(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
09 November 2017 (09.11.2017)

WIPO | PCT

(10) International Publication Number
WO 2017/192543 A1

(51) International Patent Classification:
C07D 401/04 (2006.01) *A61K 31/4523* (2006.01)
C07D 401/14 (2006.01) *A61K 31/454* (2006.01)
C07D 405/04 (2006.01) *A61K 31/4545* (2006.01)
C07D 211/34 (2006.01) *A61P 35/00* (2006.01)

(21) International Application Number:
PCT/US2017/030577

(22) International Filing Date:
02 May 2017 (02.05.2017)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/330,350 02 May 2016 (02.05.2016) US

(71) Applicant: **REGENTS OF THE UNIVERSITY OF MICHIGAN** [US/US]; Office of Technology Transfer, 1600 Huron Parkway, 2nd Floor, Ann Arbor, MI 48109-2590 (US).

(72) Inventors: **WANG, Shaomeng**; 3336 Stirling Ct., Superior Township, MI 49198 (US). **AGUILAR, Angelo**; 2364 Stone Rd., Ann Arbor, 48105 (US). **ZHANG, Ke**; 2411 Stone Rd., Ann Arbor, MI 48105 (US). **XU, Shilin**; 3578 Green Brier Blvd., Apartment 405C, Ann Arbor, MI 48105 (US). **XU, Tianfeng**; 2153 Arbor Circle West, Apartment 205, Ypsilanti, 48197 (US). **BERNARD, Denzil**; 1803 Pointe Crossing St., Apartment 101, Ann Arbor, MI 48105 (US). **HUANG, Liyue**; 3170 Otter Creek Ct., Ann Arbor, MI 48105 (US).

(74) Agent: **NAPOLI, James J.**; Marshall, Gerstein & Borun LLP, 233 S. Wacker Drive, 6300 Willis Tower, Chicago, IL 60606-6357 (US).

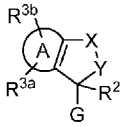
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report (Art. 21(3))*

WO 2017/192543 A1

(54) Title: PIPERIDINES AS MENIN INHIBITORS



(I)

(57) Abstract: The present disclosure provides compounds represented by Formula (I): (Formula(I)) and the pharmaceutically acceptable salts, hydrates, and solvates thereof, wherein R^2, R^{3a}, R^{3b}, A, G, X, and Y are as defined as set forth in the specification. The present disclosure also provides compounds of Formula (I) for use to treat a condition or disorder responsive to menin inhibition such as cancer.

PIPERIDINES AS MENIN INHIBITORS

BACKGROUND OF THE INVENTION

Field of the Invention

[0001] The present disclosure provides compounds as menin inhibitors and therapeutic methods of treating conditions and diseases wherein inhibition of menin provides a benefit.

Background Art

[0002] Mixed-lineage leukemia (MLL) is a proto-oncogene that was originally discovered at the site of chromosomal translocations in human leukemias. Due to chromosomal translocations, MLL is fused with more than 40 different partner proteins to yield a diverse collection of chimeric fusion proteins. The MLL protein is a histone methyltransferase that covalently modifies chromatin and is mutated in certain subsets of acute leukemia. Many of the fusion partners constitutively activate novel transcriptional effector properties of MLL that often correlate with its oncogenic potential in animal models of acute leukemia. MLL normally associates with a group of highly conserved cofactors to form a macromolecular complex that includes menin, a product of the MEN1 tumor suppressor gene. The MEN1 gene is mutated in heritable and sporadic endocrine tumors.

[0003] Menin is in involved in a diverse network of protein-protein interactions. Cierpicki and Grembecka, *Future Med. Chem. 6*:447-462 (2014). Overexpression of menin leads to inhibition of Ras-transformed cells. Menin interacts with the transcription factors JunD and NF-κB and represses their activation of gene transcription. Studies on these interacting proteins suggest that menin exerts its effects predominantly through inhibitory effects on transcription. But an alternative possibility is that menin mediates its effects through transcriptional activation of target genes. Additionally, menin interacts with RPA2, a component of a single-stranded DNA-binding protein involved in DNA repair and replication. Menin also interacts with FANCD2, a nuclear protein that plays a critical role in maintaining genome stability with breast cancer 1 gene (Brea1) product.

[0004] The mechanisms by which menin, which does not have significant homology with other proteins, functions as a tumor suppressor are not completely known. Menin

plays a role in regulating cellular proliferation because Men1 knockout mice show increased proliferation in neuroendocrine tissues, down-modulation of menin in epithelial cells increases proliferation, and Men1 knockout fibroblasts proliferate more rapidly than wild-type cells as assayed by tritiated thymidine incorporation. MEN1 cells also have increased sensitivity to DNA-damaging agents. Menin interacts with promoters of HOX genes.

[0005] Certain oncogenic MLL fusion proteins stably associate with menin through a high-affinity interaction that is required for the initiation of MLL-mediated leukemogenesis. Menin is essential for maintenance of MLL-associated but not other oncogene induced myeloid transformation. Acute genetic ablation of menin reverses Hox gene expression mediated by MLL-menin promoter-associated complexes, and specifically eliminates the differentiation arrest and oncogenic properties of MLL-transformed leukemic blasts.

[0006] MLL fusion proteins, a consequence of acquired genetic aberrations, transform hematopoietic cells through two alternate mechanisms, by either constitutive transcriptional effector activity or inducing forced MLL dimerization and oligomerization. Both mechanisms result in the inappropriate expression of a subset of HOX genes, particularly HOXA9, whose consistent expression is a characteristic feature of human MLL leukemias.

[0007] Menin interacts with transcription activators, e.g., sc-Myb, MLL1, SMAD 1,3,5, Pem, Runx2, Hlbx9,ER, PPARγ, vitamin D receptor, transcription repressors, e.g., JunD, Sin3A, HDAC, EZH2, PRMT5, NFκB, Sirt1, CHES1, cell signaling proteins, e.g., AKT, SOS1/GEF, β-catenin, SMAD 1,3,5, NFκB,ER, PPARγ, vitamin D receptor, and other proteins, e.g., cell cycle: RPA2, ASK; DNA repair: FANCD2; cell structure: GFAP, vimenten, NMMHCIIA, IQGAP1; Others: HSP70, CHIP, ("menin-interacting proteins") involved in regulating gene transcription and cell signaling. Matkar, *Trends in Biochemical Sciences 38*: 394-402 (2013). Targeting menin interactions, e.g., menin–MLL interaction, with small molecules represents an attractive strategy to develop new anticancer agents. *See, e.g.*, Cierpicki and Grembecka, *Future Med. Chem. 6*:447-462 (2014); He *et al.*, *J. Med. Chem. 57*:1543−1556 (2014); and Borkin *et al.*, *Cancer Cell 27*:589–602 (2015).

[0008] Small molecules that disrupt the interaction of MLL and menin are disclosed in U.S. Patent Nos. 9,212,180 and 9,216,993; and U.S. Patent Application Publication Nos. 2011/0065690; 2014/0275070; 2016/0045504; and 2016/0046647. Peptides that disrupt the interaction of MLL and menin are disclosed in U.S. Patent Application Publication No. 2009/0298772.

[0009] There is an ongoing need for new agents, e.g., small molecules, for treating cancer and other diseases responsive to menin inhibition.

BRIEF SUMMARY OF THE INVENTION

[0010] In one aspect, the present disclosure provides piperidines, and related analogs, represented by any one or more of Formulae **I-VI**, **VIi**, **VIII**, **VIII-A**, **VIII-B**, **VIII-C**, **VIII-D**, **VIII-E**, **VIII-F**, **VIII-G**, **VIII-H**, **IX**, **IX-A**, **IX-B**, **IX-C**, **IX-D**, **IX-E**, **IX-F**, **IX-G**, **IX-H**, **X**, **X-A**, **X-B**, **X-C**, **X-D**, **X-E**, **X-F**, **X-G**, **X-H**, **Xi**, **Xi-A**, **Xi-B**, **Xi-C**, **Xi-D**, **Xi-E**, **Xi-F**, **Xi-G**, or **Xi-H** below, and the pharmaceutically acceptable salts, hydrates, and solvates thereof, collectively referred to herein as "Compounds of the Disclosure." Compounds of the Disclosure are inhibitors of menin and/or synthetic intermediates that can be used to prepare inhibitors of menin. Compounds of the Disclosure are useful in treating diseases or conditions wherein inhibition of menin provides a therapeutic benefit to a patient.

[0011] In another aspect, the present disclosure provides methods of treating a condition or disease by administering a therapeutically effective amount of a Compound of the Disclosure to a patient, e.g., a human, in need thereof. The disease or condition is treatable by inhibition menin, for example, a cancer, e.g., leukemia, a chronic autoimmune disorder, an inflammatory condition, a proliferative disorder, sepsis, or a viral infection. Also provided are methods of preventing the proliferation of unwanted proliferating cells, such as cancer, in a subject comprising administering a therapeutically effective amount of a Compound of the Disclosure to a subject at risk of developing a condition characterized by unwanted proliferating cells. In some embodiments, the Compounds of the Disclosure reduce the proliferation of unwanted cells by inducing apoptosis and/or differentiation in those cells.

[0012] In another aspect, the present disclosure provides a method of inhibiting menin in an individual, comprising administering to the individual an effective amount of at least one Compound of the Disclosure.

[0013] In another aspect, the present disclosure provides a pharmaceutical composition comprising a Compound of the Disclosure and an excipient and/or pharmaceutically acceptable carrier.

[0014] In another aspect, the present disclosure provides a composition comprising a Compound of the Disclosure and an excipient and/or pharmaceutically acceptable carrier for use treating diseases or conditions wherein inhibition of menin provides a benefit, *e.g.*, cancer.

[0015] In another aspect, the present disclosure provides a composition comprising: (a) a Compound of the Disclosure; (b) a second therapeutically active agent; and (c) optionally an excipient and/or pharmaceutically acceptable carrier.

[0016] In another aspect, the present disclosure provides a Compound of the Disclosure for use in treatment of a disease or condition of interest, e.g., cancer.

[0017] In another aspect, the present disclosure provides a use of a Compound of the Disclosure for the manufacture of a medicament for treating a disease or condition of interest, e.g., cancer.

[0018] In another aspect, the present disclosure provides a kit comprising a Compound of the Disclosure, and, optionally, a packaged composition comprising a second therapeutic agent useful in the treatment of a disease or condition of interest, and a package insert containing directions for use in the treatment of a disease or condition, e.g., cancer.

[0019] In another aspect, the present disclosure provides methods of preparing Compounds of the Disclosure.

[0020] It is to be understood that both the foregoing summary and the following detailed description are exemplary and explanatory only, and are not restrictive of the invention as claimed.

DETAILED DESCRIPTION OF DRAWINGS

[0021] Fig. 1 is bar graph showing the effect of Cpd. No. 210 and Cpd. No. 366 on MOLM-13 genes MEIS1, HOX7, HOX10, and MYB after 4 days of treatment.

[0022] Fig. 2 is bar graph showing the effect of Cpd. No. 210 and Cpd. No. 366 on MV4-11 genes MEIS1, HOX7, HOX10, and MYB after 4 days of treatment.

[0023] Fig. 3 is bar graph showing the effect of Cpd. No. 366 and Cpd. No. 238 on MOLM-13 genes MEIS1, HOX7, HOX10, and ITGAM after 66 hours of treatment.

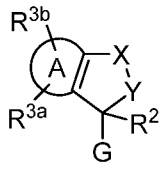
[0024] Fig. 4 is bar graph showing the effect Cpd. No. 366 and Cpd. No. 215 on MOLM-13 genes MEIS1, HOX7, HOX9, HOX10, and HOX11 after 40 hours of treatment.

[0025] Fig. 5 is bar graph showing the effect Cpd. No. 366 and Cpd. No. 215 on MV4-11 genes MEIS1, HOX7, HOX10, and HOX11 after 40 hours of treatment.

DETAILED DESCRIPTION OF THE INVENTION

[0026] Compounds of the Disclosure are menin inhibitors and/or synthetic intermediates used to prepare menin inhibitors.

[0027] In one embodiment, Compounds of the Disclosure are compounds represented by Formula **I**:



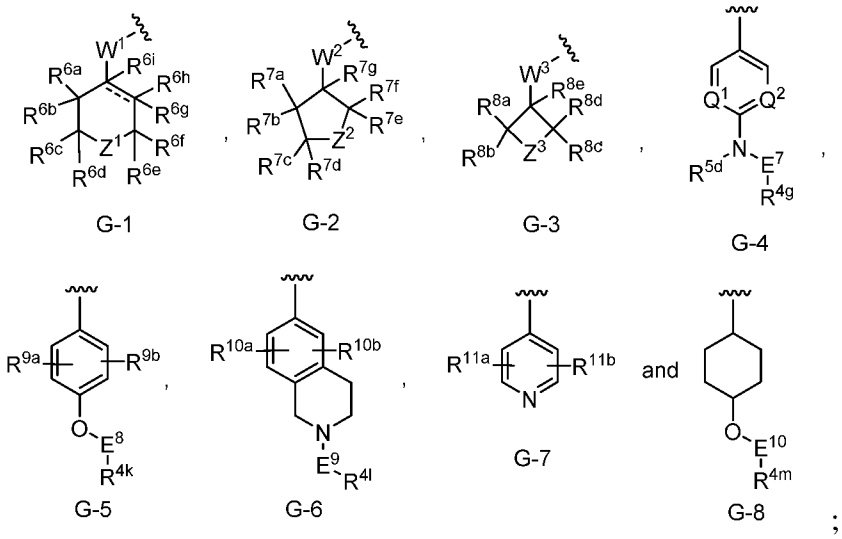
I,

and the pharmaceutically acceptable salts, hydrates, and solvates thereof, wherein:

[0028] 

is a fused thienyl or fused phenyl group,

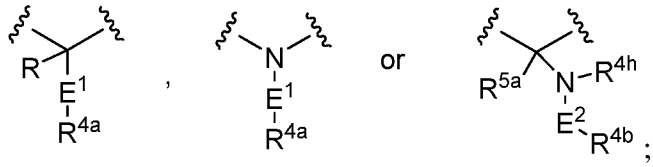
[0029] G is selected from the group consisting of:



;

[0030] W^1 is absent or $-CH_2-$;

[0031] Z^1 is selected from the group consisting of $-C(R)(-E^1-R^{4a})-$, $-N(-E^1-R^{4a})-$ and $-C[-N(-E^2-R^{4b})(R^{4h})](R^{5a})-$, i.e., Z^1 is:



;

[0032] W^2 is absent or $-CH_2-$;

[0033] Z^2 is selected from the group consisting of $-N(-E^3-R^{4c})-$ and $-C[-N(-E^4-R^{4d})(R^{4i})](R^{5b})-$;

[0034] W^3 is absent or $-CH_2-$;

[0035] Z^3 is selected from the group consisting of $-N(-E^5-R^{4e})-$ and $-C[-N(-E^6-R^{4f})(R^{4j})](R^{5c})-$;

[0036] ≡ is a single or double bond, with the proviso that when ≡ is a double bond, R^{6h} and R^{6i} are absent;

[0037] Q^1 and Q^2 are each independently CH or N;

[0038] X-Y is selected from the group consisting of:

$-N(R^{1a})-C(=O)-$;

$-C(=O)-O-$;

$-C(=O)-N(R^{1b})-$;

$-CH_2N(R^{1c})-CH_2-$;

$-C(=O)N(R^{1d})-CH_2-$;

$-CH_2CH_2-N(R^{1e})-$;

$-CH_2N(R^{1f})-C(=O)-$; and

$-CH_2O-CH_2-$; or

[0039] X and Y do not form a chemical bond, and

[0040] X is selected from the group consisting of hydrogen, alkyl, halo, hydroxy, cyano, amino, alkylamino, dialkylamino, haloalkyl, alkoxy, and haloalkoxy; and

[0041] Y is selected from the group consisting of cyano, hydroxy, and $-CH_2-R^{12}$;

[0042] E^1, E^2, E^3, E^4, E^5, E^6, E^7, E^8, E^9, and E^{10} are each independently selected from the group consisting of:

$-C(=O)-$;

$-C(=O)N(R^{13})-$;

$-[C(R^{14a})(R^{4b})]_mO-$;

$-[C(R^{14a})(R^{14b})]_mN(R^{15})-$;

$-[C(R^{14c})(R^{14d})]_n-$;

$-CH_2(=O)-$; and

$-S(=O)_2-$; or

[0043] E^1, E^2, E^3, E^4, E^5, E^6, E^7, E^8, E^9, and E^{10} are each independently absent;

