = 1.4 Hz, 1H), 7.43 – 7.25 (m, 1H), 7.21 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.11 (d, *J* = 1.6 Hz, 1H), 7.06 (t, *J* = 7.8 Hz, 1H), 6.96 – 6.78 (m, 4H), 6.73 (t, *J* = 2.0 Hz, 1H), 6.70 – 6.61 (m, 1H), 6.37 (d, *J* = 7.8 Hz, 1H), 5.27 (p, *J* = 7.1 Hz, 1H), 4.46 (br, 1H), 3.96 (s, 2H), 3.80 (d, *J* = 7.4 Hz, 2H), 2.08 (dq, *J* = 13.9, 6.9 Hz, 1H), 1.51 (d, *J* = 6.9 Hz, 3H), 1.45 (s, 6H), 1.22 (s, 9H), 0.80 (d, *J* = 6.6 Hz, 6H). ESI-MS (*m/z*): 586.89[M]⁺.

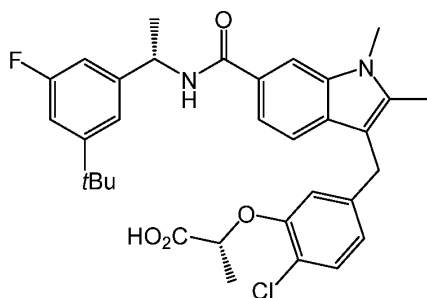
[0533] Compound 68: (*R*)-2-(5-((6-(((*S*)-1-(3-(tert-butyl)-5-fluorophenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)-2-chlorophenoxy)propanoic acid.



[0534] Step 1: (*S*)-N-(1-(3-(tert-butyl)-5-fluorophenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide. The title compound was prepared following the same general protocol as described in Step 8, Compound 1, using the (*S*)-1-(3-(tert-butyl)-5-fluorophenyl)ethanamine hydrochloride instead of the (*S*)-1-(4-(tert-butyl)phenyl)ethanamine hydrochloride. A white solid was obtained (40 mg, yield 70%).

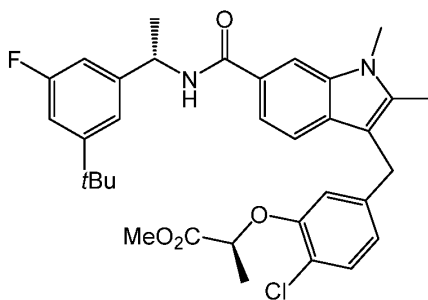


[0535] Step 2: methyl (R)-2-(5-(((6-(((S)-1-(3-(tert-butyl)-5-fluorophenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)-2-chlorophenoxy)propanoate. The title compound was prepared following the same general protocol as described in Step 9, Compound 1, using the (S)-N-(1-(3-(tert-butyl)-5-fluorophenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide and the methyl (R)-2-(2-chloro-5-formylphenoxy)propanoate instead of the ethyl 2-(4-formylphenoxy)propanoate. A yellow solid was obtained (40 mg, yield 85%).



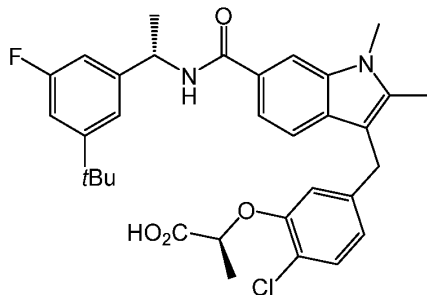
[0536] Step 3: (R)-2-(5-(((6-(((S)-1-(3-(tert-butyl)-5-fluorophenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)-2-chlorophenoxy)propanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the methyl (R)-2-(5-(((6-(((S)-1-(3-(tert-butyl)-5-fluorophenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)-2-chlorophenoxy)propanoate instead of the (ethyl 2-(4-(((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)propanoate. A brown solid was obtained (15 mg, yield 53%). ¹H NMR (400 MHz, CDCl₃) δ 7.75 (s, 1H), 7.29 – 7.20 (m, 2H), 7.19 – 7.06 (m, 2H), 6.91 (dq, J = 11.3, 1.6 Hz, 1H), 6.83 (dt, J = 9.4, 2.0 Hz, 1H), 6.72 (dd, J = 8.2, 1.9 Hz, 1H), 6.57 (dd, J = 3.4, 1.9 Hz, 1H), 6.39 (dd, J = 7.7, 4.3 Hz, 1H), 5.38 – 5.20 (m, 1H), 4.68 – 4.44 (m, 1H), 3.92 (s, 2H), 3.66 – 3.42 (m, 3H), 2.27 (s, 3H), 1.52 (d, J = 7.1 Hz, 6H), 1.23 (s, 9H). ¹⁹F NMR (376 MHz, CDCl₃) δ -113.23 (t, ³J_{HF} = 10.1 Hz). ESI-MS (m/z): 578.91 [M]⁺.

[0537] Compound 69: (S)-2-(5-(((6-(((S)-1-(3-(tert-butyl)-5-fluorophenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)-2-chlorophenoxy)propanoic acid.



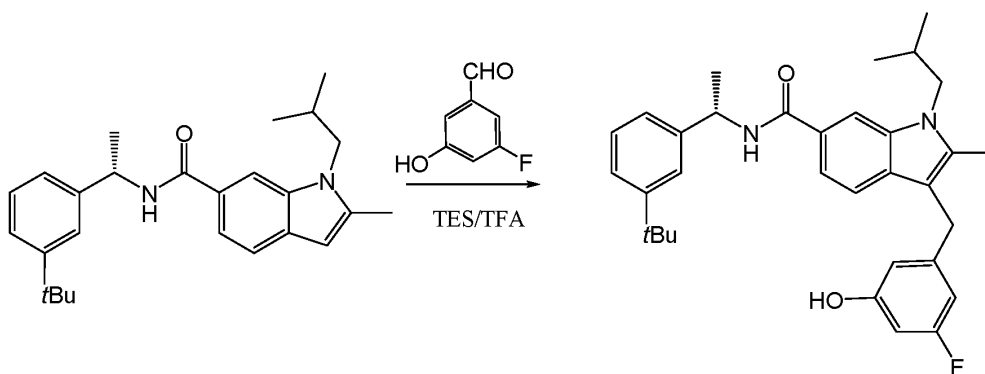
[0538] Step 1: methyl (S)-2-(5-(((6-(((S)-1-(3-(tert-butyl)-5-fluorophenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)-2-chlorophenoxy)propanoate. The title compound was prepared following the same general protocol as described in Step 9, Compound 1, using the (S)-N-(1-(3-(tert-butyl)-5-

fluorophenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide and the methyl (S)-2-(2-chloro-5-formylphenoxy)propanoate instead of the ethyl 2-(4-formylphenoxy)propanoate. A brown solid was obtained (23 mg, yield 79%).

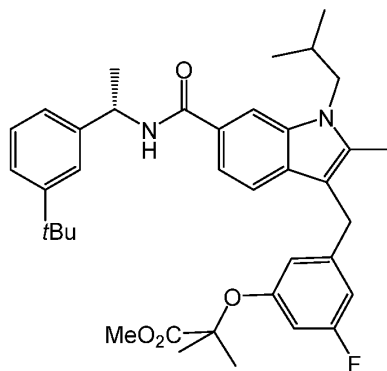


[0539] Step 2: (S)-2-(5-(((S)-1-(3-(tert-butyl)-5-fluorophenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)-2-chloro phenoxy)propanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the methyl (S)-2-(5-(((S)-1-(3-(tert-butyl)-5-fluorophenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)-2-chlorophenoxy)propanoate instead of the (ethyl 2-(4-(((S)-1-(4-(tert-butyl) phenyl) ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)propanoate. A brown solid was obtained (10 mg, yield 68 %). ¹H NMR (400 MHz, CDCl₃) δ 7.77 (s, 1H), 7.22 (d, J = 4.3 Hz, 2H), 7.17 – 7.09 (m, 2H), 6.90 (s, 1H), 6.83 (d, J = 9.4 Hz, 1H), 6.72 (d, J = 8.1 Hz, 1H), 6.58 (t, J = 2.7 Hz, 1H), 6.38 (s, 1H), 5.26 (d, J = 7.9 Hz, 1H), 4.62 – 4.48 (m, 1H), 4.04 – 3.89 (m, 2H), 3.60 (d, J = 1.8 Hz, 3H), 2.27 (d, J = 1.2 Hz, 3H), 1.53 (d, J = 7.1 Hz, 6H), 1.23 (d, J = 0.9 Hz, 9H). ¹⁹F NMR (376 MHz, CDCl₃) δ -113.24 (t, ³J_{HF} = 10.1 Hz). ESI-MS (m/z): 578.82 [M]⁺.

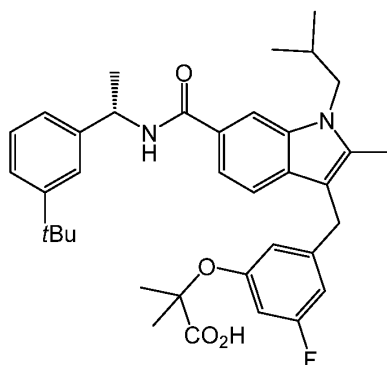
[0540] Compound 70: (S)-2-(3-(((1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-1-isobutyl-2-methyl-1H-indol-3-yl)methyl)-5-fluorophenoxy)-2-methylpropanoic acid.



[0541] Step 1: (S)-N-(1-(3-(tert-butyl)phenyl)ethyl)-3-(3-fluoro-5-hydroxybenzyl)-1-isobutyl-2-methyl-1H-indole-6-carboxamide. The title compound was prepared following the same general protocol as described in Step 9, Compound 1, using the 3-fluoro-5-hydroxybenzaldehyde instead of the ethyl 2-(4-formylphenoxy)propanoate. A light-yellow solid was obtained (40 mg, yield 83%). ESI-MS (m/z): 514.84 [M]⁺.

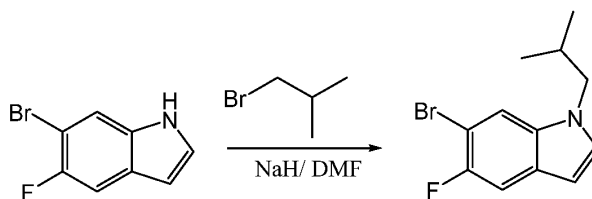


[0542] Step 2: methyl (S)-2-(3-(((6-((1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-1-isobutyl-2-methyl-1H-indol-3-yl)methyl)-5-fluorophenoxy)-2-methylpropanoate. The title compound was prepared following the same general protocol as described in Step 2, Compound 42, using the methyl 2-bromo-2-methylpropanoate instead of the (R)-2-bromopropanoate and the (S)-N-(1-(3-(tert-butyl)phenyl)ethyl)-3-(3-fluoro-5-hydroxybenzyl)-1-isobutyl-2-methyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-3-(2-chloro-3-hydroxybenzyl)-1,2-dimethyl-1H-indole-6-carboxamide. A yellow solid was obtained (38 mg, yield 80%).

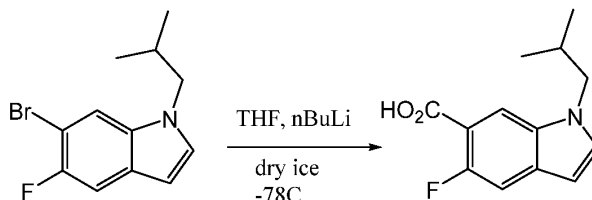


[0543] Step 3: (S)-2-(3-(((6-((1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-1-isobutyl-2-methyl-1H-indol-3-yl)methyl)-5-fluorophenoxy)-2-methylpropanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the methyl (S)-2-(3-(((6-((1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-1-isobutyl-2-methyl-1H-indol-3-yl)methyl)-5-fluorophenoxy)-2-methylpropanoate instead of the (ethyl 2-(4-(((6-((1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)propanoate. A brown solid was obtained (20 mg, yield 54 %). ¹H NMR (400 MHz, CDCl₃) δ 7.84 (s, 1H), 7.35 (d, J = 2.1 Hz, 1H), 7.26 – 7.19 (m, 3H), 7.16 (ddt, J = 6.8, 4.3, 1.9 Hz, 1H), 6.43 (dd, J = 9.4, 2.0 Hz, 1H), 6.41 – 6.29 (m, 3H), 5.30 (p, J = 7.1 Hz, 1H), 3.88 (s, 2H), 3.83 (d, J = 7.7 Hz, 2H), 2.26 (s, 3H), 2.14 (p, J = 7.1 Hz, 1H), 1.55 (d, J = 6.7 Hz, 3H), 1.45 (s, 6H), 1.25 (s, 9H), 0.82 (d, J = 6.7 Hz, 6H).

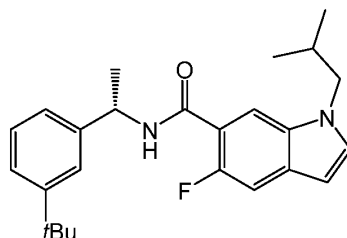
[0544] Compound 71: (S)-2-(3-(((6-((1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-5-fluoro-1-isobutyl-1H-indol-3-yl)methyl)phenoxy)-2-methyl propanoic acid.



[0545] Step 1: 6-bromo-5-fluoro-1-isobutyl-1H-indole. To a stirred solution of 6-bromo-5-fluoro-1H-indole (0.3 g, 1.4 mmol) in dry DMF (10 mL) was added NaH (60% dispersion in oil, 0.112 g, 2.8 mmol) in portions. The mixture was stirred for 30 min, then iodomethane (251 μ L, 2.8 mmol) was added in one portion. The reaction became exothermic and was cooled in an ice bath. After 16 hours at 90°C, the reaction mixture was cooled down, quenched with water (50 ml) and extracted with diethyl ether (50 ml $\times$ 2). The combined organic layers were dried over sodium sulfate and concentrated under vacuum. The residue was purified on silica gel (hexanes/EtOAc, 10:1 (v/v)) gave the title compound (0.35 g, yield 92%) as light-white solid. ESI-MS (m/z): 269.92 [M]⁺.

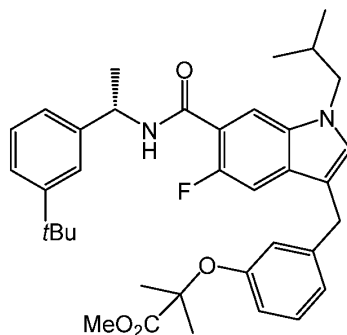


[0546] Step 2: 5-fluoro-1-isobutyl-1H-indole-6-carboxylic acid. 6-Bromo-5-fluoro-1-isobutyl-1H-indole (0.35 g, 1.3 mmol) was dissolved in dry THF (10 mL) and the reaction mixture was cooled to -78°C. Subsequently, n-BuLi (2.5M, 1 ml, 1.4 mmol) was added dropwise. After a further 20 minutes of stirring, a large excess of dry ice was added. The reaction was monitored by analytical-HPLC until the consumption of the starting material and then was quenched by water (10 mL) and HCl (1N) until a pH of 2 was reached. The aqueous layer was extracted with EtOAc (2 x 50 mL) and the organic layer was dried over sodium sulfate and concentrated under vacuum. The residue was purified by flash column chromatography and the product was isolated as white powder (0.2 g, yield 65%). ¹H NMR (600 MHz, CDCl₃) δ 11.24 (br, 1H), 7.97 (dd, J = 5.9, 0.9 Hz, 1H), 7.22 (d, J = 11.9 Hz, 1H), 7.18 (d, J = 3.1 Hz, 1H), 6.37 (dd, J = 3.0, 0.9 Hz, 1H), 3.84 (d, J = 7.5 Hz, 2H), 2.15 – 2.06 (m, 1H), 0.82 (d, J = 6.8 Hz, 6H). ESI-MS (m/z): 235.73 [M]⁺.

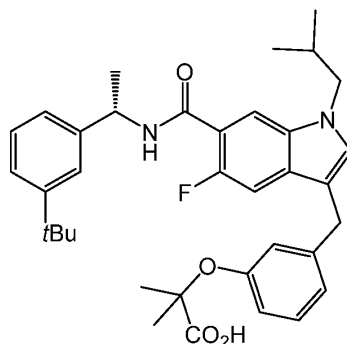


[0547] Step 3: (S)-N-(1-(3-(tert-butyl)phenyl)ethyl)-5-fluoro-1-isobutyl-1H-indole-6-carboxamide. The title compound was prepared following the same general protocol as described in Step 8, Compound 1, using the (S)-1-(3-(tert-butyl)-5-fluorophenyl)ethanamine hydrochloride instead of the (S)-1-(4-(tert-

butyl)phenyl)ethanamine hydrochloride and the 5-fluoro-1-isobutyl-1H-indole-6-carboxylic acid instead of the 1,2-dimethyl-1H-indole-6-carboxylic acid. A white solid was obtained (45 mg, yield 90%). ¹H NMR (400 MHz, CDCl₃) δ 8.08 (dd, J = 6.5, 0.9 Hz, 1H), 7.47 – 7.30 (m, 1H), 7.28 – 7.04 (m, 6H), 6.36 (dd, J = 3.1, 0.9 Hz, 1H), 5.31 (pd, J = 6.9, 2.7 Hz, 1H), 3.85 (d, J = 7.5 Hz, 2H), 2.13 (dp, J = 13.7, 6.8 Hz, 1H), 1.55 (d, J = 6.9 Hz, 3H), 1.25 (s, 9H), 0.81 (d, J = 6.7 Hz, 6H).

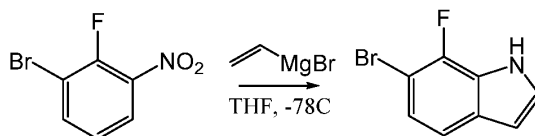


[0548] Step 5: methyl (S)-2-(3-((6-((1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-5-fluoro-1-isobutyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoate. The title compound was prepared following the same general protocol as described in Step 9, Compound 1, using the (S)-N-(1-(3-(tert-butyl)phenyl)ethyl)-5-fluoro-1-isobutyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide and the methyl 2-(3-formylphenoxy)-2-methylpropanoate instead of the ethyl 2-(4-formylphenoxy)propanoate. A brown solid was obtained (50 mg, yield 65%).

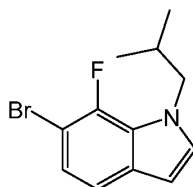


[0549] Step 6: (S)-2-(3-((6-((1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-5-fluoro-1-isobutyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the methyl (S)-2-(3-((6-((1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-5-fluoro-1-isobutyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoate instead of the (ethyl 2-(4-((6-((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)propanoate. A brown solid was obtained (45 mg, yield 93%). ¹H NMR (400 MHz, CDCl₃) δ 8.05 (d, J = 6.3 Hz, 1H), 7.33 (q, J = 1.5 Hz, 1H), 7.25 – 7.10 (m, 4H), 7.06 (t, J = 7.9 Hz, 1H), 6.99 (d, J = 13.4 Hz, 1H), 6.87 (s, 1H), 6.82 (dt, J = 7.8, 1.1 Hz, 1H), 6.72 (t, J = 2.0 Hz, 1H), 6.67 (ddd, J = 8.1, 2.5, 0.9 Hz, 1H), 5.30 (qt, J = 7.8, 3.7 Hz, 1H), 5.10 (br, 1H), 3.89 (s, 2H), 3.78 (d, J = 7.4 Hz, 2H), 2.07 (dh, J = 13.8, 6.8 Hz, 1H), 1.53 (d, J = 6.9 Hz, 3H), 1.47 (s, 6H), 1.24 (s, 9H), 0.78 (d, J = 6.6 Hz, 6H). ¹⁹F NMR (565 MHz, CDCl₃) δ -125.14 – -126.11 (m). ESI-MS (m/z): 586.77 [M]⁺.

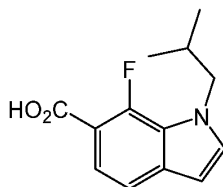
[0550] **Compound 72: (S)-2-(3-((6-((1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-7-fluoro-1-isobutyl-1H-indol-3-yl)methyl) phenoxy)-2-methylpropanoic acid.**



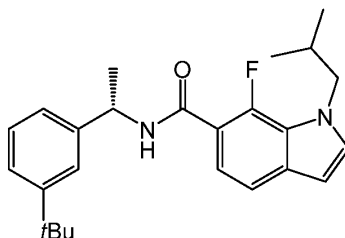
[0551] **Step 1: 6-bromo-7-fluoro-1H-indole.** To a solution of 1-bromo-2-fluoro-3-nitrobenzene (0.5 g, 2.27 mmol) in THF (25 mL) at -50 °C was added vinyl magnesium bromide (9.75 mL, 6.83 mmol) and the mixture was stirred at -40 °C for 1 h. The reaction was quenched with saturated ammonium chloride solution and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and evaporated under reduced pressure to yield a gum, which was purified by column chromatography over silica gel eluting with EtOAc/hexane to afford pure 6-bromo-7-fluoro-1H-indole. ¹H NMR (400 MHz, CDCl₃) δ = 8.51 (br, 1H), 7.19 (d, J = 8.4 Hz 1H), 7.11-7.07 (m, 2H), 6.47 (m, 1H).



[0552] **Step 2: 6-bromo-7-fluoro-1-isobutyl-1H-indole.** The title compound was prepared following the same general protocol as described in Step 2, Compound 71, using the 6-bromo-7-fluoro-1H-indole instead of the 6-bromo-5-fluoro-1H-indole. A white solid was obtained (90 mg, yield 83%). ESI-MS (m/z): 269.91 [M]⁺.

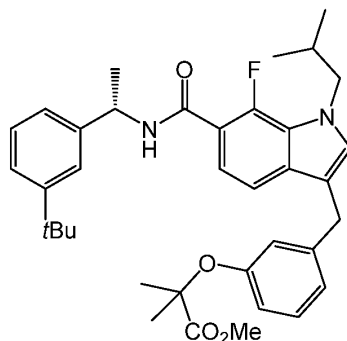


[0553] **Step 3: 7-fluoro-1-isobutyl-1H-indole-6-carboxylic acid.** The title compound was prepared following the same general protocol as described in Step 3, Compound 71, using the 6-bromo-7-fluoro-1-isobutyl-1H-indole instead of the 6-bromo-5-fluoro-1-isobutyl-1H-indole. A white solid was obtained (70 mg, yield 89%).

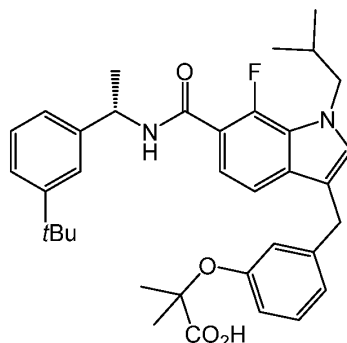


[0554] **Step 4: (S)-N-(1-(3-(tert-butyl)phenyl)ethyl)-7-fluoro-1-isobutyl-1H-indole-6-carboxamide.** The title compound was prepared following the same general protocol as described in Step 4, Compound 71,

using the 7-fluoro-1-isobutyl-1H-indole-6-carboxylic acid instead of the 5-fluoro-1-isobutyl-1H-indole-6-carboxylic acid. A yellow solid was obtained (60 mg, yield 41%). ESI-MS (m/z): 394.77 $[M]^+$.

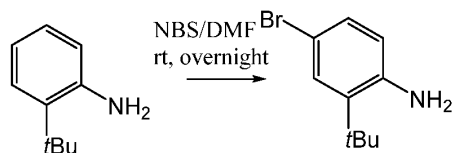


[0555] Step 5: methyl (S)-2-(3-(((6-((1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-7-fluoro-1-isobutyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoate. The title compound was prepared following the same general protocol as described in Step 5, Compound 71, using the (S)-N-(1-(3-(tert-butyl)phenyl)ethyl)-7-fluoro-1-isobutyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(3-(tert-butyl)phenyl)ethyl)-5-fluoro-1-isobutyl-1H-indole-6-carboxamide. A yellow solid was obtained (75 mg, yield 82%). ESI-MS (m/z): 600.89 $[M]^+$.

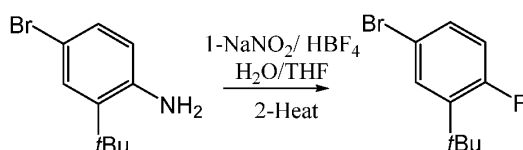


[0556] Step 6: (S)-2-(3-(((6-((1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-7-fluoro-1-isobutyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoic acid. The title compound was prepared following the same general protocol as described in Step 6, Compound 71, using the methyl (S)-2-(3-(((6-((1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-7-fluoro-1-isobutyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoate instead of the (methyl (S)-2-(3-(((6-((1-(3-(tert-butyl)phenyl)ethyl)carbamoyl)-5-fluoro-1-isobutyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoate. A yellow solid was obtained (35 mg, yield 47%). ^1H NMR (400 MHz, CDCl_3) δ 7.52 (dd, J = 8.4, 6.6 Hz, 1H), 7.38 (s, 1H), 7.28 – 7.21 (m, 2H), 7.18 – 7.03 (m, 3H), 6.89 (d, J = 7.5 Hz, 1H), 6.80 (s, 1H), 6.74 – 6.61 (m, 2H), 5.34 (q, J = 7.2 Hz, 1H), 4.06 – 3.84 (m, 4H), 2.05 (dd, J = 13.6, 6.8 Hz, 1H), 1.56 (d, J = 6.9 Hz, 3H), 1.45 (s, 6H), 1.26 (s, 9H), 0.82 (dd, J = 6.7, 1.8 Hz, 6H).

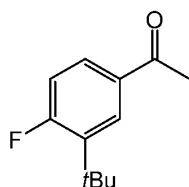
[0557] Compound 73: (S)-2-(3-(((6-((1-(3-(tert-butyl)-4-fluorophenyl)ethyl)carbamoyl)-1-isobutyl-2-methyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoic acid.



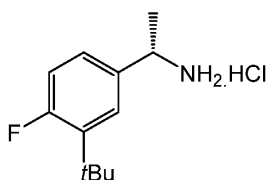
[0558] Step 1: 4-bromo-2-(tert-butyl)aniline. To a solution of 2-(tert-butyl)aniline (3 g, 0.02 mmol) was added a solution of NBS (17.8 g, 100 mol) in DMF (10 ml). The mixture was stirred overnight at rt, diluted with water (30 mL) and extracted with Et₂O (3x 50 mL). The organic layer was washed with brine, dried over sodium sulfate, concentrated and purified by flash column chromatography and the product was isolated as brown oil (1.5 g, yield 33%). ¹H NMR (400 MHz, CDCl₃) δ 7.34 (d, J = 2.3 Hz, 1H), 7.15 (dd, J = 8.4, 2.3 Hz, 1H), 6.54 (d, J = 8.4 Hz, 1H), 3.76 (br, 2H), 1.43 (s, 9H). ESI-MS (m/z): 227.75 [M]⁺.



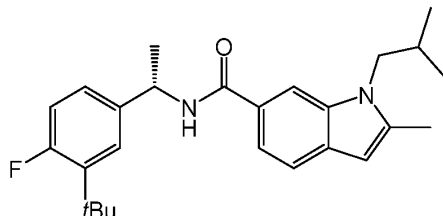
[0559] Step 2: 4-bromo-2-(tert-butyl)-1-fluorobenzene. To a solution of 4-bromo-2-(tert-butyl)aniline (1.5 g, 6.6 mmol) in THF (2 ml) at 0°C was added 48% HBF₄ (5 ml). An aqueous solution of sodium nitrite (0.45 g, 5.78 mmol) was then added dropwise and the resultant yellow suspension stirred at 0°C for 1h. The solid was collected by vacuum filtration yielding the corresponding diazonium salt. Subsequently, the salt was heated to 50°C until the evolution BF₃ has ceased. The remaining material was dissolved in CH₂Cl₂ (100 ml), filtrated through a short pad of silica gel, dried over sodium sulfate and concentrated under vacuum. The residue was purified by flash column chromatography and the product was isolated as light-yellow oil. (0.6 g, yield 39%). ¹H NMR (400 MHz, CDCl₃) δ 7.29 (dd, J = 7.3, 2.5 Hz, 1H), 7.16 (ddd, J = 8.6, 4.1, 2.5 Hz, 1H), 6.76 (dd, J = 12.0, 8.6 Hz, 1H), 1.25 (d, J = 1.1 Hz, 9H). ESI-MS (m/z): 230.89 [M]⁺.



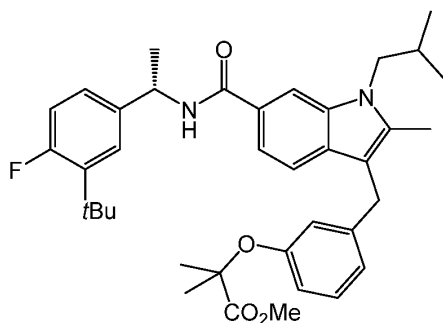
[0560] Step 3: 1-(3-(tert-butyl)-4-fluorophenyl)ethenone. The title compound was prepared following the same general protocol as described in Step 1, Compound 67, using the 4-bromo-2-(tert-butyl)-1-fluorobenzene instead of the 1-bromo-3-(tert-butyl)-5-fluorobenzene. A transparent oil was obtained (330 mg, yield 66%).



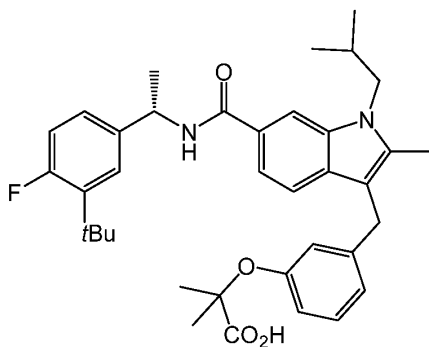
[0561] Step 4: (S)-1-(3-(tert-butyl)-4-fluorophenyl)ethanamine hydrochloride. The title compound was prepared following the same general protocol as described in Step 6, Compound 1, using the 1-(3-(tert-butyl)-4-fluorophenyl)ethenone instead of the 1-(4-*tert*-butylphenyl)ethenone. A yellow solid was obtained (250 mg, yield 63%).



[0562] Step 5: (S)-N-(1-(3-(tert-butyl)-4-fluorophenyl)ethyl)-1-isobutyl-2-methyl-1H-indole-6-carboxamide. The title compound was prepared following the same general protocol as described in Step 8, Compound 1, using the (S)-1-(3-(tert-butyl)-4-fluorophenyl)ethanamine hydrochloride instead of the (S)-1-(4-(tert-butyl)phenyl)ethanamine hydrochloride and the 1-isobutyl-1H-indole-6-carboxylic acid instead of the 1-methyl-2-methyl-1H-indole-6-carboxylic acid. A yellow solid was obtained (27 mg, yield 90%). ESI-MS (*m/z*): 408.77 [*M*]⁺.