[0044] R is selected from the group consisting of hydrogen and alkyl;

[0045] R^{1a} is selected from the group consisting of hydrogen and alkyl;

[0046] R^{1b} is selected from the group consisting of hydrogen, alkyl, and aralkyl;

[0047] R^{1c} is selected from the group consisting of hydrogen, alkyl, haloalkyl, optionally substituted cycloalkyl, optionally substituted heterocyclo, (cycloalkyl)alkyl, (heterocycloalkyl)alkyl, aralkyl, (heteroaryl)alkyl, alkylcarbonyl, arylcarbonyl, and alkoxycarbonyl;

[0048] R^{1d} is selected from the group consisting of hydrogen, alkyl, and aralkyl;

[0049] R^{1e} is selected from the group consisting of hydrogen, alkyl, and (aryloxy)alkyl;

[0050] R^{1f} is selected from the group consisting of hydrogen and alkyl;

[0051] R^2 is selected from the group consisting of hydrogen, alkyl, alkenyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclo, optionally substituted heteroaryl, and aralkyl;

[0052] R^{3a} and R^{3b} are each independently selected from the group consisting of hydrogen, alkyl, halo, hydroxy, cyano, amino, alkylamino, dialkylamino, haloalkyl, alkoxy, and haloalkoxy;

[0053] R^{4a}, R^{4b}, R^{4c}, R^{4d}, R^{4e}, R^{4f}, R^{4g}, R^{4k}, R^{4l}, and R^{4m} are each independently selected from the group consisting of hydrogen, alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclo, optionally substituted heteroaryl, aralkyl, (heterocyclo)alkyl, and (heteroaryl)alkyl;

[0054] R^{4h}, R^{4i}, and R^{4j} are each independently selected from the group consisting of hydrogen and alkyl;

[0055] R^{5a}, R^{5b}, R^{5c}, and R^{5d} are each independently selected from the group consisting of hydrogen and alkyl;

[0056] R^{6a}, R^{6b}, R^{6c}, R^{6d}, R^{6e}, R^{6f}, R^{6g}, and R^{6h} are each independently selected from the group consisting of hydrogen and alkyl;

[0057] R^{6i} is selected from the group consisting of hydrogen, alkyl, and halo;

[0058] R^{7a}, R^{7b}, R^{7c}, R^{7d}, R^{7e}, and R^{7f} are each independently selected from the group consisting of hydrogen and alkyl;

[0059] R^{7g} is selected from the group consisting of hydrogen, alkyl, and halo;

[0060] R^{8a}, R^{8b}, R^{8c}, and R^{8d} are each independently selected from the group consisting of hydrogen and alkyl;

[0061] R^{8e} is selected from the group consisting of hydrogen, alkyl, and halo;

[0062] R^{9a} and R^{9b} are each independently selected from the group consisting of hydrogen, alkyl, halo, hydroxy, cyano, amino, alkylamino, dialkylamino, haloalkyl, alkoxy, and haloalkoxy;

[0063] R^{10a} and R^{10b} are each independently selected from the group consisting of hydrogen, alkyl, halo, hydroxy, cyano, amino, alkylamino, dialkylamino, haloalkyl, alkoxy, and haloalkoxy;

[0064] R^{11a} and R^{11b} are each independently selected from the group consisting of hydrogen, alkyl, halo, hydroxy, cyano, amino, alkylamino, dialkylamino, haloalkyl, alkoxy, and haloalkoxy;

[0065] R^{12} is selected from the group consisting of hydroxy, amino, optionally substituted heteroaryl, optionally substituted heterocyclo, and -NHC(=O)-R^{16};

[0066] m is 2, 3, 4, or 5,

[0067] n is 1, 2, 3, 4, or 5

[0068] R^{13} is selected from the group consisting of hydrogen and alkyl;

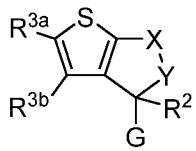
[0069] R^{14a} and R^{14b} are each independently selected from the group consisting of hydrogen and alkyl;

[0070] R^{14c} and R^{14d} are each independently selected from the group consisting of hydrogen and alkyl;

[0071] R^{15} is selected from the group consisting of hydrogen and alkyl; and

[0072] R^{16} is selected from the group consisting of alkyl, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted cycloalkyl.

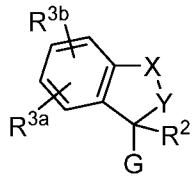
[0073] In another embodiment, Compounds of the Disclosure are compounds represented by Formula **II**:



II,

and the pharmaceutically acceptable salts, hydrates, and solvates thereof, wherein R^2, R^{3a}, R^{3b}, G, X, and Y are as defined in connection with Formula **I**.

[0074] In another embodiment, Compounds of the Disclosure are compounds represented by Formula **III**:



III,

and the pharmaceutically acceptable salts, hydrates, and solvates thereof, wherein R^2, R^{3a}, R^{3b}, G, X, and Y are as defined in connection with Formula **I**.

[0075] In another embodiment, Compounds of the Disclosure are compounds represented by any one of Formulae **I-III**, and the pharmaceutically acceptable salts, hydrates, and solvates thereof, wherein G is G-1. In another embodiment, W^1 is absent. In another embodiment, ═══ is a single bond and R^{6a}, R^{6b}, R^{6c}, R^{6d}, R^{6e}, R^{6f}, R^{6g}, R^{6h}, and R^{6i} are each independently selected from the group consisting of hydrogen and $C_{1\text{-}3}$ alkyl. In another embodiment, W^1 is absent, ═══ is a single bond, and R^{6a}, R^{6b}, R^{6c}, R^{6d}, R^{6e}, R^{6f}, R^{6g}, R^{6h}, and R^{6i} are each independently selected from the group consisting of hydrogen and $C_{1\text{-}3}$ alkyl. In another embodiment, R^{6a}, R^{6b}, R^{6c}, R^{6d}, R^{6e}, R^{6f}, R^{6g}, R^{6h}, and R^{6i} are each hydrogen.

[0076] In another embodiment, E^1 is -C(=O)-. In another embodiment, E^1 is -C(=O)N(R^{13})-. In another embodiment, E^1 is -[C(R^{14a})(R^{14b})]$_m$O-. In another embodiment, E^1 is -[C(R^{14a})(R^{14b})]$_m$N(R^{15})-. In another embodiment, E^1 is -[C(R^{14c})(R^{14d})]$_n$-. In another embodiment, E^1 is -[C(R^{14c})(R^{14d})]$_n$- and n is 1 or 2 and R^{14c} and R^{14d} are each hydrogen. In another embodiment, E^1 is -CH_2(=O)-. In another embodiment, E^1 is -S(=O)$_2$-. In another embodiment, E^1 is absent.

[0077] In another embodiment, Compounds of the Disclosure are compounds represented by any one of Formulae **I-III**, and the pharmaceutically acceptable salts, hydrates, and solvates thereof, wherein G is G-2. In another embodiment, W^2 is absent. In another embodiment, R^{7a}, R^{7b}, R^{7c}, R^{7d}, R^{7e}, R^{7f}, and R^{7g} are each independently selected from the group consisting of hydrogen and C_{1-3} alkyl. In another embodiment, W^2 is absent and R^{7a}, R^{7b}, R^{7c}, R^{7d}, R^{7e}, R^{7f}, and R^{7g} are each independently selected from the group consisting of hydrogen and C_{1-3} alkyl. In another embodiment, R^{7a}, R^{7b}, R^{7c}, R^{7d}, R^{7e}, R^{7f}, and R^{7g} are each hydrogen.

[0078] In another embodiment, Compounds of the Disclosure are compounds represented by any one of Formulae **I-III**, and the pharmaceutically acceptable salts, hydrates, and solvates thereof, wherein G is G-3. In another embodiment, W^3 is absent. In another embodiment, R^{8a}, R^{8b}, R^{8c}, R^{8d}, and R^{8e} are each independently selected from the group consisting of hydrogen and C_{1-3} alkyl. In another embodiment, W^3 is absent and R^{8a}, R^{8b}, R^{8c}, R^{8d}, and R^{8e} are each independently selected from the group consisting of hydrogen and C_{1-3} alkyl. In another embodiment, R^{8a}, R^{8b}, R^{8c}, R^{8d}, and R^{8e} are each hydrogen.

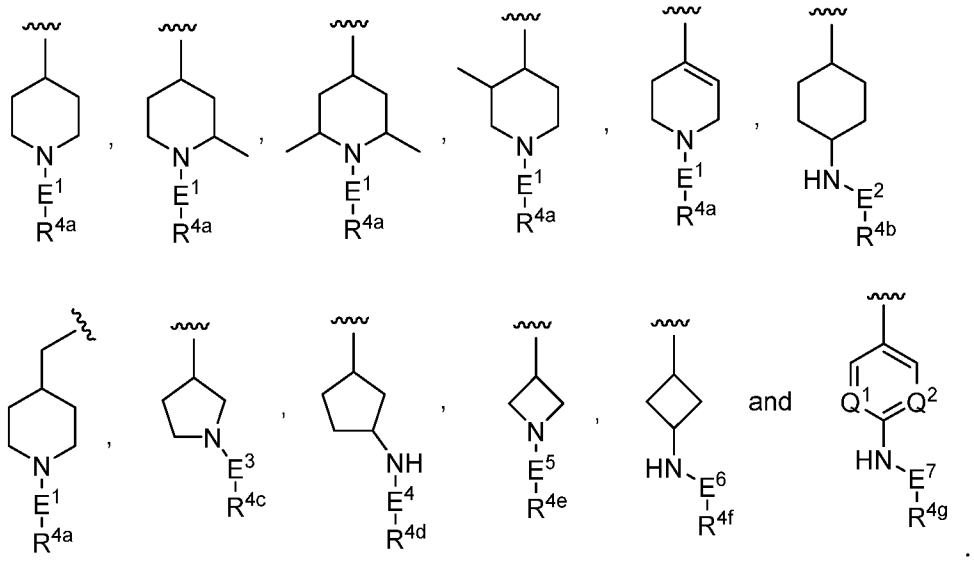
[0079] In another embodiment, Compounds of the Disclosure are compounds represented by any one of Formulae **I-III**, and the pharmaceutically acceptable salts, hydrates, and solvates thereof, wherein G is G-4.

[0080] In another embodiment, Compounds of the Disclosure are compounds represented by any one of Formulae **I-III**, and the pharmaceutically acceptable salts, hydrates, and solvates thereof, wherein G is G-5.

[0081] In another embodiment, Compounds of the Disclosure are compounds represented by any one of Formulae **I-III**, and the pharmaceutically acceptable salts, hydrates, and solvates thereof, wherein G is G-6.

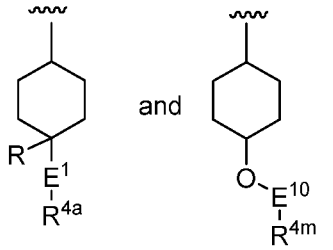
[0082] In another embodiment, Compounds of the Disclosure are compounds represented by any one of Formulae **I-III**, and the pharmaceutically acceptable salts, hydrates, and solvates thereof, wherein G is G-7.

[0083] In another embodiment, Compounds of the Disclosure are compounds represented by any one of Formulae **I-III**, and the pharmaceutically acceptable salts, hydrates, and solvates thereof, wherein G is selected from the group consisting of:



with the proviso that Q^1 is N and Q^2 is selected from the group consisting of CH and N, and R^{4a}, R^{4b}, R^{4c}, R^{4d}, R^{4e}, R^{4f}, R^{4g}, E^1, E^2, E^3, E^4, E^5, E^6, and E^7 are as defined in connection with Formula **I**. In another embodiment, E^1, E^2, E^3, E^4, E^5, E^6, and E^7 are each independently selected from the group consisting of -C(=O)-, -C(=O)N(R^{13})-, -[C(R^{14a})(R^{14b})]$_m$O-, -[C(R^{14a})(R^{14b})]$_m$N(R^{15})-, -[C(R^{14c})(R^{14d})]$_n$-, -CH_2(=O)-, and -$S(=O)_2$-. In another embodiment, E^1, E^2, E^3, E^4, E^5, E^6, and E^7 are each absent.

[0084] In another embodiment, Compounds of the Disclosure are compounds represented by any one of Formulae **I-III**, and the pharmaceutically acceptable salts, hydrates, and solvates thereof, wherein G is selected from the group consisting of:

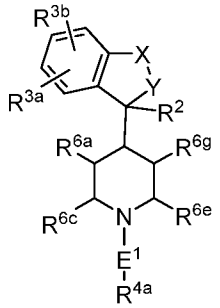


R, R^{4a}, R^{4m}, E^1, and E^{10} are as defined in connection with Formula **I**. In another embodiment, E^1 is -[C(R^{14c})(R^{14d})]$_n$-, R^{14c} and R^{14d} are hydrogen, and n is 1 or 2. In

another embodiment, E^{10} is $-[C(R^{14a})(R^{14b})]_mO-$, R^{14c} and R^{14d} are hydrogen, and m is 2, 3, or 4.

[0085] In another embodiment, Compounds of the Disclosure are compounds represented by any one of Formulae **I**-**III**, and the pharmaceutically acceptable salts, hydrates, and solvates thereof, wherein G is G^1, G^2, G^3, or G^4; R^{4a}, R^{4b}, R^{4c}, R^{4d}, R^{4e}, R^{4f}, and R^{4g} are each independently selected from the group consisting of alkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclo, optionally substituted heteroaryl, aralkyl, and (heteroaryl)alkyl; and R^2, R^{3a}, R^{3b}, E^1, E^2, E^3, E^4, E^5, E^6, E^7, X, and Y are as defined in connection with Formula **I**. In another embodiment, R^{4a}, R^{4b}, R^{4c}, R^{4d}, R^{4e}, R^{4f}, and R^{4g} are each alkyl. In another embodiment, R^{4a}, R^{4b}, R^{4c}, R^{4d}, R^{4e}, R^{4f}, and R^{4g} are each optionally substituted cycloalkyl. In another embodiment, R^{4a}, R^{4b}, R^{4c}, R^{4d}, R^{4e}, R^{4f}, and R^{4g} are each optionally substituted aryl. In another embodiment, R^{4a}, R^{4b}, R^{4c}, R^{4d}, R^{4e}, R^{4f}, and R^{4g} are each optionally substituted heterocyclo. In another embodiment, R^{4a}, R^{4b}, R^{4c}, R^{4d}, R^{4e}, R^{4f}, and R^{4g} are each optionally substituted heteroaryl. In another embodiment, R^{4a}, R^{4b}, R^{4c}, R^{4d}, R^{4e}, R^{4f}, and R^{4g} are each aralkyl. In another embodiment, R^{4a}, R^{4b}, R^{4c}, R^{4d}, R^{4e}, R^{4f}, and R^{4g} are each (heteroaryl)alkyl.

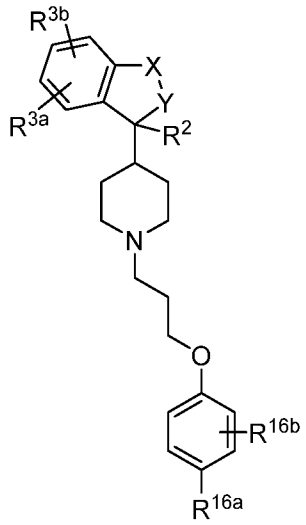
[0086] In another embodiment, Compounds of the Disclosure are compounds represented by Formula **IV**:



IV,

and the pharmaceutically acceptable salts, hydrates, and solvates thereof, wherein R^2, R^{3a}, R^{3b}, R^{4a}, R^{6a}, R^{6c}, R^{6e}, R^{6g}, E^1, X, and Y are as defined in connection with Formula **I**. In another embodiment, E^1 is $-[C(R^{14a})(R^{14b})]_mO-$ and R^{4a} is selected from the group consisting of optionally substituted aryl and optionally substituted heteroaryl.