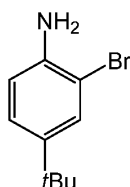


[0563] Step 6: methyl (S)-2-(3-(((1-(3-(tert-butyl)-4-fluorophenyl)ethyl)carbamoyl)-1-isobutyl-2-methyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoate. The title compound was prepared following the same general protocol as described in Step 9, Compound 1, using the (S)-N-(1-(3-(tert-butyl)-4-fluorophenyl)ethyl)-1-isobutyl-2-methyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide and the methyl 2-(3-formylphenoxy)-2-methylpropanoate instead of the ethyl 2-(4-formylphenoxy)propanoate. A yellow solid was obtained (43 mg, yield 95%). ESI-MS (*m/z*): 614.74 [*M*]⁺.

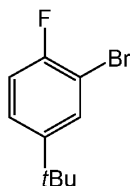


[0564] Step 7: (S)-2-(3-((6-((1-(3-(tert-butyl)-4-fluorophenyl)ethyl)carbamoyl)-1-isobutyl-2-methyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the methyl (S)-2-(3-((6-((1-(3-(tert-butyl)-4-fluorophenyl)ethyl)carbamoyl)-1-isobutyl-2-methyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoate instead of the (ethyl 2-(4-((6-((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)propanoate. A yellow solid was obtained (20 mg, yield 47%). ¹H NMR (600 MHz, CDCl₃) δ 7.79 (d, J = 1.5 Hz, 1H), 7.22 – 7.15 (m, 2H), 7.11 (dd, J = 8.3, 1.5 Hz, 1H), 7.07 (ddd, J = 8.4, 4.4, 2.4 Hz, 1H), 6.95 (td, J = 7.5, 1.3 Hz, 1H), 6.83 (dd, J = 12.3, 8.3 Hz, 1H), 6.72 (d, J = 7.6 Hz, 1H), 6.56 (dd, J = 8.5, 1.9 Hz, 2H), 6.29 (d, J = 7.7 Hz, 1H), 5.20 (p, J = 7.0 Hz, 1H), 4.12 (br, 1H), 3.89 (s, 2H), 3.78 (d, J = 7.7 Hz, 2H), 2.22 (s, 3H), 2.09 (dt, J = 13.8, 7.0 Hz, 1H), 1.46 (d, J = 6.9 Hz, 3H), 1.37 (s, 6H), 1.24 (d, J = 1.0 Hz, 9H), 0.77 (d, J = 6.6 Hz, 6H). ESI-MS (m/z): 600.79 [M]⁺.

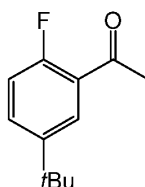
[0565] Compound 74: (S)-2-(3-((6-((1-(5-(tert-butyl)-2-fluorophenyl)ethyl)carbamoyl)-1-isobutyl-2-methyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoic acid.



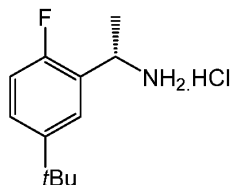
[0566] Step 1: 2-bromo-4-(tert-butyl)aniline. The title compound was prepared following the same general protocol as described in Step 1, Compound 73, using the 4-(tert-butyl)aniline instead of the 2-(tert-butyl)aniline. A brown liquid was obtained (1.85 g, yield 81%). ¹H NMR (600 MHz, CDCl₃) δ 7.53 – 7.31 (m, 1H), 7.17 (ddd, J = 8.4, 2.2, 0.8 Hz, 1H), 6.75 (d, J = 8.3 Hz, 1H), 3.91 (br, 2H), 1.30 (d, J = 1.9 Hz, 9H). ESI-MS (m/z): 227.75 [M]⁺.



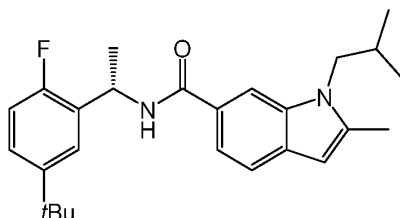
[0567] Step 2: 2-bromo-4-(tert-butyl)-1-fluorobenzene. The title compound was prepared following the same general protocol as described in Step 2, Compound 73, using the 2-bromo-4-(tert-butyl)aniline instead of the 4-bromo-2-(tert-butyl)aniline. A light-red liquid was obtained (0.55 g, yield 29%). ¹H NMR (400 MHz, CDCl₃) δ 7.41 (dd, J = 6.6, 2.4 Hz, 1H), 7.14 (ddd, J = 8.7, 4.6, 2.4 Hz, 1H), 6.87 (t, J = 8.5 Hz, 1H), 1.16 (s, 9H). ESI-MS (m/z): 230.89 [M]⁺.



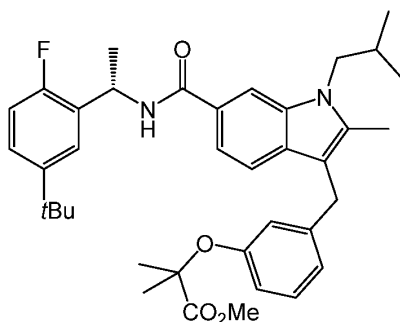
[0568] Step 3: 1-(5-(tert-butyl)-2-fluorophenyl)ethenone. The title compound was prepared following the same general protocol as described in Step 1, Compound 67, using the 2-bromo-4-(tert-butyl)-1-fluorobenzene instead of the 1-bromo-3-(tert-butyl)-5-fluorobenzene. A transparent oil was obtained (0.45 g, yield 97%).



[0569] Step 4: (S)-1-(5-(tert-butyl)-2-fluorophenyl)ethanamine hydrochloride. The title compound was prepared following the same general protocol as described in Step 6, Compound 1, using the 1-(5-(tert-butyl)-2-fluorophenyl)ethanone instead of the 1-(4-tert-butylphenyl)ethenone. A yellow solid was obtained (450 mg, yield 69%).

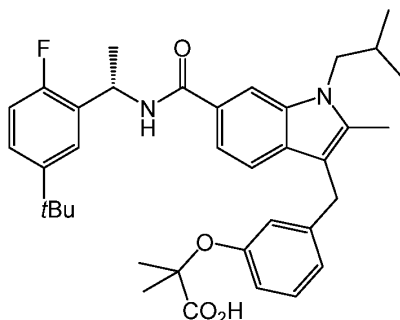


[0570] Step 5: (S)-N-(1-(5-(tert-butyl)-2-fluorophenyl)ethyl)-1-isobutyl-2-methyl-1H-indole-6-carboxamide. The title compound was prepared following the same general protocol as described in Step 8, Compound 1, using the (S)-1-(5-(tert-butyl)-2-fluorophenyl)ethanamine hydrochloride instead of the (S)-1-(4-(tert-butyl)phenyl)ethanamine hydrochloride and the 1-isobutyl-1H-indole-6-carboxylic acid instead of the 1-methyl-2-methyl-1H-indole-6-carboxylic acid. A yellow solid was obtained (27 mg, yield 90%). ESI-MS (m/z): 408.77 [M]⁺.



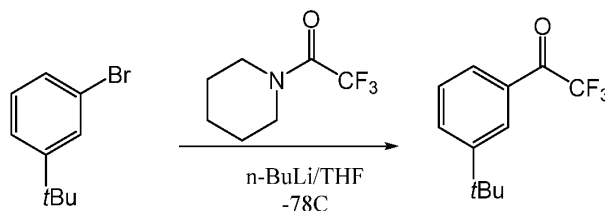
[0571] Step 6: methyl (S)-2-(3-(((1-(5-(tert-butyl)-2-fluorophenyl)ethyl)carbamoyl)-1-isobutyl-2-methyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoate. The title compound was prepared following the same general protocol as described in Step 9, Compound 1, using the (S)-N-(1-(5-(tert-butyl)-2-fluorophenyl)ethyl)-1-isobutyl-2-methyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide and the methyl 2-(3-formylphenoxy)-2-

methylpropanoate instead of the ethyl 2-(4-formylphenoxy)propanoate. A yellow solid was obtained (32 mg, yield 72%). ESI-MS (m/z): 614.87 [M]⁺.



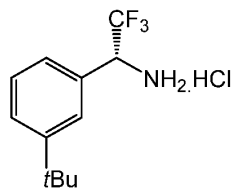
[0572] Step 7: (S)-2-(3-((6-((1-(5-(tert-butyl)-2-fluorophenyl)ethyl)carbamoyl)-1-isobutyl-2-methyl-1H-indol-3-yl)methyl) phenoxy)-2-methylpropanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the methyl (S)-2-(3-((6-((1-(5-(tert-butyl)-2-fluorophenyl)ethyl)carbamoyl)-1-isobutyl-2-methyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoate instead of the (ethyl 2-(4-((6-(((S)-1-(4-(tert-butyl) phenyl) ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)propanoate. A brown solid was obtained (15 mg, yield 48%). ¹H NMR (600 MHz, CDCl₃) δ 7.81 (d, J = 1.5 Hz, 1H), 7.32 – 7.21 (m, 2H), 7.20 – 7.11 (m, 2H), 6.99 (dd, J = 8.8, 7.7 Hz, 1H), 6.89 (dd, J = 10.8, 8.6 Hz, 1H), 6.78 – 6.73 (m, 1H), 6.60 (dd, J = 6.4, 1.2 Hz, 2H), 5.42 – 5.34 (m, 1H), 3.92 (s, 2H), 3.81 (d, J = 7.7 Hz, 2H), 2.25 (s, 3H), 2.12 (dt, J = 13.8, 6.8 Hz, 1H), 1.52 (d, J = 7.0 Hz, 3H), 1.40 (s, 6H), 1.20 (s, 9H), 0.80 (d, J = 6.8 Hz, 6H). ESI-MS (m/z): 600.82 [M]⁺.

[0573] Compound 75: (R)-2-(3-((6-((1-(3-(tert-butyl)phenyl)-2,2,2-trifluoroethyl)carbamoyl)-1-isobutyl-2-methyl-1H-indol-3-yl)methyl) phenoxy)-2-methyl propanoic acid.

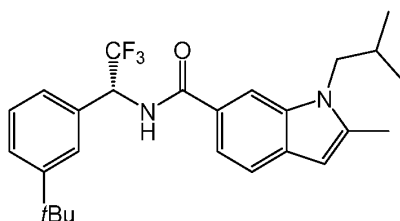


[0574] Step 1: 1-(3-(tert-butyl)phenyl)-2,2,2-trifluoroethanone. In a Schlenk flask under an argon atmosphere, 1-bromo-3-(tert-butyl)benzene (0.5 g, 2.35 mmol) was dissolved in dry tetrahydrofuran (5 mL). The solution was cooled to –78°C. n-BuLi (2.5M, 1.41 mL, 3.5 mmol) was added dropwise. The resulting yellow solution was further stirred for 3h at 0°C. The reaction mixture was cooled down to –78°C and N-trifluoro acetylpyridine (0.5 mL, 2.82 mmol) in dry tetrahydrofuran (2 mL) was added dropwise. Dry ice bath was removed and the mixture was allowed to stir at rt overnight. The reaction was quenched by adding a saturated aqueous solution of ammonium chloride (10 mL) and the mixture was extracted with EtOAc (2X 50 mL). The combined extracts were dried over sodium sulfate, filtered, and concentrated in vacuo. The resulting crude product was purified by flash column chromatography on silica gel (Hex:EtOAc = 50:1) and the product was isolated as transparent oil (0.25 g, yield 47%). ¹H

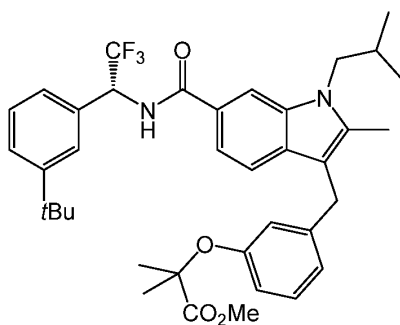
NMR (400 MHz, CDCl₃) δ 8.09 – 7.88 (m, 1H), 7.76 (dt, J = 7.8, 1.5 Hz, 1H), 7.63 (ddd, J = 7.9, 2.1, 1.1 Hz, 1H), 7.35 (td, J = 7.8, 0.5 Hz, 1H), 1.24 (s, 9H). ¹⁹F NMR (376 MHz, CDCl₃) δ -71.29.



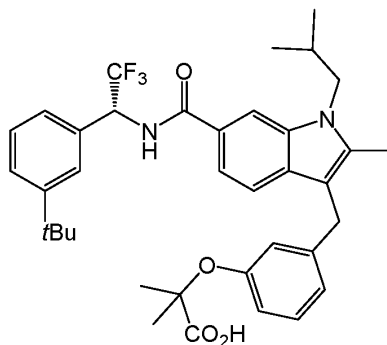
[0575] Step 2: (R)-1-(3-(tert-butyl)phenyl)-2,2,2-trifluoroethanamine hydrochloride. The title compound was prepared following the same general protocol as described in Step 6, Compound 1, using the Step 1: 1-(3-(tert-butyl)phenyl)-2,2,2-trifluoroethanone instead of the 1-(4-*tert*-butylphenyl)ethanone. A yellow solid was obtained (200 mg, yield 68%). ESI-MS (m/z): 231. 62 [M]⁺.



[0576] Step 3: (R)-N-(1-(3-(tert-butyl)phenyl)-2,2,2-trifluoroethyl)-1-isobutyl-2-methyl-1H-indole-6-carboxamide. The title compound was prepared following the same general protocol as described in Step 8, Compound 1, using the (R)-1-(3-(tert-butyl)phenyl)-2,2,2-trifluoroethanamine hydrochloride instead of the (S)-1-(4-(tert-butyl)phenyl)ethanamine hydrochloride and the 1-isobutyl-1H-indole-6-carboxylic acid instead of the 1-methyl-2-methyl-1H-indole-6-carboxylic acid. A yellow solid was obtained (20 mg, yield 40%).

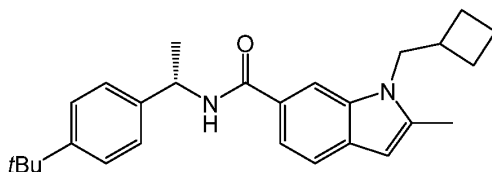


[0577] Step 4: methyl (R)-2-(3-(((6-((1-(3-(tert-butyl)phenyl)-2,2,2-trifluoroethyl)carbamoyl)-1-isobutyl-2-methyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoate. The title compound was prepared following the same general protocol as described in Step 9, Compound 1, using the (R)-N-(1-(3-(tert-butyl)phenyl)-2,2,2-trifluoroethyl)-1-isobutyl-2-methyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide and the methyl 2-(3-formylphenoxy)-2-methylpropanoate instead of the ethyl 2-(4-formylphenoxy)propanoate. A yellow solid was obtained (22 mg, yield 75%). ESI-MS (m/z): 651.78 [M+H]⁺.

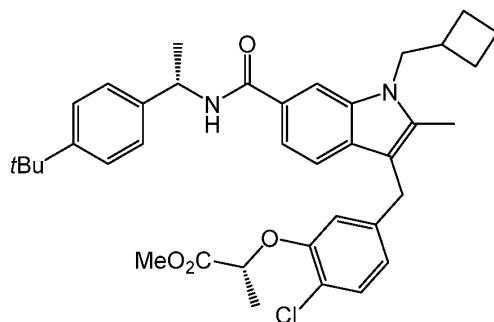


[0578] Step 5: (R)-2-(3-((6-((1-(3-(tert-butyl)phenyl)-2,2,2-trifluoroethyl)carbamoyl)-1-isobutyl-2-methyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the methyl (R)-2-(3-((6-((1-(3-(tert-butyl)phenyl)-2,2,2-trifluoroethyl)carbamoyl)-1-isobutyl-2-methyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoate instead of the (ethyl 2-(4-((6-(((S)-1-(4-(tert-butyl) phenyl) ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)propanoate. A yellow solid was obtained (18 mg, yield 85%). ¹H NMR (400 MHz, CDCl₃) δ 8.12 (d, J = 2.6 Hz, 1H), 7.97 (s, 1H), 7.78 (d, J = 7.9 Hz, 1H), 7.64 – 7.27 (m, 5H), 7.02 (s, 1H), 6.92 (d, J = 8.1 Hz, 1H), 6.32 (d, J = 3.8 Hz, 1H), 6.18 (s, 1H), 6.01 (s, 1H), 4.25 (d, J = 3.5 Hz, 2H), 4.00 (d, J = 7.3 Hz, 3H), 3.75 (dd, J = 7.4, 2.9 Hz, 2H), 2.44 (s, 2H), 1.36 (t, J = 2.2 Hz, 5H), 1.01 – 0.82 (m, 12H).

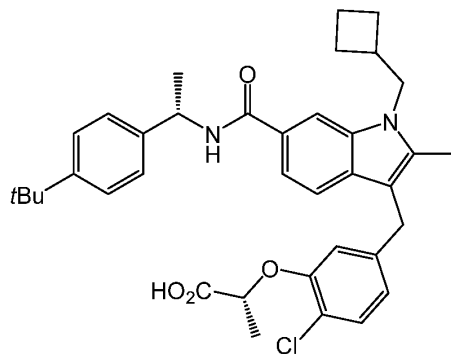
[0579] Compound 76: (R)-2-(5-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1-(cyclobutylmethyl)-2-methyl-1H-indol-3-yl)methyl)-2-chlorophenoxy)propanoic acid.



[0580] Step 1: (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1-(cyclobutylmethyl)-2-methyl-1H-indole-6-carboxamide. The title compound was prepared following the same general protocol as described in Step 8, Compound 1, using the 1-(cyclobutylmethyl)-2-methyl-1H-indole-6-carboxylic acid instead of the 1-methyl-2-methyl-1H-indole-6-carboxylic acid. A white solid was obtained (190 mg, yield 94%). ¹H NMR (400 MHz, CDCl₃) δ 7.90 (d, J = 1.5 Hz, 1H), 7.36 (d, J = 8.2 Hz, 1H), 7.31 – 7.19 (m, 5H), 6.47 (d, J = 7.8 Hz, 1H), 6.31 – 5.95 (m, 1H), 5.28 (p, J = 7.1 Hz, 1H), 4.00 (d, J = 7.1 Hz, 2H), 2.71 (p, J = 7.6 Hz, 1H), 2.35 (d, J = 0.9 Hz, 3H), 1.92 – 1.81 (m, 2H), 1.79 – 1.62 (m, 4H), 1.52 (d, J = 6.9 Hz, 3H), 1.22 (s, 9H). ESI-MS (m/z): 402. 68 [M]⁺.

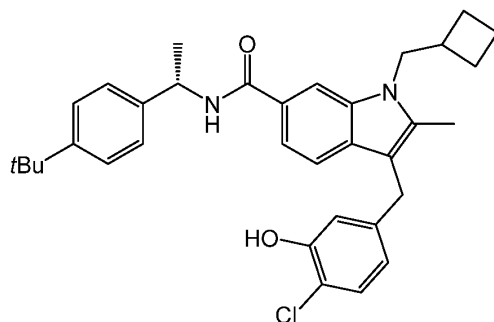


[0581] Step 2: methyl (R)-2-(5-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1-(cyclobutylmethyl)-2-methyl-1H-indol-3-yl)methyl)-2-chlorophenoxy)propanoate. The title compound was prepared following the same general protocol as described in Step 9, Compound 1, using the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1-(cyclobutylmethyl)-2-methyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide and the methyl (R)-2-(2-chloro-5-formylphenoxy)propanoate instead of the ethyl 2-(4-formylphenoxy)propanoate. A yellow solid was obtained (39 mg, yield 87%). ESI-MS (m/z): 628.84[M]⁺.

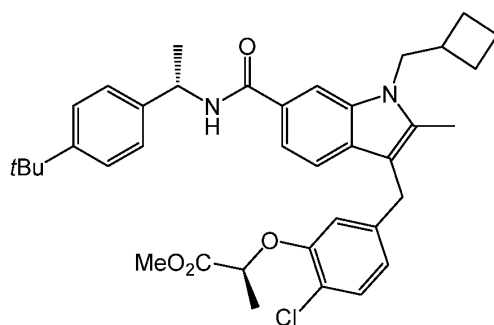


[0582] Step 3: (R)-2-(5-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1-(cyclobutylmethyl)-2-methyl-1H-indol-3-yl)methyl)-2-chlorophenoxy)propanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the methyl (R)-2-(5-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1-(cyclobutylmethyl)-2-methyl-1H-indol-3-yl)methyl)-2-chlorophenoxy)propanoate instead of the (ethyl 2-(4-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)propanoate. A light-yellow solid was obtained (34 mg, yield 89%). ¹H NMR (400 MHz, CDCl₃) δ 7.78 (q, J = 1.2 Hz, 1H), 7.28 – 7.16 (m, 4H), 7.12 (d, J = 2.4 Hz, 2H), 7.06 (dd, J = 8.1, 0.8 Hz, 1H), 6.59 (dt, J = 8.2, 1.8 Hz, 1H), 6.48 (dd, J = 4.0, 1.9 Hz, 1H), 6.33 (d, J = 7.9 Hz, 1H), 5.21 (p, J = 7.1 Hz, 1H), 4.44 (qd, J = 6.9, 2.4 Hz, 2H), 3.94 (dd, J = 7.1, 1.7 Hz, 2H), 3.80 (d, J = 4.1 Hz, 2H), 2.63 (p, J = 7.5 Hz, 1H), 2.19 (d, J = 0.8 Hz, 3H), 1.87 – 1.76 (m, 2H), 1.75 – 1.55 (m, 4H), 1.53 – 1.43 (m, 6H), 1.17 (s, 9H). ESI-MS (m/z): 614.71 [M]⁺.

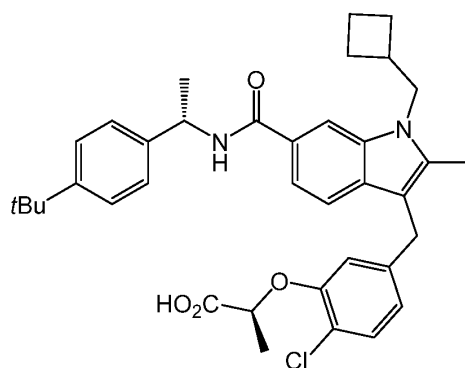
[0583] Compound 77: (S)-2-(5-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1-(cyclobutylmethyl)-2-methyl-1H-indol-3-yl)methyl)-2-chlorophenoxy)propanoic acid.



[0584] Step 1: (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-3-(4-chloro-3-hydroxybenzyl)-1-(cyclobutylmethyl)-2-methyl-1H-indole-6-carboxamide. The title compound was prepared following the same general protocol as described in Step 1, Compound 42, using the 4-chloro-3-hydroxybenzaldehyde instead of the 2-chloro-3-hydroxybenzaldehyde and the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1-(cyclobutylmethyl)-2-methyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide. A yellow solid was obtained (28 mg, yield 93%). ESI-MS (m/z): 542. 64 [M]⁺.

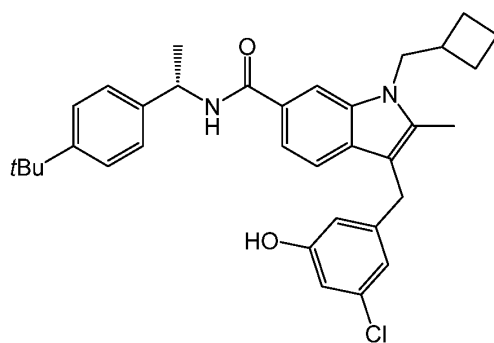


[0585] Step 2: methyl (S)-2-(5-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1-(cyclobutylmethyl)-2-methyl-1H-indol-3-yl)methyl)-2-chlorophenoxy)propanoate. The title compound was prepared following the same general protocol as described in Step 2, Compound 42, using the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-3-(4-chloro-3-hydroxybenzyl)-1-(cyclobutylmethyl)-2-methyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-3-(2-chloro-3-hydroxybenzyl)-1,2-dimethyl-1H-indole-6-carboxamide and the methyl (S)-2-bromopropanoate instead of the (R)-2-bromopropanoate. A white solid was obtained (25mg, yield 78%). ESI-MS (m/z): 628.82 [M]⁺.

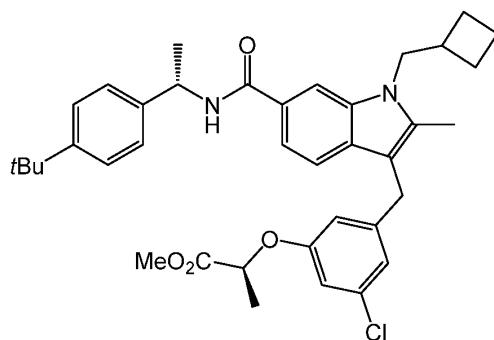


[0586] Step 3: (S)-2-(5-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1-(cyclobutylmethyl)-2-methyl-1H-indol-3-yl)methyl)-2-chlorophenoxy)propanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the methyl (S)-2-(5-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1-(cyclobutylmethyl)-2-methyl-1H-indol-3-yl)methyl)-2-chlorophenoxy)propanoate instead of the (ethyl 2-(4-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)propanoate. A light-yellow solid was obtained (22 mg, yield 91%). ¹H NMR (400 MHz, CDCl₃) δ 7.85 (q, J = 1.2 Hz, 1H), 7.39 – 7.22 (m, 4H), 7.18 (d, J = 3.6 Hz, 2H), 7.13 (dd, J = 8.1, 1.2 Hz, 1H), 6.66 (dd, J = 8.1, 2.1 Hz, 1H), 6.61 – 6.48 (m, 1H), 6.37 (d, J = 7.9 Hz, 1H), 5.28 (p, J = 7.0 Hz, 1H), 4.51 (qd, J = 6.9, 2.7 Hz, 1H), 4.02 (d, J = 6.9 Hz, 2H), 3.87 (d, J = 5.0 Hz, 2H), 2.70 (p, J = 7.6 Hz, 1H), 2.26 (d, J = 1.0 Hz, 3H), 1.96 – 1.83 (m, 2H), 1.81 – 1.59 (m, 4H), 1.56 – 1.48 (m, 6H), 1.24 (s, 9H). ESI-MS (m/z): 614.71 [M]⁺.

[0587] Compound 78: (S)-2-(3-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1-(cyclobutylmethyl)-2-methyl-1H-indol-3-yl)methyl)-5-chlorophenoxy)propanoic acid.

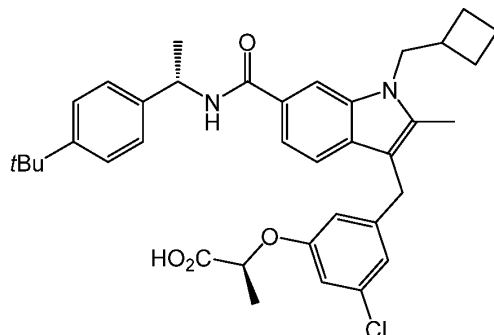


[0588] Step 1: (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-3-(3-chloro-5-hydroxybenzyl)-1-(cyclobutylmethyl)-2-methyl-1H-indole-6-carboxamide. The title compound was prepared following the same general protocol as described in Step 1, Compound 42, using the 3-chloro-5-hydroxybenzaldehyde instead of the 2-chloro-3-hydroxybenzaldehyde and the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1-(cyclobutylmethyl)-2-methyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide. A yellow solid was obtained (25 mg, yield 97%). ESI-MS (m/z): 542. 64 [M]⁺.



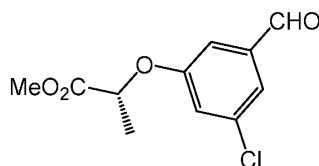
[0589] Step 2: methyl (S)-2-(3-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1-(cyclobutylmethyl)-2-methyl-1H-indol-3-yl)methyl)-5-chlorophenoxy)propanoate. The title compound was prepared following the same general protocol as described in Step 2, Compound 42, using the (S)-N-(1-(4-(tert-

butyl)phenyl)ethyl)-3-(3-chloro-5-hydroxybenzyl)-1-(cyclobutylmethyl)-2-methyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-3-(2-chloro-3-hydroxybenzyl)-1,2-dimethyl-1H-indole-6-carboxamide and the methyl (S)-2-bromopropanoate instead of the (R)-2-bromopropanoate. A white solid was obtained (27mg, yield 93%). ESI-MS (m/z): 628.82 [M]⁺.

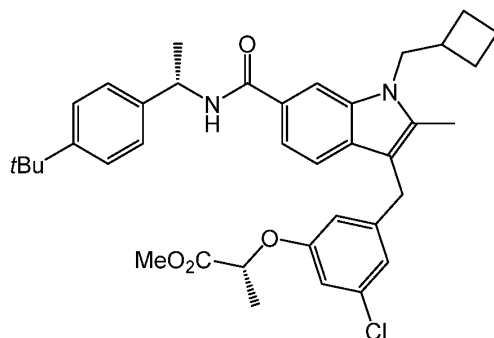


[0590] Step 3: (S)-2-(3-(((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1-(cyclobutylmethyl)-2-methyl-1H-indol-3-yl)methyl)-5-chlorophenoxy)propanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the methyl (S)-2-(3-(((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1-(cyclobutylmethyl)-2-methyl-1H-indol-3-yl)methyl)-5-chlorophenoxy)propanoate instead of the (ethyl 2-(4-(((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)propanoate. A yellow solid was obtained (24 mg, yield 92%). ¹H NMR (400 MHz, CDCl₃) δ 7.87 (s, 1H), 7.39 – 7.23 (m, 4H), 7.24 – 7.10 (m, 2H), 6.69 (q, J = 1.7 Hz, 1H), 6.60 (t, J = 2.1 Hz, 1H), 6.44 (d, J = 3.1 Hz, 1H), 6.36 (d, J = 7.9 Hz, 1H), 5.29 (t, J = 7.1 Hz, 1H), 4.67 – 4.42 (m, 1H), 4.02 (d, J = 7.1 Hz, 2H), 3.88 (d, J = 4.7 Hz, 2H), 2.81 – 2.58 (m, 1H), 2.26 (s, 3H), 1.96 – 1.81 (m, 0H), 1.81 – 1.64 (m, 4H), 1.59 – 1.33 (m, 6H), 1.24 (s, 9H). ESI-MS (m/z): 614.58 [M]⁺.

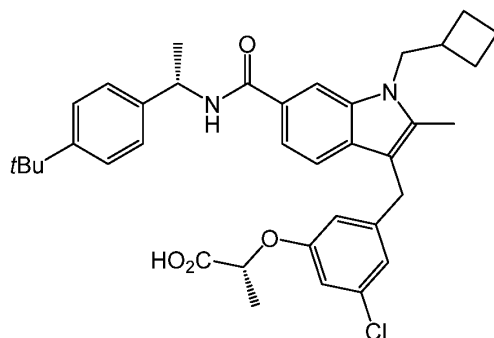
[0591] Compound 79: (R)-2-(3-(((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1-(cyclobutylmethyl)-2-methyl-1H-indol-3-yl)methyl)-5-chlorophenoxy)propanoic acid.