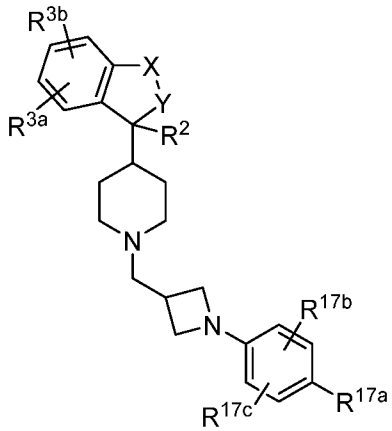
[0087] In another embodiment, Compounds of the Disclosure are compounds represented by Formula **V**:



V,

and the pharmaceutically acceptable salts, hydrates, and solvates thereof, wherein R^{16a} is selected from the group consisting of hydrogen, alkyl, halo, hydroxy, cyano, amino, alkylamino, dialkylamino, haloalkyl, alkoxy, haloalkoxy, alkylsulfonyl, haloalkylsulfonyl, cycloalkylsulfonyl, (cycloalkyl)alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, heterocyclosulfonyl, sulfonamido, optionally substituted heteroaryl, optionally substituted heterocyclo, carboxamido, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, carboxy, and carboxyalkyl; R^{16b} is selected from the group consisting of hydrogen, alkyl, halo, hydroxy, cyano, amino, alkylamino, dialkylamino, haloalkyl, alkoxy, and haloalkoxy; and R^2, R^{3a}, R^{3b}, X, and Y are as defined in connection with Formula **I**.

[0088] In another embodiment, Compounds of the Disclosure are compounds represented by Formula **VIi**:



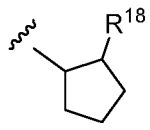
VIi,

and the pharmaceutically acceptable salts, hydrates, and solvates thereof, wherein R^{17a} is selected from the group consisting of hydrogen, alkyl, halo, hydroxy, cyano,

amino, alkylamino, dialkylamino, haloalkyl, alkoxy, haloalkoxy, alkylsulfonyl, haloalkylsulfonyl, cycloalkylsulfonyl, (cycloalkyl)alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, heterocyclosulfonyl, sulfonamido, optionally substituted heteroaryl, optionally substituted heterocyclo, carboxamido, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, carboxy, and carboxyalkyl; R^{17b} and R^{17c} are independently selected from the group consisting of hydrogen, alkyl, halo, hydroxy, cyano, amino, alkylamino, dialkylamino, haloalkyl, alkoxy, and haloalkoxy; and R^2, R^{3a}, R^{3b}, X, and Y are as defined in connection with Formula **I**. In another embodiment, R^{17a} is selected from the group consisting of alkylsulfonyl, cycloalkylsulfonyl, arylsulfonyl, and heteroarylsulfonyl; R^{17b} is hydrogen; and R^{17c} is hydrogen.

[0089] In another embodiment, Compounds of the Disclosure are compounds represented by any one of Formulae **I-VI**, and the pharmaceutically acceptable salts, hydrates, and solvates thereof, wherein R^2 is selected from the group consisting of alkyl, alkenyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclo, optionally substituted heteroaryl, and aralkyl. In another embodiment, R^2 is unsubstituted cycloalkyl. In another embodiment, R^2 is substituted cycloalkyl.

[0090] In another embodiment, Compounds of the Disclosure are compounds represented by any one of Formulae **I-VI**, and the pharmaceutically acceptable salts, hydrates, and solvates thereof, wherein R^2 is a radical, i.e., a substituted cycloalkyl, having Formula **VII**:

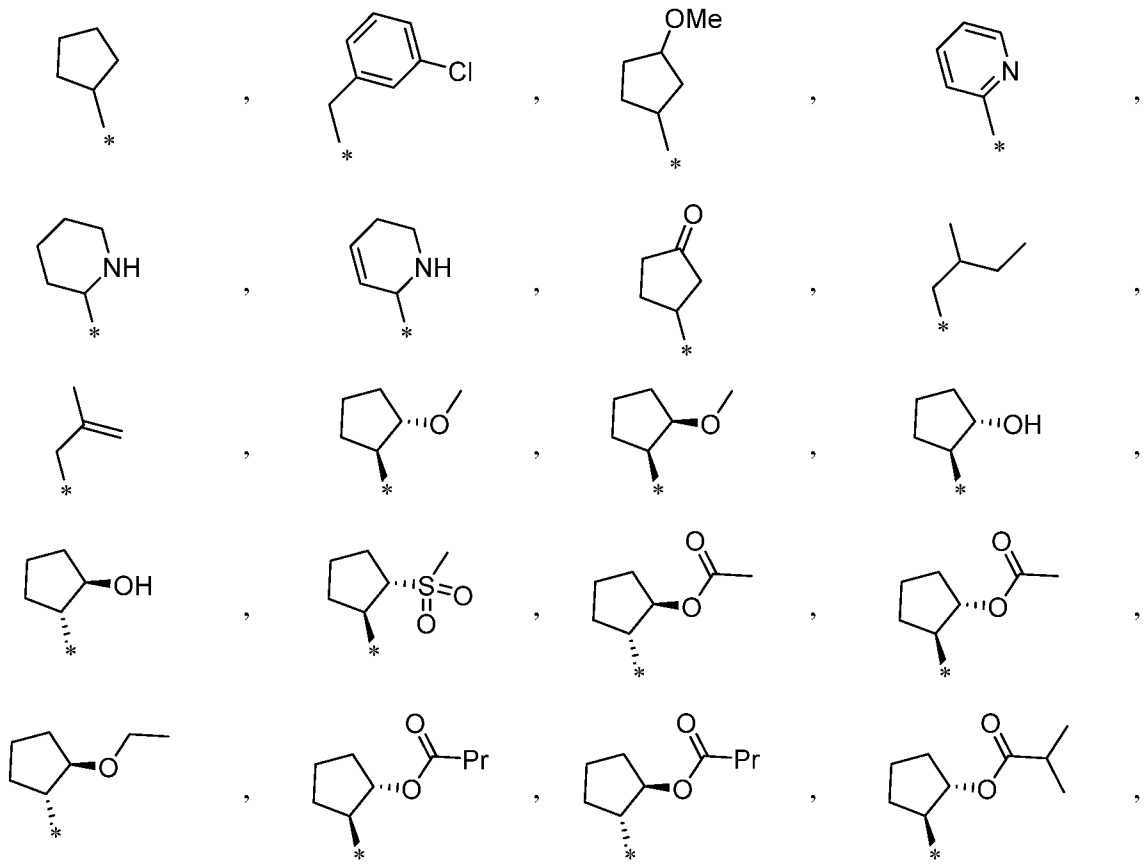


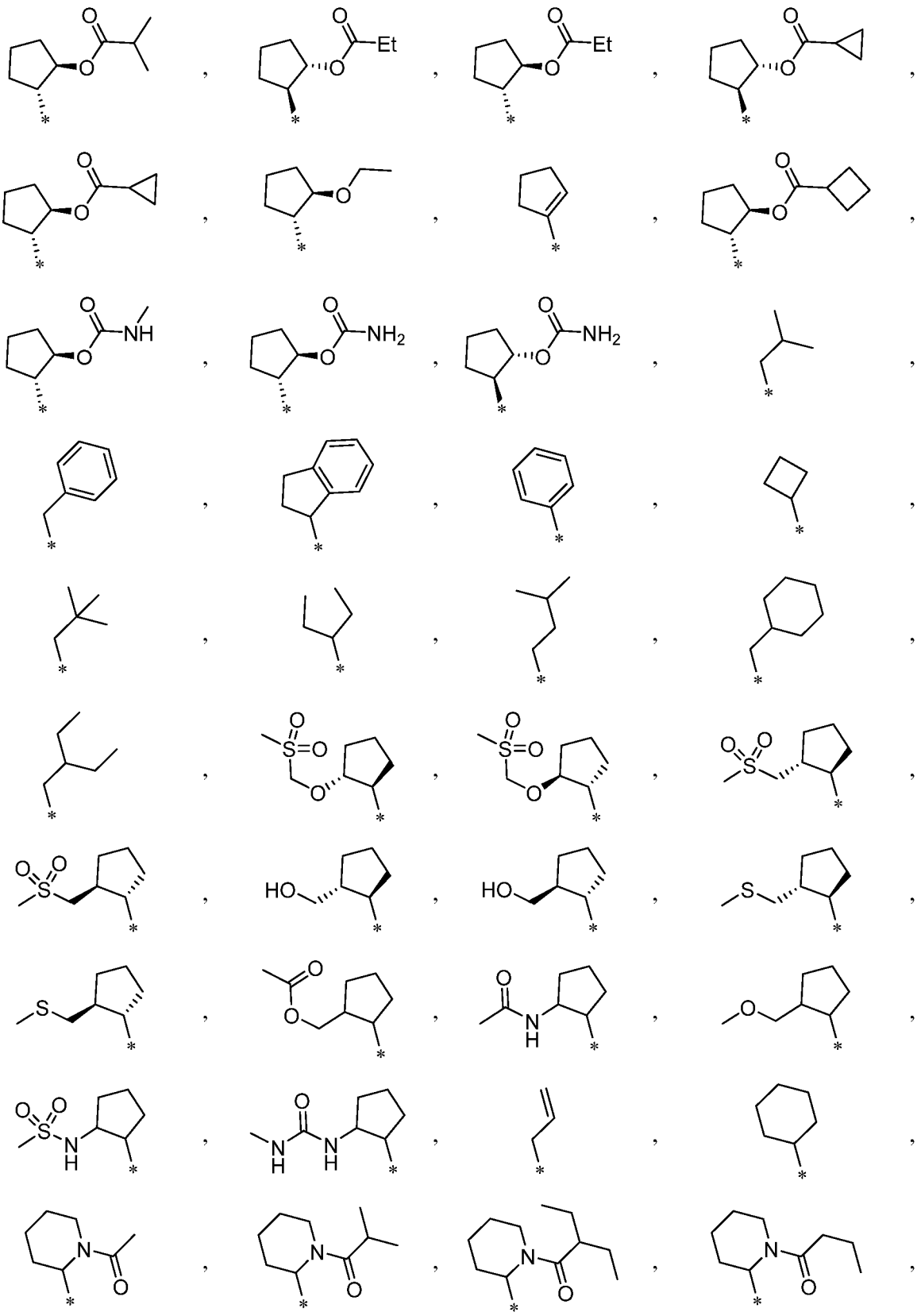
VII,

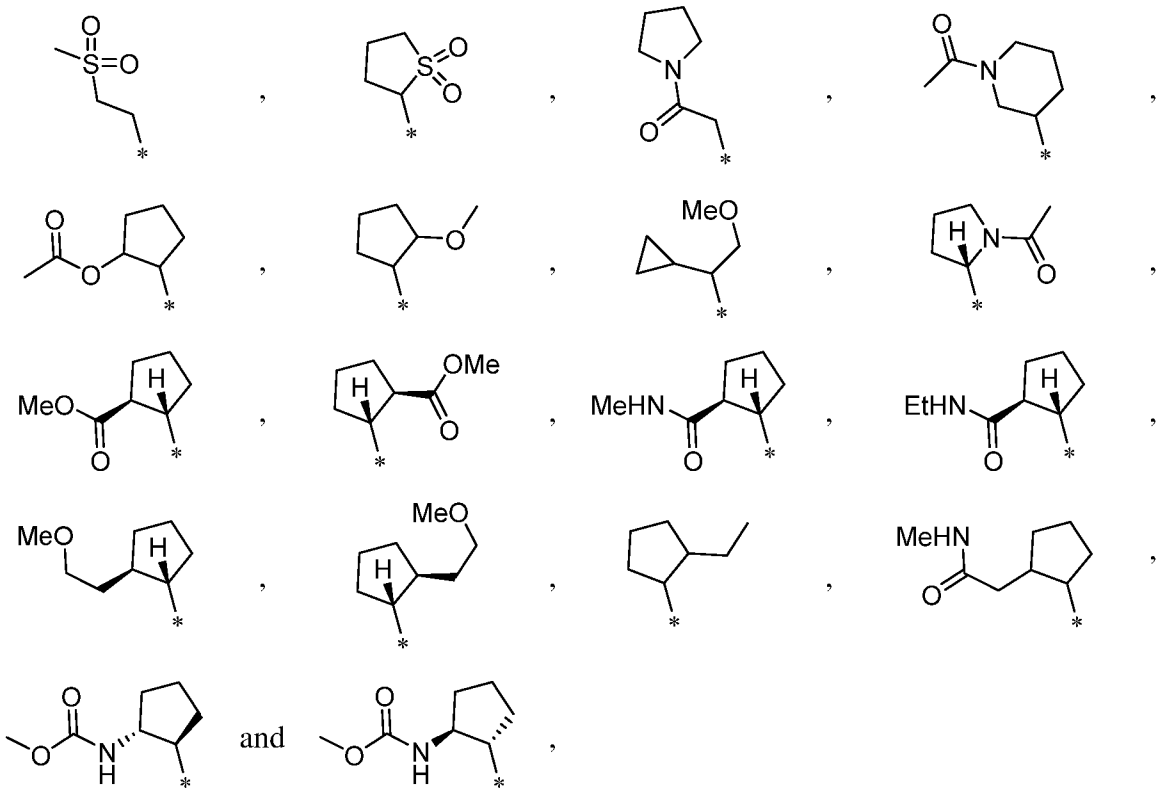
R^{18} is selected from the group consisting of halo, nitro, cyano, hydroxy, alkylcarbonyloxy, cycloalkylcarbonyloxy, amino, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, aryloxy, aralkyloxy, alkylthio, carboxamido, sulfonamido, alkylcarbonyl, arylcarbonyl, alkylsulfonyl, arylsulfonyl, carboxy, carboxyalkyl, optionally substituted alkyl, optionally substituted cycloalkyl, alkenyl, alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclo, alkoxyalkyl, (amino)alkyl, (carboxamido)alkyl, (heterocyclo)alkyl, -OC(=O)-amino, -N(R^{19a})C(=O)-R^{19b}, and -N(R^{20a})SO_2-R^{20b}; R^{19a} is selected from the group consisting of hydrogen and

alkyl; R^{19b} is selected from the group consisting of amino, alkoxy, alkyl, and optionally substituted aryl; and R^{20a} is selected from the group consisting of hydrogen and alkyl; and R^{20b} is selected from the group consisting of amino, alkyl, and optionally substituted aryl. In another embodiment, R^{18} is selected from the group consisting of alkylcarbonyloxy, cycloalkylcarbonyloxy, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, aryloxy, aralkyloxy, alkylthio, carboxamido, sulfonamido, alkylcarbonyl, arylcarbonyl, alkylsulfonyl, arylsulfonyl, carboxy, carboxyalkyl, optionally substituted alkyl, optionally substituted cycloalkyl, alkenyl, alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclo, alkoxyalkyl, (amino)alkyl, (carboxamido)alkyl, and (heterocyclo)alkyl. In another embodiment, R^{18} is selected from the group consisting of -OC(=O)-amino and -NHC(=O)-R^{19b}.

[0091] In another embodiment, Compounds of the Disclosure are compounds represented by any one of Formulae **I-VI**, and the pharmaceutically acceptable salts, hydrates, and solvates thereof, wherein R^2 is selected from the group consisting of:

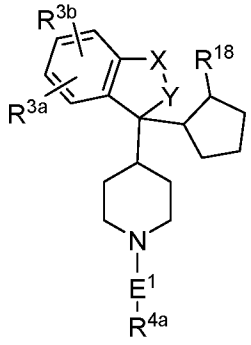






wherein " * " indicates the point of attachment to the remainder of the molecule.

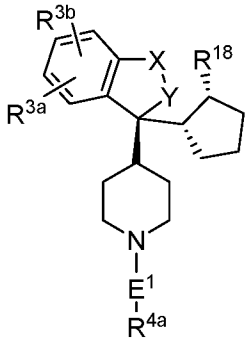
[0092] In another embodiment, Compounds of the Disclosure are compounds represented by Formula **VIII**:



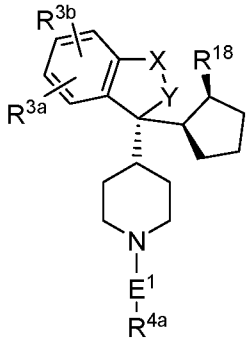
VIII,

and the pharmaceutically acceptable salts, hydrates, and solvates thereof, wherein R^{3a}, R^{3b}, R^{4a}, R^{18}, E^1, X, and Y are as defined in connection with Formula **I**. In another embodiment, R^{18} is selected from the group consisting of -OC(=O)-amino and -NHC(=O)-R^{19b}, wherein R^{19b} is selected from the group consisting of amino, alkoxy, and alkyl.