[0592] Step 1: methyl (R)-2-(3-chloro-5-formylphenoxy)propanoate. The title compound was prepared following the same general protocol as described in Step 7, Compound 1, using the 3-chloro-5-hydroxybenzaldehyde instead of the 4-hydroxybenzaldehyde and the methyl (S)-2-bromopropanoate instead of the ethyl bromopropionate. A light-yellow solid was obtained (0.14 g, yield 59%).

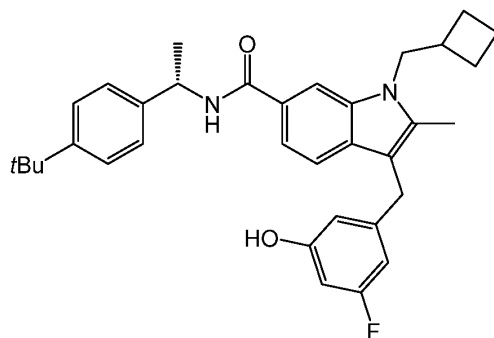


[0593] Step 2: methyl (R)-2-(3-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1-(cyclobutylmethyl)-2-methyl-1H-indol-3-yl)methyl)-5-chlorophenoxy)propanoate. The title compound was prepared following the same general protocol as described in Step 9, Compound 1, using the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1-(cyclobutylmethyl)-2-methyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide and the methyl (R)-2-(3-chloro-5-formylphenoxy)propanoate instead of the ethyl 2-(4-formylphenoxy)propanoate. A yellow solid was obtained (19 mg, yield 92%). ESI-MS (m/z): 628.58[M]⁺.

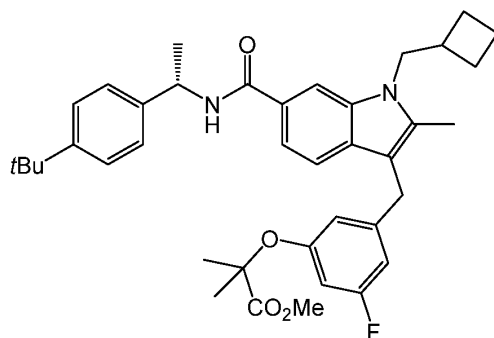


[0594] Step 3: (R)-2-(3-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1-(cyclobutylmethyl)-2-methyl-1H-indol-3-yl)methyl)-5-chlorophenoxy)propanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the methyl (R)-2-(3-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1-(cyclobutylmethyl)-2-methyl-1H-indol-3-yl)methyl)-5-chlorophenoxy)propanoate instead of the (ethyl 2-(4-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)propanoate. A yellow solid was obtained (10 mg, yield 55%). ¹H NMR (600 MHz, CDCl₃) δ 7.88 (s, 1H), 7.33 – 7.24 (m, 4H), 7.24 – 7.15 (m, 2H), 6.68 (dt, J = 3.2, 1.6 Hz, 1H), 6.60 (q, J = 2.0 Hz, 1H), 6.50 – 6.43 (m, 1H), 6.41 (dd, J = 8.1, 2.3 Hz, 1H), 5.37 – 5.18 (m, 1H), 4.54 (qd, J = 6.8, 1.3 Hz, 1H), 4.03 – 3.93 (m, 2H), 3.89 (d, J = 3.0 Hz, 2H), 2.68 (p, J = 7.6 Hz, 1H), 2.26 (s, 3H), 1.92 – 1.83 (m, 2H), 1.79 – 1.61 (m, 4H), 1.51 (ddd, J = 22.5, 6.9, 1.8 Hz, 6H), 1.23 (s, 9H). ESI-MS (m/z): 614.54 [M]⁺.

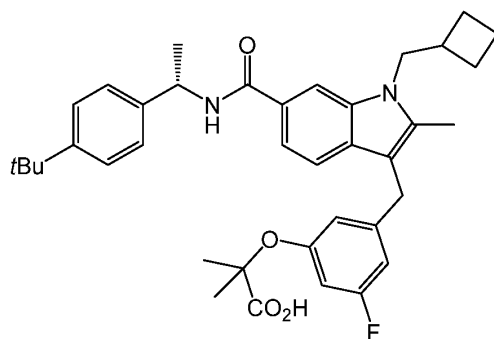
[0595] Compound 80: (S)-2-(3-((6-(((1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1-(cyclobutylmethyl)-2-methyl-1H-indol-3-yl)methyl)-5-fluorophenoxy)-2-methyl propanoic acid.



[0596] Step 1: (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1-(cyclobutylmethyl)-3-(3-fluoro-5-hydroxybenzyl)-2-methyl-1H-indole-6-carboxamide. The title compound was prepared following the same general protocol as described in Step 1, Compound 42, using the 3-fluoro-5-hydroxybenzaldehyde instead of the 2-chloro-3-hydroxybenzaldehyde and the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1-(cyclobutylmethyl)-2-methyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide. A yellow solid was obtained (34 mg, yield 97%). ESI-MS (m/z): 526. 62 [M]⁺.

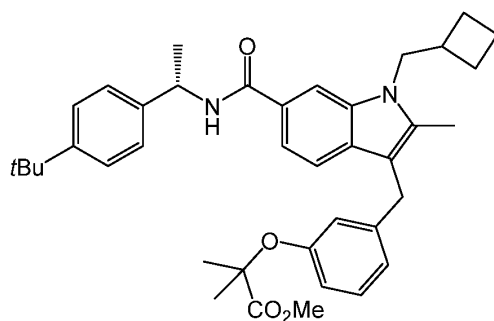


[0597] Step 2: methyl (S)-2-(3-(((1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1-(cyclobutylmethyl)-2-methyl-1H-indol-3-yl)methyl)-5-fluorophenoxy)-2-methylpropanoate. The title compound was prepared following the same general protocol as described in Step 2, Compound 42, using the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1-(cyclobutylmethyl)-3-(3-fluoro-5-hydroxybenzyl)-2-methyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-3-(2-chloro-3-hydroxybenzyl)-1,2-dimethyl-1H-indole-6-carboxamide and the methyl 2-bromo-2-methylpropanoate instead of the (R)-2-bromopropanoate. A white solid was obtained (37mg, yield 92%). ESI-MS (m/z): 626. 62 [M]⁺.

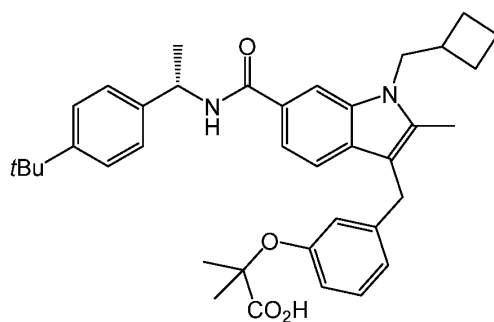


[0598] Step 3: (S)-2-(3-((6-((1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1-(cyclobutylmethyl)-2-methyl-1H-indol-3-yl)methyl)-5-fluorophenoxy)-2-methylpropanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the methyl (S)-2-(3-((6-((1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1-(cyclobutylmethyl)-2-methyl-1H-indol-3-yl)methyl)-5-fluorophenoxy)-2-methylpropanoate instead of the ethyl 2-(4-((6-((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)propanoate. A yellow solid was obtained (30 mg, yield 83%). ¹H NMR (400 MHz, CDCl₃) δ 7.89 (s, 1H), 7.38 – 7.22 (m, 4H), 7.19 (dd, J = 2.3, 1.2 Hz, 2H), 6.52 – 6.26 (m, 4H), 5.35 – 5.23 (m, 1H), 4.04 (d, J = 7.1 Hz, 2H), 3.85 (s, 2H), 2.71 (p, J = 7.6 Hz, 1H), 2.26 (s, 3H), 1.94 – 1.84 (m, 2H), 1.78 – 1.65 (m, 4H), 1.54 (d, J = 6.8 Hz, 3H), 1.46 (s, 6H), 1.24 (s, 9H). ESI-MS (m/z): 612.71 [M]⁺.

[0599] Compound 81: (S)-2-(3-((6-((1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1-(cyclobutylmethyl)-2-methyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoic acid.



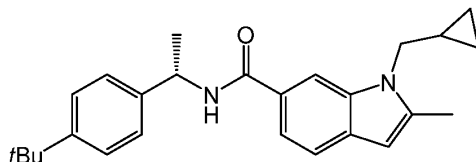
[0600] Step 1: methyl (S)-2-(3-((6-((1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1-(cyclobutylmethyl)-2-methyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoate. The title compound was prepared following the same general protocol as described in Step 9, Compound 1, using the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1-(cyclobutylmethyl)-2-methyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide and the methyl 2-(3-formylphenoxy)-2-methylpropanoate instead of the ethyl 2-(4-formylphenoxy)propanoate. A yellow solid was obtained (39 mg, yield 75%). ESI-MS (m/z): 608.79[M]⁺.



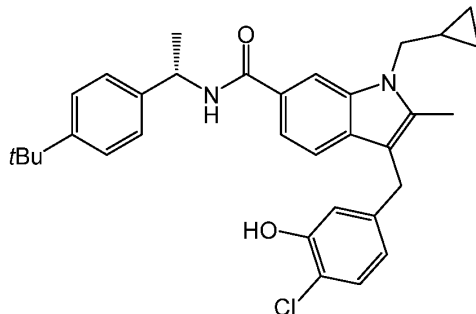
[0601] Step 2: (S)-2-(3-((6-((1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1-(cyclobutylmethyl)-2-methyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the methyl (S)-2-(3-((6-((1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1-(cyclobutylmethyl)-2-methyl-1H-indol-3-yl)methyl)phenoxy)-2-

methylpropanoate instead of the (ethyl 2-(4-((6-(((S)-1-(4-(tert-butyl) phenyl) ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)propanoate. A yellow solid was obtained (32 mg, yield 84%). ¹H NMR (400 MHz, CDCl₃) δ 7.84 (t, J = 2.4 Hz, 1H), 7.30 – 7.19 (m, 4H), 7.19 – 7.07 (m, 2H), 6.99 – 6.90 (m, 1H), 6.72 (d, J = 7.6 Hz, 1H), 6.60 – 6.52 (m, 2H), 6.27 (d, J = 7.8 Hz, 1H), 5.23 (p, J = 6.5 Hz, 1H), 3.98 (d, J = 7.1 Hz, 2H), 3.87 (s, 1H), 2.66 (p, J = 7.8 Hz, 1H), 2.22 (s, 3H), 1.89 – 1.79 (m, 2H), 1.76 – 1.60 (m, 4H), 1.48 (d, J = 6.8 Hz, 3H), 1.37 (s, 6H), 1.18 (s, 9H). ESI-MS (m/z): 594. 65 [M]⁺.

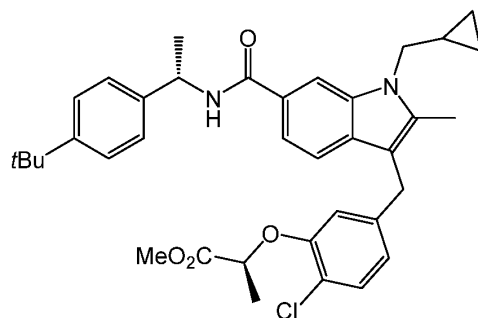
[0602] Compound 82: (S)-2-(5-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1-(cyclopropylmethyl)-2-methyl-1H-indol-3-yl)methyl)-2-chlorophenoxy)propanoic acid.



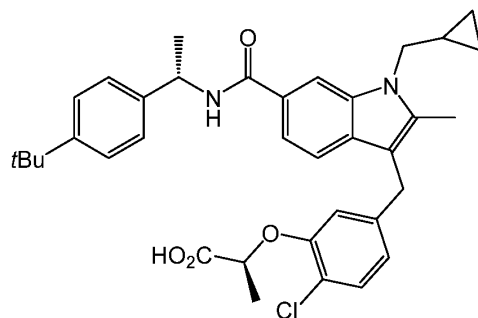
[0603] Step 1: (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1-(cyclopropylmethyl)-2-methyl-1H-indole-6-carboxamide. The title compound was prepared following the same general protocol as described in Step 8, Compound 1, using the 1-(cyclopropylmethyl)-2-methyl-1H-indole-6-carboxylic acid instead of the 1-methyl-2-methyl-1H-indole-6-carboxylic acid. A yellow solid was obtained (29 mg, yield 87%). ESI-MS (m/z): 388.74 [M]⁺.



[0604] Step 2: (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-3-(4-chloro-3-hydroxybenzyl)-1-(cyclopropylmethyl)-2-methyl-1H-indole-6-carboxamide. The title compound was prepared following the same general protocol as described in Step 1, Compound 42, using the 4-chloro-3-hydroxybenzaldehyde instead of the 2-chloro-3-hydroxybenzaldehyde and the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1-(cyclopropylmethyl)-2-methyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide. A brown solid was obtained (35 mg, yield 89%). ESI-MS (m/z): 528.56 [M]⁺.

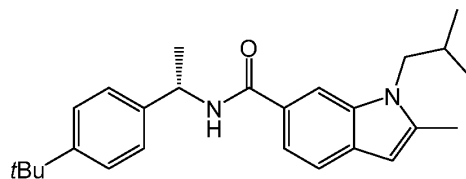


[0605] Step 3: methyl (S)-2-(5-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1-(cyclopropylmethyl)-2-methyl-1H-indol-3-yl)methyl)-2-chlorophenoxy)propanoate. The title compound was prepared following the same general protocol as described in Step 2, Compound 42, using the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-3-(4-chloro-3-hydroxybenzyl)-1-(cyclopropylmethyl)-2-methyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-3-(2-chloro-3-hydroxybenzyl)-1,2-dimethyl-1H-indole-6-carboxamide and the methyl (S)-2-bromopropanoate instead of the (R)-2-bromopropanoate. A white solid was obtained (37mg, yield 92%). ESI-MS (m/z): 614. 63 [M]⁺.

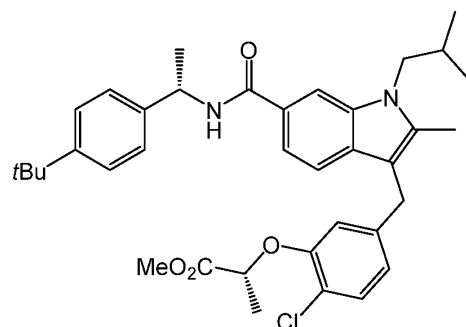


[0606] Step 4: (S)-2-(5-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1-(cyclopropylmethyl)-2-methyl-1H-indol-3-yl)methyl)-2-chlorophenoxy)propanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the methyl (S)-2-(5-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1-(cyclopropylmethyl)-2-methyl-1H-indol-3-yl)methyl)-2-chlorophenoxy)propanoate instead of the (ethyl 2-(4-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)propanoate. A yellow solid was obtained (30 mg, yield 83%). ¹H NMR (400 MHz, CDCl₃) δ 7.93 (s, 1H), 7.40 – 7.29 (m, 5H), 7.29 – 7.16 (m, 2H), 6.74 (d, J = 8.1 Hz, 1H), 6.65 (d, J = 6.1 Hz, 1H), 6.47 (d, J = 7.8 Hz, 1H), 5.39 – 5.31 (m, 1H), 4.64 – 4.56 (m, 1H), 3.96 (dd, J = 17.1, 6.2 Hz, 4H), 2.34 (s, 3H), 1.60 (s, 6H), 1.30 (s, 9H), 1.15 (s, 1H), 0.50 (d, J = 7.8 Hz, 2H), 0.31 (s, 2H).

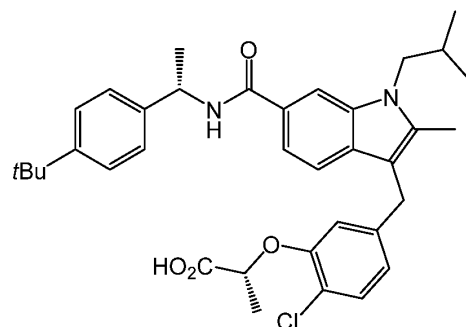
[0607] Compound 83: (R)-2-(5-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1-isobutyl-2-methyl-1H-indol-3-yl)methyl)-2-chlorophenoxy)propanoic acid.



[0608] Step 1: (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1-isobutyl-2-methyl-1H-indole-6-carboxamide. The title compound was prepared following the same general protocol as described in Step 8, Compound 1, using the 1-isobutyl-2-methyl-1H-indole-6-carboxylic acid instead of the 1-methyl-2-methyl-1H-indole-6-carboxylic acid. A yellow solid was obtained (27 mg, yield 98%). ESI-MS (m/z): 390.70 [M]⁺.



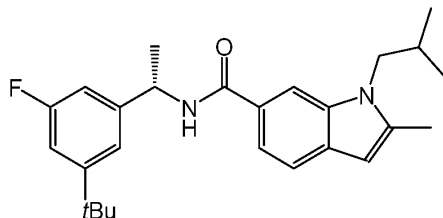
[0609] Step 2: methyl (R)-2-(5-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1-isobutyl-2-methyl-1H-indol-3-yl)methyl)-2-chlorophenoxy)propanoate. The title compound was prepared following the same general protocol as described in Step 9, Compound 1, using the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1-isobutyl-2-methyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide and the methyl (R)-2-(2-chloro-5-formylphenoxy)propanoate instead of the ethyl 2-(4-formylphenoxy)propanoate. A yellow solid was obtained (32 mg, yield 77%). ESI-MS (m/z): 616.56 [M]⁺.



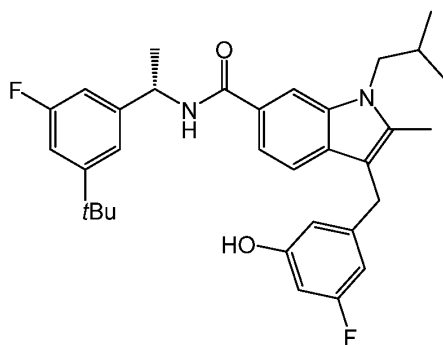
[0610] Step 3: (R)-2-(5-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1-isobutyl-2-methyl-1H-indol-3-yl)methyl)-2-chlorophenoxy)propanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the methyl (R)-2-(5-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1-isobutyl-2-methyl-1H-indol-3-yl)methyl)-2-chlorophenoxy)propanoate instead of the (ethyl 2-(4-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)propanoate. A yellow solid was obtained (28 mg, yield 90%). ¹H NMR (400 MHz, CDCl₃) δ 7.83 (s, 1H), 7.27 (q, J = 8.2 Hz, 4H), 7.18 (d, J = 7.2 Hz, 2H), 7.08 (dd, J = 11.3, 8.0 Hz, 1H),

6.61 (d, J = 14.4 Hz, 2H), 6.38 (d, J = 7.8 Hz, 1H), 4.51 (d, J = 7.2 Hz, 1H), 3.87 (s, 2H), 3.79 (d, J = 7.7 Hz, 2H), 2.23 (s, 3H), 2.17 – 1.96 (m, 1H), 1.57 – 1.46 (m, 6H), 1.22 (s, 9H), 0.79 (d, J = 6.6 Hz, 6H).

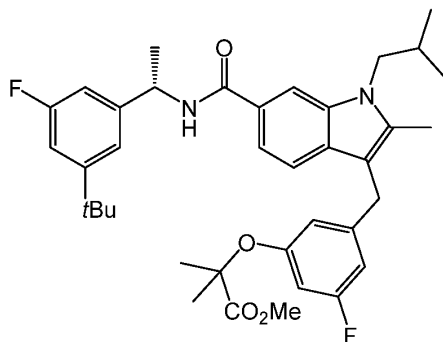
[0611] Compound 84: (S)-2-(3-((6-((1-(3-(tert-butyl)-5-fluorophenyl)ethyl)carbamoyl)-1-isobutyl-2-methyl-1H-indol-3-yl)methyl)-5-fluorophenoxy)-2-methylpropanoic acid.



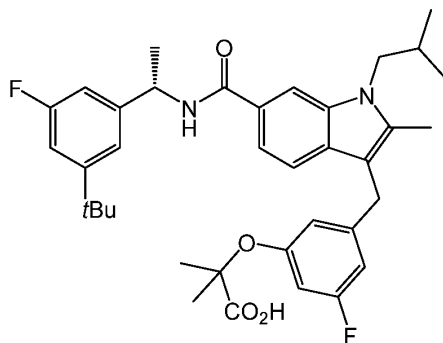
[0612] Step 1: (S)-N-(1-(3-(tert-butyl)-5-fluorophenyl)ethyl)-1-isobutyl-2-methyl-1H-indole-6-carboxamide. The title compound was prepared following the same general protocol as described in Step 8, Compound 1, using the 1-isobutyl-2-methyl-1H-indole-6-carboxylic acid instead of the 1-methyl-2-methyl-1H-indole-6-carboxylic acid and the (S)-1-(3-(tert-butyl)-5-fluorophenyl)ethanamine hydrochloride instead of the (S)-1-(4-(tert-butyl)phenyl)ethanamine hydrochloride. A yellow solid was obtained (15 mg, yield 85%). ESI-MS (m/z): 408.77 [M]⁺.



[0613] Step 2: (S)-N-(1-(3-(tert-butyl)-5-fluorophenyl)ethyl)-3-(3-fluoro-5-hydroxybenzyl)-1-isobutyl-2-methyl-1H-indole-6-carboxamide. The title compound was prepared following the same general protocol as described in Step 1, Compound 42, using the 3-fluoro-5-hydroxybenzaldehyde instead of the 2-chloro-3-hydroxybenzaldehyde and the (S)-N-(1-(3-(tert-butyl)-5-fluorophenyl)ethyl)-1-isobutyl-2-methyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide. A brown solid was obtained (18 mg, yield 92%). ESI-MS (m/z): 532.68 [M]⁺.

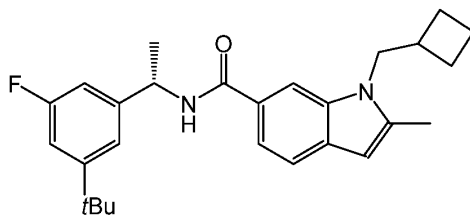


[0614] Step 3: methyl (S)-2-(3-(((6-((1-(3-(tert-butyl)-5-fluorophenyl)ethyl)carbamoyl)-1-isobutyl-2-methyl-1H-indol-3-yl)methyl)-5-fluorophenoxy)-2-methylpropanoate. The title compound was prepared following the same general protocol as described in Step 2, Compound 42, using the (S)-N-(1-(3-(tert-butyl)-5-fluorophenyl)ethyl)-3-(3-fluoro-5-hydroxybenzyl)-1-isobutyl-2-methyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-3-(2-chloro-3-hydroxybenzyl)-1,2-dimethyl-1H-indole-6-carboxamide and the methyl 2-bromo-2-methylpropanoate instead of the (R)-2-bromopropanoate. A white solid was obtained (17mg, yield 79%). ESI-MS (m/z): 632.70 [M]⁺.



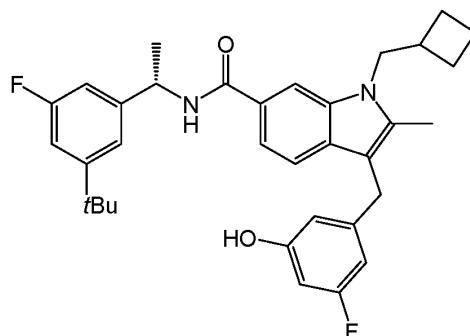
[0615] Step 4: (S)-2-(3-(((6-((1-(3-(tert-butyl)-5-fluorophenyl)ethyl)carbamoyl)-1-isobutyl-2-methyl-1H-indol-3-yl)methyl)-5-fluorophenoxy)-2-methylpropanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the methyl (S)-2-(3-(((6-((1-(3-(tert-butyl)-5-fluorophenyl)ethyl)carbamoyl)-1-isobutyl-2-methyl-1H-indol-3-yl)methyl)-5-fluorophenoxy)-2-methylpropanoate instead of the (ethyl 2-(4-(((S)-1-(4-(tert-butyl) phenyl) ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)propanoate. A yellow solid was obtained (9 mg, yield 57%). ¹H NMR (400 MHz, CDCl₃) δ 7.90 (d, J = 1.3 Hz, 1H), 7.36 – 7.27 (m, 2H), 7.18 (d, J = 1.7 Hz, 1H), 6.98 (dt, J = 10.8, 2.0 Hz, 1H), 6.91 (d, J = 9.3 Hz, 1H), 6.54 (d, J = 9.3 Hz, 1H), 6.49 – 6.33 (m, 3H), 5.34 (t, J = 7.1 Hz, 1H), 4.00 (s, 2H), 3.92 (d, J = 7.7 Hz, 2H), 2.21-1.95 (m, 1H), 2.17 (s, 3H), 1.60 (d, J = 6.9 Hz, 3H), 1.52 (s, 6H), 1.30 (s, 9H), 0.91 (d, J = 6.7 Hz, 6H). ESI-MS (m/z): 618.71 [M]⁺.

[0616] Compound 85: (S)-2-(3-(((6-((1-(3-(tert-butyl)-5-fluorophenyl)ethyl)carbamoyl)-1-(cyclobutylmethyl)-2-methyl-1H-indol-3-yl)methyl)-5-fluorophenoxy)-2-methylpropanoic acid.

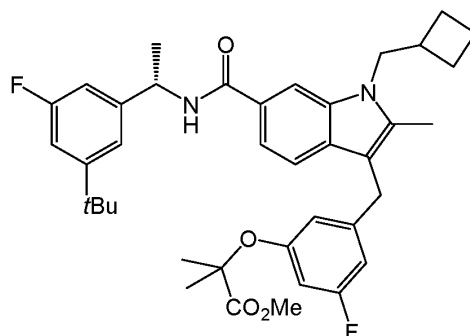


[0617] Step 1: (S)-N-(1-(3-(tert-butyl)-5-fluorophenyl)ethyl)-1-(cyclobutylmethyl)-2-methyl-1H-indole-6-carboxamide. The title compound was prepared following the same general protocol as described in Step 8, Compound 1, using the 1-(cyclobutylmethyl)-2-methyl-1H-indole-6-carboxylic acid instead of the 1-methyl-2-methyl-1H-indole-6-carboxylic acid and the (S)-1-(3-(tert-butyl)-5-fluorophenyl)ethanamine

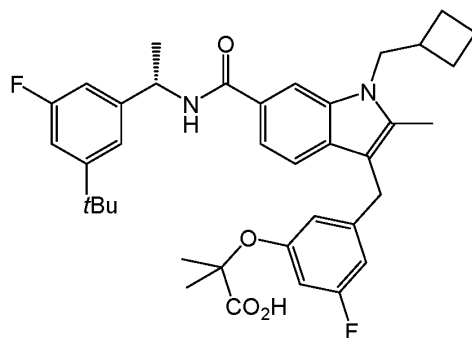
hydrochloride instead of the (S)-1-(4-(tert-butyl)phenyl)ethanamine hydrochloride. A yellow solid was obtained (10 mg, yield 90%). ESI-MS (m/z): 420.70 [M]⁺.



[0618] Step 2: (S)-N-(1-(3-(tert-butyl)-5-fluorophenyl)ethyl)-1-(cyclobutylmethyl)-3-(3-fluoro-5-hydroxybenzyl)-2-methyl-1H-indole-6-carboxamide. The title compound was prepared following the same general protocol as described in Step 1, Compound 42, using the 3-fluoro-5-hydroxybenzaldehyde instead of the 2-chloro-3-hydroxybenzaldehyde and the (S)-N-(1-(3-(tert-butyl)-5-fluorophenyl)ethyl)-1-(cyclobutylmethyl)-2-methyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide. A yellow solid was obtained (12 mg, yield 92%). ESI-MS (m/z): 544.70 [M]⁺.

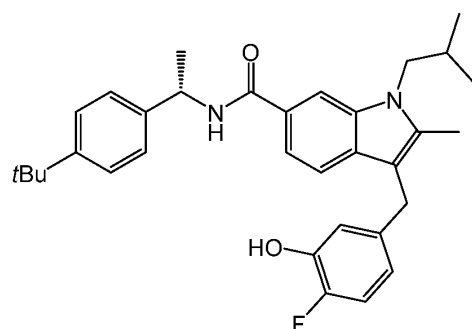


[0619] Step 3: methyl (S)-2-(3-(((1-(3-(tert-butyl)-5-fluorophenyl)ethyl)carbamoyl)-1-(cyclobutylmethyl)-2-methyl-1H-indol-3-yl)methyl)-5-fluorophenoxy)-2-methylpropanoate. The title compound was prepared following the same general protocol as described in Step 2, Compound 42, using the (S)-N-(1-(3-(tert-butyl)-5-fluorophenyl)ethyl)-1-(cyclobutylmethyl)-3-(3-fluoro-5-hydroxybenzyl)-2-methyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-3-(2-chloro-3-hydroxybenzyl)-1,2-dimethyl-1H-indole-6-carboxamide and the methyl 2-bromo-2-methylpropanoate instead of the (R)-2-bromopropanoate. A white solid was obtained (10mg, yield 70%).

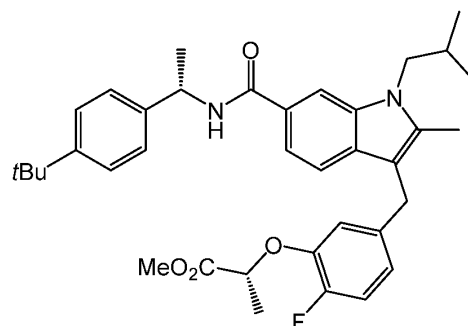


[0620] Step 4: (S)-2-(3-((6-((1-(3-(tert-butyl)-5-fluorophenyl)ethyl)carbamoyl)-1-(cyclobutylmethyl)-2-methyl-1H-indol-3-yl)methyl)-5-fluorophenoxy)-2-methylpropanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the methyl (S)-2-(3-((6-((1-(3-(tert-butyl)-5-fluorophenyl)ethyl)carbamoyl)-1-(cyclobutylmethyl)-2-methyl-1H-indol-3-yl)methyl)-5-fluorophenoxy)-2-methylpropanoate instead of the (ethyl 2-(4-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)propanoate. A yellow solid was obtained (7 mg, yield 71%). ¹H NMR (400 MHz, CDCl₃) δ 7.93 (s, 1H), 7.54 (d, J = 8.5 Hz, 1H), 7.35 (dd, J = 7.2, 2.6 Hz, 1H), 7.30 (s, 2H), 6.99 (dd, J = 10.9, 8.6 Hz, 1H), 6.75 (d, J = 8.4 Hz, 1H), 6.55 (d, J = 9.3 Hz, 1H), 6.49 – 6.39 (m, 2H), 5.47 (q, J = 7.3 Hz, 1H), 4.13 (d, J = 7.0 Hz, 2H), 3.99 (s, 2H), 2.36 (s, 3H), 2.12 (m, 2H), 1.82 (qt, J = 7.9, 4.0 Hz, 4H), 1.62 (d, J = 6.9 Hz, 3H), 1.52 (s, 6H), 1.30 (s, 9H).

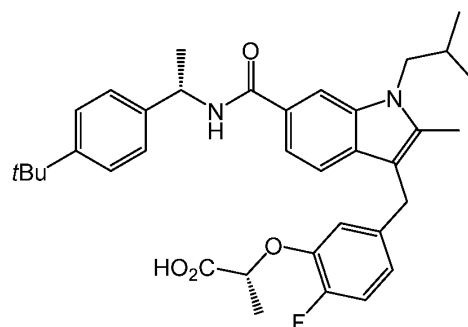
[0621] Compound 86: (R)-2-(5-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1-isobutyl-2-methyl-1H-indol-3-yl)methyl)-2-fluorophenoxy)propanoic acid.



[0622] Step 1: (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-3-(4-fluoro-3-hydroxybenzyl)-1-isobutyl-2-methyl-1H-indole-6-carboxamide. The title compound was prepared following the same general protocol as described in Step 1, Compound 42, using the 4-fluoro-3-hydroxybenzaldehyde instead of the 2-chloro-3-hydroxybenzaldehyde and the ((S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1-isobutyl-2-methyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide. A yellow solid was obtained (23 mg, yield 87%). ESI-MS (m/z): 514. 16 [M]⁺.

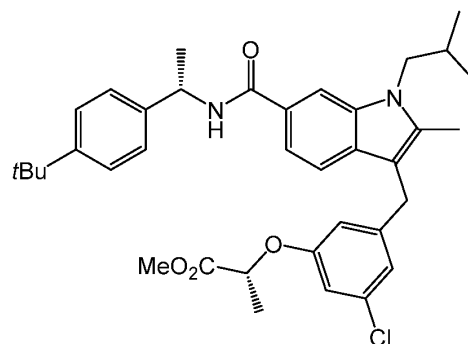


[0623] Step 2: methyl (R)-2-(5-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1-isobutyl-2-methyl-1H-indol-3-yl)methyl)-2-fluorophenoxy)propanoate. The title compound was prepared following the same general protocol as described in Step 2, Compound 42, using the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-3-(4-fluoro-3-hydroxybenzyl)-1-isobutyl-2-methyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-3-(2-chloro-3-hydroxybenzyl)-1,2-dimethyl-1H-indole-6-carboxamide and the methyl (S)-2-bromopropanoate instead of the (R)-2-bromopropanoate. A white solid was obtained (24mg, yield 88%). ESI-MS (m/z): 600.61 [M]⁺.

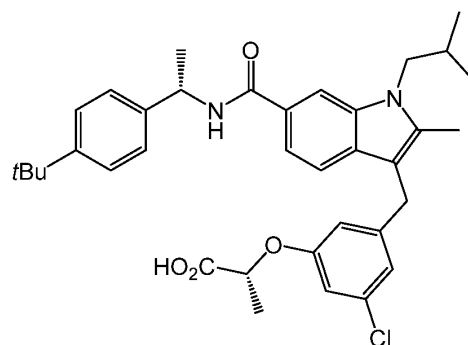


[0624] Step 3: (R)-2-(5-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1-isobutyl-2-methyl-1H-indol-3-yl)methyl)-2-fluorophenoxy)propanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the methyl (R)-2-(5-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1-isobutyl-2-methyl-1H-indol-3-yl)methyl)-2-fluorophenoxy)propanoate instead of the (ethyl 2-(4-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)propanoate. A yellow solid was obtained (20 mg, yield 85%). ¹H NMR (400 MHz, CDCl₃) δ 7.87 (s, 1H), 7.40 - 7.30 (m, 5H), 6.93 (dd, J = 11.21, 8.3 Hz, 1H), 6.78 - 6.70 (m, 1H), 5.34 (p, J = 7.0 Hz, 1H), 4.60 (q, J = 6.8 Hz, 1H), 3.98 (s, 2H), 3.90 (d, J = 7.7 Hz, 2H), 3.72-3.64 (m, 1H), 2.34 (s, 3H), 2.22 (dd, J = 13.7, 7.0 Hz, 1H), 1.59 (dd, J = 14.5, 6.8 Hz, 6H), 1.31 (s, 9H), 0.89 (d, J = 6.6 Hz, 6H). ESI-MS (m/z): 586.619[M]⁺.

[0625] Compound 87: (R)-2-(3-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1-isobutyl-2-methyl-1H-indol-3-yl)methyl)-5-chlorophenoxy)propanoic acid.

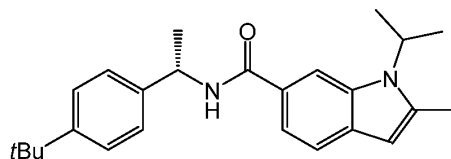


[0626] Step 1: methyl (R)-2-(3-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1-isobutyl-2-methyl-1H-indol-3-yl)methyl)-5-chlorophenoxy)propanoate. The title compound was prepared following the same general protocol as described in Step 9, Compound 1, using the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1-isobutyl-2-methyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide and the methyl (R)-2-(3-chloro-5-formylphenoxy)propanoate instead of the ethyl 2-(4-formylphenoxy)propanoate. A yellow solid was obtained (25 mg, yield 92%). ESI-MS (m/z): 616.68 [M]⁺.



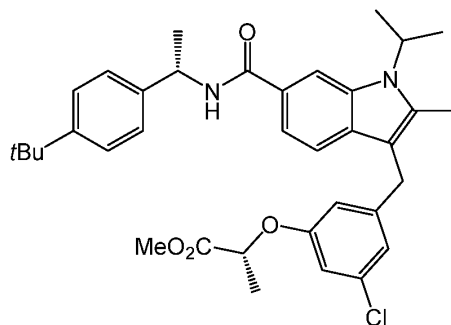
[0627] Step 2: (R)-2-(3-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1-isobutyl-2-methyl-1H-indol-3-yl)methyl)-5-chlorophenoxy)propanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the methyl (R)-2-(3-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1-isobutyl-2-methyl-1H-indol-3-yl)methyl)-5-chlorophenoxy)propanoate instead of the (ethyl 2-(4-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)propanoate. A brown solid was obtained (20 mg, yield 83%). ¹H NMR (400 MHz, CDCl₃) δ 7.89 (s, 1H), 7.45 -7.27 (m, 5H), 6.78 (s, 1H), 6.68 (s, 1H), 6.50 (s, 1H), 6.42 (d, J = 7.9 Hz, 1H), 5.34 (t, J = 7.2 Hz, 1H) 3.98 (s, 2H), 3.89 (d, J = 7.8 Hz, 2H), 2.33 (s, 3H), 2.21 (dt, J = 13.7, 7.1 Hz, 1H), 1.59 (d, J = 6.9 Hz, 3H), 1.55 (d, J = 6.9 Hz, 3H), 1.31 (s, 9H), 0.89 (d, J = 6.5 Hz, 6H). ESI-MS (m/z): 602.61 [M]⁺.

[0628] Compound 88: (R)-2-(3-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1-isopropyl-2-methyl-1H-indol-3-yl)methyl)-5-chlorophenoxy)propanoic acid.

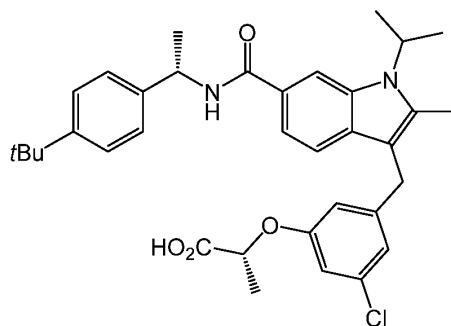


[0629] Step 1: (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1-isopropyl-2-methyl-1H-indole-6-carboxamide.

The title compound was prepared following the same general protocol as described in Step 8, Compound 1, using the 1-isopropyl-2-methyl-1H-indole-6-carboxylic acid instead of the 1-methyl-2-methyl-1H-indole-6-carboxylic acid. A yellow solid was obtained (18 mg, yield 72%). ESI-MS (m/z): 376.70 [M]⁺.



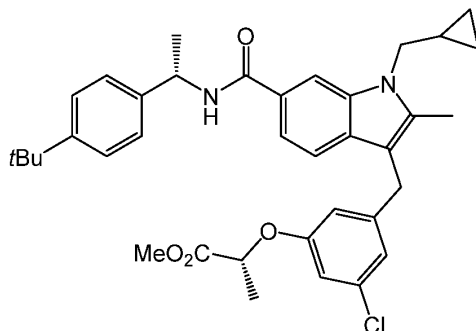
[0630] Step 2: methyl (R)-2-(3-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1-isopropyl-2-methyl-1H-indol-3-yl)methyl)-5-chlorophenoxy)propanoate. The title compound was prepared following the same general protocol as described in Step 9, Compound 1, using the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1-isopropyl-2-methyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide and the methyl (R)-2-(3-chloro-5-formylphenoxy)propanoate instead of the ethyl 2-(4-formylphenoxy)propanoate. A yellow solid was obtained (20 mg, yield 71%). ESI-MS (m/z): 602.63 [M]⁺.



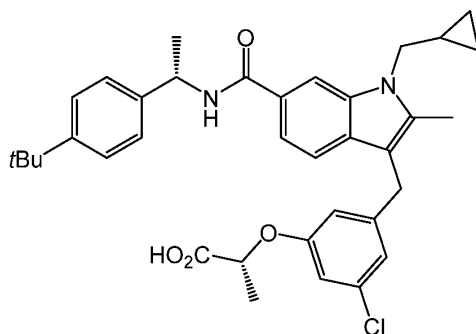
[0631] Step 3: (R)-2-(3-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1-isopropyl-2-methyl-1H-indol-3-yl)methyl)-5-chlorophenoxy)propanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the methyl (R)-2-(3-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1-isopropyl-2-methyl-1H-indol-3-yl)methyl)-5-chlorophenoxy)propanoate instead of the (ethyl 2-(4-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)propanoate. A brown powder was obtained (14 mg, yield 71%). ¹H NMR (600 MHz, CDCl₃) δ 8.07 (s, 1H), 7.37 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.5 Hz, 2H), 7.29 (d, J = 8.2 Hz, 1H), 7.26 – 7.21 (m, 1H), 6.79 (d, J = 1.6 Hz, 1H), 6.70 – 6.66 (m, 1H), 6.48 (s, 1H), 6.44 (t, J = 7.0 Hz, 1H), 5.35

(dq, $J = 14.2, 6.7$ Hz, 1H), 4.69 (p, $J = 7.0$ Hz, 1H), 4.60 (q, $J = 7.4$ Hz, 1H), 3.95 (s, 2H), 2.36 (d, $J = 1.5$ Hz, 3H), 1.60 (td, $J = 7.2, 2.8$ Hz, 9H), 1.56 (dd, $J = 7.0, 3.1$ Hz, 3H), 1.31 (s, 9H). ESI-MS (m/z): 588.55 $[M]^+$.

[0632] Compound 89: (R)-2-(3-(((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1-(cyclopropylmethyl)-2-methyl-1H-indol-3-yl)methyl)-5-chlorophenoxy)propanoic acid.

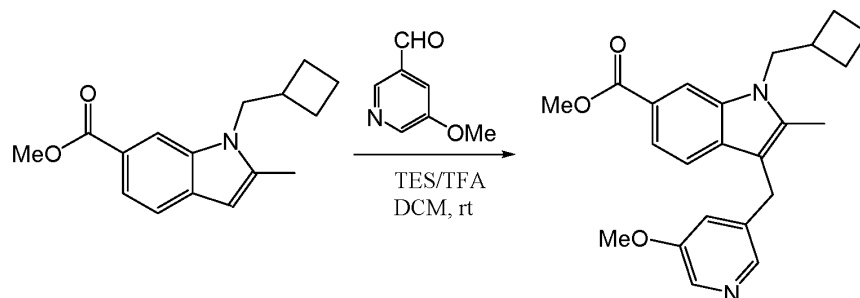


[0633] Step 1: methyl (R)-2-(3-(((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1-(cyclopropylmethyl)-2-methyl-1H-indol-3-yl)methyl)-5-chlorophenoxy)propanoate. The title compound was prepared following the same general protocol as described in Step 9, Compound 1, using the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1-(cyclopropylmethyl)-2-methyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide and the methyl (R)-2-(3-chloro-5-formylphenoxy)propanoate instead of the ethyl 2-(4-formylphenoxy)propanoate. A yellow solid was obtained (49 mg, yield 98%). ESI-MS (m/z): 614.79 $[M]^+$.

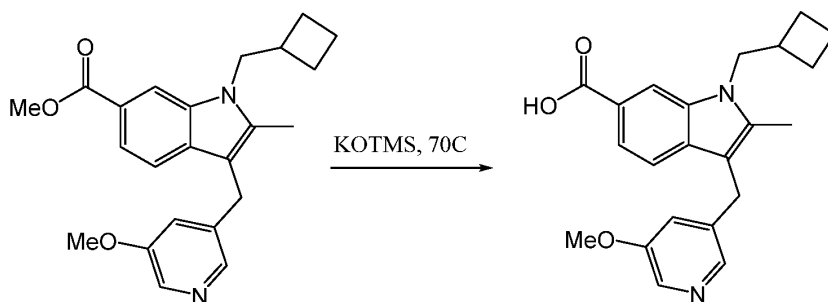


[0634] Step 2: (R)-2-(3-(((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1-(cyclopropylmethyl)-2-methyl-1H-indol-3-yl)methyl)-5-chlorophenoxy)propanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the methyl (R)-2-(3-(((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1-(cyclopropylmethyl)-2-methyl-1H-indol-3-yl)methyl)-5-chlorophenoxy)propanoate instead of the (ethyl 2-(4-(((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)propanoate. A yellow solid was obtained (43 mg, yield 91%). ^1H NMR (400 MHz, CDCl_3) δ 7.93 (s, 1H), 7.46 – 7.24 (m, 6H), 6.77 (d, $J = 3.5$ Hz, 1H), 6.67 (s, 1H), 6.59 – 6.37 (m, 2H), 5.34 (t, $J = 7.2$ Hz, 1H), 4.60 (s, 1H), 3.95 (d, $J = 4.3$ Hz, 4H), 2.33 (s, 3H), 1.66 – 1.45 (m, 6H), 1.30 (s, 9H), 1.20 – 1.00 (m, 1H), 0.59 – 0.42 (m, 2H), 0.31 (d, $J = 5.1$ Hz, 2H). ESI-MS (m/z): 600. 60 $[M]^+$.

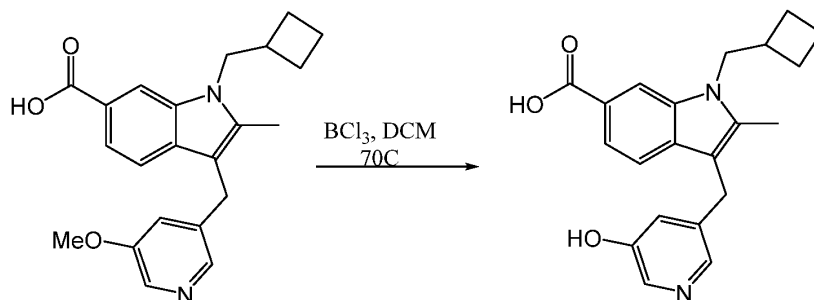
[0635] Compound 90: (R)-2-((5-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1-(cyclobutylmethyl)-2-methyl-1H-indol-3-yl)methyl)pyridin-3-yl)oxy)propanoic acid.



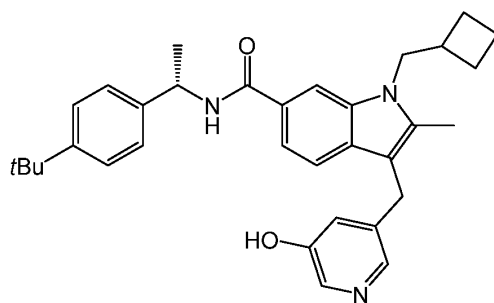
[0636] Step1: methyl 1-(cyclobutylmethyl)-3-((5-methoxypyridin-3-yl)methyl)-2-methyl-1H-indole-6-carboxylate. Triethylsilane (30 μ L, 1.8 mmol) and trifluoroacetic acid (83 μ L, 1.1 mmol) were sequentially added dropwise over 1 min to a stirred solution of methyl 1-(cyclobutylmethyl)-2-methyl-1H-indole-6-carboxylate (85 mg, 0.35 mmol) and 5-methoxynicotinaldehyde (49 mg, 0.35 mmol) in DCM (1 ml) at 0° C. The mixture was then warmed to rt and stirred for 2 h. The reaction was monitored by anal. HPLC until the complete consumption of the starting materials. The resulting mixture was quenched by a saturated solution of sodium bicarbonate (20 mL) and diluted with ethyl acetate (50 ml). The organic layer was separated, dried and concentrated in vacuo. The crude product was used for the next step without any further purification (45 mg, yield 34%). ESI-MS (m/z): 378.95 $[M]^+$.



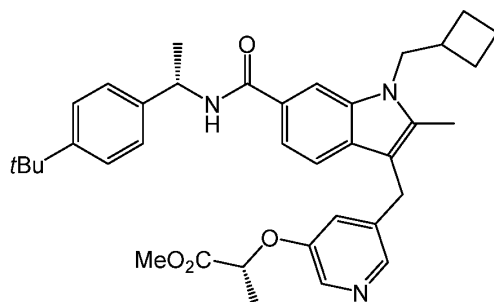
[0637] Step 2: 1-(cyclobutylmethyl)-3-((5-methoxypyridin-3-yl)methyl)-2-methyl-1H-indole-6-carboxylic acid. To a stirred solution of potassium trimethylsilonate in THF (120 μ l, 2M in THF, 0.24 mmol) was added methyl 1-(cyclobutylmethyl)-3-((5-methoxypyridin-3-yl)methyl)-2-methyl-1H-indole-6-carboxylate (45 mg, 0.12 mmol) in one portion and the reaction mixture was heated at 70°C for 10 minutes. The mixture was allowed to cool down and quenched with 5 N HCl aqueous solution (10 ml) and extracted with ethyl acetate (20 ml $\times$ 2). The combined organic layers were washed with a saturated NaHCO_3 and brine, dried over sodium sulfate and concentrated in vacuo. The obtained brown solid was used in the next step without further purification (42 mg, Yield 97%). ESI-MS (m/z): 364.85 $[M]^+$.



[0638] Step 3: 1-(cyclobutylmethyl)-3-((5-hydroxypyridin-3-yl)methyl)-2-methyl-1H-indole-6-carboxylic acid. To a solution of 1-(cyclobutylmethyl)-3-((5-methoxypyridin-3-yl)methyl)-2-methyl-1H-indole-6-carboxylic acid (42 mg, 1 mmol) in dry DCM (10 mL) under argon was added an excess of BCl_3 (2M in DCM , 5 mL). The reaction mixture was allowed to reflux until the complete consumption of the starting material. The reaction was quenched by adding a saturated aqueous solution of sodium bicarbonate (50 mL) at 0°C and extracted with ethyl acetate (50 mL $\times$ 2). The combined organic layers were washed with brine, dried over sodium sulfate and concentrated in vacuo. The residue was purified by column chromatography on silica gel (DCM/MeOH , 20:1 (v/v)). The desired product was obtained as a sticky yellow oil (32 mg, yield 74%). ESI-MS (m/z): 350.79 $[\text{M}]^+$.

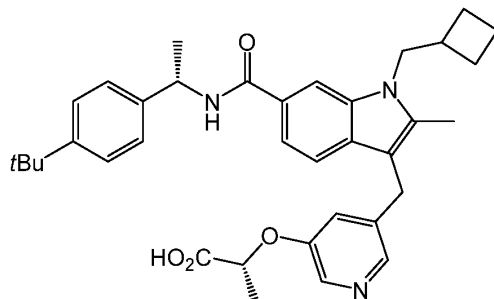


[0639] Step 4: (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1-(cyclobutylmethyl)-3-((5-hydroxypyridin-3-yl)methyl)-2-methyl-1H-indole-6-carboxamide. The title compound was prepared following the same general protocol as described in Step 8, Compound 1, using the 1-(cyclobutylmethyl)-3-((5-hydroxypyridin-3-yl)methyl)-2-methyl-1H-indole-6-carboxylic acid instead of 1,2-dimethyl-1H-indole-6-carboxylic acid. A yellow solid was obtained (15 mg, yield 32%). ESI-MS (m/z): 509.90 $[\text{M}]^+$.



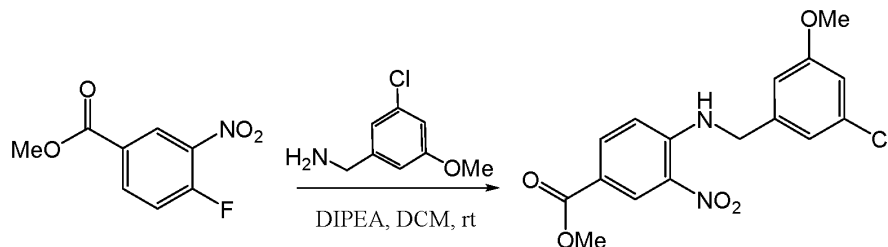
[0640] Step 5: methyl (R)-2-((5-((1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1-(cyclobutylmethyl)-2-methyl-1H-indol-3-yl)methyl)pyridin-3-yl)oxy)propanoate. The title compound was prepared following

the same general protocol as described in Step 2, Compound 42, using the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1-(cyclobutylmethyl)-3-((5-hydroxypyridin-3-yl)methyl)-2-methyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-3-(2-chloro-3-hydroxybenzyl)-1,2-dimethyl-1H-indole-6-carboxamide and the methyl (S)-2-bromopropanoate instead of the (R)-2-bromopropanoate. A grey solid was obtained (5 mg, yield 28%). ESI-MS (m/z): 595.88 [M]⁺.

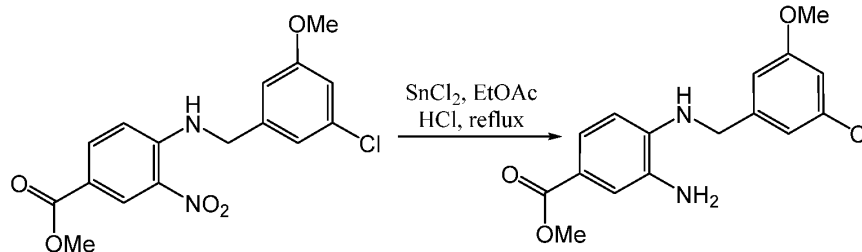


[0641] Step 6: (R)-2-((5-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1-(cyclobutylmethyl)-2-methyl-1H-indol-3-yl)methyl)pyridin-3-yl)oxy)propanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the methyl (R)-2-((5-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1-(cyclobutylmethyl)-2-methyl-1H-indol-3-yl)methyl)pyridin-3-yl)oxy)propanoate instead of the (ethyl 2-(4-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)propanoate. A grey solid was obtained (3 mg, yield 61%). ESI-MS (m/z): 581.68 [M]⁺.

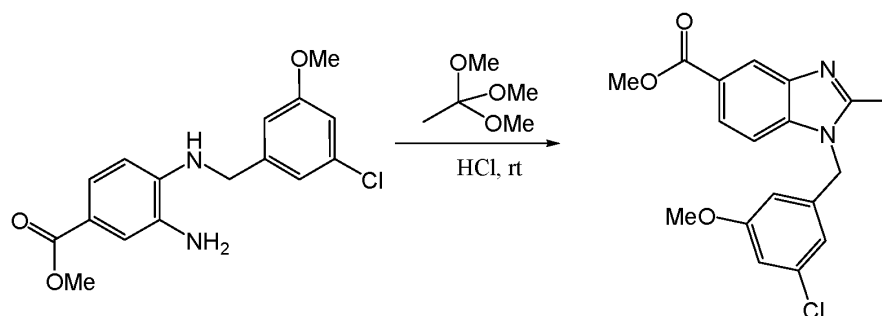
[0642] Compound 91: (R)-2-(3-((5-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-2-methyl-1H-benzo[d]imidazol-1-yl)methyl)-5-chlorophenoxy)propanoic acid.



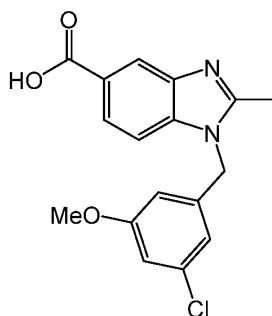
[0643] Step 1: methyl 4-((3-chloro-5-methoxybenzyl)amino)-3-nitrobenzoate. Methyl 4-fluoro-3-nitrobenzoate (325 mg, 1.55 mmol), (3-chloro-5-methoxyphenyl)methanamine (308 mg, 1.55 mmol) and N,N-diisopropylethylamine (214 μ l, 1.55 mmol) were stirred in CH₂Cl₂ (25 mL) at room temperature for 2 hours. The solvent was evaporated and the crude mixture was dissolved in dichloromethane and washed with water. The dichloromethane was evaporated in vacuo to collect the title compound as light-red powder (520 mg, yield 95%). ¹H NMR (400 MHz, CDCl₃) δ 11.19 (br, 1H), 8.89 (d, J = 2.0 Hz, 1H), 8.72 (t, J = 5.8 Hz, 1H), 8.01 (dd, J = 8.9, 2.1 Hz, 1H), 6.91 (t, J = 1.7 Hz, 1H), 6.87 – 6.64 (m, 3H), 4.56 (d, J = 5.8 Hz, 2H), 3.89 (s, 3H), 3.78 (s, 3H). ESI-MS (m/z): 350.51 [M]⁺.



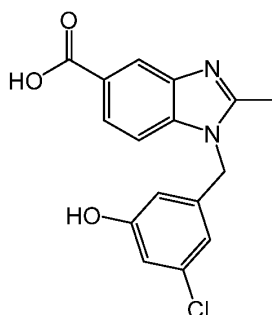
[0644] Step 2: methyl 3-amino-4-((3-chloro-5-methoxybenzyl)amino)benzoate. Methyl 4-((3-chloro-5-methoxybenzyl)amino)-3-nitrobenzoate (520 mg, 1.48 mmol) was suspended in ethyl acetate (50ml) and $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (1.4g, 7.4 mmol) and concentrated HCl (1 mL) were added. It was heated to reflux for 2 hours then cooled to room temperature. The reaction mixture was poured onto cold water (200mL) and cooled in an ice bath. It was basified with careful addition of saturated sodium bicarbonate solution (50mL). The precipitate was removed by filtration through celite, washed with EtOAc (50 mL). The filtrate was transferred to separating funnel and aqueous phase separated and extracted with EtOAc (50 mL). The combined organics were dried over anhydrous sodium sulfate and evaporated to dryness. The crude product was used for the next step without any further purification (400 mg, yield 84%). ^1H NMR (600 MHz, CDCl_3) δ 7.39 (dd, J = 8.3, 2.0 Hz, 1H), 7.29 (d, J = 2.1 Hz, 1H), 6.80 (t, J = 1.6 Hz, 1H), 6.66 (dt, J = 11.0, 2.3 Hz, 2H), 6.36 (d, J = 8.4 Hz, 1H), 4.48 (br, 1H), 4.16 (s, 2H), 3.70 (s, 3H), 3.62 (s, 3H), 3.39 (br, 2H).



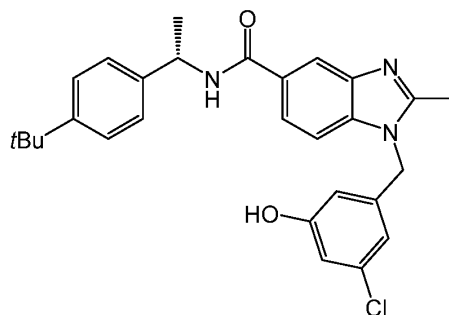
[0645] Step 3: methyl 1-(3-chloro-5-methoxybenzyl)-2-methyl-1H-benzo[d]imidazole-5-carboxylate. To a suspension solution of methyl 3-amino-4-((3-chloro-5-methoxybenzyl)amino)benzoate (400 mg, 1.25 mmol) in 5 mL of trimethyl orthoacetate was added a concentrated HCl (1 mL) and the reaction mixture was stirred for 1h at rt. The reaction was quenched with a saturated solution of sodium bicarbonate (50 mL). The aqueous solution was extracted with EtOAc (50 mL) and organic phase was dried over anhydrous sodium sulfate and evaporated to dryness. The residue was purified by flash chromatography and the desired product was isolated as light-brown solid (200 mg, yield 47%). ^1H NMR (400 MHz, CDCl_3) δ 8.31 (s, 1H), 7.82 (d, J = 8.4 Hz, 1H), 7.10 (d, J = 8.6 Hz, 1H), 6.68 (s, 1H), 6.47 (d, J = 14.2 Hz, 1H), 6.30 (s, 1H), 5.12 (s, 2H), 3.81 (s, 3H), 3.58 (d, J = 6.9 Hz, 3H), 2.45 (s, 3H). ESI-MS (m/z): 344.76 $[\text{M}]^+$.



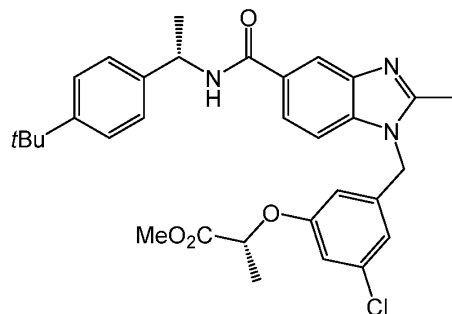
[0646] Step 4: 1-(3-chloro-5-methoxybenzyl)-2-methyl-1H-benzo[d]imidazole-5-carboxylic acid. The title compound was prepared following the same general protocol as described in Step 2, Compound 90, using the methyl 1-(3-chloro-5-methoxybenzyl)-2-methyl-1H-benzo[d]imidazole-5-carboxylate instead of the methyl 1-(cyclobutylmethyl)-3-((2-methoxypyridin-4-yl)methyl)-2-methyl-1H-indole-6-carboxylate. A yellow solid was obtained (150 mg, yield 78%). ESI-MS (m/z): 330.76 $[M]^+$.



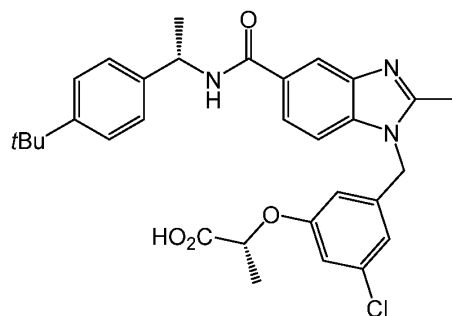
[0647] Step 5: 1-(3-chloro-5-hydroxybenzyl)-2-methyl-1H-benzo[d]imidazole-5-carboxylic acid. The title compound was prepared following the same general protocol as described in Step 3, Compound 90, using the 1-(3-chloro-5-methoxybenzyl)-2-methyl-1H-benzo[d]imidazole-5-carboxylic acid instead of the 1-(cyclobutylmethyl)-3-((2-methoxypyridin-4-yl)methyl)-2-methyl-1H-indole-6-carboxylic acid. A yellow solid was obtained (49 mg, yield 34%). ESI-MS (m/z): 316.78 $[M]^+$.