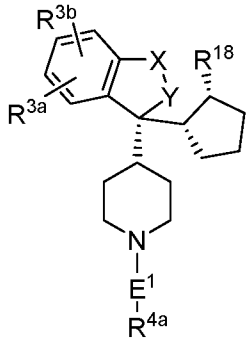
[0093] In another embodiment, Compounds of the Disclosure are compounds represented by any one or more of Formulae **VIII-A**, **VIII-B**, **VIII-C**, **VIII-D**, **VIII-E**, **VIII-F**, **VIII-G**, or **VIII-H**:



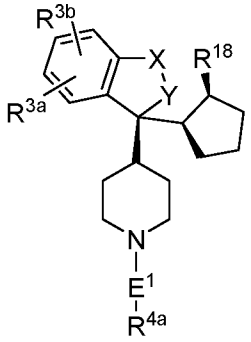
Formula **VIII-A**



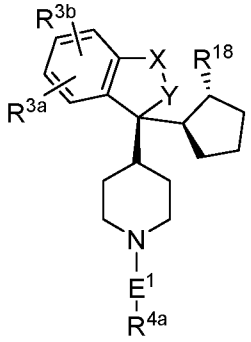
Formula **VIII-B**



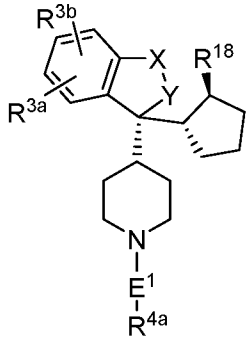
Formula **VIII-C**



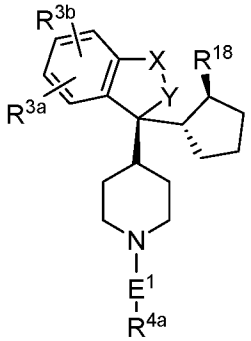
Formula **VIII-D**



Formula **VIII-E**

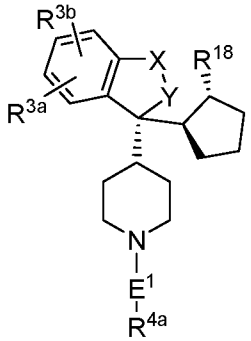


Formula **VIII-F**



Formula **VIII-G**

and



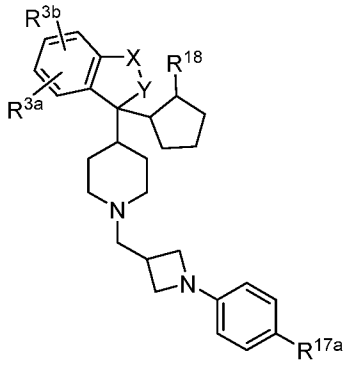
Formula **VIII-H**

and the pharmaceutically acceptable salts, hydrates, and solvates thereof, wherein R^{3a}, R^{3b}, R^{4a}, R^{18}, E^1, X, and Y are as defined in connection with Formula **VIII**. In another embodiment, R^{18} is selected from the group consisting of -OC(=O)-amino and -NHC(=O)-R^{19b}, wherein R^{19b} is selected from the group consisting of amino, alkoxy, and alkyl.

[0094] In another embodiment, Compounds of the Disclosure are compounds represented by any one of Formulae **I-VI**, **VIII**, **VIII-A**, **VIII-B**, **VIII-C**, **VIII-D**, **VIII-E**, **VIII-F**, **VIII-G**, or **VIII-H**, and the pharmaceutically acceptable salts, hydrates, and solvates thereof, wherein X-Y is selected from the group consisting of $-N(R^{1a})-C(=O)-$, $-C(=O)-O-$, $-C(=O)-N(R^{1b})-$, $-CH_2N(R^{1c})-CH_2-$, $-C(=O)N(R^{1d})-CH_2-$, $-CH_2CH_2-N(R^{1e})-$, $-CH_2N(R^{1f})-C(=O)-$, and $-CH_2O-CH_2-$. In this embodiment, X and Y are taken together to form a chemical bond, and the radial listed to the left of the chemical bond corresponds to X, and is attached to the A-ring, and the radical listed to the right corresponds to Y and is attached to $-C(R^2)(G)-$. For example, when X-Y is $-N(R^{1a})-C(=O)-$, X is $-N(R^{1a})-$, and is attached to the A-ring and Y is $-C(=O)-$, and is attached to $-C(R^2)(G)-$; when X-Y is $-C(=O)-O-$, X is $-C(=O)-$, and is attached to the A-ring and Y is $-O-$, and is attached to $-C(R^2)(G)-$; when X-Y is $-C(=O)-N(R^{1b})-$, X is $-C(=O)-$, and is attached to the A-ring and Y is $-N(R^{1b})-$, and is attached to $-C(R^2)(G)-$; etc.

[0095] In another embodiment, Compounds of the Disclosure are compounds represented by any one of Formulae **I-VI**, **VIII**, **VIII-A**, **VIII-B**, **VIII-C**, **VIII-D**, **VIII-E**, **VIII-F**, **VIII-G**, or **VIII-H**, and the pharmaceutically acceptable salts, hydrates, and solvates thereof, wherein X and Y do not form a chemical bond and X is hydrogen. In another embodiment, Y is selected from the group consisting of cyano and $-CH_2-R^{12}$. In another embodiment, Y is cyano. In another embodiment, Y is $-CH_2-R^{12}$.

[0096] In another embodiment, Compounds of the Disclosure are compounds represented by Formula **IX**:

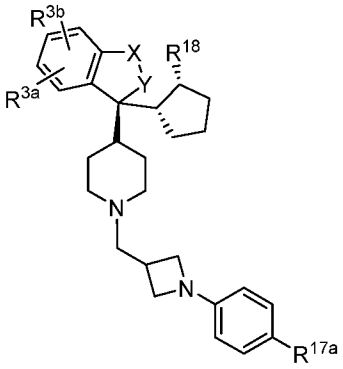


IX,

and the pharmaceutically acceptable salts, hydrates, and solvates thereof, wherein X-Y is $-CH_2N(R^{1c})-CH_2-$, or X and Y do not form a chemical bond, and X is hydrogen;

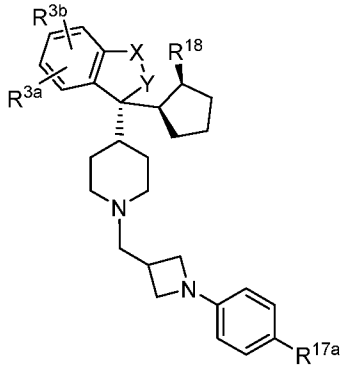
and Y is selected from the group consisting of -CN and -CH_2-R^{12}; R^{1c} is C_{1-3} alkyl; R^{12} is selected from the group consisting of amino and heteroaryl; R^{17a} is selected from the group consisting of chloro, cyano, alkylsulfonyl, haloalkylsulfonyl,cycloalkylsulfonyl, arylsulfonyl, and heteroarylsulfonyl; R^{18} is selected from the group consisting of -OC(=O)-amino and -NHC(=O)-R^{19b}; and R^{19b} is selected from the group consisting of amino, alkoxy, alkyl, and optionally substituted aryl, and R^{3a} and R^{3b} are as defined are as defined in connection with Formula **I**. In another embodiment, X-Y is -$CH_2N(R^{1c})$-CH_2-; and R^{1c} is selected from the group consisting of hydrogen and C_{1-6} alkyl.

[0097] In another embodiment, Compounds of the Disclosure are compounds represented by one or more of Formulae **IX-A**, **IX-B**, **IX-C**, **IX-D**, **IX-E**, **IX-F**, **IX-G**, or **IX-H**:



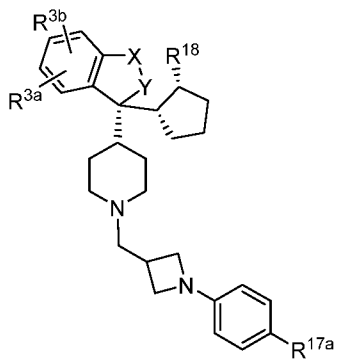
Formula **IX-A**

,

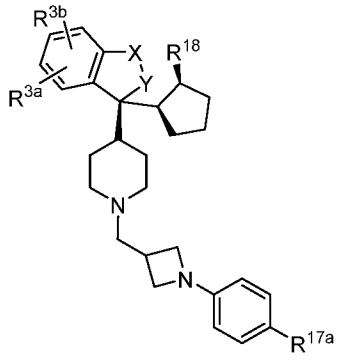


Formula **IX-B**

,

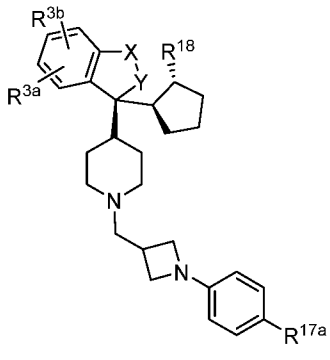


Formula **IX-C**



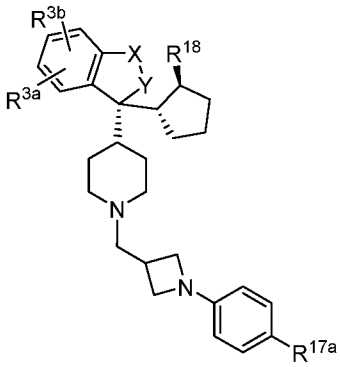
Formula **IX-D**

,

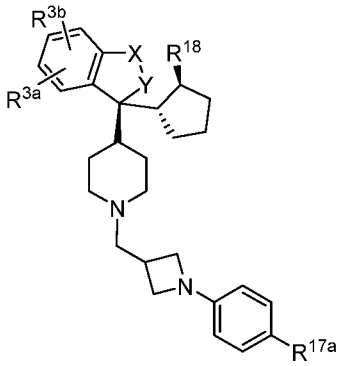


Formula **IX-E**

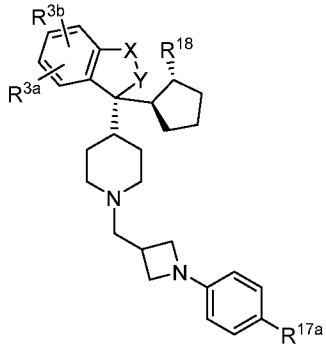
,



Formula **IX-F**



and

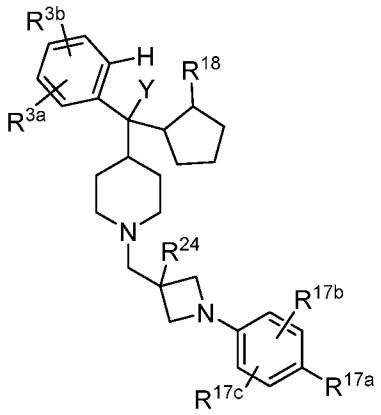


,

Formula **IX-G** Formula **IX-H**

and the pharmaceutically acceptable salts, hydrates, and solvates thereof, wherein X-Y is -$CH_2N(R^{1c})$-CH_2-, or X and Y do not form a chemical bond, and X is hydrogen and Y is selected from the group consisting of -CN and -CH_2-R^{12}; R^{1c} is C_{1-3} alkyl; R^{12} is selected from the group consisting of amino and heteroaryl; R^{17a} is selected from the group consisting of alkylsulfonyl, cycloalkylsulfonyl, arylsulfonyl, and heteroarylsulfonyl; R^{18} is selected from the group consisting of -OC(=O)-amino and -NHC(=O)-R^{19b}; and R^{19b} is selected from the group consisting of amino, alkoxy, alkyl, and optionally substituted aryl, and R^{3a} and R^{3b} are as defined are as defined in connection with Formula **I**. In another embodiment, X-Y is -$CH_2N(R^{1c})$-CH_2-; and R^{1c} is selected from the group consisting of hydrogen and C_{1-6} alkyl.

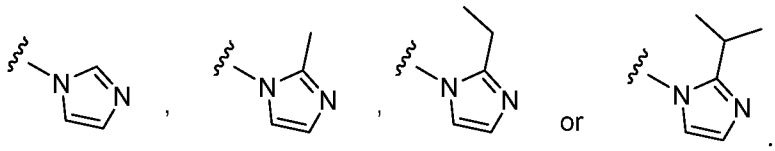
[0098] In another embodiment, Compounds of the Disclosure are compounds represented by Formula **Xi**:



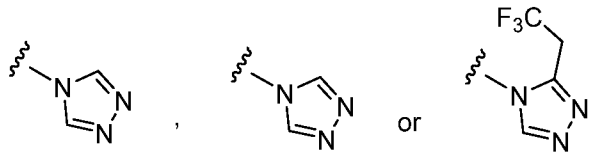
Xi,

and the pharmaceutically acceptable salts, hydrates, and solvates thereof, wherein Y is selected from the group consisting of cyano and -CH_2-R^{12}; R^{12} is selected from the group consisting of amino and heteroaryl; R^{17a} is selected from the group consisting of chloro, cyano, alkylsulfonyl, haloalkylsulfonyl, cycloalkylsulfonyl, arylsulfonyl, and

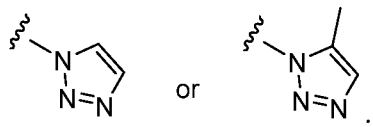
heteroarylsulfonyl; R^{17b} and R^{17c} are independently selected from the group consisting of hydrogen and halo; R^{18} is selected from the group consisting of -OC(=O)-amino, e.g., $-OC(=O)N(H)CH_3$, and $-NHC(=O)-R^{19b}$, e.g., $-NHC(=O)OCH_3$; R^{19b} is selected from the group consisting of amino, alkoxy, alkyl, and optionally substituted aryl; R^{24} is selected from the group consisting of hydrogen and fluoro, and R^{3a} and R^{3b} are as defined are as defined in connection with Formula **I**. In another embodiment, R^{12} is optionally substituted 5-membered heteroaryl. In another embodiment, R^{12} is optionally substituted imidazol-1-yl, e.g.,



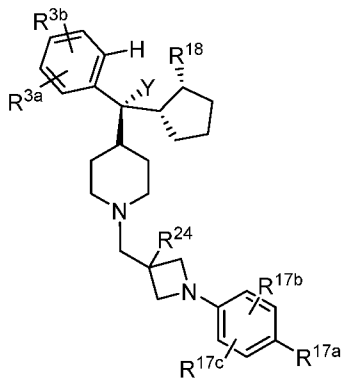
[0099] In another embodiment, R^{12} is optionally substituted 1,3,4-triazole, e.g.,



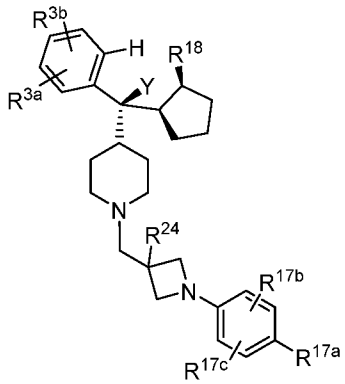
[0100] In another embodiment, R^{12} is optionally substituted 1,2,3-triazole, e.g.,



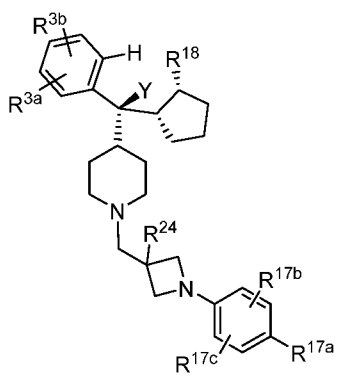
[0101] In another embodiment, Compounds of the Disclosure are compounds represented by one or more of Formulae **Xi-A**, **Xi-B**, **Xi-C**, **Xi-D**, **Xi-E**, **Xi-F**, **Xi-G**, or **Xi-H**:



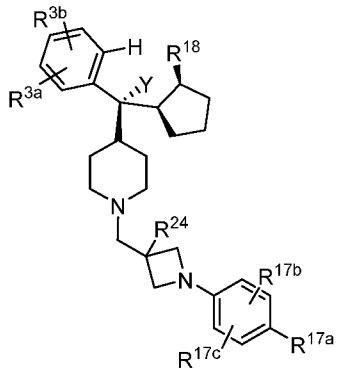
Formula **Xi-A**



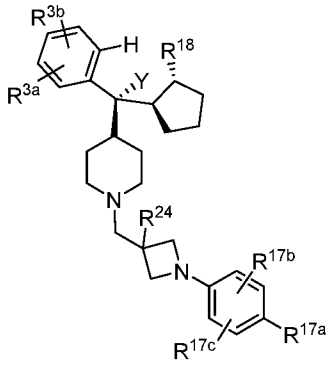
Formula **Xi-B**



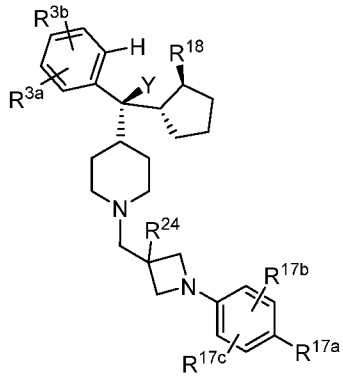
Formula **Xi-C**



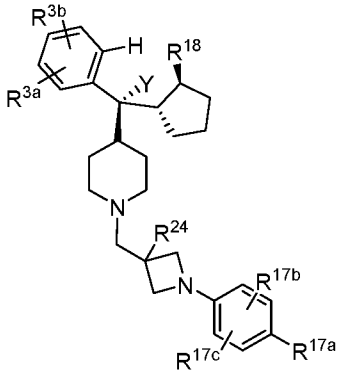
,



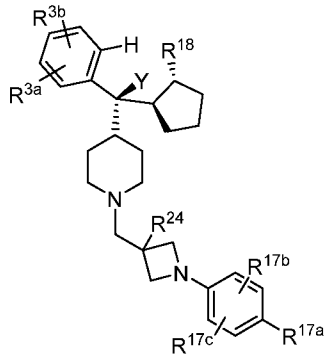
,



Formula **Xi-D** Formula **Xi-E** Formula **Xi-F**



and



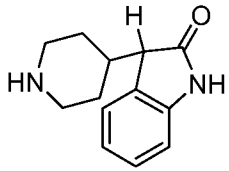
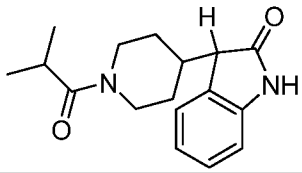
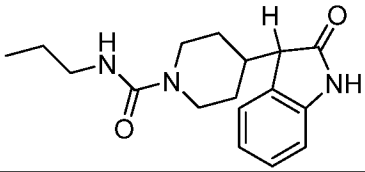
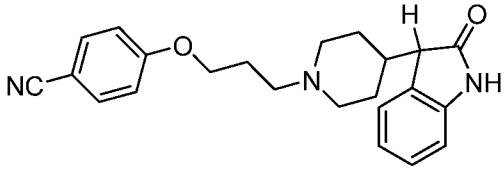
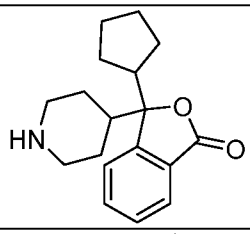
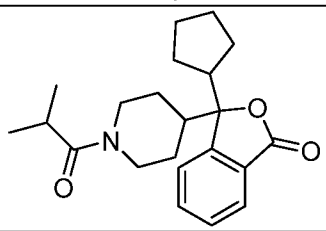
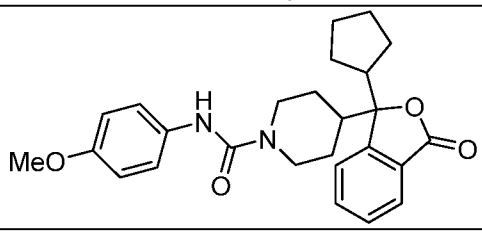
,

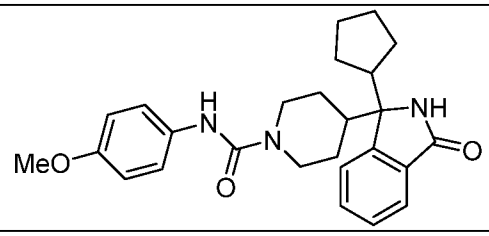
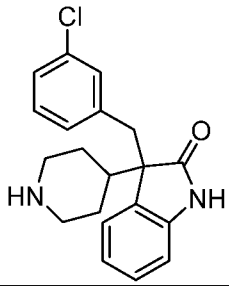
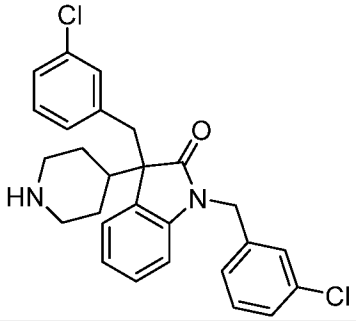
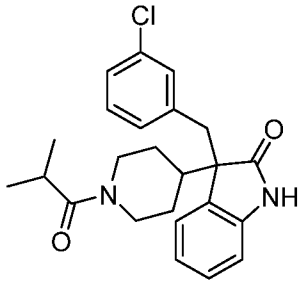
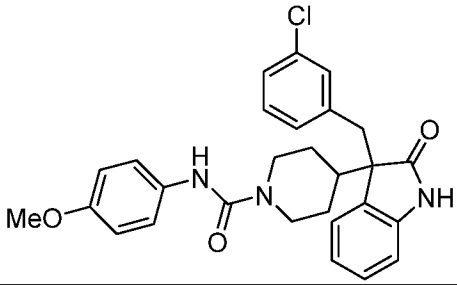
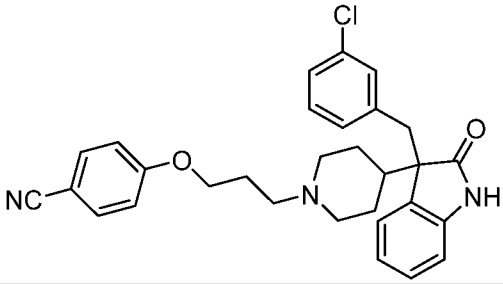
Formula **Xi-G** Formula **Xi-H**

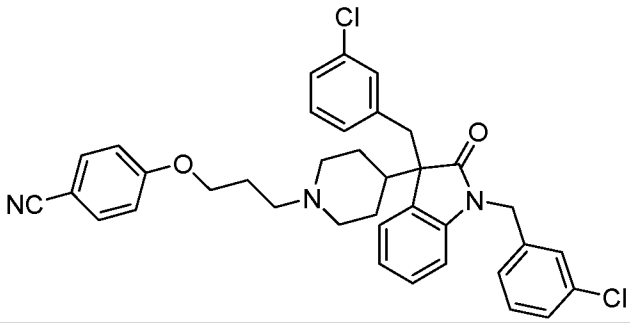
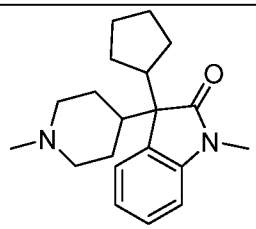
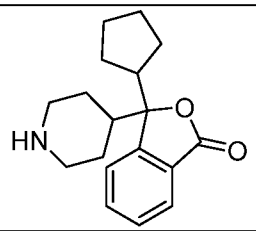
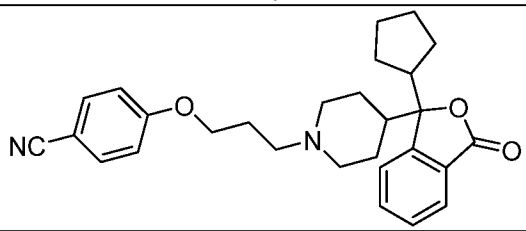
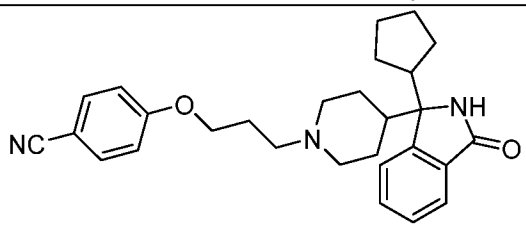
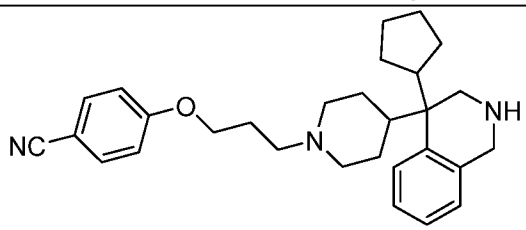
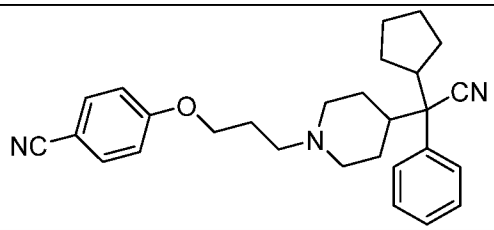
and the pharmaceutically acceptable salts, hydrates, and solvates thereof, wherein Y is selected from the group consisting of cyano and -CH_2-R^{12}; R^{12} is selected from the group consisting of amino and heteroaryl; R^{17a} is selected from the group consisting of chloro, cyano, alkylsulfonyl, haloalkylsulfonyl, cycloalkylsulfonyl, arylsulfonyl, and heteroarylsulfonyl; R^{17b} and R^{17c} are independently selected from the group consisting of hydrogen and halo; R^{18} is selected from the group consisting of -OC(=O)-amino and -NHC(=O)-R^{19b}; R^{19b} is selected from the group consisting of amino, alkoxy, alkyl, and optionally substituted aryl; R^{24} is selected from the group consisting of hydrogen and fluoro,, and R^{3a} and R^{3b} are as defined are as defined in connection with Formula **I**. In another embodiment, R^{12} is an optionally substituted 5-membered heteroaryl. In another embodiment, R^{12} is an optionally substituted imidazol-1-yl. In another embodiment, R^{12} is optionally substituted 1,3,4-triazole. In another embodiment, R^{12} is optionally substituted 1,2,3-triazole.

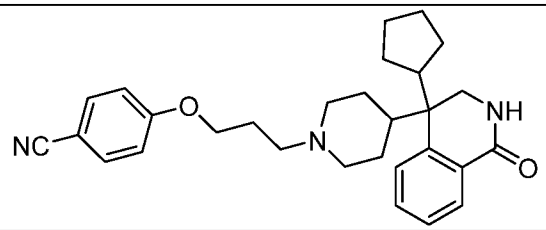
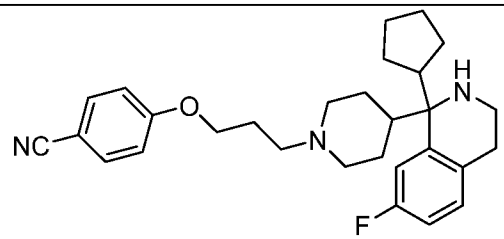
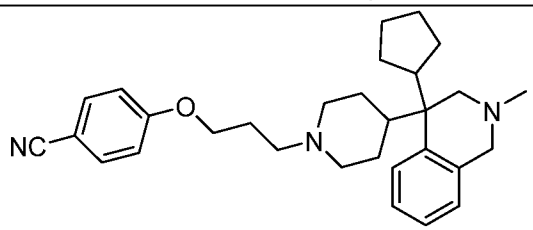
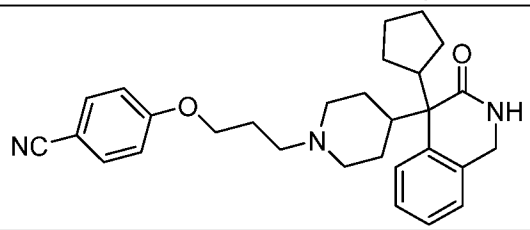
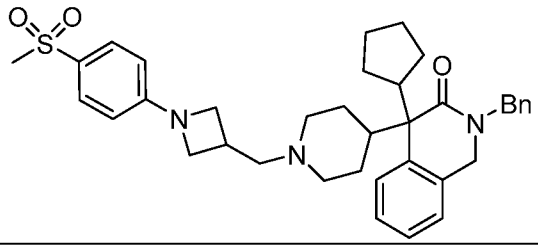
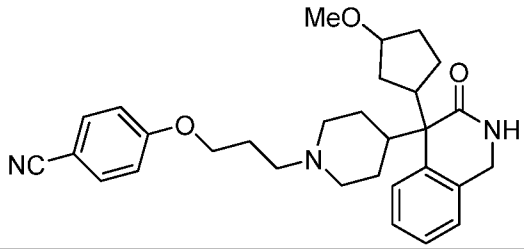
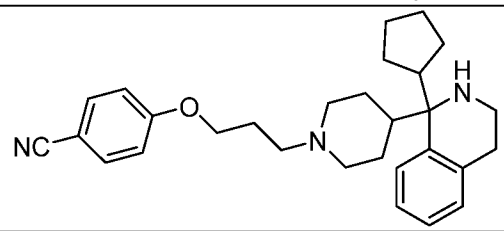
[0102] In another embodiment, Compounds of the Disclosure are one or more of the compounds of Table 1, and the pharmaceutically acceptable salts, hydrates, and solvates

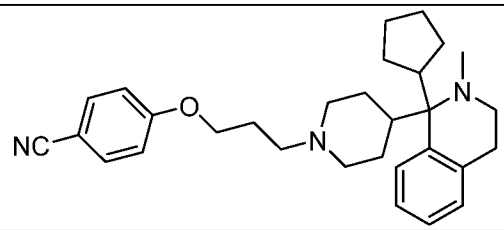
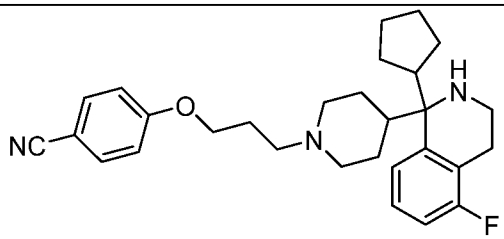
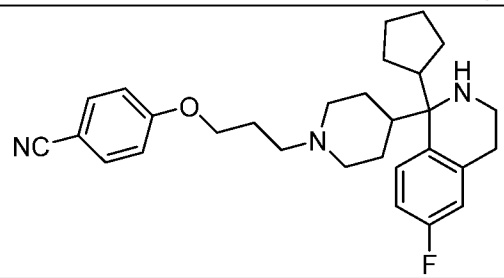
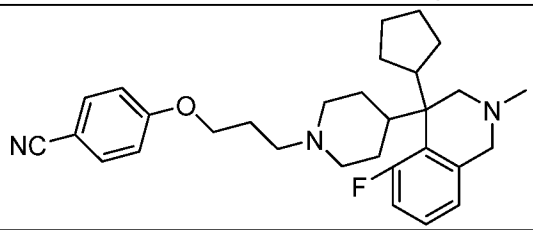
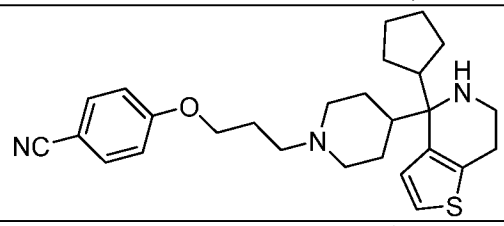
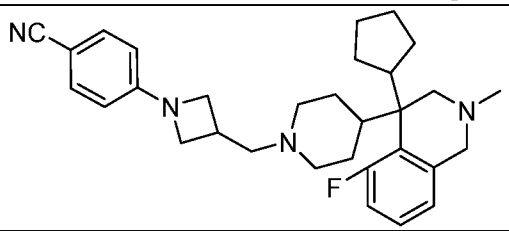
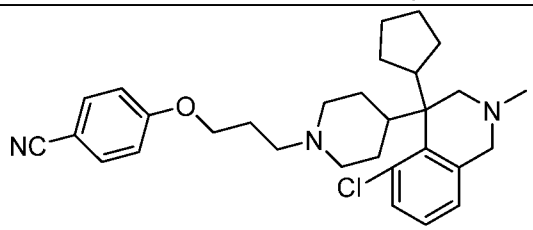
Table 1