[0648] Step 6: (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1-(3-chloro-5-hydroxybenzyl)-2-methyl-1H-benzo[d]imidazole-5-carboxamide. The title compound was prepared following the same general protocol as described in Step 8, Compound 1, using the 1-(3-chloro-5-hydroxybenzyl)-2-methyl-1H-benzo[d]imidazole-5-carboxylic acid instead of 1,2-dimethyl-1H-indole-6-carboxylic acid. A brown solid was obtained (35 mg, yield 47%). ESI-MS (m/z): 475.78 $[M]^+$.

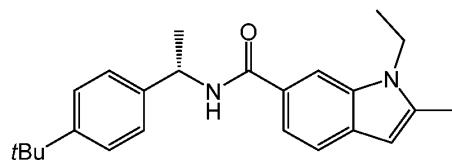


[0649] Step 7: methyl (R)-2-(3-((5-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-2-methyl-1H-benzo[d]imidazol-1-yl)methyl)-5-chlorophenoxy)propanoate. The title compound was prepared following the same general protocol as described in Step 2, Compound 42, using the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1-(3-chloro-5-hydroxybenzyl)-2-methyl-1H-benzo[d]imidazole-5-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-3-(2-chloro-3-hydroxybenzyl)-1,2-dimethyl-1H-indole-6-carboxamide and the methyl (S)-2-bromopropanoate instead of the (R)-2-bromopropanoate. A brown solid was obtained (12 mg, yield 29%). ESI-MS (m/z): 561.99 [M]⁺.

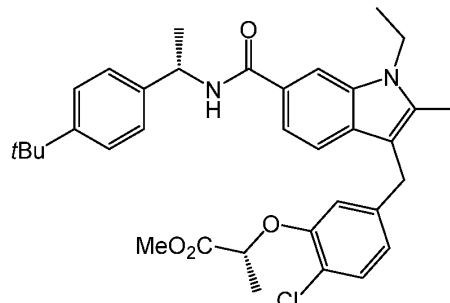


[0650] Step 8: (R)-2-(3-((5-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-2-methyl-1H-benzo[d]imidazol-1-yl)methyl)-5-chlorophenoxy)propanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the methyl (R)-2-(3-((5-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-2-methyl-1H-benzo[d]imidazol-1-yl)methyl)-5-chlorophenoxy)propanoate instead of the (ethyl 2-(4-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)propanoate. A grey solid was obtained (10 mg, yield 97%). ¹H NMR (400 MHz, CDCl₃) δ 8.05 (s, 1H), 7.93 (s, 1H), 7.37 (s, 6H), 7.05 (s, 1H), 6.91 (s, 1H), 6.85 (d, J = 14.0 Hz, 1H), 5.83 (s, 1H), 5.44 (s, 1H), 5.29 (d, J = 11.7 Hz, 2H), 2.71 (s, 3H), 1.62 (d, J = 6.7 Hz, 3H), 1.51 (s, 3H), 1.29 (s, 9H). ESI-MS (m/z): 548.10 [M]⁺.

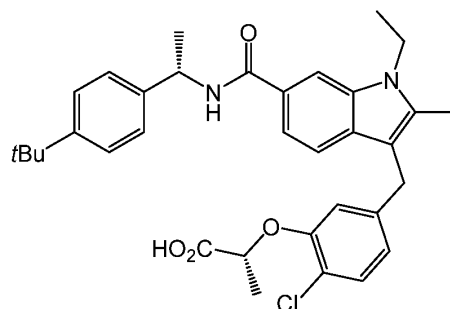
[0651] Compound 92: (R)-2-(5-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1-ethyl-2-methyl-1H-indol-3-yl)methyl)-2-chlorophenoxy)propanoic acid.



[0652] Step 1: (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1-ethyl-2-methyl-1H-indole-6-carboxamide. The title compound was prepared following the same general protocol as described in Step 8, Compound 1, using the 1-ethyl-2-methyl-1H-indole-6-carboxylic acid instead of the 1-methyl-2-methyl-1H-indole-6-carboxylic acid. A light-yellow solid was obtained (30 mg, yield 84%). ESI-MS (m/z): 362.70 [M]⁺.

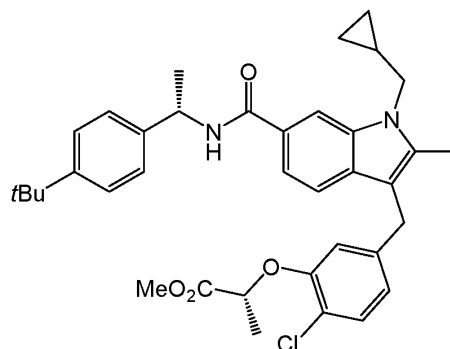


[0653] Step 2: methyl (R)-2-(5-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1-ethyl-2-methyl-1H-indol-3-yl)methyl)-2-chlorophenoxy)propanoate. The title compound was prepared following the same general protocol as described in Step 9, Compound 1, using the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1-ethyl-2-methyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide and the methyl (R)-2-(2-chloro-5-formylphenoxy)propanoate instead of the ethyl 2-(4-formylphenoxy)propanoate. A yellow solid was obtained (35 mg, yield 72%). ESI-MS (m/z): 588.66 [M]⁺.

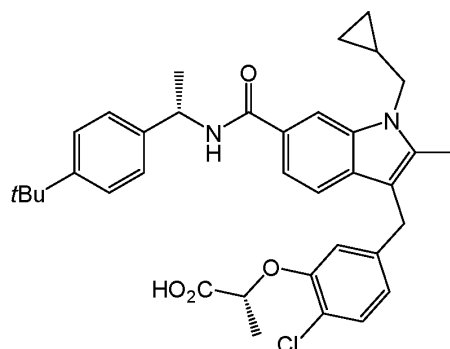


[0654] Step 3: (R)-2-(5-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1-ethyl-2-methyl-1H-indol-3-yl)methyl)-2-chlorophenoxy)propanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the methyl (R)-2-(5-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1-ethyl-2-methyl-1H-indol-3-yl)methyl)-2-chlorophenoxy)propanoate instead of the (ethyl 2-(4-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)propanoate. A light-yellow solid was obtained (31 mg, yield 90%). ¹H NMR (400 MHz, CDCl₃) δ 7.86 (s, 1H), 7.29 (m, 6H), 7.08 (s, 1H), 6.72 (s, 1H), 6.58 (d, J = 31.4 Hz, 2H), 5.33 (t, J = 6.3 Hz, 1H), 4.52 (s, 1H), 4.21 – 3.98 (m, 2H), 3.89 (s, 2H), 2.27 (s, 3H), 1.57 (d, J = 6.8 Hz, 3H), 1.46 (d, J = 6.8 Hz, 3H), 1.26 (d, J = 14.9 Hz, 12H). ESI-MS (m/z): 574.61 [M]⁺.

[0655] Compound 93: (R)-2-(5-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1-(cyclopropylmethyl)-2-methyl-1H-indol-3-yl)methyl)-2-chlorophenoxy)propanoic acid.

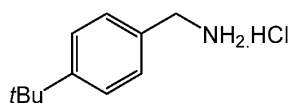


[0656] Step 1: methyl (R)-2-(5-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1-(cyclopropylmethyl)-2-methyl-1H-indol-3-yl)methyl)-2-chlorophenoxy)propanoate. The title compound was prepared following the same general protocol as described in Step 9, Compound 1, using the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1-(cyclopropylmethyl)-2-methyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide and the methyl (R)-2-(2-chloro-5-formylphenoxy)propanoate instead of the ethyl 2-(4-formylphenoxy)propanoate. A yellow solid was obtained (13 mg, yield 70%). ESI-MS (m/z): 614.74 $[M]^+$.

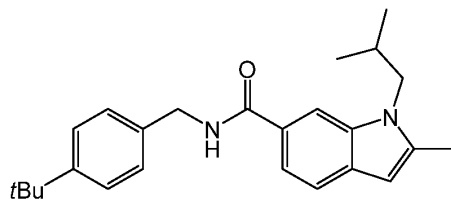


[0657] Step 2: (R)-2-(5-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1-(cyclopropylmethyl)-2-methyl-1H-indol-3-yl)methyl)-2-chlorophenoxy)propanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the methyl (R)-2-(5-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1-(cyclopropylmethyl)-2-methyl-1H-indol-3-yl)methyl)-2-chlorophenoxy)propanoate instead of the (ethyl 2-(4-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)propanoate. A brown solid was obtained (9 mg, yield 70%). ^1H NMR (600 MHz, CDCl_3) δ 7.90 (s, 1H), 7.52 – 7.23 (m, 6H), 7.18 (d, $J = 7.3$ Hz, 1H), 6.69 (d, $J = 33.7$ Hz, 2H), 6.48 (s, 1H), 5.44 – 5.20 (m, 1H), 4.58 (s, 1H), 4.00 (s, 2H), 3.95 (s, 2H), 2.34 (s, 3H), 1.76 – 1.53 (m, 6H), 1.30 (s, 9H), 1.14-1.12 (m, 1H), 0.61 – 0.39 (m, 2H), 0.39 – 0.22 (m, 2H). ESI-MS (m/z): 600.72 $[M]^+$.

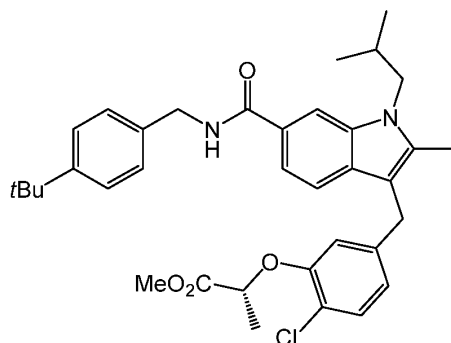
[0658] Compound 94: (R)-2-(5-((4-(tert-butyl)benzyl)carbamoyl)-1-isobutyl-2-methyl-1H-indol-3-yl)methyl)-2-chlorophenoxy)propanoic acid.



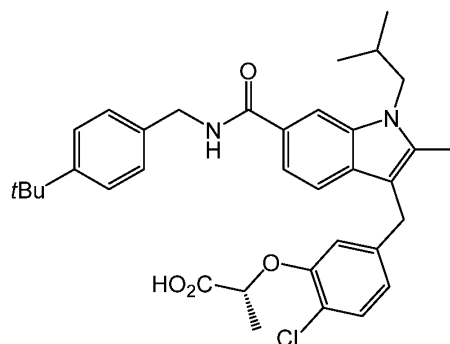
[0659] Step 1: (4-(tert-butyl)phenyl)methanamine hydrochloride. 4-(tert-butyl)benzonitrile (1g, 6.28 mmol) was dissolved in MeOH (20 mL) and NiCl_2 (0.81g, 6.28 mmol) was added to the mixture in one portion. The reaction was cooled to 0°C and NaBH_4 (0.72g, 19 mmol) was added in small portion over 30 minutes and the mixture was stirred at rt for 5 hours. The reaction mixture was filtrated through the celite and the filtrate was evaporated to dryness under vacuum. The residue was dissolved in ether (50 mL) and an aqueous solution of HCl (5M, 5 mL) was added dropwise into the mixture. The precipitate was filtrated and further washed by ether (50 mL). The salt was obtained as light-green powder (1.2g, yield 95%). ^1H NMR (600 MHz, DMSO) δ 8.41 (br, 2H), 7.50 – 6.85 (m, 4H), 3.71 (s, 2H), 1.04 (s, 9H).



[0660] Step 2: N-(4-(tert-butyl)benzyl)-1-isobutyl-2-methyl-1H-indole-6-carboxamide. The title compound was prepared following the same general protocol as described in Step 8, Compound 1, using the (4-(tert-butyl)phenyl)methanamine hydrochloride instead of the (S)-1-(4-(tert-butyl)phenyl)ethanamine hydrochloride and the 1-isobutyl-2-methyl-1H-indole-6-carboxylic acid instead of the 1,2-dimethyl-1H-indole-6-carboxylic acid. A light-yellow solid was obtained (38 mg, yield 95%). ESI-MS (m/z): 376.77 $[\text{M}]^+$.

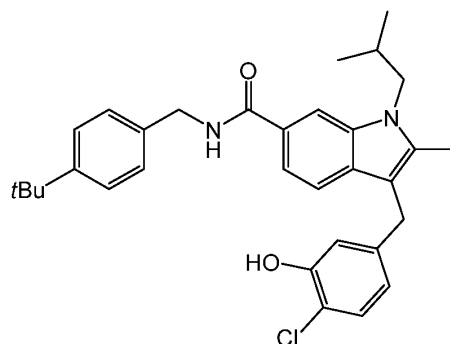


[0661] Step 3: methyl (R)-2-(5-((6-((4-(tert-butyl)benzyl)carbamoyl)-1-isobutyl-2-methyl-1H-indol-3-yl)methyl)-2-chlorophenoxy)propanoate. The title compound was prepared following the same general protocol as described in Step 9, Compound 1, using the N-(4-(tert-butyl)benzyl)-1-isobutyl-2-methyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide and the methyl (R)-2-(2-chloro-5-formyl phenoxy)propanoate instead of the ethyl 2-(4-formylphenoxy)propanoate. A yellow solid was obtained (15 mg, yield 78%). ESI-MS (m/z): 602.62 $[\text{M}]^+$.

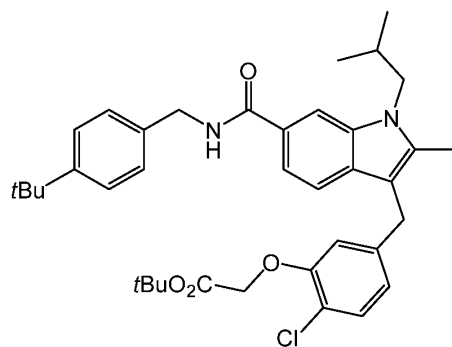


[0662] Step 4: (R)-2-(5-((6-((4-(tert-butyl)benzyl)carbamoyl)-1-isobutyl-2-methyl-1H-indol-3-yl)methyl)-2-chlorophenoxy)propanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the methyl (R)-2-(5-((6-((4-(tert-butyl)benzyl)carbamoyl)-1-isobutyl-2-methyl-1H-indol-3-yl)methyl)-2-chlorophenoxy)propanoate instead of the (ethyl 2-(4-(((S)-1-(4-(tert-butyl) phenyl) ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)propanoate. A brown solid was obtained (7 mg, yield 42%). ESI-MS (m/z): 588.75 [M]⁺.

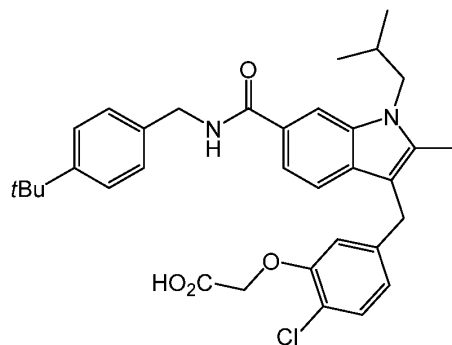
[0663] Compound 95: 2-(5-((6-((4-(tert-butyl)benzyl)carbamoyl)-1-isobutyl-2-methyl-1H-indol-3-yl)methyl)-2-chlorophenoxy)acetic acid.



[0664] Step 1: N-(4-(tert-butyl)benzyl)-3-(4-chloro-3-hydroxybenzyl)-1-isobutyl-2-methyl-1H-indole-6-carboxamide. The title compound was prepared following the same general protocol as described in Step 1, Compound 42, using the 4-chloro-3-hydroxybenzaldehyde instead of the 2-chloro-3-hydroxybenzaldehyde and N-(4-(tert-butyl)benzyl)-1-isobutyl-2-methyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide. A yellow solid was obtained (17 mg, yield 87%). ESI-MS (m/z): 516.69 [M]⁺.

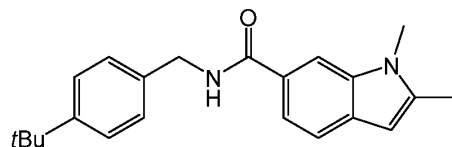


[0665] Step 2: tert-butyl 2-(5-((6-((4-(tert-butyl)benzyl)carbamoyl)-1-isobutyl-2-methyl-1H-indol-3-yl)methyl)-2-chlorophenoxy)acetate. The title compound was prepared following the same general protocol as described in Step 2, Compound 42, using the N-(4-(tert-butyl)benzyl)-3-(4-chloro-3-hydroxybenzyl)-1-isobutyl-2-methyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-3-(2-chloro-3-hydroxybenzyl)-1,2-dimethyl-1H-indole-6-carboxamide and the tert-butyl 2-bromoacetate instead of the (R)-2-bromopropanoate. A brown solid was obtained (12 mg, yield 29%). ESI-MS (m/z): 630.25 [M]⁺.



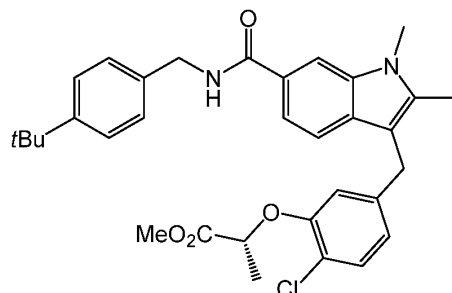
[0666] Step 3: 2-(5-((6-((4-(tert-butyl)benzyl)carbamoyl)-1-isobutyl-2-methyl-1H-indol-3-yl)methyl)-2-chlorophenoxy)acetic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the tert-butyl 2-(5-((6-((4-(tert-butyl)benzyl)carbamoyl)-1-isobutyl-2-methyl-1H-indol-3-yl)methyl)-2-chlorophenoxy)acetate instead of the (ethyl 2-(4-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)propanoate. A brown solid was obtained (4 mg, yield 37%). ESI-MS (m/z): 574.72 [M]⁺.

[0667] Compound 96: (R)-2-(5-((6-((4-(tert-butyl)benzyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)-2-chlorophenoxy) propanoic acid.

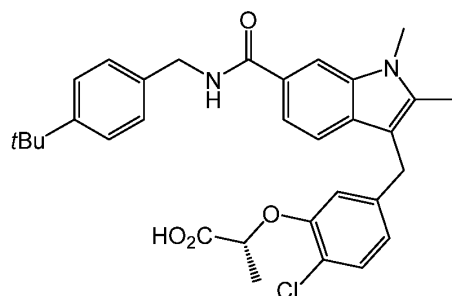


[0668] Step 1: N-(4-(tert-butyl)benzyl)-1,2-dimethyl-1H-indole-6-carboxamide. The title compound was prepared following the same general protocol as described in Step 8, Compound 1, using the (4-(tert-

butyl)phenyl)methanamine hydrochloride instead of the (S)-1-(4-(tert-butyl)phenyl)ethanamine hydrochloride. A brown solid was obtained (35 mg, yield 45%). ESI-MS (m/z): 334.75 [M]⁺.

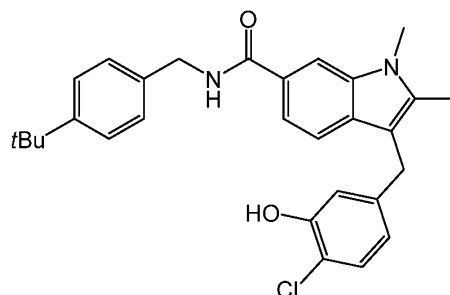


[0669] Step 2: methyl (R)-2-(5-(((6-((4-(tert-butyl)benzyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)-2-chlorophenoxy)propanoate. The title compound was prepared following the same general protocol as described in Step 9, Compound 1, using the N-(4-(tert-butyl)benzyl)-1,2-dimethyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide and the methyl (R)-2-(2-chloro-5-formyl phenoxy)propanoate instead of the ethyl 2-(4-formylphenoxy)propanoate. A yellow solid was obtained (12 mg, yield 42%). ESI-MS (m/z): 560.67 [M]⁺.

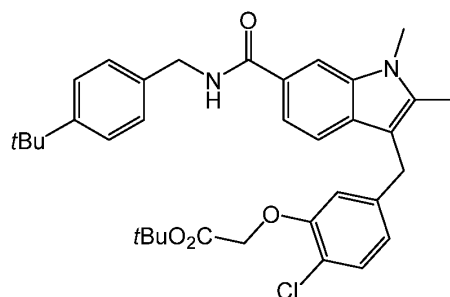


[0670] Step 3: (R)-2-(5-(((6-((4-(tert-butyl)benzyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)-2-chlorophenoxy)propanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the methyl (R)-2-(5-(((6-((4-(tert-butyl)benzyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)-2-chlorophenoxy)propanoate instead of the (ethyl 2-(4-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)propanoate. A yellow sticky oil was obtained (9 mg, yield 73%). ¹H NMR (600 MHz, CDCl₃) δ 7.81 (s, 1H), 7.36 (d, J = 7.9 Hz, 2H), 7.33 – 7.27 (m, 4H), 7.21 (d, J = 8.2 Hz, 1H), 6.78 (dd, J = 8.0, 1.7 Hz, 1H), 4.57 (d, J = 5.6 Hz, 2H), 4.14 (q, J = 7.2, 1H), 3.96 (s, 2H), 2.33 (d, J = 1.0 Hz, 3H), 2.17 (s, 3H), 1.59 (d, J = 6.7 Hz, 3H), 1.31 (s, 9H). ESI-MS (m/z): 546.73 [M]⁺.

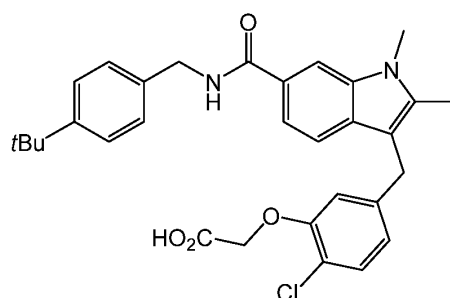
[0671] **Compound 97: 2-(5-(((6-((4-(tert-butyl)benzyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)-2-chlorophenoxy)acetic acid.**



[0672] Step 1: N-(4-(tert-butyl)benzyl)-3-(4-chloro-3-hydroxybenzyl)-1,2-dimethyl-1H-indole-6-carboxamide. The title compound was prepared following the same general protocol as described in Step 1, Compound 42, using the 4-chloro-3-hydroxybenzaldehyde instead of the 2-chloro-3-hydroxybenzaldehyde and N-(4-(tert-butyl)benzyl)-1,2-dimethyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide. A yellow solid was obtained (14 mg, yield 89%). ESI-MS (m/z): 474.64 [M]⁺.



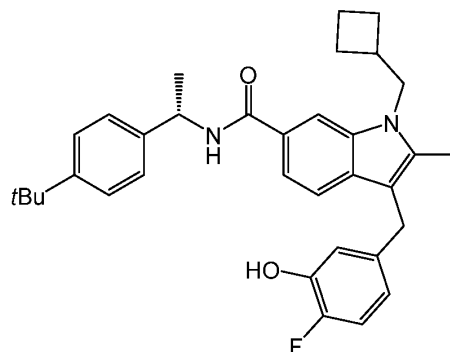
[0673] Step 2: tert-butyl 2-(5-(((6-((4-(tert-butyl)benzyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)-2-chlorophenoxy) acetate. The title compound was prepared following the same general protocol as described in Step 2, Compound 42, using the N-(4-(tert-butyl)benzyl)-3-(4-chloro-3-hydroxybenzyl)-1,2-dimethyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-3-(2-chloro-3-hydroxybenzyl)-1,2-dimethyl-1H-indole-6-carboxamide and the tert-butyl 2-bromoacetate instead of the (R)-2-bromopropanoate. A brown solid was obtained (10 mg, yield 70%). ESI-MS (m/z): 580.31 [M]⁺.



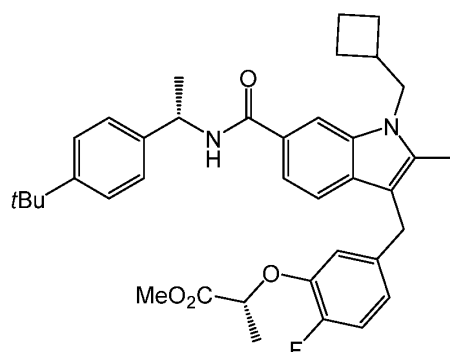
[0674] Step 3: 2-(5-(((6-((4-(tert-butyl)benzyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)-2-chlorophenoxy) acetic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the tert-butyl 2-(5-(((6-((4-(tert-butyl)benzyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)-2-chlorophenoxy) acetate instead of the (ethyl 2-(4-(((S)-1-(4-(tert-

butyl) phenyl) ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)propanoate. A brown solid was obtained (8 mg, yield 82%). ¹H NMR (400 MHz, CDCl₃) δ 7.82 (s, 1H), 7.40 – 7.35 (m, 2H), 7.35 – 7.27 (m, 4H), 7.22 (d, J = 8.1 Hz, 1H), 6.80 (dd, J = 8.1, 1.8 Hz, 1H), 6.62 – 6.52 (m, 2H), 4.60 (d, J = 5.4 Hz, 2H), 4.51 (s, 2H), 4.00 (s, 2H), 2.35 (s, 3H), 2.17 (s, 3H), 1.31 (s, 9H).. ESI-MS (m/z): 532.67 [M]⁺.

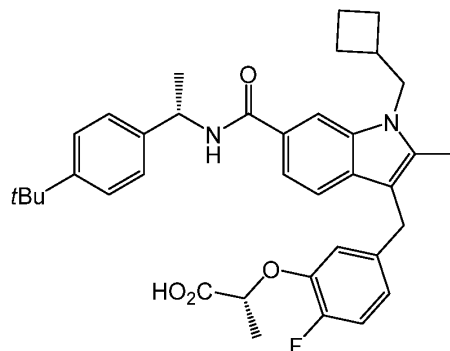
[0675] Compound 98: (R)-2-(5-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1-(cyclobutylmethyl)-2-methyl-1H-indol-3-yl)methyl)-2-fluorophenoxy)propanoic acid.



[0676] Step 1: (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1-(cyclobutylmethyl)-3-(4-fluoro-3-hydroxybenzyl)-2-methyl-1H-indole-6-carboxamide. The title compound was prepared following the same general protocol as described in Step 1, Compound 42, using the 4-fluoro-3-hydroxybenzaldehyde instead of the 2-chloro-3-hydroxybenzaldehyde and (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1-(cyclobutylmethyl)-2-methyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide. A yellow solid was obtained (19 mg, yield 77%). ESI-MS (m/z): 526.69 [M]⁺.

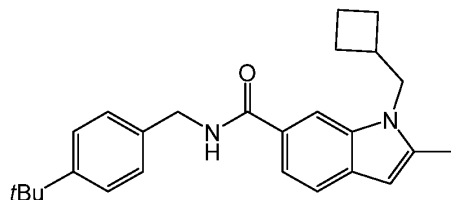


[0677] Step 2: methyl (R)-2-(5-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1-(cyclobutylmethyl)-2-methyl-1H-indol-3-yl)methyl)-2-fluorophenoxy)propanoate. The title compound was prepared following the same general protocol as described in Step 2, Compound 42, using the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1-(cyclobutylmethyl)-3-(4-fluoro-3-hydroxybenzyl)-2-methyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-3-(2-chloro-3-hydroxybenzyl)-1,2-dimethyl-1H-indole-6-carboxamide and the methyl (S)-2-bromopropanoate instead of the (R)-2-bromopropanoate. A brown solid was obtained (14 mg, yield 63%). ESI-MS (m/z): 612.66 [M]⁺.

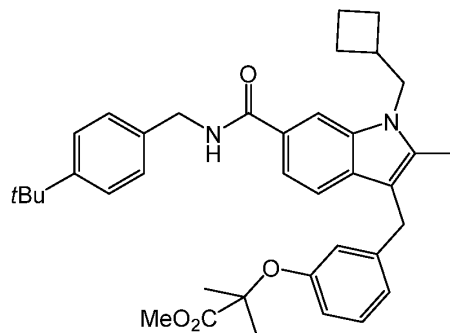


[0678] Step 3: (R)-2-(5-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1-(cyclobutylmethyl)-2-methyl-1H-indol-3-yl)methyl)-2-fluorophenoxy)propanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the methyl (R)-2-(5-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1-(cyclobutylmethyl)-2-methyl-1H-indol-3-yl)methyl)-2-fluorophenoxy)propanoate instead of the (ethyl 2-(4-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)propanoate. A brown solid was obtained (10 mg, yield 73%). ¹H NMR (400 MHz, CDCl₃) δ 7.91 (s, 1H), 7.46 – 7.30 (m, 4H), 6.93 (dd, J = 11.1, 8.3 Hz, 1H), 6.77 – 6.70 (m, 1H), 6.66 (dd, J = 8.0, 2.1 Hz, 1H), 6.43 (d, J = 7.8 Hz, 1H), 5.35 (p, J = 7.0 Hz, 1H), 4.60 (q, J = 6.8 Hz, 1H), 4.10 (d, J = 7.1 Hz, 2H), 3.95 (s, 2H), 2.79 (h, J = 7.5 Hz, 1H), 2.34 (s, 3H), 2.03 – 1.90 (m, 2H), 1.91 – 1.71 (m, 4H), 1.59 (dd, J = 11.6, 6.9 Hz, 6H), 1.31 (s, 9H). ESI-MS (m/z): 598.65 [M]⁺.

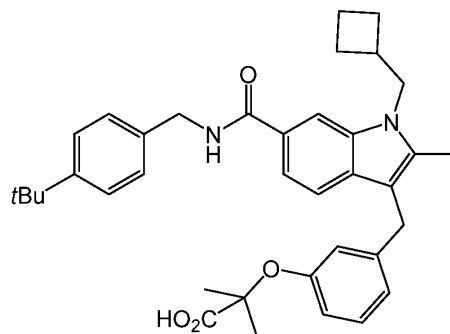
[0679] Compound 99: 2-(3-((6-((4-(tert-butyl)benzyl)carbamoyl)-1-(cyclobutylmethyl)-2-methyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoic acid.



[0680] Step 1: N-(4-(tert-butyl)benzyl)-1-(cyclobutylmethyl)-2-methyl-1H-indole-6-carboxamide. The title compound was prepared following the same general protocol as described in Step 8, Compound 1, using the (4-(tert-butyl)phenyl)methanamine hydrochloride instead of the (S)-1-(4-(tert-butyl)phenyl)ethanamine hydrochloride and the 1-(cyclobutylmethyl)-2-methyl-1H-indole-6-carboxylic acid instead of the 1,2-dimethyl-1H-indole-6-carboxylic acid. A brown solid was obtained (10 mg, yield 75%). ESI-MS (m/z): 388.75 [M]⁺.