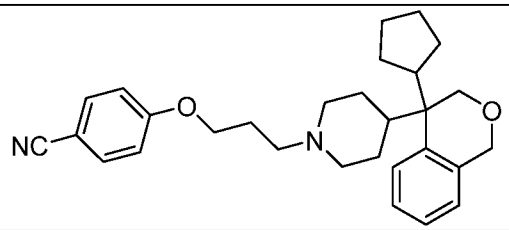
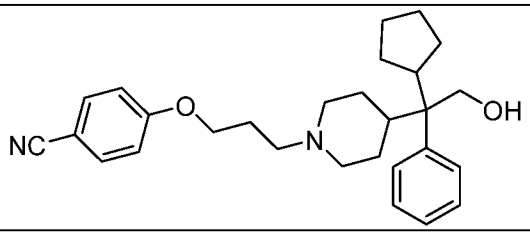
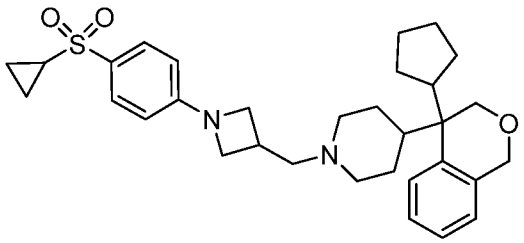
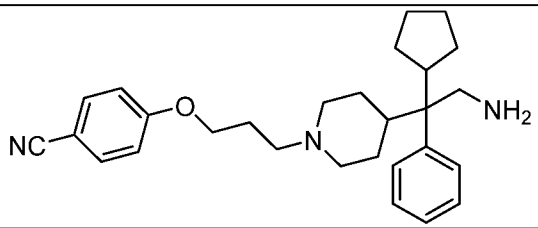
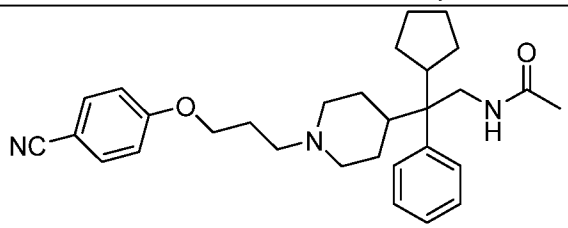
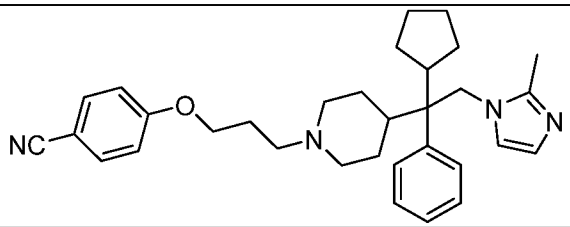
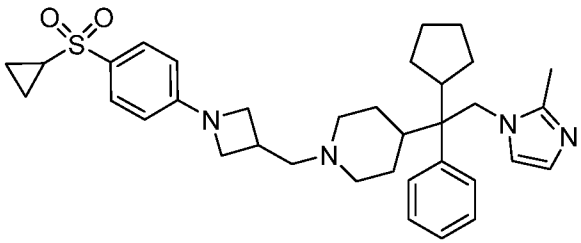
Cpd. No.	Chemical Structure	Chemical Name
1		3-(piperidin-4-yl)indolin-2-one
2		3-(1-isobutyrylpiperidin-4-yl)indolin-2-one
3		4-(2-oxoindolin-3-yl)-N-propylpiperidine-1-carboxamide
4		4-(3-(4-(2-oxoindolin-3-yl)piperidin-1-yl)propoxy)benzonitrile
5		3-cyclopentyl-3-(piperidin-4-yl)isobenzofuran-1(3H)-one
6		3-cyclopentyl-3-(1-isobutyrylpiperidin-4-yl)isobenzofuran-1(3H)-one
7		4-(1-cyclopentyl-3-oxo-1,3-dihydroisobenzofuran-1-yl)-N-(4-methoxyphenyl)piperidine-1-carboxamide

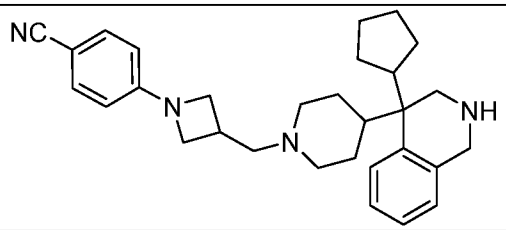
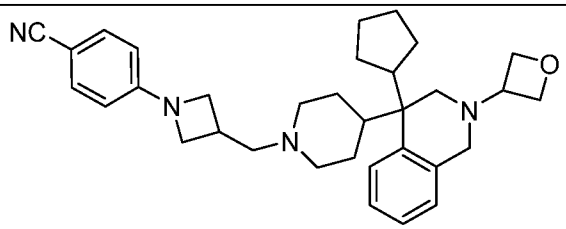
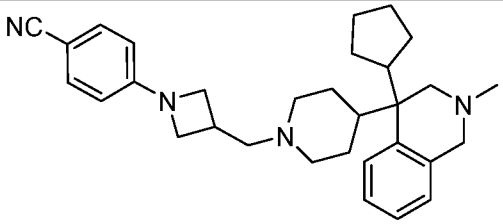
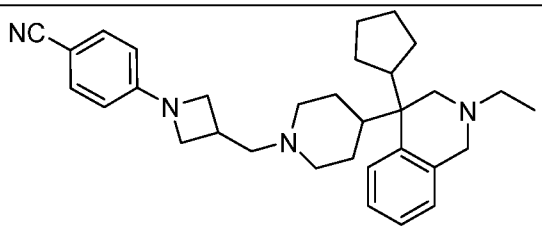
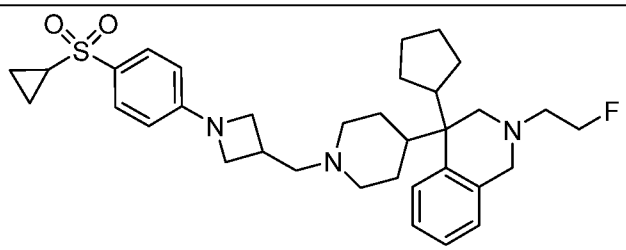
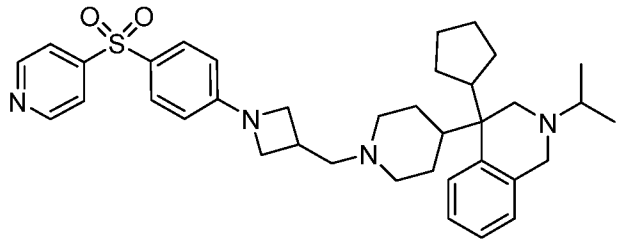
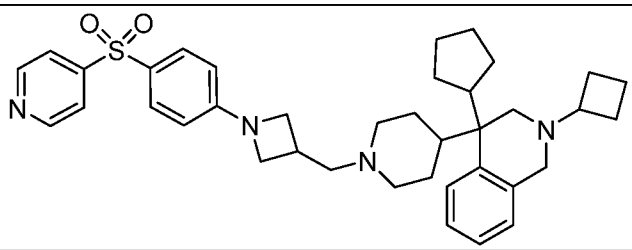
Cpd. No.	Chemical Structure	Chemical Name
8		4-(1-cyclopentyl-3-oxoisoindolin-1-yl)-N-(4-methoxyphenyl)piperidine-1-carboxamide
9		3-(3-chlorobenzyl)-3-(piperidin-4-yl)indolin-2-one
10		1,3-bis(3-chlorobenzyl)-3-(piperidin-4-yl)indolin-2-one
11		3-(3-chlorobenzyl)-3-(1-isobutyrylpiperidin-4-yl)indolin-2-one
12		4-(3-(3-chlorobenzyl)-2-oxoindolin-3-yl)-N-(4-methoxyphenyl)piperidine-1-carboxamide
13		4-(3-(4-(3-(3-chlorobenzyl)-2-oxoindolin-3-yl)piperidin-1-yl)propoxy)benzonitrile

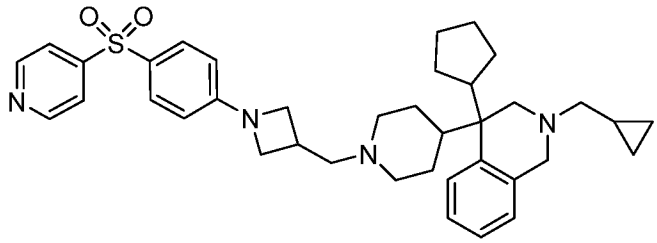
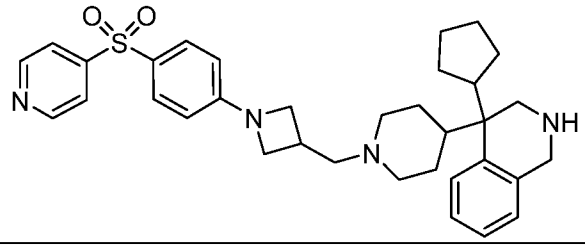
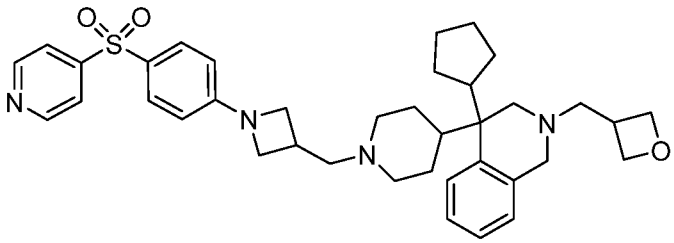
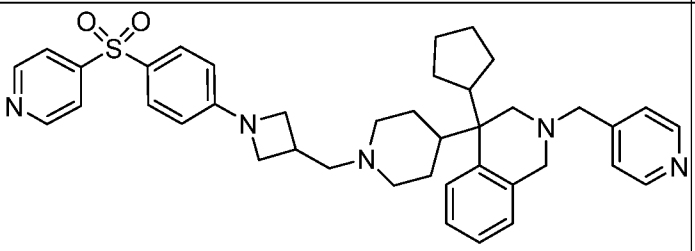
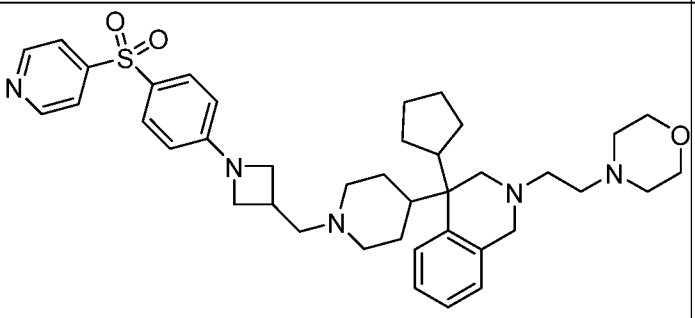
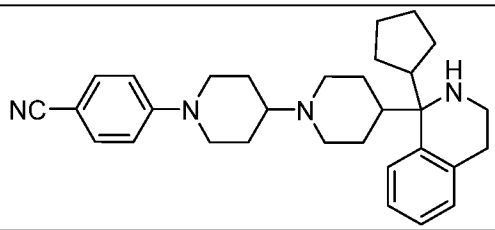
Cpd. No.	Chemical Structure	Chemical Name
14		4-(3-(4-(1,3-bis(3-chlorobenzyl)-2-oxoindolin-3-yl)piperidin-1-yl)propoxy)benzonitrile
15		3-cyclopentyl-1-methyl-3-(1-methylpiperidin-4-yl)indolin-2-one
16		3-cyclopentyl-3-(piperidin-4-yl)isobenzofuran-1(3H)-one
17		4-(3-(4-(1-cyclopentyl-3-oxo-1,3-dihydroisobenzofuran-1-yl)piperidin-1-yl)propoxy)benzonitrile
18		4-(3-(4-(1-cyclopentyl-3-oxoisoindolin-1-yl)piperidin-1-yl)propoxy)benzonitrile
19		4-(3-(4-(4-cyclopentyl-1,2,3,4-tetrahydroisoquinolin-4-yl)piperidin-1-yl)propoxy)benzonitrile
20		4-(3-(4-(cyano(cyclopentyl)(phenyl)methyl)piperidin-1-yl)propoxy)benzonitrile

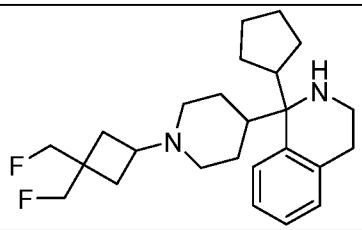
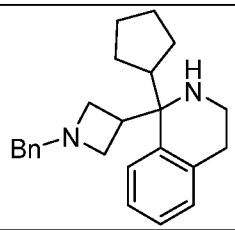
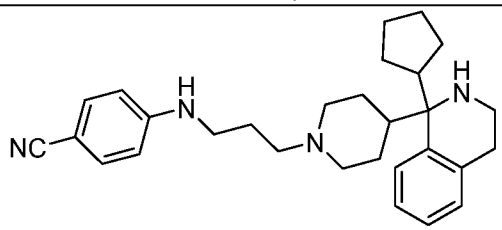
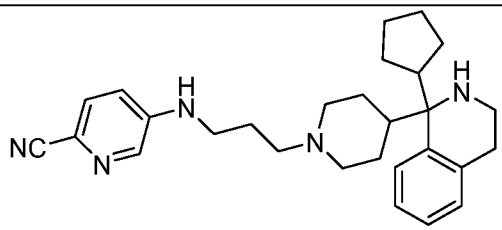
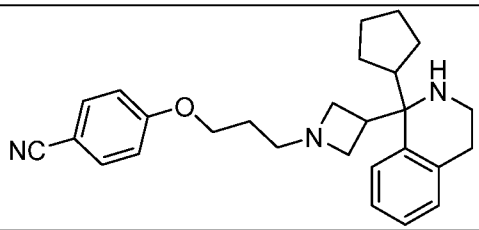
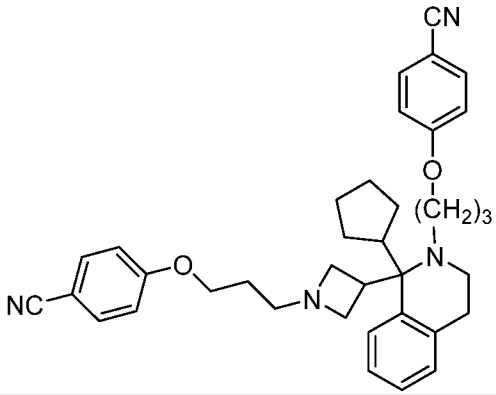
Cpd. No.	Chemical Structure	Chemical Name
21		4-(3-(4-(4-cyclopentyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl)piperidin-1-yl)propoxy)benzonitrile
22		4-(3-(4-(1-cyclopentyl-7-fluoro-1,2,3,4-tetrahydroisoquinolin-1-yl)piperidin-1-yl)propoxy)benzonitrile
23		4-(3-(4-(4-cyclopentyl-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)piperidin-1-yl)propoxy)benzonitrile
24		4-(3-(4-(4-cyclopentyl-3-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl)piperidin-1-yl)propoxy)benzonitrile
25		2-benzyl-4-cyclopentyl-4-(1-((1-(4-(methylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1,4-dihydroisoquinolin-3(2H)-one
26		4-(3-(4-(4-(3-methoxycyclopentyl)-3-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl)piperidin-1-yl)propoxy)benzonitrile
27		4-(3-(4-(1-cyclopentyl-1,2,3,4-tetrahydroisoquinolin-1-yl)piperidin-1-yl)propoxy)benzonitrile