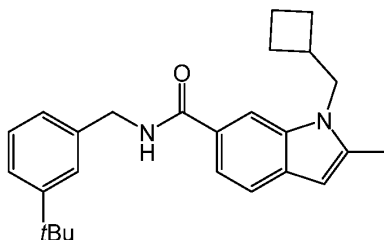


[0681] Step 2: methyl 2-(3-((6-((4-(tert-butyl)benzyl)carbamoyl)-1-(cyclobutylmethyl)-2-methyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoate. The title compound was prepared following the same general protocol as described in Step 9, Compound 1, using the N-(4-(tert-butyl)benzyl)-1-(cyclobutylmethyl)-2-methyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide and the methyl 2-(3-formylphenoxy)-2-methylpropanoate instead of the ethyl 2-(4-formylphenoxy)propanoate. A white powder was obtained (12 mg, yield 78%). ESI-MS (m/z): 594.93 [M]⁺.

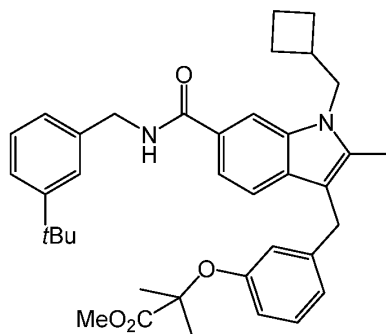


[0682] Step 3: 2-(3-((6-((4-(tert-butyl)benzyl)carbamoyl)-1-(cyclobutylmethyl)-2-methyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the methyl 2-(3-((6-((4-(tert-butyl)benzyl)carbamoyl)-1-(cyclobutylmethyl)-2-methyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoate instead of the (ethyl 2-(4-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)propanoate. A brown solid was obtained (5 mg, yield 42%). ESI-MS (m/z): 580.75 [M]⁺.

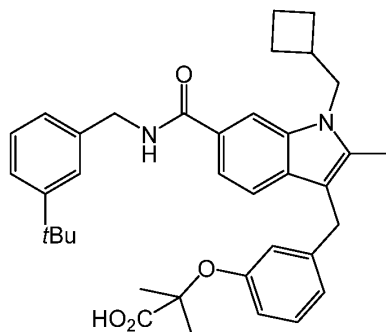
[0683] **Compound 100: 2-(3-((6-((3-(tert-butyl)benzyl)carbamoyl)-1-(cyclobutylmethyl)-2-methyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoic acid.**



[0684] Step 1: N-(3-(tert-butyl)benzyl)-1-(cyclobutylmethyl)-2-methyl-1H-indole-6-carboxamide. The title compound was prepared following the same general protocol as described in Step 8, Compound 1, using the (3-(tert-butyl)phenyl)methanamine hydrochloride instead of the (S)-1-(4-(tert-butyl)phenyl)ethanamine hydrochloride and the 1-(cyclobutylmethyl)-2-methyl-1H-indole-6-carboxylic acid instead of the 1,2-dimethyl-1H-indole-6-carboxylic acid. A brown solid was obtained (48 mg, yield 75%). ESI-MS (m/z): 388.75 [M]⁺.



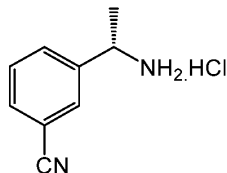
[0685] Step 2: methyl 2-(3-((6-((3-(tert-butyl)benzyl)carbamoyl)-1-(cyclobutylmethyl)-2-methyl-1H-indol-3-yl)methyl) phenoxy)-2-methylpropanoate. The title compound was prepared following the same general protocol as described in Step 9, Compound 1, using the N-(3-(tert-butyl)benzyl)-1-(cyclobutylmethyl)-2-methyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(tert-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide and the methyl 2-(3-formylphenoxy)-2-methylpropanoate instead of the ethyl 2-(4-formylphenoxy)propanoate. A white powder was obtained (42 mg, yield 57%). ESI-MS (m/z): 594.92 [M]⁺.



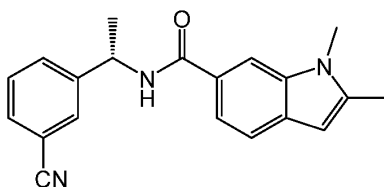
[0686] Step 3: 2-(3-((6-((3-(tert-butyl)benzyl)carbamoyl)-1-(cyclobutylmethyl)-2-methyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the methyl 2-(3-((6-((3-(tert-butyl)benzyl)carbamoyl)-1-(cyclobutylmethyl)-2-methyl-1H-indol-3-yl)methyl) phenoxy)-2-methylpropanoate instead of the (ethyl 2-(4-((6-(((S)-1-(4-(tert-butyl) phenyl) ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)propanoate. A yellow solid was obtained (30 mg, yield 73%). ¹H NMR (400 MHz, CDCl₃) δ 7.96 (s, 1H), 7.39 (s, 1H), 7.37 – 7.25 (m, 4H), 7.20 (d, J = 7.1 Hz, 1H), 7.12 (t, J = 7.7 Hz, 1H), 6.89 (d, J = 7.6 Hz, 1H), 6.76 – 6.63 (m, 2H), 6.44 (t, J = 5.8 Hz, 1H), 4.68 (d, J = 5.4

Hz, 2H), 4.15 (d, J = 7.1 Hz, 2H), 4.03 (s, 2H), 2.81 (td, J = 14.2, 6.6 Hz, 1H), 2.38 (s, 3H), 2.09 – 1.93 (m, 2H), 1.91 – 1.71 (m, 4H), 1.49 (s, 6H), 1.32 (s, 9H). ESI-MS (m/z): 580.78 [M]⁺.

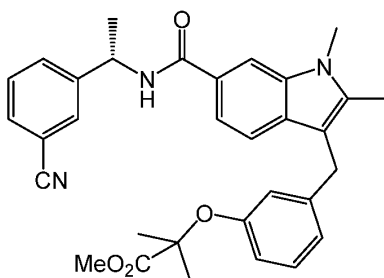
[0687] Compound 101: (S)-2-(3-((6-((1-(3-cyanophenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoic acid.



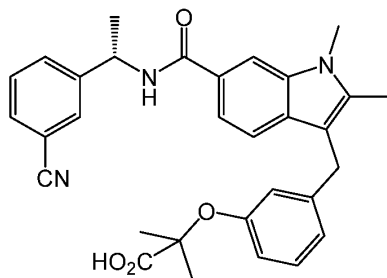
[0688] Step 1: (S)-3-(1-aminoethyl)benzonitrile hydrochloride. The title compound was prepared following the same general protocol as described in Step 6, Compound 1, using the 3-acetylbenzonitrile instead of the 1-(4-*tert*-butylphenyl)ethenone. A grey solid was obtained (500 mg, yield 71%).



[0689] Step 2: (S)-N-(1-(3-cyanophenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide. The title compound was prepared following the same general protocol as described in Step 8, Compound 1, using the (S)-3-(1-aminoethyl)benzonitrile hydrochloride instead of (S)-1-(4-(*tert*-butyl)phenyl)ethanamine hydrochloride. A yellow solid was obtained (20 mg, yield 90%).



[0690] Step 3: methyl (S)-2-(3-((6-((1-(3-cyanophenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoate. The title compound was prepared following the same general protocol as described in Step 9, Compound 1, using the (S)-N-(1-(3-cyanophenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide instead of the (S)-N-(1-(4-(*tert*-butyl)phenyl)ethyl)-1,2-dimethyl-1H-indole-6-carboxamide and the methyl 2-(3-formylphenoxy)-2-methylpropanoate instead of the ethyl 2-(4-formylphenoxy)propanoate. A yellow solid was obtained (22 mg, yield 68%).



[0691] Step 4: (S)-2-(3-((6-((1-(3-cyanophenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoic acid. The title compound was prepared following the same general protocol as described in Step 10, Compound 1, using the methyl (S)-2-(3-((6-((1-(3-cyanophenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)-2-methylpropanoate instead of the (ethyl 2-(4-((6-(((S)-1-(4-(tert-butyl)phenyl)ethyl)carbamoyl)-1,2-dimethyl-1H-indol-3-yl)methyl)phenoxy)propanoate. A white solid was obtained (19 mg, yield 90%). ¹H NMR (400 MHz, CDCl₃) δ 7.80 (s, 1H), 7.60 (d, J = 1.9 Hz, 1H), 7.55 (d, J = 7.8 Hz, 1H), 7.46 (dt, J = 7.8, 1.4 Hz, 1H), 7.35 (t, J = 7.8 Hz, 1H), 7.30 – 7.19 (m, 2H), 7.03 (t, J = 7.7 Hz, 1H), 6.81 (d, J = 7.9 Hz, 1H), 6.74 – 6.47 (m, 2H), 6.08 (br, 1H), 5.25 (dd, J = 14.0, 6.8 Hz, 1H), 3.95 (s, 2H), 3.59 (s, 3H), 2.29 (s, 3H), 1.51 (d, J = 6.9 Hz, 3H), 1.44 (s, 6H).

Example 2: Biological Data.

[0692] GAL4 transactivation Assay: The GAL4 constructs for NR1C2 (PPAR_γ – NP_056953.2) and NR1C1 (PPAR_α – NP_005027) were built by replacing the endogenous N terminus and DNA binding domain (DBD) of receptors with a GAL4 DBD. The fusion constructs consist of the GAL4 DBD, the hinge domain, and LBD of the human receptors. The sequence verified constructs were co-transfected with UAS luciferase reporter pGL4.31 (Promega) into HEK293T cells. After overnight incubation, 20μL cells (0.5x10⁶ cells/mL) were seeded into 384-well plates in quadruplicate and allowed to incubate for 3 hours before the addition of 20μL of compounds (12 serial 1:3 dilutions starting at 30μM final concentration) or DMSO incubated for 18 hours before the addition of 20μL of BriteLite (PerkinElmer Life and Analytical Sciences) to measure luciferase activity. Compounds that attenuate the GAL4-VP16-dependent luciferase activity in the positive control were considered promiscuous or cytotoxic. Replicates were averaged for luciferase and compared with DMSO-only controls.

[0693] LanthaScreen TR-FRET Competitive Binding assay for PPAR_γ: The PPAR_γ competitive binding assay (Invitrogen) was performed according to the manufacturer's protocol. A mixture of 0.5nM GST-PPAR_γ LBD, 5nM Tb-GST antibody, 5nM fluormone Pan-PPAR Green, and serial dilutions of compound beginning at 30μM downwards was added in 384-well low-volume black plates (Greiner) to a total volume of 20μl (2% DMSO in all wells). DMSO at 2% concentration was used as a no-ligand control. All dilutions were made in TRFRET PPAR assay buffer. Experiments were performed in triplicate and incubated for 2 hours in the dark before analysis in Perkin Elmer ViewLux ultra HTS microplate reader. TR-FRET signal was measured by excitation at 340nm with emission at 520nm for

fluorescein and 490nm for terbium. Data were plotted as the TR-FRET ratio 520/490nm using GraphPad Prism software.

Table 1. PPAR γ and PPAR α assays

Compound	GAL4 – PPAR γ (IC50 μ M)	GAL4 – PPAR α (IC50 μ M)	LanthaScreen – PPAR γ (IC50 μ M)	LanthaScreen – PPAR α (IC50 μ M)
1	3.457	2.463	0.401	0.377
2	33.467	2.686	0.503	0.082
3	Flat Curve	3.299	0.119	0.696
4	4.424	3.301	0.067	1.033
5	6.717	4.920	0.171	1.383
6	1019.827	15.073	3.279	N/A
7	0.148	484.730	0.003	N/A
8	0.736	1.229	0.328	N/A
9	7.873	1.729	0.029	N/A
10	0.792	9.322	0.042	N/A
11	0.849	9.486	0.002	N/A
12	1.585	0.658	0.039	N/A
13	15.958	12.668	0.971	N/A
14	0.384	0.156	0.001	N/A
15	2.848	3.604	0.006	N/A
16	1.643	0.627	0.056	N/A
17	6.759	1.927	0.054	N/A
18	1.354	3.170	0.005	N/A
19	2.062	25.187	0.003	N/A
20	1.616	2.192	0.003	N/A
21	6.935	12.395	0.038	N/A
22	3.690	18.746	0.001	N/A
23	3.381	5.162	0.001	N/A
24	2.404	4.562	0.025	N/A
25	5.369	4.441	0.073	N/A
26	0.504	0.871	0.001	N/A
27	1.939	6.140	0.013	N/A
28	1.781	4.114	0.012	N/A
29	1.954	4.599	0.082	N/A
30	1.194	18.987	0.0003	N/A
31	2.080	31.943	0.0004	N/A
32	3.021	3.007	0.007	N/A
33	7.473	19.796	0.057	N/A
34	31.370	Flat Curve	0.262	N/A
35	43.390	Flat Curve	0.012	N/A
36	35.081	33.960	1.177	N/A
37	18.820	3.349	0.109	N/A
38	4.206	27.63	0.058	N/A
39	0.0452	5.474	0.0015	0.6168
40	0.316	213.600	0.018	N/A
41	535.593	1531.000	0.020	N/A
42	42.780	0.858	0.015	N/A
43	14.889	8.965	0.0004	0.187
44	Flat Curve	36.16	0.002	N/A
45	1496.000	74.600	0.002	N/A
46	Flat Curve	89.86	Flat Curve	0.241
47	195.940	262.800	0.006	N/A

Compound	GAL4 – PPAR γ (IC50 μ M)	GAL4 – PPAR α (IC50 μ M)	LanthaScreen – PPAR γ (IC50 μ M)	LanthaScreen – PPAR α (IC50 μ M)
48	8.297	157.7	0.0005	N/A
49	372.627	26.380	0.001	N/A
50	4.524	60.56	0.0007	N/A
51	1.530	36.680	0.001	N/A
52	537.488	11.730	0.002	N/A
53	294.300	13.910	0.001	N/A
54	43.500	20.140	0.002	N/A
55	0.965	50.64	0.004	N/A
56	1.742	791.737	0.001	2.159
57	5.514	Flat Curve	0.010	N/A
58	Flat Curve	6.341	0.003	N/A
59	37.250	41.150	0.187	N/A
60	140.700	48.490	0.308	N/A
61	134.100	3.015	0.381	N/A
62	23.940	1.387	0.118	N/A
63	77.730	Flat Curve	0.158	N/A
64	2.065	> 100 μ M	0.017	N/A
65	0.558	3.293	0.009	Flat curve
66	0.056	0.237	0.024	N/A
67	0.019	0.017	0.023	N/A
68	0.280	> 100 μ M	0.014	N/A
69	0.312	3.703	0.015	N/A
70	0.292	5.892	0.009	Flat Curve
71	0.351	0.678	0.156	0.722
72	0.047	> 100 μ M	0.085	N/A
73	0.521	1.668	0.003	0.210
74	0.442	8.641	0.002	Flat Curve
75	3.685	0.039	0.154	Flat Curve
76	6.422	1.587	0.002	N/A
77	Flat Curve	5.872	0.005	Flat Curve
78	Flat Curve	> 100 μ M	0.0116	N/A
79	0.9407	0.2335	.020058	N/A
80	0.4807	> 100 μ M	0.004129	N/A
81	0.5926	0.0102	0.003513	N/A
82	0.6163	> 100 μ M	0.001421	N/A
83	Flat Curve	1.112	0.000391	N/A
84	0.216	> 100 μ M	0.008953	N/A
85	Flat Curve	> 100 μ M	0.002738	N/A
86	Flat Curve	0.6822	0.008457	N/A
87	Flat Curve	10.41	0.1067	N/A
88	Flat Curve	1.132	0.2198	N/A
89	Flat Curve	1.504	0.05987	N/A
90	Flat Curve	0.1083	0.7226	N/A
91	Flat Curve	0.0097	0.03714	N/A
92	57.59	2.493	0.00423	N/A
93	Flat Curve	2.779	0.00075	N/A
94	6.001	2.642	0.00193	N/A
95	24.35	Flat Curve	0.00079	N/A
96	20.10	3.941	0.00612	N/A
97	0.1532	Flat Curve	0.00554	N/A
98	0.01569	2.666	0.000493	N/A
99	0.2296	0.247	0.03015	N/A

Compound	GAL4 – PPAR γ (IC50 μ M)	GAL4 – PPAR α (IC50 μ M)	LanthaScreen – PPAR γ (IC50 μ M)	LanthaScreen – PPAR α (IC50 μ M)
100	0.1644	4.271	0.00726	N/A
101	0.940	85.930	0.018	N/A

INCORPORATION BY REFERENCE

[0694] The present application refers to various issued patent, published patent applications, scientific journal articles, and other publications, all of which are incorporated herein by reference. The details of one or more embodiments of the invention are set forth herein. Other features, objects, and advantages of the invention will be apparent from the Detailed Description, the Examples, and the Claims.

EQUIVALENTS AND SCOPE

[0695] In the articles such as “a,” “an,” and “the” may mean one or more than one unless indicated to the contrary or otherwise evident from the context. Embodiments or descriptions that include “or” between one or more members of a group are considered satisfied if one, more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process unless indicated to the contrary or otherwise evident from the context. The invention includes embodiments in which exactly one member of the group is present in, employed in, or otherwise relevant to a given product or process. The invention includes embodiments in which more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process.

[0696] Furthermore, the disclosure encompasses all variations, combinations, and permutations in which one or more limitations, elements, clauses, and descriptive terms from one or more of the listed claims is introduced into another claim. For example, any claim that is dependent on another claim can be modified to include one or more limitations found in any other claims that is dependent on the same base claim. Where elements are presented as lists, *e.g.*, in Markush group format, each subgroup of the elements is also disclosed, and any element(s) can be removed from the group. It should be understood that, in general, where the invention, or aspects of the invention, is/are referred to as comprising particular elements and/or features, certain embodiments of the disclosure or aspects of the disclosure consist, or consist essentially of, such elements and/or features. For purposes of simplicity, those embodiments have not been specifically set forth *in haec verba* herein. It is also noted that the terms “comprising” and “containing” are intended to be open and permits the inclusion of additional elements or steps. Where ranges are given, endpoints are included. Furthermore, unless otherwise indicated or otherwise evident from the context and understanding of one of ordinary skill in the art, values that are expressed as ranges can assume any specific value or sub-range within the stated ranges in different embodiments of the invention, to the tenth of the unit of the lower limit of the range, unless the context clearly dictates otherwise.

[0697] This application refers to various issued patents, published patent applications, journal articles, and other publications, all of which are incorporated herein by reference. If there is a conflict between any

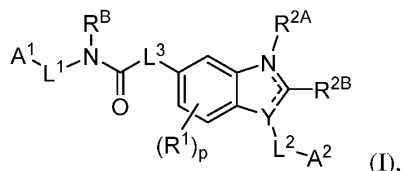
of the incorporated references and the instant specification, the specification shall control. In addition, any particular embodiment of the present invention that falls within the prior art may be explicitly excluded from any one or more of the embodiments. Because such embodiments are deemed to be known to one of ordinary skill in the art, they may be excluded even if the exclusion is not set forth explicitly herein. Any particular embodiment of the invention can be excluded from any embodiment, for any reason, whether or not related to the existence of prior art.

[0698] Those skilled in the art will recognize or be able to ascertain using no more than routine experimentation many equivalents to the specific embodiments described herein. The scope of the present embodiments described herein is not intended to be limited to the above Description, but rather is as set forth in the appended embodiments. Those of ordinary skill in the art will appreciate that various changes and modifications to this description may be made without departing from the spirit or scope of the present invention, as defined in the following claims.

CLAIMS

What is claimed is:

1. A compound of Formula (I):



or a pharmaceutically acceptable salt or prodrug thereof, wherein:

A¹ is substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

A² is substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl;

each of L¹, L², and L³ is independently a bond or substituted or unsubstituted alkylene;

Y is C or N;

each occurrence of R¹ is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroalkenyl, substituted or unsubstituted heteroalkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -CN, -OR^A, -SCN, -SR^A, -SSR^A, -N₃, -NO, -N(R^A)₂, -NO₂, -C(=O)R^A, -C(=O)OR^A, -C(=O)SR^A, -C(=O)N(R^A)₂, -C(=NR^A)R^A, -C(=NR^A)OR^A, -C(=NR^A)SR^A, -C(=NR^A)N(R^A)₂, -S(=O)R^A, -S(=O)OR^A, -S(=O)SR^A, -S(=O)N(R^A)₂, -S(=O)₂R^A, -S(=O)₂OR^A, -S(=O)₂SR^A, -S(=O)₂N(R^A)₂, -OC(=O)R^A, -OC(=O)OR^A, -OC(=O)SR^A, -OC(=O)N(R^A)₂, -OC(=NR^A)R^A, -OC(=NR^A)OR^A, -OC(=NR^A)SR^A, -OC(=NR^A)N(R^A)₂, -OS(=O)R^A, -OS(=O)OR^A, -OS(=O)SR^A, -OS(=O)N(R^A)₂, -OS(=O)₂R^A, -OS(=O)₂OR^A, -OS(=O)₂SR^A, -OS(=O)₂N(R^A)₂, -ON(R^A)₂, -SC(=O)R^A, -SC(=O)OR^A, -SC(=O)SR^A, -SC(=O)N(R^A)₂, -SC(=NR^A)R^A, -SC(=NR^A)OR^A, -SC(=NR^A)SR^A, -SC(=NR^A)N(R^A)₂, -NR^AC(=O)R^A, -NR^AC(=O)OR^A, -NR^AC(=O)SR^A, -NR^AC(=O)N(R^A)₂, -NR^AC(=NR^A)R^A, -NR^AC(=NR^A)OR^A, -NR^AC(=NR^A)SR^A, -NR^AC(=NR^A)N(R^A)₂, -NR^AS(=O)R^A, -NR^AS(=O)OR^A, -NR^AS(=O)SR^A, -NR^AS(=O)N(R^A)₂, -NR^AS(=O)₂R^A, -NR^AS(=O)₂OR^A, -NR^AS(=O)₂SR^A, -NR^AS(=O)₂N(R^A)₂, -Si(R^A)₃, -Si(R^A)₂OR^A, -Si(R^A)(OR^A)₂, -Si(OR^A)₃, -OSi(R^A)₃, -OSi(R^A)₂OR^A, -OSi(R^A)(OR^A)₂, -OSi(OR^A)₃, or -B(OR^A)₂;

R^{2A} is absent, hydrogen, substituted or unsubstituted alkyl, or a nitrogen protecting group, provided that when Y is N, R^{2A} is absent;

R^{2B} is hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroalkenyl, substituted or unsubstituted heteroalkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or

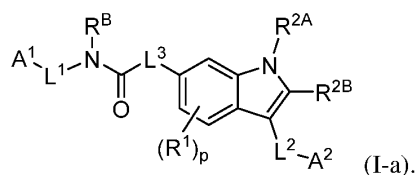
unsubstituted heteroaryl, $-\text{CN}$, $-\text{OR}^A$, $-\text{SCN}$, $-\text{SR}^A$, $-\text{SSR}^A$, $-\text{N}_3$, $-\text{NO}$, $-\text{N}(\text{R}^A)_2$, $-\text{NO}_2$, $-\text{C}(=\text{O})\text{R}^A$, $-\text{C}(=\text{O})\text{OR}^A$, $-\text{C}(=\text{O})\text{SR}^A$, $-\text{C}(=\text{O})\text{N}(\text{R}^A)_2$, $-\text{C}(=\text{NR}^A)\text{R}^A$, $-\text{C}(=\text{NR}^A)\text{OR}^A$, $-\text{C}(=\text{NR}^A)\text{SR}^A$, $-\text{C}(=\text{NR}^A)\text{N}(\text{R}^A)_2$, $-\text{S}(=\text{O})\text{R}^A$, $-\text{S}(=\text{O})\text{OR}^A$, $-\text{S}(=\text{O})\text{SR}^A$, $-\text{S}(=\text{O})\text{N}(\text{R}^A)_2$, $-\text{S}(=\text{O})_2\text{R}^A$, $-\text{S}(=\text{O})_2\text{OR}^A$, $-\text{S}(=\text{O})_2\text{SR}^A$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^A)_2$, $-\text{OC}(=\text{O})\text{R}^A$, $-\text{OC}(=\text{O})\text{OR}^A$, $-\text{OC}(=\text{O})\text{SR}^A$, $-\text{OC}(=\text{O})\text{N}(\text{R}^A)_2$, $-\text{OC}(=\text{NR}^A)\text{R}^A$, $-\text{OC}(=\text{NR}^A)\text{OR}^A$, $-\text{OC}(=\text{NR}^A)\text{SR}^A$, $-\text{OC}(=\text{NR}^A)\text{N}(\text{R}^A)_2$, $-\text{OS}(=\text{O})\text{R}^A$, $-\text{OS}(=\text{O})\text{OR}^A$, $-\text{OS}(=\text{O})\text{SR}^A$, $-\text{OS}(=\text{O})\text{N}(\text{R}^A)_2$, $-\text{OS}(=\text{O})_2\text{R}^A$, $-\text{OS}(=\text{O})_2\text{OR}^A$, $-\text{OS}(=\text{O})_2\text{SR}^A$, $-\text{OS}(=\text{O})_2\text{N}(\text{R}^A)_2$, $-\text{ON}(\text{R}^A)_2$, $-\text{SC}(=\text{O})\text{R}^A$, $-\text{SC}(=\text{O})\text{OR}^A$, $-\text{SC}(=\text{O})\text{SR}^A$, $-\text{SC}(=\text{O})\text{N}(\text{R}^A)_2$, $-\text{SC}(=\text{NR}^A)\text{R}^A$, $-\text{SC}(=\text{NR}^A)\text{OR}^A$, $-\text{SC}(=\text{NR}^A)\text{SR}^A$, $-\text{SC}(=\text{NR}^A)\text{N}(\text{R}^A)_2$, $-\text{NR}^A\text{C}(=\text{O})\text{R}^A$, $-\text{NR}^A\text{C}(=\text{O})\text{OR}^A$, $-\text{NR}^A\text{C}(=\text{O})\text{SR}^A$, $-\text{NR}^A\text{C}(=\text{O})\text{N}(\text{R}^A)_2$, $-\text{NR}^A\text{C}(=\text{NR}^A)\text{R}^A$, $-\text{NR}^A\text{C}(=\text{NR}^A)\text{OR}^A$, $-\text{NR}^A\text{C}(=\text{NR}^A)\text{SR}^A$, $-\text{NR}^A\text{C}(=\text{NR}^A)\text{N}(\text{R}^A)_2$, $-\text{NR}^A\text{S}(=\text{O})\text{R}^A$, $-\text{NR}^A\text{S}(=\text{O})\text{OR}^A$, $-\text{NR}^A\text{S}(=\text{O})\text{SR}^A$, $-\text{NR}^A\text{S}(=\text{O})\text{N}(\text{R}^A)_2$, $-\text{NR}^A\text{S}(=\text{O})_2\text{R}^A$, $-\text{NR}^A\text{S}(=\text{O})_2\text{OR}^A$, $-\text{NR}^A\text{S}(=\text{O})_2\text{SR}^A$, $-\text{NR}^A\text{S}(=\text{O})_2\text{N}(\text{R}^A)_2$, $-\text{Si}(\text{R}^A)_3$, $-\text{Si}(\text{R}^A)_2\text{OR}^A$, $-\text{Si}(\text{R}^A)(\text{OR}^A)_2$, $-\text{Si}(\text{OR}^A)_3$, $-\text{OSi}(\text{R}^A)_3$, $-\text{OSi}(\text{R}^A)_2\text{OR}^A$, $-\text{OSi}(\text{R}^A)(\text{OR}^A)_2$, $-\text{OSi}(\text{OR}^A)_3$, or $-\text{B}(\text{OR}^A)_2$;

each occurrence of R^A is independently hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroalkenyl, substituted or unsubstituted heteroalkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, a nitrogen protecting group when attached to a nitrogen atom, an oxygen protecting group when attached to an oxygen atom, or a sulfur protecting group when attached to a sulfur atom, or two occurrences of R^A are joined together with their intervening atom(s) to form an substituted or unsubstituted heterocyclic ring or substituted or unsubstituted heteroaryl ring;

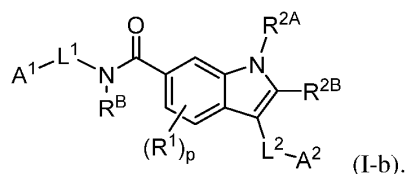
R^B is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted acyl, or a nitrogen protecting group; and

p is 0, 1, 2, or 3.

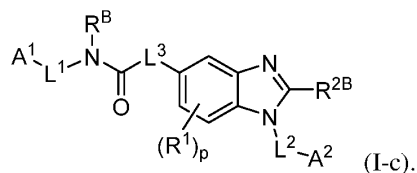
2. The compound of claim 1, or a pharmaceutically acceptable salt or prodrug thereof, wherein the compound is of Formula (I-a):



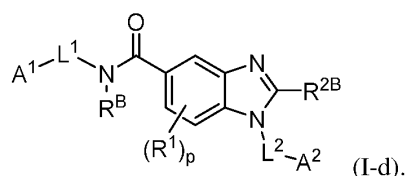
3. The compound of claim 1, or a pharmaceutically acceptable salt or prodrug thereof, wherein the compound is of Formula (I-b):



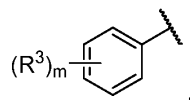
4. The compound of claim 1, or a pharmaceutically acceptable salt or prodrug thereof, wherein the compound is of Formula (I-c):



5. The compound of claim 1, or a pharmaceutically acceptable salt or prodrug thereof, wherein the compound is of Formula (I-d):



6. The compound of any one of claims 1-5, or a pharmaceutically acceptable salt or prodrug thereof, wherein A¹ is substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl.
7. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt or prodrug thereof, wherein A¹ is substituted or unsubstituted aryl.
8. The compound of any one of claims 1-7, or a pharmaceutically acceptable salt or prodrug thereof, wherein A¹ is substituted or unsubstituted phenyl.
9. The compound of any one of claims 1-8, or a pharmaceutically acceptable salt or prodrug thereof, wherein A¹ is of formula:



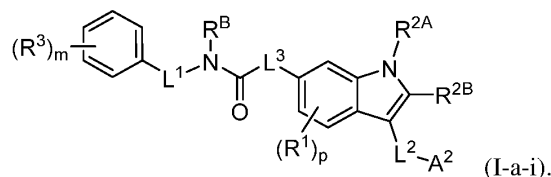
wherein:

each occurrence of R³ is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heteroalkyl,

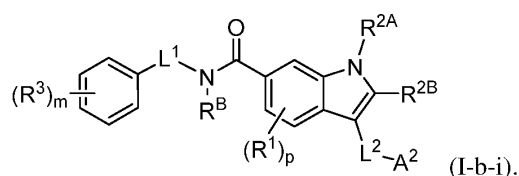
substituted or unsubstituted heteroalkenyl, substituted or unsubstituted heteroalkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-\text{CN}$, $-\text{OR}^A$, $-\text{SCN}$, $-\text{SR}^A$, $-\text{SSR}^A$, $-\text{N}_3$, $-\text{NO}$, $-\text{N}(\text{R}^A)_2$, $-\text{NO}_2$, $-\text{C}(=\text{O})\text{R}^A$, $-\text{C}(=\text{O})\text{OR}^A$, $-\text{C}(=\text{O})\text{SR}^A$, $-\text{C}(=\text{O})\text{N}(\text{R}^A)_2$, $-\text{C}(=\text{NR}^A)\text{R}^A$, $-\text{C}(=\text{NR}^A)\text{OR}^A$, $-\text{C}(=\text{NR}^A)\text{SR}^A$, $-\text{C}(=\text{NR}^A)\text{N}(\text{R}^A)_2$, $-\text{S}(=\text{O})\text{R}^A$, $-\text{S}(=\text{O})\text{OR}^A$, $-\text{S}(=\text{O})\text{SR}^A$, $-\text{S}(=\text{O})\text{N}(\text{R}^A)_2$, $-\text{S}(=\text{O})_2\text{R}^A$, $-\text{S}(=\text{O})_2\text{OR}^A$, $-\text{S}(=\text{O})_2\text{SR}^A$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^A)_2$, $-\text{OC}(=\text{O})\text{R}^A$, $-\text{OC}(=\text{O})\text{OR}^A$, $-\text{OC}(=\text{O})\text{SR}^A$, $-\text{OC}(=\text{O})\text{N}(\text{R}^A)_2$, $-\text{OC}(=\text{NR}^A)\text{R}^A$, $-\text{OC}(=\text{NR}^A)\text{OR}^A$, $-\text{OC}(=\text{NR}^A)\text{SR}^A$, $-\text{OC}(=\text{NR}^A)\text{N}(\text{R}^A)_2$, $-\text{OS}(=\text{O})\text{R}^A$, $-\text{OS}(=\text{O})\text{OR}^A$, $-\text{OS}(=\text{O})\text{SR}^A$, $-\text{OS}(=\text{O})\text{N}(\text{R}^A)_2$, $-\text{OS}(=\text{O})_2\text{R}^A$, $-\text{OS}(=\text{O})_2\text{OR}^A$, $-\text{OS}(=\text{O})_2\text{SR}^A$, $-\text{OS}(=\text{O})_2\text{N}(\text{R}^A)_2$, $-\text{ON}(\text{R}^A)_2$, $-\text{SC}(=\text{O})\text{R}^A$, $-\text{SC}(=\text{O})\text{OR}^A$, $-\text{SC}(=\text{O})\text{SR}^A$, $-\text{SC}(=\text{O})\text{N}(\text{R}^A)_2$, $-\text{SC}(=\text{NR}^A)\text{R}^A$, $-\text{SC}(=\text{NR}^A)\text{OR}^A$, $-\text{SC}(=\text{NR}^A)\text{SR}^A$, $-\text{SC}(=\text{NR}^A)\text{N}(\text{R}^A)_2$, $-\text{NR}^A\text{C}(=\text{O})\text{R}^A$, $-\text{NR}^A\text{C}(=\text{O})\text{OR}^A$, $-\text{NR}^A\text{C}(=\text{O})\text{SR}^A$, $-\text{NR}^A\text{C}(=\text{O})\text{N}(\text{R}^A)_2$, $-\text{NR}^A\text{C}(=\text{NR}^A)\text{R}^A$, $-\text{NR}^A\text{C}(=\text{NR}^A)\text{OR}^A$, $-\text{NR}^A\text{C}(=\text{NR}^A)\text{SR}^A$, $-\text{NR}^A\text{C}(=\text{NR}^A)\text{N}(\text{R}^A)_2$, $-\text{NR}^A\text{S}(=\text{O})\text{R}^A$, $-\text{NR}^A\text{S}(=\text{O})\text{OR}^A$, $-\text{NR}^A\text{S}(=\text{O})\text{SR}^A$, $-\text{NR}^A\text{S}(=\text{O})\text{N}(\text{R}^A)_2$, $-\text{NR}^A\text{S}(=\text{O})_2\text{R}^A$, $-\text{NR}^A\text{S}(=\text{O})_2\text{OR}^A$, $-\text{NR}^A\text{S}(=\text{O})_2\text{SR}^A$, $-\text{NR}^A\text{S}(=\text{O})_2\text{N}(\text{R}^A)_2$, $-\text{Si}(\text{R}^A)_3$, $-\text{Si}(\text{R}^A)_2\text{OR}^A$, $-\text{Si}(\text{R}^A)(\text{OR}^A)_2$, $-\text{Si}(\text{OR}^A)_3$, $-\text{OSi}(\text{R}^A)_3$, $-\text{OSi}(\text{R}^A)_2\text{OR}^A$, $-\text{OSi}(\text{R}^A)(\text{OR}^A)_2$, $-\text{OSi}(\text{OR}^A)_3$, or $-\text{B}(\text{OR}^A)_2$; and

m is 0, 1, 2, 3, 4, or 5.

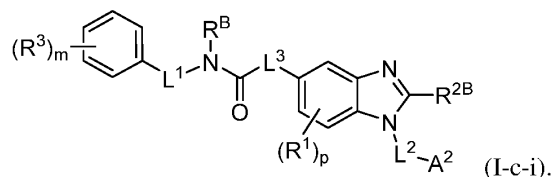
10. The compound of any one of claims 1, 2, or 6-9, or a pharmaceutically acceptable salt or prodrug thereof, wherein the compound is of Formula (I-a-i):



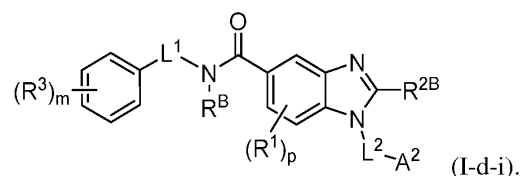
11. The compound of any one of claims 1, 3, or 6-9, or a pharmaceutically acceptable salt or prodrug thereof, wherein the compound is of Formula (I-b-i):



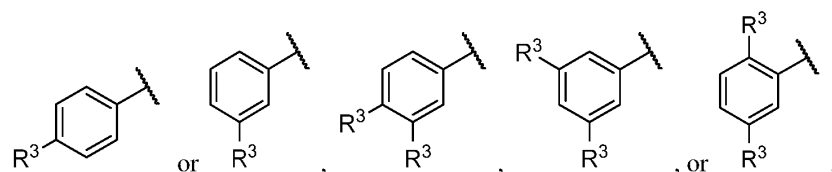
12. The compound of any one of claims 1, 4, or 6-9, or a pharmaceutically acceptable salt or prodrug thereof, wherein the compound is of Formula (I-c-i):



13. The compound of any one of claims 1, 5, or 6-9, or a pharmaceutically acceptable salt or prodrug thereof, wherein the compound is of Formula (I-d-i):



14. The compound of any one of claims 1-13, or a pharmaceutically acceptable salt or prodrug thereof, wherein A¹ is of formula:



15. The compound of any one of claims 9-14, or a pharmaceutically acceptable salt or prodrug thereof, wherein each occurrence of R³ is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, -CN, or -OR^A.

16. The compound of any one of claims 9-15, or a pharmaceutically acceptable salt or prodrug thereof, wherein at least one occurrence of R³ is C₁₋₆ alkyl.

17. The compound of any one of claims 9-16, or a pharmaceutically acceptable salt or prodrug thereof, wherein at least one occurrence of R³ is methyl, trifluoromethyl, ethyl, isopropyl, or *tert*-butyl.

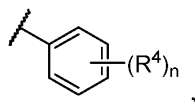
18. The compound of any one of claims 9-17, or a pharmaceutically acceptable salt or prodrug thereof, wherein at least one occurrence of R³ is C₁₋₆ cycloalkyl.

19. The compound of any one of claims 9-18, or a pharmaceutically acceptable salt or prodrug thereof, wherein at least one occurrence of R³ is cyclopropyl.

20. The compound of any one of claims 9-19, or a pharmaceutically acceptable salt or prodrug thereof, wherein at least one occurrence of R³ is -F, -Cl, -Br, -OMe, -OCF₃, or -CN.

21. The compound of any one of claims 1-20, or a pharmaceutically acceptable salt or prodrug thereof, wherein R^{2A} is absent.

22. The compound of any one of claims 1-20, or a pharmaceutically acceptable salt or prodrug thereof, wherein R^{2A} is substituted or unsubstituted alkyl.
23. The compound of any one of claims 1-20 or 22, or a pharmaceutically acceptable salt or prodrug thereof, wherein R^{2A} is substituted or unsubstituted C_{1-6} alkyl.
24. The compound of any one of claims 1-20, 22, or 23, or a pharmaceutically acceptable salt or prodrug thereof, wherein R^{2A} is methyl, ethyl, isopropyl, 2-methylpropyl, 2,2-dimethylpropyl, cyclopropylmethyl, or cyclobutylmethyl.
25. The compound of any one of claims 1-24, or a pharmaceutically acceptable salt or prodrug thereof, wherein R^{2B} is substituted or unsubstituted alkyl.
26. The compound of any one of claims 1-25, or a pharmaceutically acceptable salt or prodrug thereof, wherein R^{2B} is substituted or unsubstituted C_{1-6} alkyl.
27. The compound of any one of claims 1-26, or a pharmaceutically acceptable salt or prodrug thereof, wherein R^{2B} is methyl.
28. The compound of any one of claims 1-27, or a pharmaceutically acceptable salt or prodrug thereof, wherein A^2 is substituted or unsubstituted aryl.
29. The compound of any one of claims 1-28, or a pharmaceutically acceptable salt or prodrug thereof, wherein A^2 is substituted or unsubstituted phenyl.
30. The compound of any one of claims 1-29, or a pharmaceutically acceptable salt or prodrug thereof, wherein A^2 is of formula:



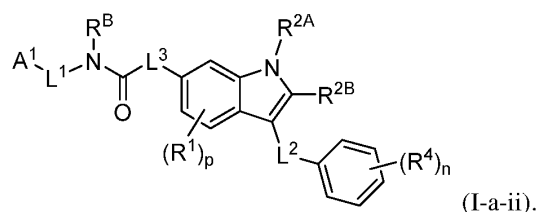
wherein:

each occurrence of R^4 is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heteroalkenyl, substituted or unsubstituted heteroalkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-CN$, $-OR^A$, $-SCN$, $-SR^A$, $-SSR^A$, $-N_3$, $-NO$, $-N(R^A)_2$, $-NO_2$,

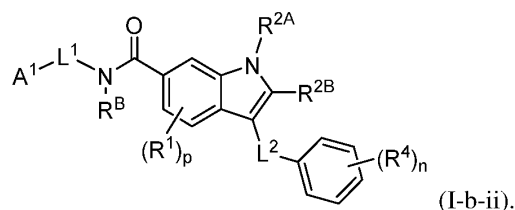
$-C(=O)R^A$, $-C(=O)OR^A$, $-C(=O)SR^A$, $-C(=O)N(R^A)_2$, $-C(=NR^A)R^A$, $-C(=NR^A)OR^A$, $-C(=NR^A)SR^A$,
 $-C(=NR^A)N(R^A)_2$, $-S(=O)R^A$, $-S(=O)OR^A$, $-S(=O)SR^A$, $-S(=O)N(R^A)_2$, $-S(=O)_2R^A$, $-S(=O)_2OR^A$, $-$
 $S(=O)_2SR^A$, $-S(=O)_2N(R^A)_2$, $-OC(=O)R^A$, $-OC(=O)OR^A$, $-OC(=O)SR^A$, $-OC(=O)N(R^A)_2$, $-$
 $OC(=NR^A)R^A$, $-OC(=NR^A)OR^A$, $-OC(=NR^A)SR^A$, $-OC(=NR^A)N(R^A)_2$, $-OS(=O)R^A$, $-OS(=O)OR^A$, $-$
 $OS(=O)SR^A$, $-OS(=O)N(R^A)_2$, $-OS(=O)_2R^A$, $-OS(=O)_2OR^A$, $-OS(=O)_2SR^A$, $-OS(=O)_2N(R^A)_2$, $-$
 $ON(R^A)_2$, $-SC(=O)R^A$, $-SC(=O)OR^A$, $-SC(=O)SR^A$, $-SC(=O)N(R^A)_2$, $-SC(=NR^A)R^A$, $-$
 $SC(=NR^A)OR^A$, $-SC(=NR^A)SR^A$, $-SC(=NR^A)N(R^A)_2$, $-NR^AC(=O)R^A$, $-NR^AC(=O)OR^A$, $-$
 $NR^AC(=O)SR^A$, $-NR^AC(=O)N(R^A)_2$, $-NR^AC(=NR^A)R^A$, $-NR^AC(=NR^A)OR^A$, $-NR^AC(=NR^A)SR^A$, $-$
 $NR^AC(=NR^A)N(R^A)_2$, $-NR^AS(=O)R^A$, $-NR^AS(=O)OR^A$, $-NR^AS(=O)SR^A$, $-NR^AS(=O)N(R^A)_2$, $-$
 $NR^AS(=O)_2R^A$, $-NR^AS(=O)_2OR^A$, $-NR^AS(=O)_2SR^A$, $-NR^AS(=O)_2N(R^A)_2$, $-Si(R^A)_3$, $-Si(R^A)_2OR^A$, $-$
 $Si(R^A)(OR^A)_2$, $-Si(OR^A)_3$, $-OSi(R^A)_3$, $-OSi(R^A)_2OR^A$, $-OSi(R^A)(OR^A)_2$, $-OSi(OR^A)_3$, or $-B(OR^A)_2$;
 and

n is 0, 1, 2, 3, 4, or 5.

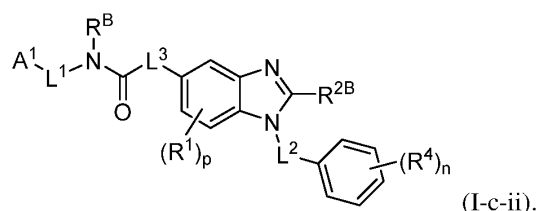
31. The compound of any one of claims 1, 2, 6-10, or 14-30, or a pharmaceutically acceptable salt or prodrug thereof, wherein the compound is of Formula (I-a-ii):



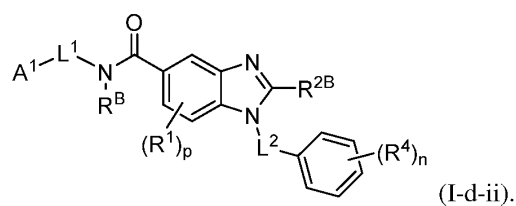
32. The compound of any one of claims 1, 3, 6-9, 11, or 14-30, or a pharmaceutically acceptable salt or prodrug thereof, wherein the compound is of Formula (I-b-ii):



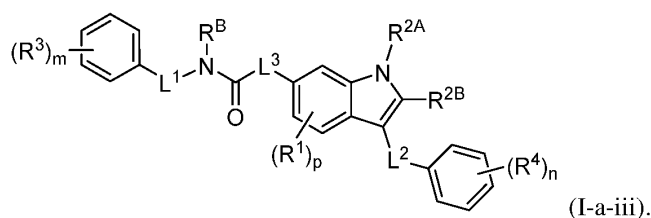
33. The compound of any one of claims 1, 4, 6-9, 12, or 14-30, or a pharmaceutically acceptable salt or prodrug thereof, wherein the compound is of Formula (I-c-ii):



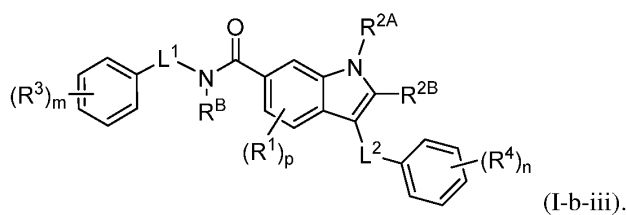
34. The compound of any one of claims 1, 5-9, or 13-30, or a pharmaceutically acceptable salt or prodrug thereof, wherein the compound is of Formula (I-d-ii):



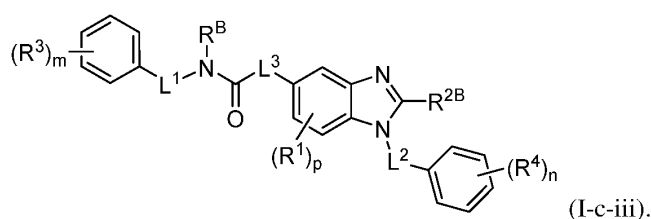
35. The compound of any one of claims 1, 2, 6-10, or 14-31, or a pharmaceutically acceptable salt or prodrug thereof, wherein the compound is of Formula (I-a-iii):



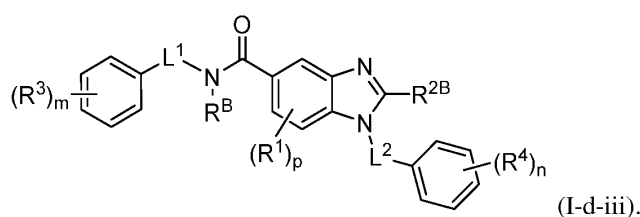
36. The compound of any one of claims 1, 3, 6-9, 11, 14-30, or 32, or a pharmaceutically acceptable salt or prodrug thereof, wherein the compound is of Formula (I-b-iii):



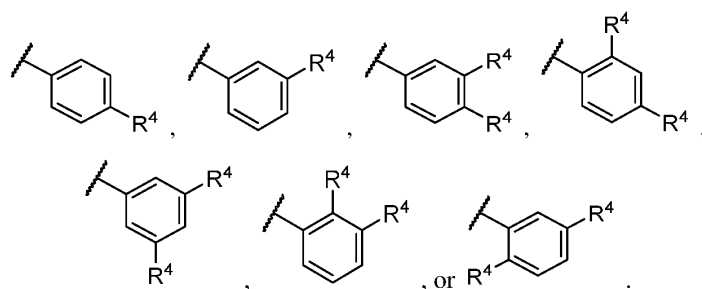
37. The compound of any one of claims 1, 4, 6-9, 12, 14-30, or 33, or a pharmaceutically acceptable salt or prodrug thereof, wherein the compound is of Formula (I-c-iii):



38. The compound of any one of claims 1, 5-9, 13-30, or 34, or a pharmaceutically acceptable salt or prodrug thereof, wherein the compound is of Formula (I-d-iii):



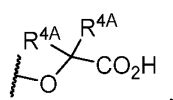
39. The compound of any one of claims 1-38, or a pharmaceutically acceptable salt or prodrug thereof, wherein A² is of formula:



40. The compound of any one of claims 1-39, or a pharmaceutically acceptable salt or prodrug thereof, wherein each occurrence of R⁴ is independently halogen, substituted or unsubstituted alkyl, or -OR^A.

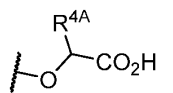
41. The compound of any one of claims 1-40, or a pharmaceutically acceptable salt or prodrug thereof, wherein at least one occurrence of R⁴ is -OR^A.

42. The compound of any one of claims 1-41, or a pharmaceutically acceptable salt or prodrug thereof, wherein at least one occurrence of R⁴ is of formula:

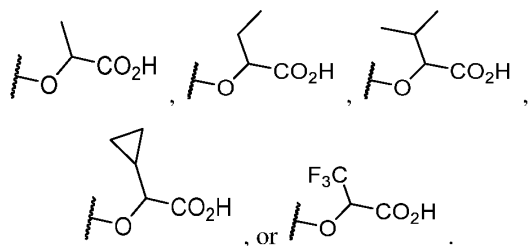


wherein each occurrence of R^{4A} is independently hydrogen, substituted or unsubstituted alkyl, or substituted or unsubstituted cycloalkyl.

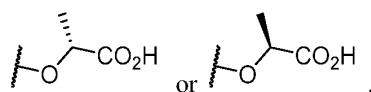
43. The compound of any one of claims 1-42, or a pharmaceutically acceptable salt or prodrug thereof, wherein at least one occurrence of R⁴ is of formula:



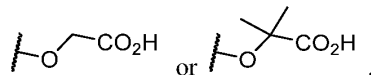
44. The compound of any one of claims 1-43, or a pharmaceutically acceptable salt or prodrug thereof, wherein at least one occurrence of R^4 is of formula:



45. The compound of any one of claims 1-44, or a pharmaceutically acceptable salt or prodrug thereof, wherein at least one occurrence of R^4 is of formula:



46. The compound of any one of claims 1-45, or a pharmaceutically acceptable salt or prodrug thereof, wherein at least one occurrence of R^4 is of formula:



47. The compound of any one of claims 1-46, or a pharmaceutically acceptable salt or prodrug thereof, wherein at least one occurrence of R^{4A} is methyl, ethyl, isopropyl, trifluoromethyl, or cyclopropyl.

48. The compound of any one of claims 1-47, or a pharmaceutically acceptable salt or prodrug thereof, wherein L^1 is substituted or unsubstituted alkylene.

49. The compound of any one of claims 1-48, or a pharmaceutically acceptable salt or prodrug thereof, wherein L^1 is substituted or unsubstituted C_{1-6} alkylene.

50. The compound of any one of claims 1-49, or a pharmaceutically acceptable salt or prodrug thereof, wherein L^1 is $-\text{CH}(\text{CH}_3)-$ or $-\text{CH}(\text{CF}_3)-$.

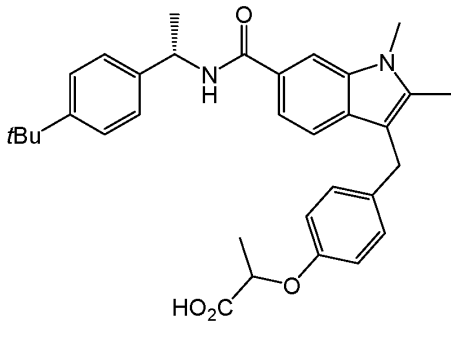
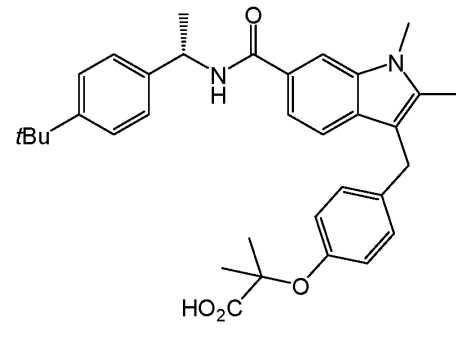
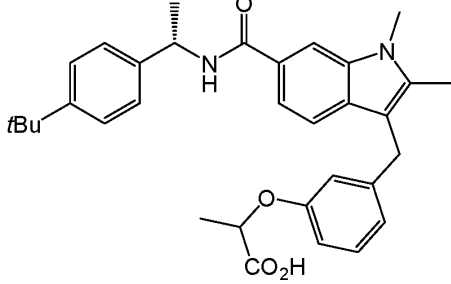
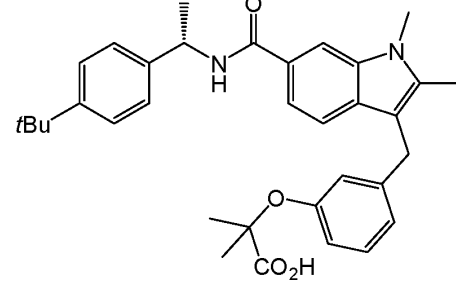
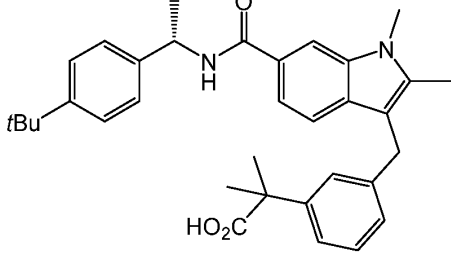
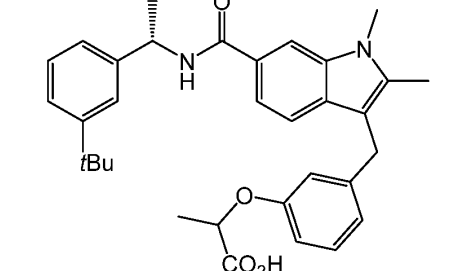
51. The compound of any one of claims 1-50, or a pharmaceutically acceptable salt or prodrug thereof, wherein L^2 is substituted or unsubstituted alkylene.

52. The compound of any one of claims 1-51, or a pharmaceutically acceptable salt or prodrug thereof, wherein L^2 is substituted or unsubstituted C_{1-6} alkylene.

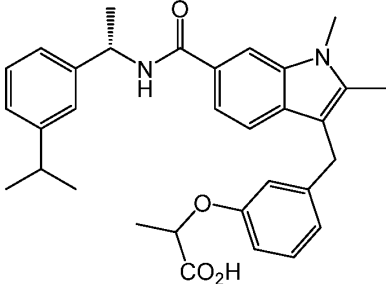
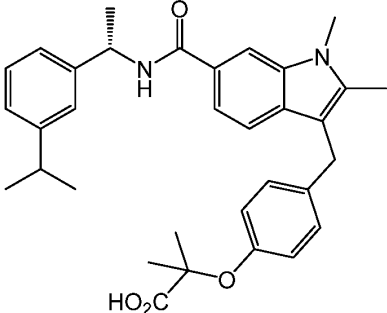
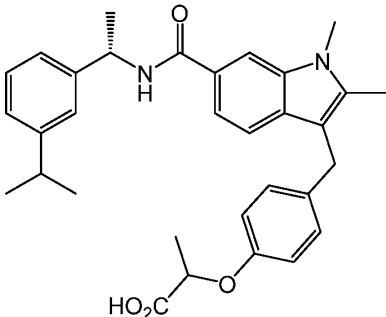
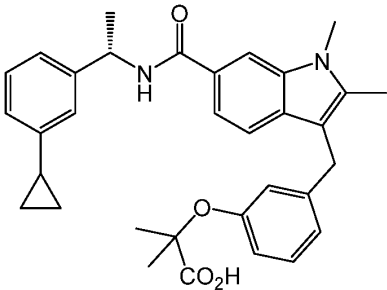
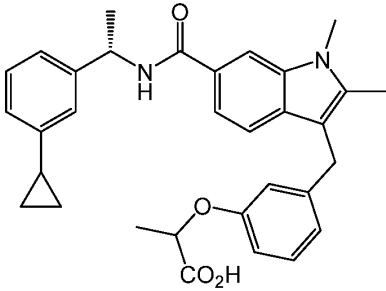
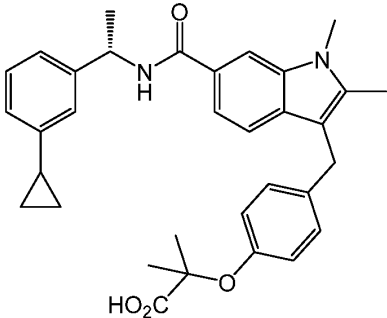
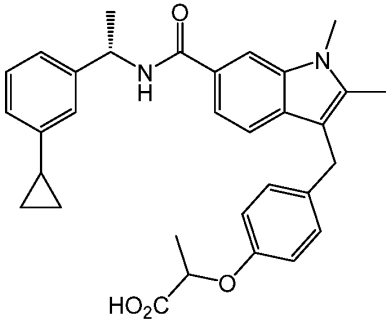
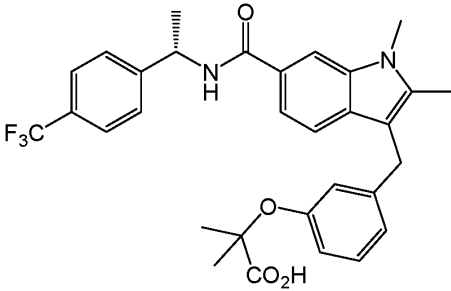
53. The compound of any one of claims 1-52, or a pharmaceutically acceptable salt or prodrug thereof, wherein L^2 is substituted or unsubstituted methylene.

54. The compound of any one of claims 1-53, or a pharmaceutically acceptable salt or prodrug thereof, wherein L^3 is a bond.