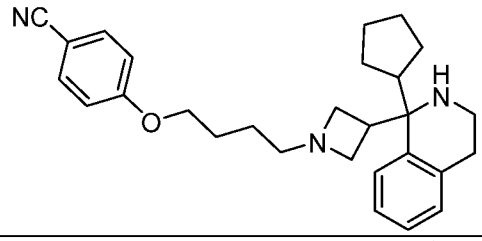
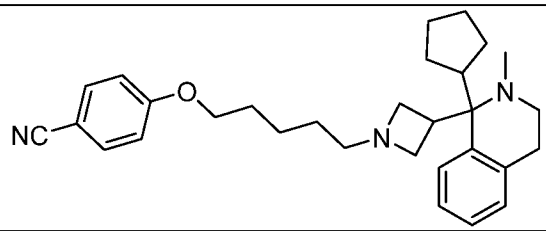
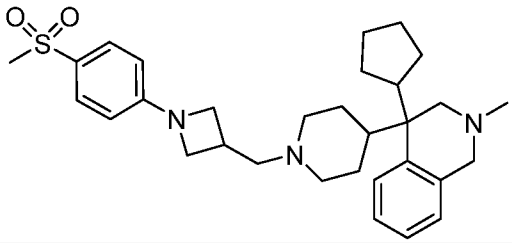
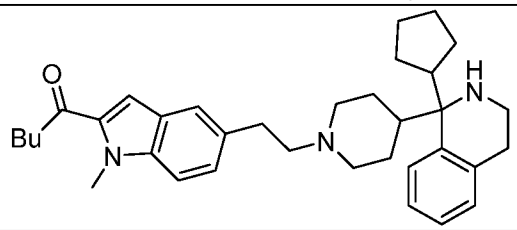
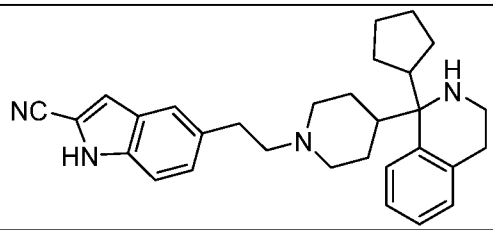
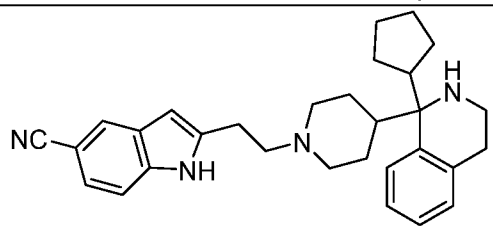
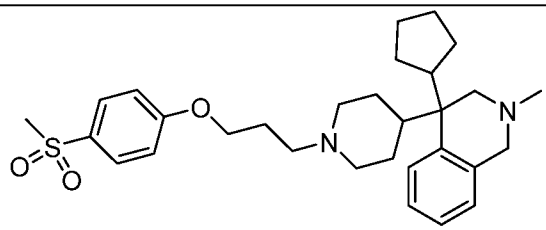
Cpd. No.	Chemical Structure	Chemical Name
28		4-(3-(4-(1-cyclopentyl-2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)piperidin-1-yl)propoxy)benzonitrile
29		4-(3-(4-(1-cyclopentyl-5-fluoro-1,2,3,4-tetrahydroisoquinolin-1-yl)piperidin-1-yl)propoxy)benzonitrile
30		4-(3-(4-(1-cyclopentyl-6-fluoro-1,2,3,4-tetrahydroisoquinolin-1-yl)piperidin-1-yl)propoxy)benzonitrile
31		4-(3-(4-(4-cyclopentyl-5-fluoro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)piperidin-1-yl)propoxy)benzonitrile
32		4-(3-(4-(4-cyclopentyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-4-yl)piperidin-1-yl)propoxy)benzonitrile
33		4-(3-((4-(4-cyclopentyl-5-fluoro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)piperidin-1-yl)methyl)azetidin-1-yl)benzonitrile
34		4-(3-(4-(5-chloro-4-cyclopentyl-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)piperidin-1-yl)propoxy)benzonitrile

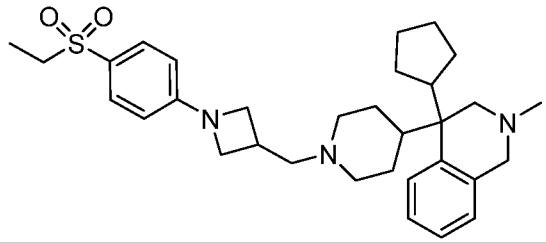
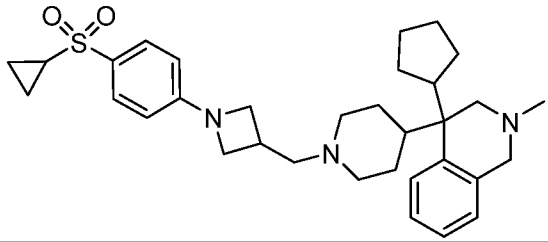
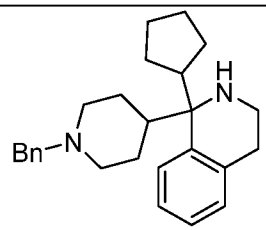
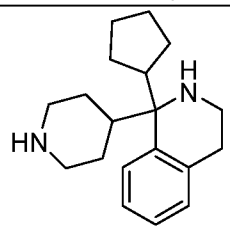
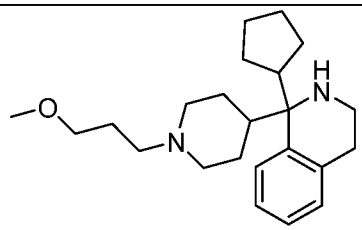
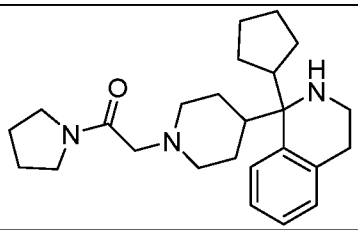
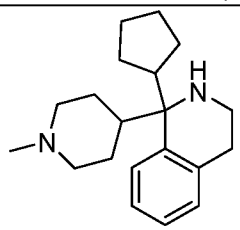
Cpd. No.	Chemical Structure	Chemical Name
35		4-(3-(4-(4-cyclopentylisochroman-4-yl)piperidin-1-yl)propoxy)benzonitrile
37		4-(3-(4-(1-cyclopentyl-2-hydroxy-1-phenylethyl)piperidin-1-yl)propoxy)benzonitrile
38		4-(4-cyclopentylisochroman-4-yl)-1-((1-(4-(cyclopropylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidine
39		4-(3-(4-(2-amino-1-cyclopentyl-1-phenylethyl)piperidin-1-yl)propoxy)benzonitrile
40		N-(2-(1-(3-(4-cyanophenoxy)propyl)piperidin-4-yl)-2-cyclopentyl-2-phenylethyl)acetamide
41		4-(3-(4-(1-cyclopentyl-2-(2-methyl-1H-imidazol-1-yl)-1-phenylethyl)piperidin-1-yl)propoxy)benzonitrile
42		4-(1-cyclopentyl-2-(2-methyl-1H-imidazol-1-yl)-1-phenylethyl)-1-((1-(4-(cyclopropylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidine

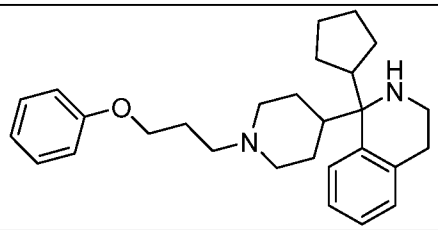
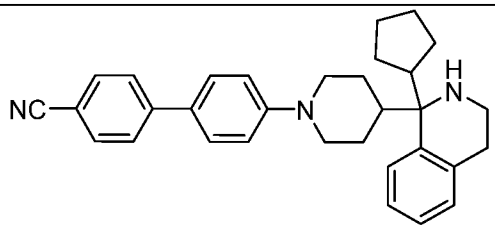
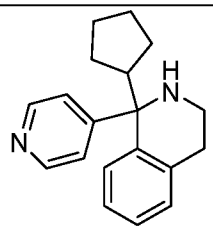
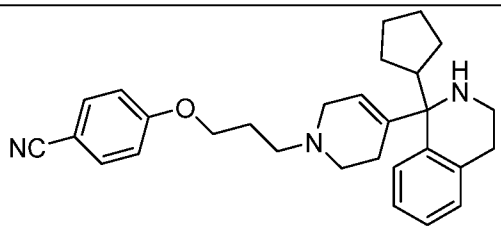
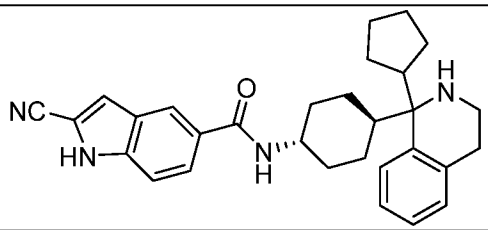
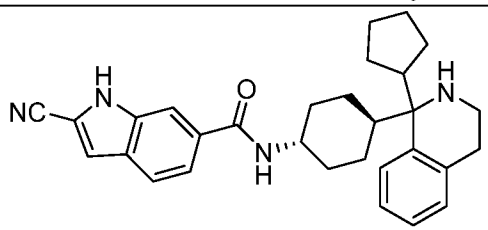
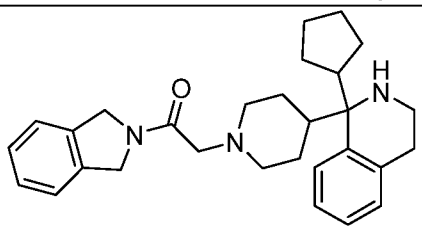
Cpd. No.	Chemical Structure	Chemical Name
43		4-(3-((4-(4-cyclopentyl-1,2,3,4-tetrahydroisoquinolin-4-yl)piperidin-1-yl)methyl)azetidin-1-yl)benzonitrile
44		4-(3-((4-(4-cyclopentyl-2-(oxetan-3-yl)-1,2,3,4-tetrahydroisoquinolin-4-yl)piperidin-1-yl)methyl)azetidin-1-yl)benzonitrile
45		4-(3-((4-(4-cyclopentyl-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)piperidin-1-yl)methyl)azetidin-1-yl)benzonitrile
46		4-(3-((4-(4-cyclopentyl-2-ethyl-1,2,3,4-tetrahydroisoquinolin-4-yl)piperidin-1-yl)methyl)azetidin-1-yl)benzonitrile
47		4-cyclopentyl-4-(1-((1-(4-(cyclopropylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-2-(2-fluoroethyl)-1,2,3,4-tetrahydroisoquinoline
48		4-cyclopentyl-2-isopropyl-4-(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1,2,3,4-tetrahydroisoquinoline
49		2-cyclobutyl-4-cyclopentyl-4-(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1,2,3,4-tetrahydroisoquinoline

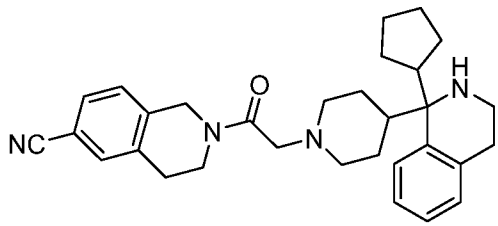
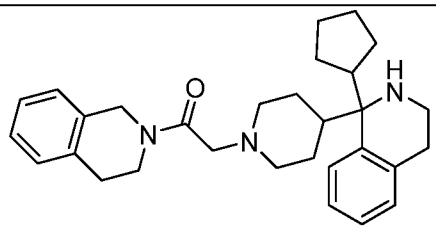
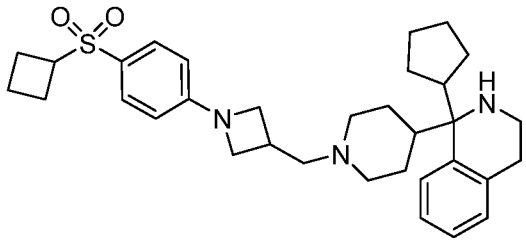
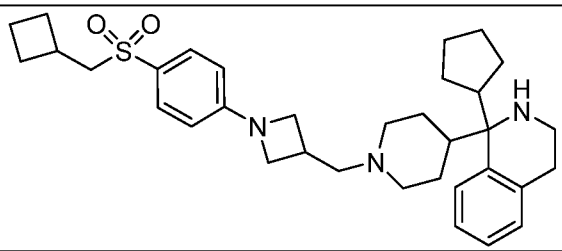
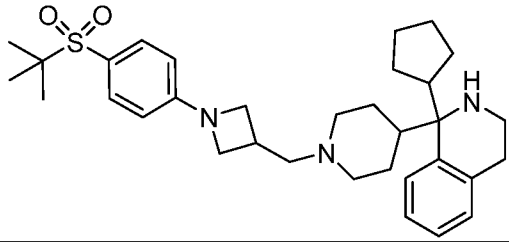
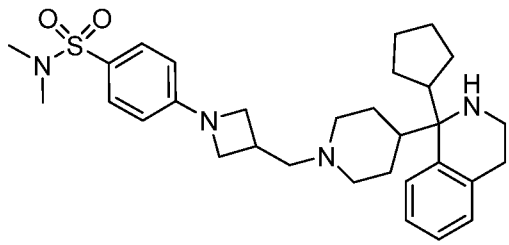
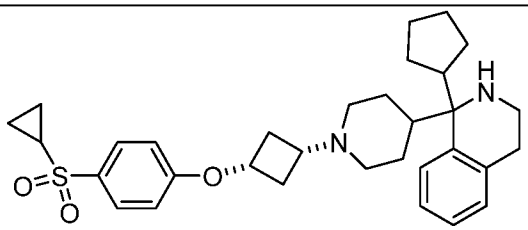
Cpd. No.	Chemical Structure	Chemical Name
50		4-cyclopentyl-2-(cyclopropylmethyl)-4-(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1,2,3,4-tetrahydroisoquinoline
51		4-cyclopentyl-4-(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1,2,3,4-tetrahydroisoquinoline
52		4-cyclopentyl-2-(oxetan-3-ylmethyl)-4-(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1,2,3,4-tetrahydroisoquinoline
53		4-cyclopentyl-2-(pyridin-4-ylmethyl)-4-(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1,2,3,4-tetrahydroisoquinoline
54		4-(2-(4-cyclopentyl-4-(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-3,4-dihydroisoquinolin-2(1H)-yl)ethyl)morpholine
55		4-(4-(1-cyclopentyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-[1,4'-bipiperidin]-1'-yl)benzonitrile

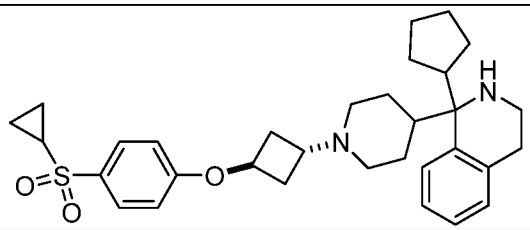
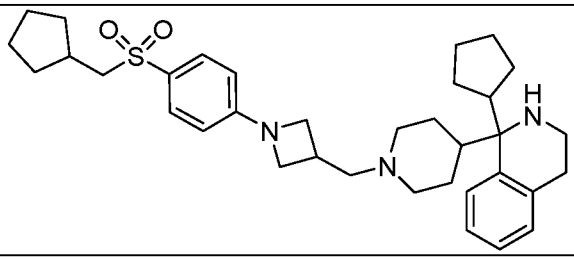
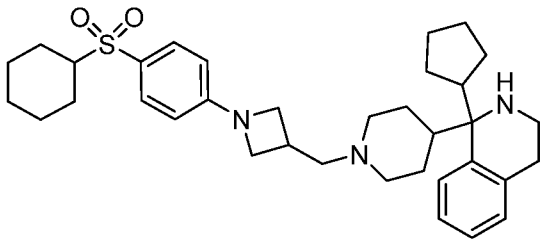
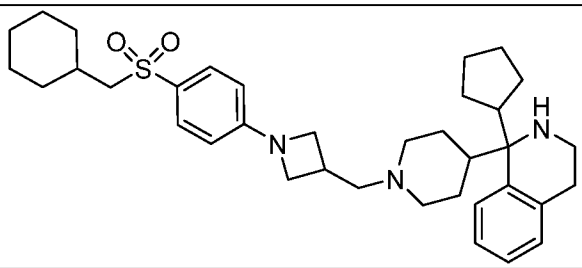
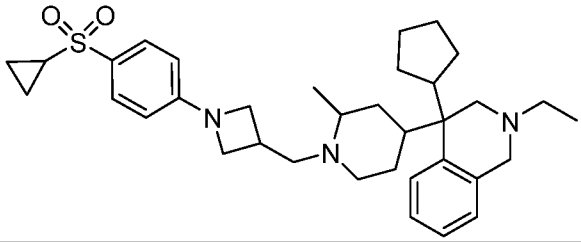
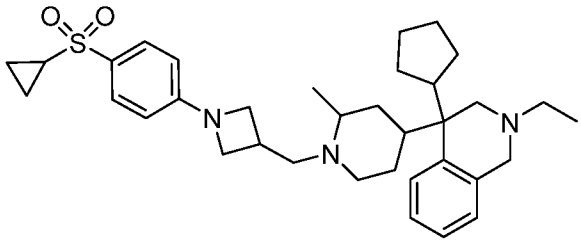
Cpd. No.	Chemical Structure	Chemical Name
56		1-(1-(3,3-bis(fluoromethyl)cyclobutyl) piperidin-4-yl)-1-cyclopentyl-1,2,3,4-tetrahydroisoquinoline
57		1-(1-benzylazetidin-3-yl)-1-cyclopentyl-1,2,3,4-tetrahydroisoquinoline
58		4-((3-(4-(1-cyclopentyl-1,2,3,4-tetrahydroisoquinolin-1-yl)piperidin-1-yl)propyl)amino)benzonitrile
59		5-((3-(4-(1-cyclopentyl-1,2,3,4-tetrahydroisoquinolin-1-yl)piperidin-1-yl)propyl)amino)picolinonitrile
60		4-(3-(3-(1-cyclopentyl-1,2,3,4-tetrahydroisoquinolin-1-yl)azetidin-1-yl)propoxy)benzonitrile
61		4-(3-(3-(2-((4-cyanophenoxy)methyl)-1-cyclopentyl-1,2,3,4-tetrahydroisoquinolin-1-yl)azetidin-1-yl)propoxy)benzonitrile compound with ethene (1:1)