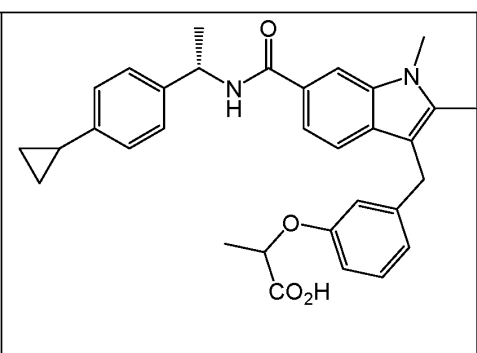
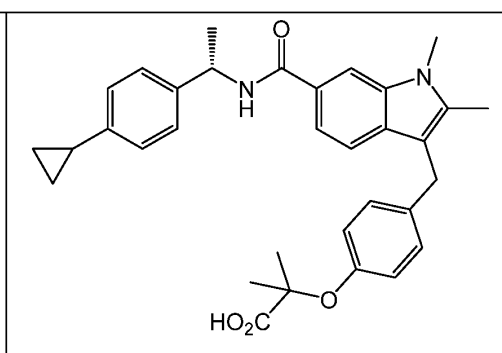
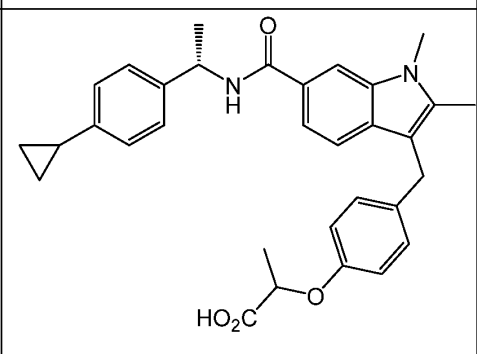
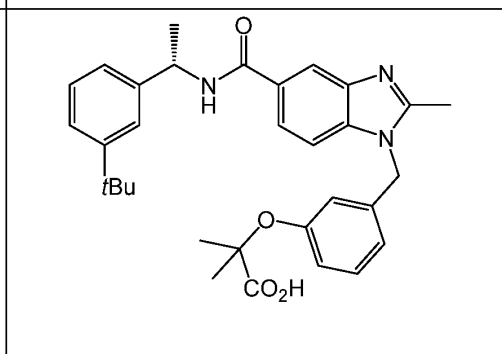
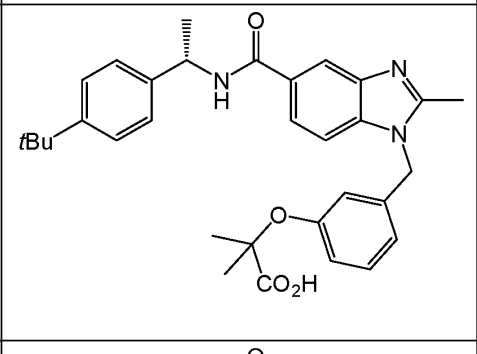
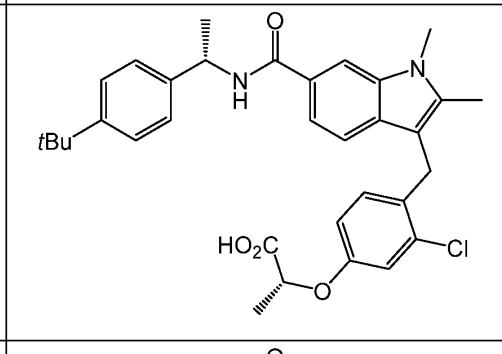
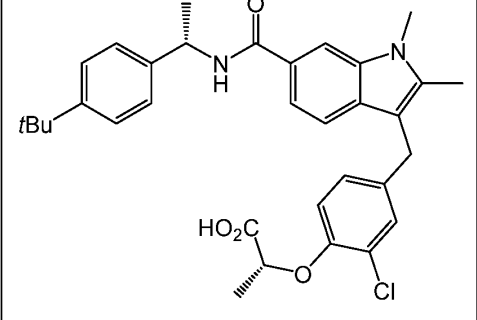
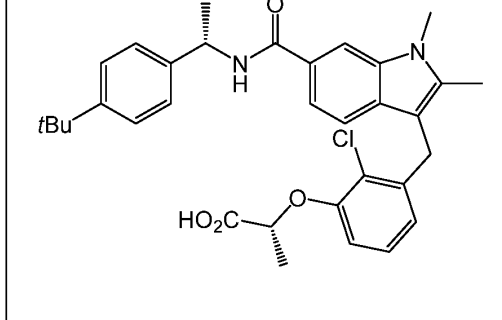
55. The compound of any one of claims 1-54, wherein the compound is of formula:

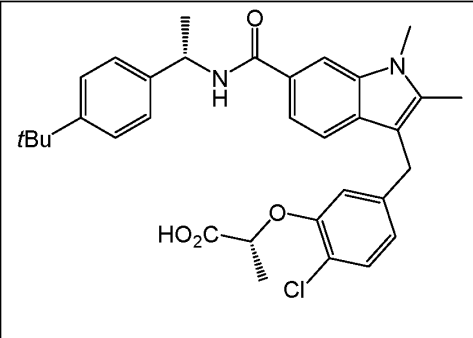
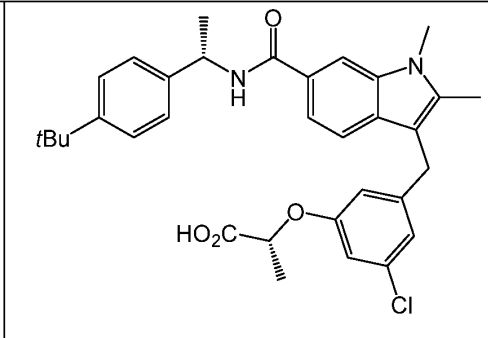
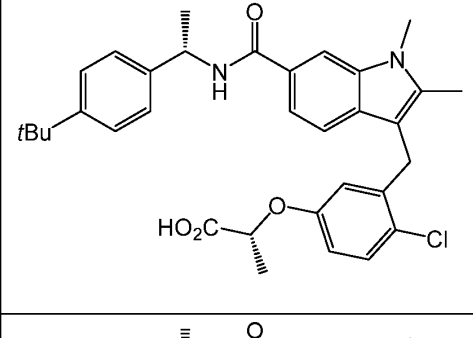
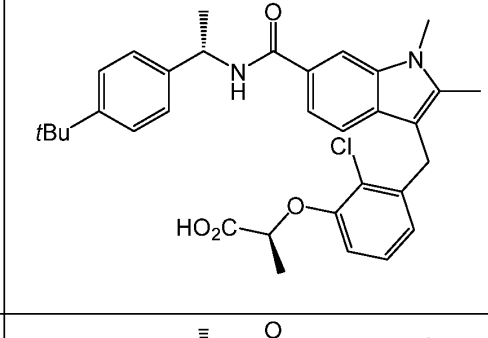
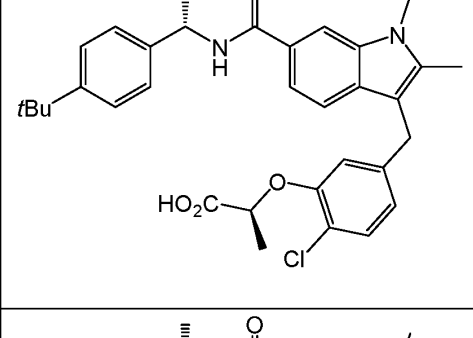
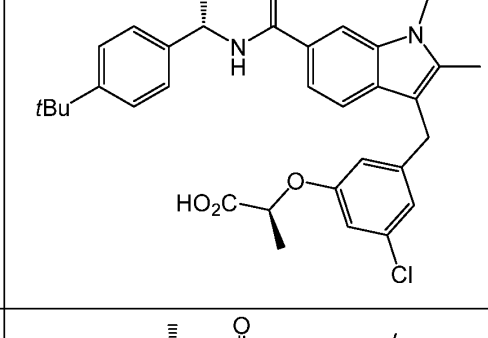
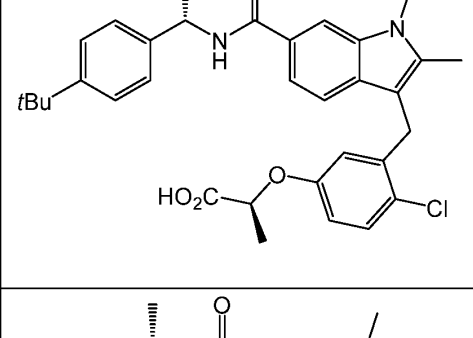
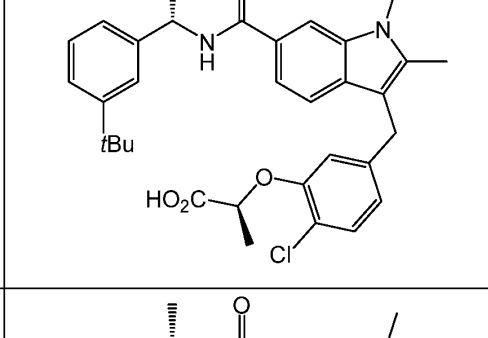
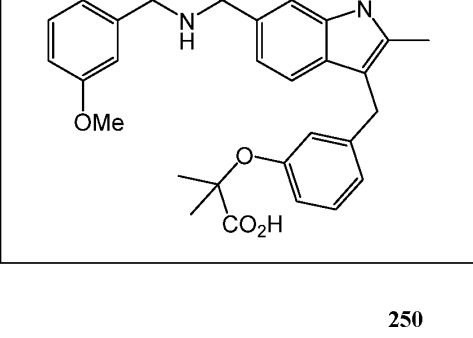
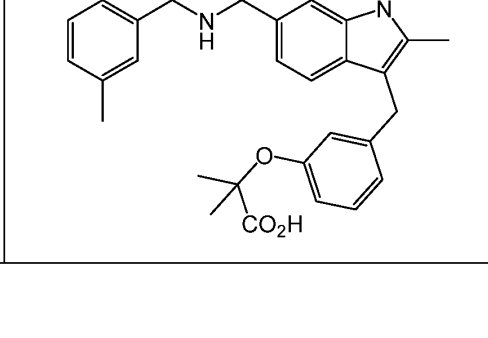
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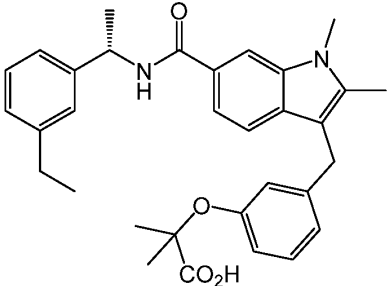
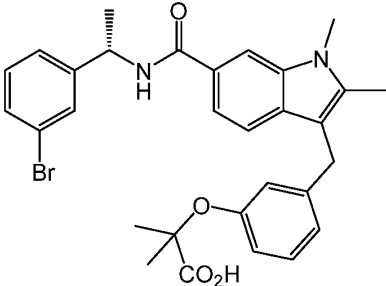
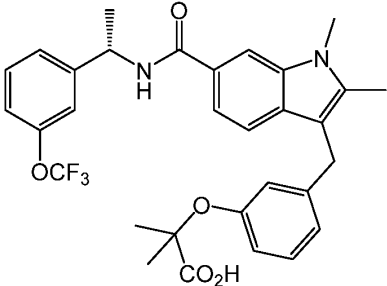
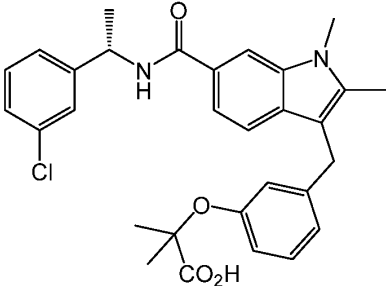
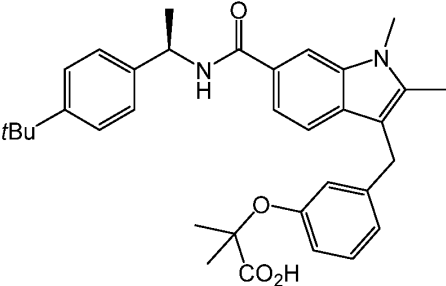
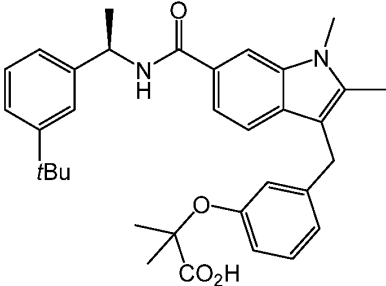
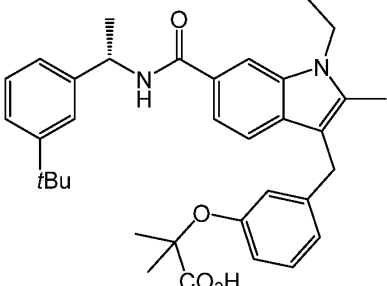
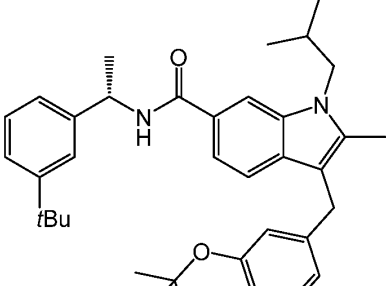
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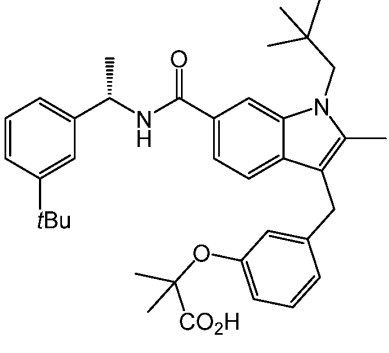
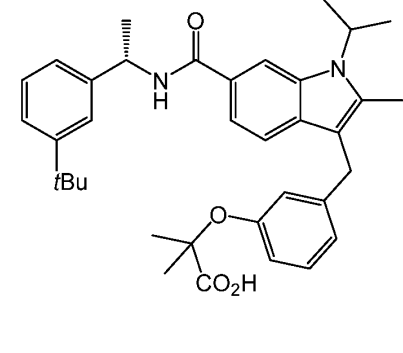
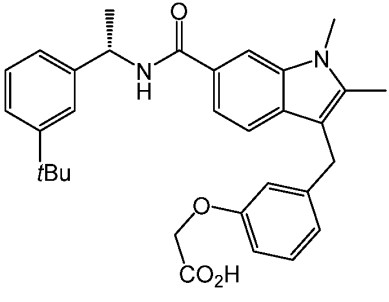
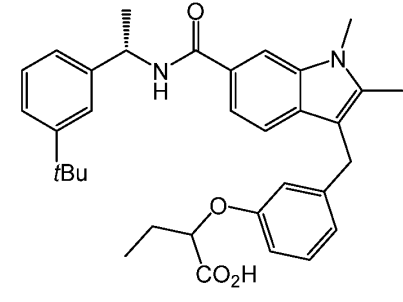
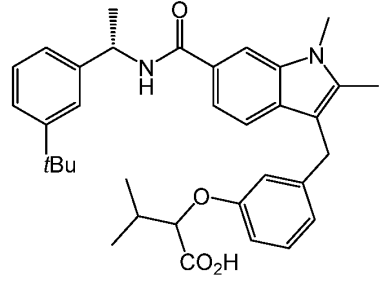
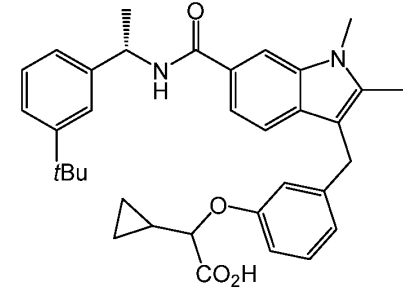
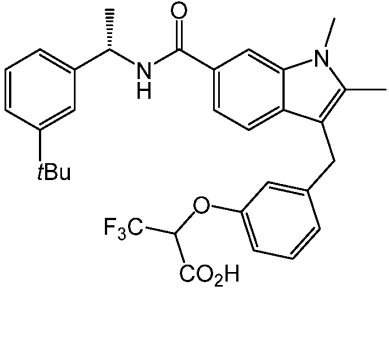
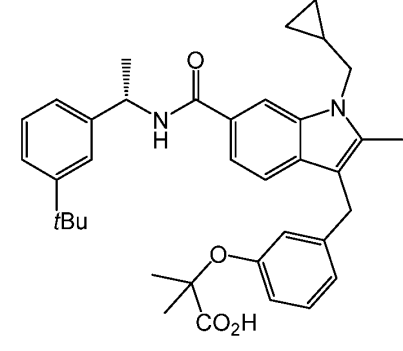
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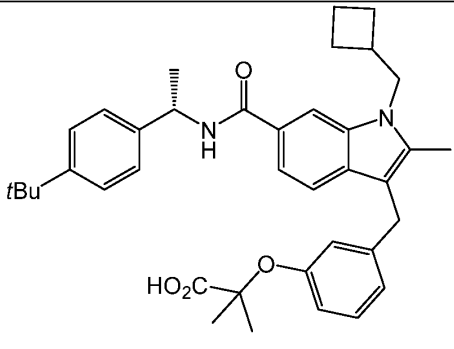
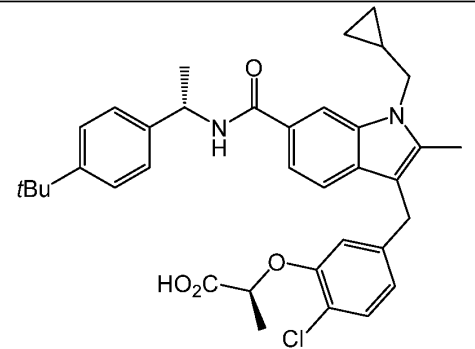
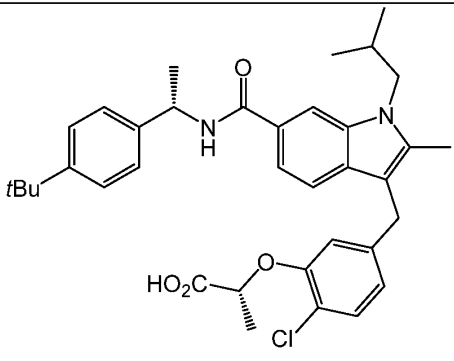
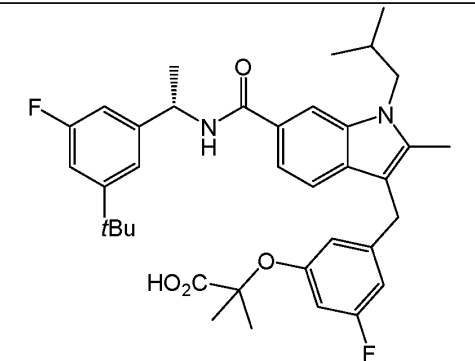
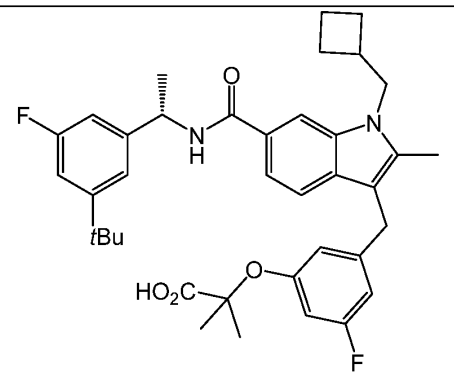
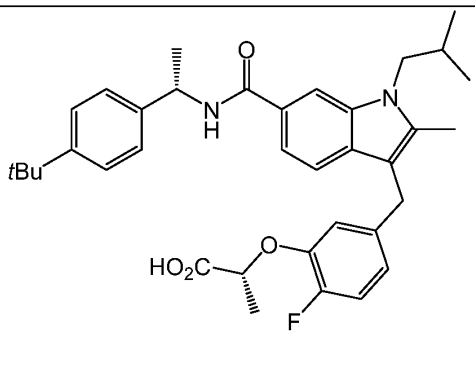
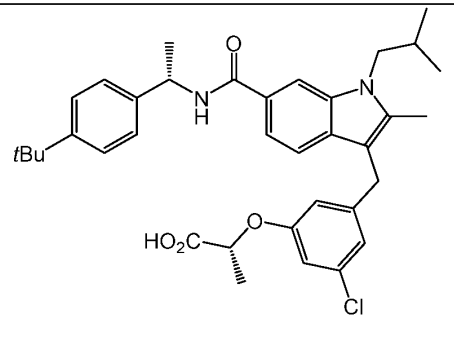
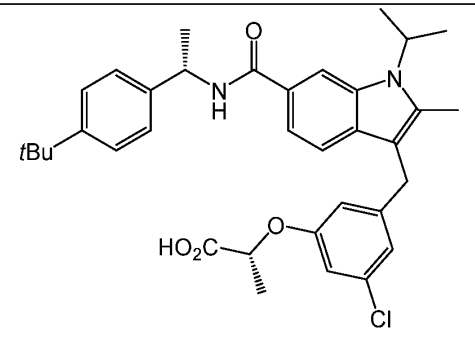
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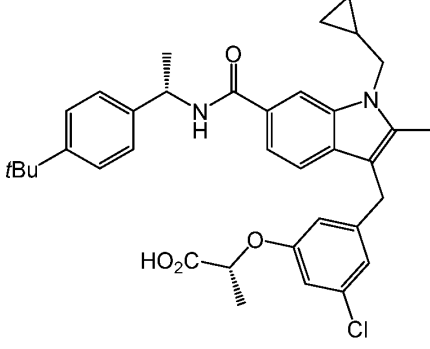
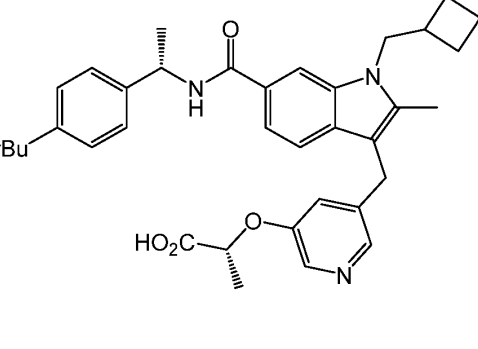
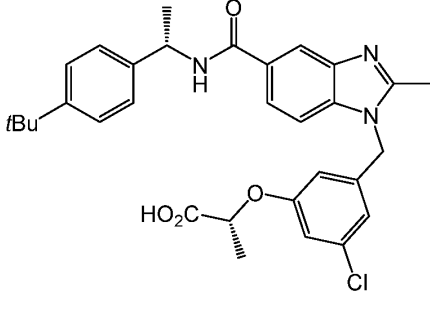
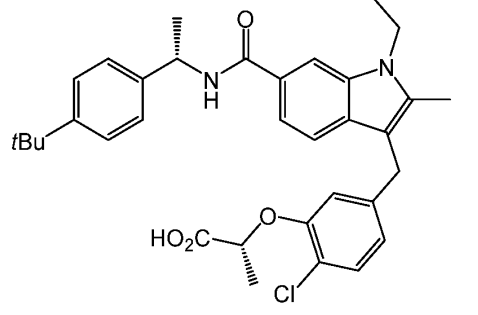
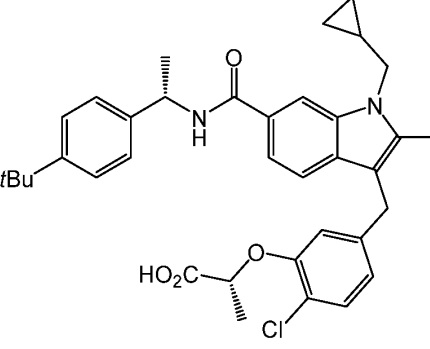
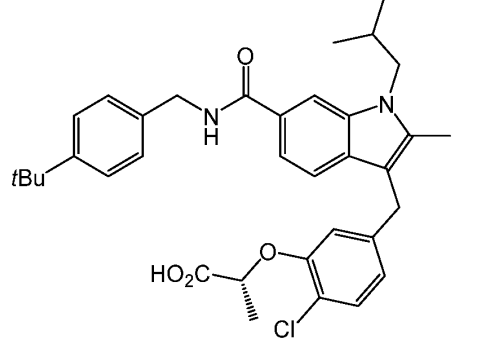
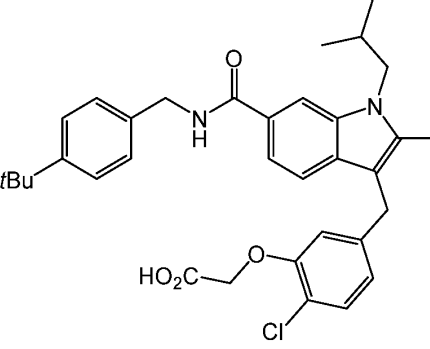
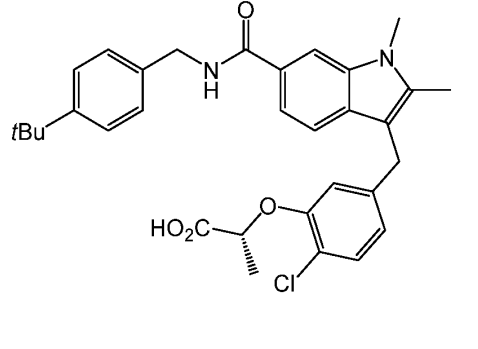
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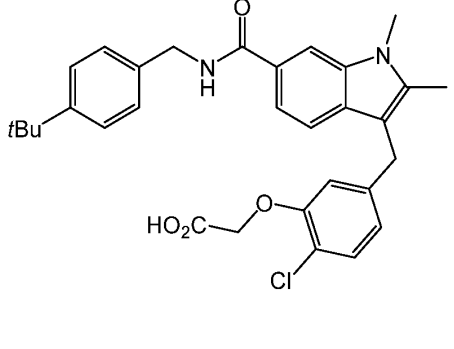
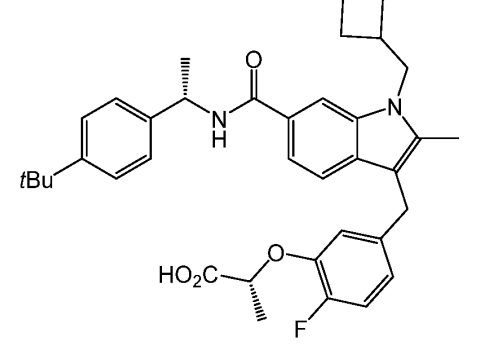
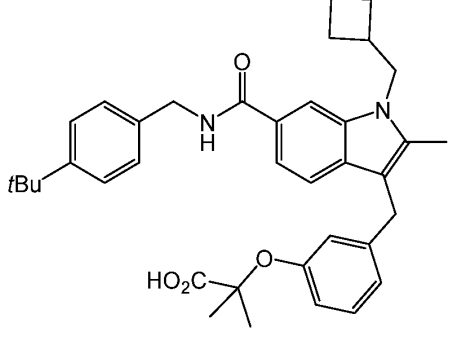
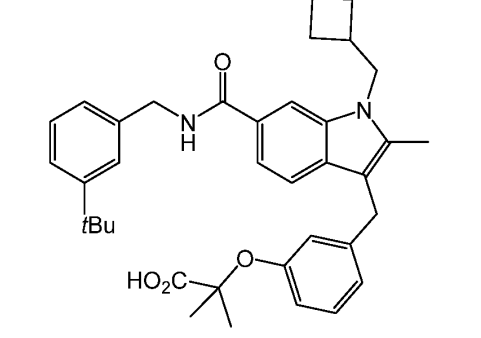
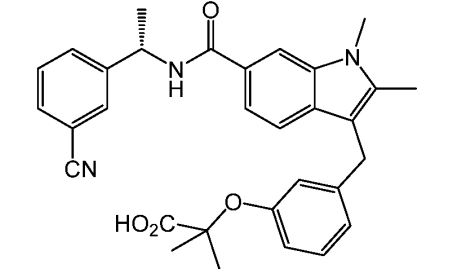
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or a pharmaceutically acceptable salt or prodrug thereof.

56. A composition comprising the compound of any one of claims 1-55, or a pharmaceutically acceptable salt or prodrug thereof, and an excipient.

57. A method of treating or preventing a disease or disorder in a subject in need thereof, comprising administering to the subject in need thereof an effective amount of:

the compound of any one of claims 1- 55, or a pharmaceutically acceptable salt or prodrug thereof;

or the composition of claim 56.

58. The compound of any one of claims 1-55, or a pharmaceutically acceptable salt or prodrug thereof, or the composition of claim 56, for use in treating a disease or disorder in a subject in need thereof.
59. The compound of any one of claims 1-55, or a pharmaceutically acceptable salt or prodrug thereof, or the composition of claim 56, for use in the manufacture of a medicament for treatment of a disease or disorder in a subject in need thereof.
60. The method, compound for use, pharmaceutically acceptable salt or prodrug thereof for use, or composition for use of any one of claims 57-59, wherein the disease or disorder is associated with peroxisome proliferator-activated receptor γ (PPAR γ).
61. The method, compound for use, pharmaceutically acceptable salt or prodrug thereof for use, or composition for use of any one of claims 57-60, wherein the disease or disorder is a progressive bone disease.
62. The method, compound for use, pharmaceutically acceptable salt or prodrug thereof for use, or composition for use of claim 61, wherein the progressive bone disease is osteoporosis or Paget's Disease.
63. The method, compound for use, pharmaceutically acceptable salt or prodrug thereof for use, or composition for use of any one of claims 57-60, wherein the disease or disorder is a proliferative disease.
64. The method, compound for use, pharmaceutically acceptable salt or prodrug thereof for use, or composition for use of claim 63, wherein the proliferative disease is cancer.
65. The method, compound for use, pharmaceutically acceptable salt or prodrug thereof for use, or composition for use of claim 64, wherein the cancer is colorectal cancer, pancreatic cancer, bladder cancer, esophageal cancer, breast cancer, prostate cancer, blood cancer, or bone cancer.
66. The method, compound for use, pharmaceutically acceptable salt or prodrug thereof for use, or composition for use of any one of claims 64 or 65, wherein the cancer is multiple myeloma.
67. The method, compound for use, pharmaceutically acceptable salt or prodrug thereof for use, or composition for use of any one of claims 57-60, wherein the disease or disorder is a metabolic disease.

68. The method, compound for use, pharmaceutically acceptable salt or prodrug thereof for use, or composition for use of claim 67, wherein the metabolic disease is diabetes, obesity, metabolic syndrome, atherosclerotic vascular disease, non-alcoholic steatohepatitis (NASH), fatty liver disease, weight loss, adipose tissue remodeling, metabolic bone disease, or hyperparathyroidism.

69. The method, compound for use, pharmaceutically acceptable salt or prodrug thereof for use, or composition for use of any one of claims 57-68, wherein side effects experienced by the subject are reduced compared with administration of a PPAR γ agonist.

70. The method, compound for use, pharmaceutically acceptable salt or prodrug thereof for use, or composition for use of claim 69, wherein the side effects comprise weight gain, edema, impairment of bone growth or formation, cardiac hypertrophy, congestive heart failure, vascular leak syndrome, and/or hepatotoxicity.

71. A method of inhibiting cell proliferation or promoting apoptosis in a subject in need thereof or in a cell, tissue, or biological sample, comprising administering to the subject in need thereof or contacting the cell, tissue, or biological sample with an effective amount of:

a compound of any one of claims 1-55, or a pharmaceutically acceptable salt or prodrug thereof;

or the composition of claim 56;

wherein the cell, tissue, or biological sample is *in vivo*.

72. A method of inhibiting cell proliferation or promoting apoptosis in a cell, tissue, or biological sample, comprising contacting the cell, tissue, or biological sample with an effective amount of:

a compound of any one of claims 1-55, or a pharmaceutically acceptable salt or prodrug thereof;

or the composition of claim 56;

wherein the cell, tissue, or biological sample is *in vitro*.

73. A method of modulating peroxisome proliferator-activated receptor γ (PPAR γ) in a subject in need thereof or in a cell, tissue, or biological sample, comprising administering to the subject in need thereof or contacting the cell, tissue, or biological sample with an effective amount of:

a compound of any one of claims 1-55, or a pharmaceutically acceptable salt or prodrug thereof;

or the composition of claim 56.

74. The method, compound for use, pharmaceutically acceptable salt or prodrug thereof for use, or composition for use of any one of claims 57-73, comprising not activating PPAR γ .
75. The method, compound for use, pharmaceutically acceptable salt or prodrug thereof for use, or composition for use of any one of claims 57-74, comprising reducing phosphorylation of PPAR γ at serine 273.
76. The method, compound for use, pharmaceutically acceptable salt or prodrug thereof for use, or composition for use of any one of claims 57-75, comprising normalizing the functional remodeling activities of osteocytes, osteoblasts, and/or osteoclasts to result in healthy bone structure and/or strength.
77. The method, compound for use, pharmaceutically acceptable salt or prodrug thereof for use, or composition for use of any one of claims 57-76, comprising decreasing marrow adiposity.
78. The method, compound for use, pharmaceutically acceptable salt or prodrug thereof for use, or composition for use of any one of claims 57-77, comprising increasing trabecular and cortical bone and/or improving metabolic parameters.
79. The method, compound for use, pharmaceutically acceptable salt or prodrug thereof for use, or composition for use of claim 78, wherein improving metabolic parameters comprises reducing fasting plasma glucose into a normal range less than 100 mg/dl and HbA1c less than 6%.
80. A kit comprising:
the compound of any one of claims 1-55, or a pharmaceutically acceptable salt or prodrug thereof, or the composition of claim 56;
and instructions for its use.