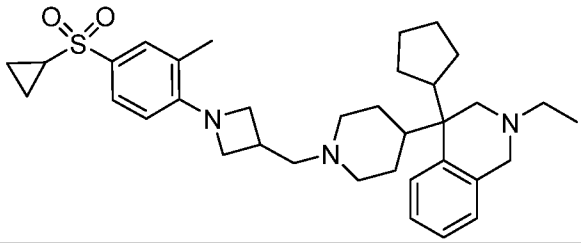
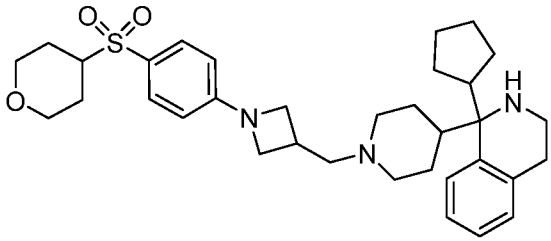
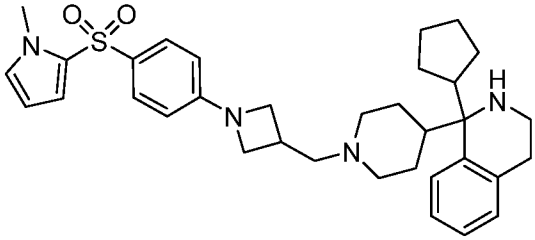
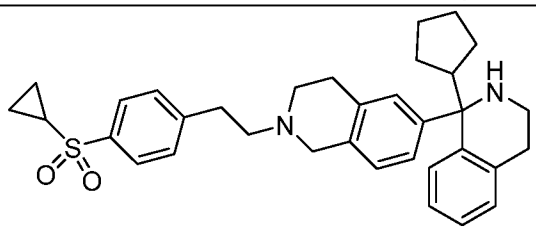
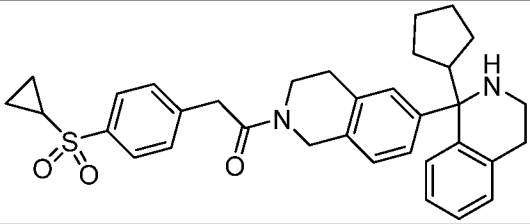
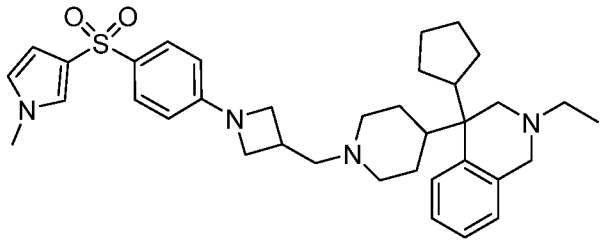
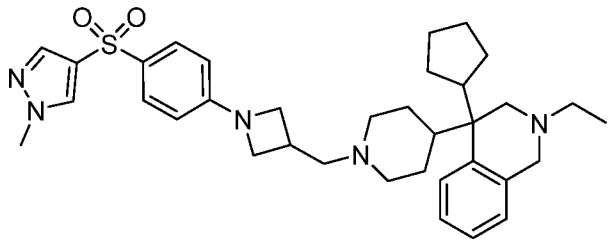
Cpd. No.	Chemical Structure	Chemical Name
62		4-(4-(3-(1-cyclopentyl-1,2,3,4-tetrahydroisoquinolin-1-yl)azetidin-1-yl)butoxy)benzonitrile
63		4-((5-(3-(1-cyclopentyl-2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)azetidin-1-yl)pentyl)oxy)benzonitrile
64		4-cyclopentyl-2-methyl-4-(1-((1-(4-(methylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1,2,3,4-tetrahydroisoquinoline
65		1-(5-(2-(4-(1-cyclopentyl-1,2,3,4-tetrahydroisoquinolin-1-yl)piperidin-1-yl)ethyl)-1-methyl-1H-indol-2-yl)pentan-1-one
66		5-(2-(4-(1-cyclopentyl-1,2,3,4-tetrahydroisoquinolin-1-yl)piperidin-1-yl)ethyl)-1H-indole-2-carbonitrile
67		2-(2-(4-(1-cyclopentyl-1,2,3,4-tetrahydroisoquinolin-1-yl)piperidin-1-yl)ethyl)-1H-indole-5-carbonitrile
68		4-cyclopentyl-2-methyl-4-(1-(3-(4-(methylsulfonyl)phenoxy)propyl)piperidin-4-yl)-1,2,3,4-tetrahydroisoquinoline

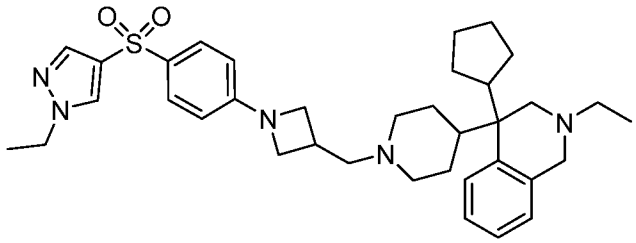
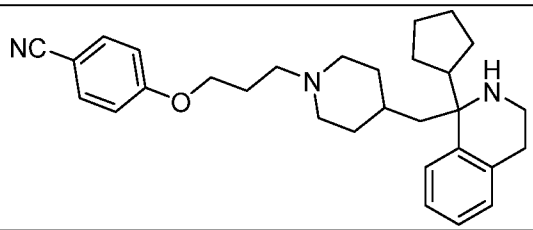
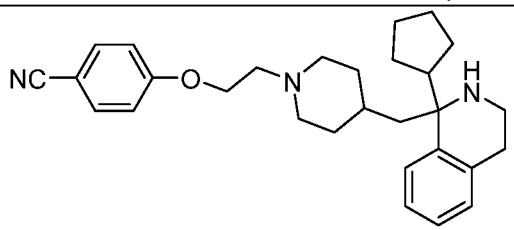
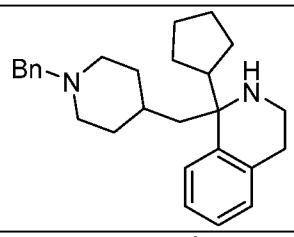
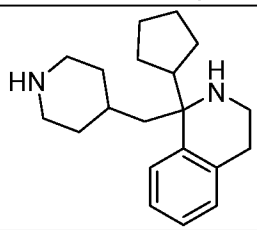
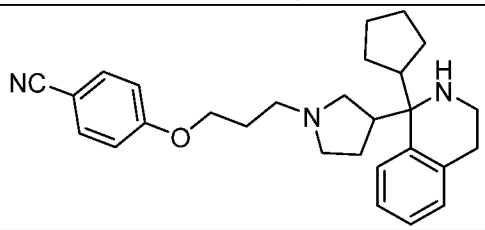
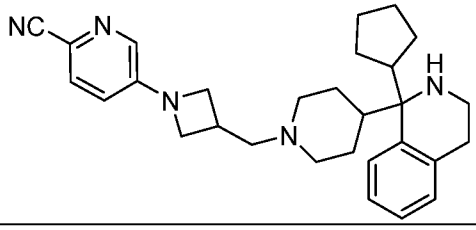
Cpd. No.	Chemical Structure	Chemical Name
69		4-cyclopentyl-4-(1-((1-(4-(ethylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-2-methyl-1,2,3,4-tetrahydroisoquinoline
70		4-cyclopentyl-4-(1-((1-(4-(cyclopropylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-2-methyl-1,2,3,4-tetrahydroisoquinoline
71		1-(1-benzylpiperidin-4-yl)-1-cyclopentyl-1,2,3,4-tetrahydroisoquinoline
72		1-cyclopentyl-1-(piperidin-4-yl)-1,2,3,4-tetrahydroisoquinoline
73		1-cyclopentyl-1-(1-(3-methoxypropyl)piperidin-4-yl)-1,2,3,4-tetrahydroisoquinoline
74		2-(4-(1-cyclopentyl-1,2,3,4-tetrahydroisoquinolin-1-yl)piperidin-1-yl)-1-(pyrrolidin-1-yl)ethan-1-one
75		1-cyclopentyl-1-(1-methylpiperidin-4-yl)-1,2,3,4-tetrahydroisoquinoline

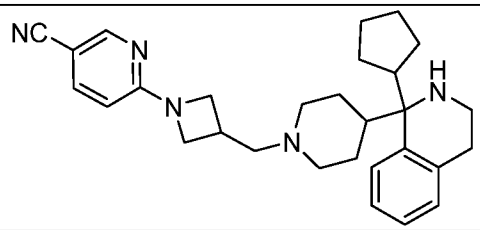
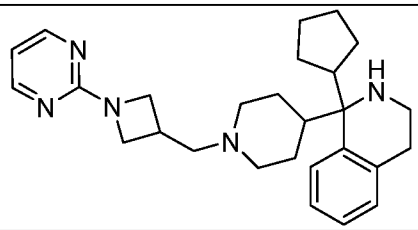
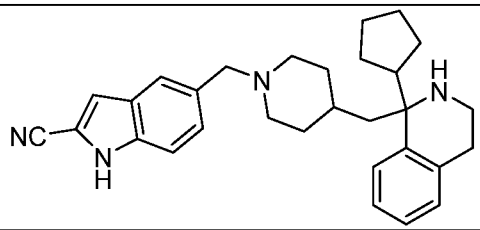
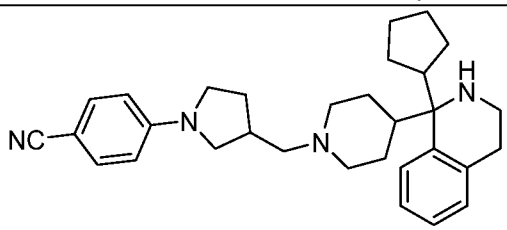
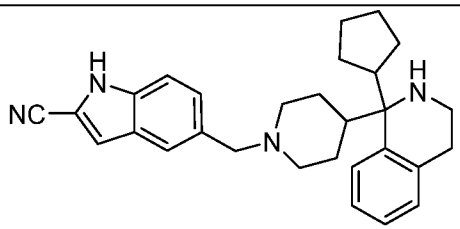
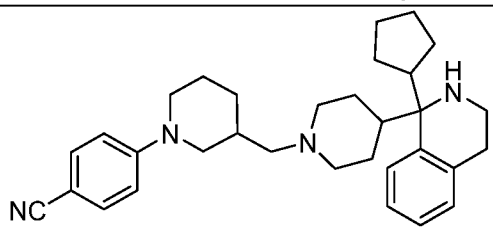
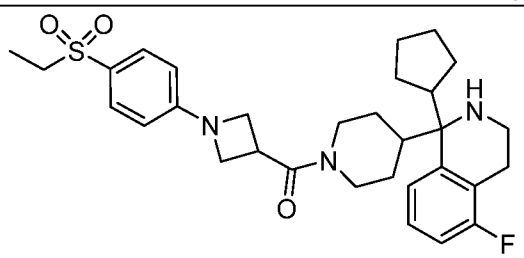
Cpd. No.	Chemical Structure	Chemical Name
76		1-cyclopentyl-1-(1-(3-phenoxypropyl)piperidin-4-yl)-1,2,3,4-tetrahydroisoquinoline
77		4'-(4-(1-cyclopentyl-1,2,3,4-tetrahydroisoquinolin-1-yl)piperidin-1-yl)-[1,1'-biphenyl]-4-carbonitrile
78		1-cyclopentyl-1-(pyridin-4-yl)-1,2,3,4-tetrahydroisoquinoline
79		4-(3-(4-(1-cyclopentyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-3,6-dihydropyridin-1(2H)-yl)propoxy)benzonitrile
80		2-cyano-N-((1r,4r)-4-(1-cyclopentyl-1,2,3,4-tetrahydroisoquinolin-1-yl)cyclohexyl)-1H-indole-5-carboxamide
81		2-cyano-N-((1r,4r)-4-(1-cyclopentyl-1,2,3,4-tetrahydroisoquinolin-1-yl)cyclohexyl)-1H-indole-6-carboxamide
82		2-(4-(1-cyclopentyl-1,2,3,4-tetrahydroisoquinolin-1-yl)piperidin-1-yl)-1-(isoindolin-2-yl)ethan-1-one

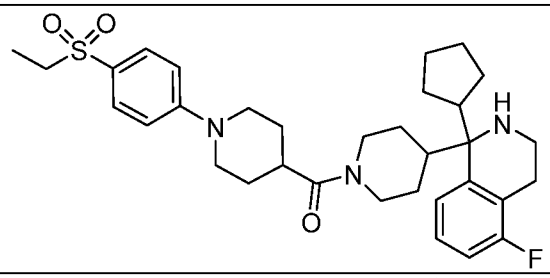
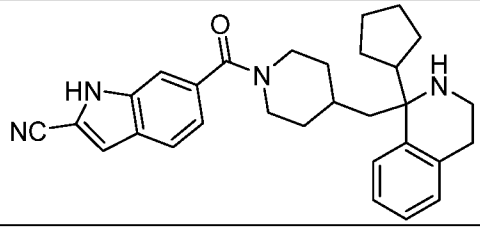
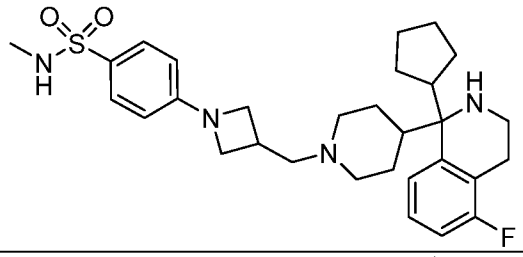
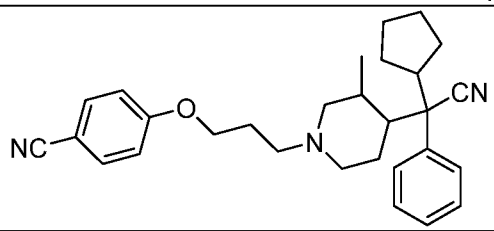
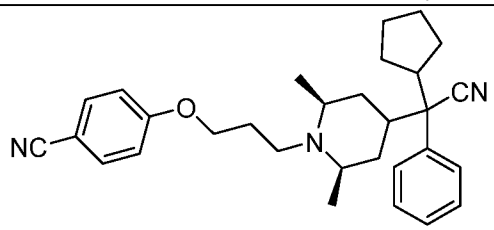
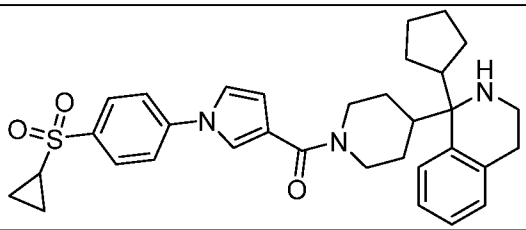
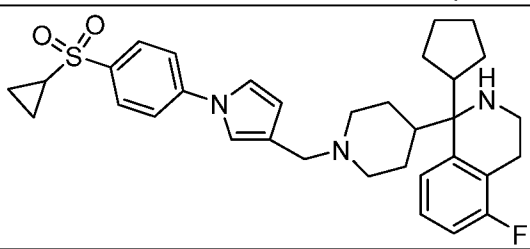
Cpd. No.	Chemical Structure	Chemical Name
83		2-(2-(4-(1-cyclopentyl-1,2,3,4-tetrahydroisoquinolin-1-yl)piperidin-1-yl)acetyl)-1,2,3,4-tetrahydroisoquinoline-6-carbonitrile
84		2-(4-(1-cyclopentyl-1,2,3,4-tetrahydroisoquinolin-1-yl)piperidin-1-yl)-1-(3,4-dihydroisoquinolin-2(1H)-yl)ethan-1-one
85		1-(1-((1-(4-(cyclobutylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1-cyclopentyl-1,2,3,4-tetrahydroisoquinoline
86		1-(1-((1-(4-((cyclobutylmethyl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1-cyclopentyl-1,2,3,4-tetrahydroisoquinoline
87		1-(1-((1-(4-(tert-butylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1-cyclopentyl-1,2,3,4-tetrahydroisoquinoline
88		4-(3-((4-(1-cyclopentyl-1,2,3,4-tetrahydroisoquinolin-1-yl)piperidin-1-yl)methyl)azetidin-1-yl)-N,N-dimethylbenzenesulfonamide
89		1-cyclopentyl-1-(1-((1s,3s)-3-(4-(cyclopropylsulfonyl)phenoxy)cyclobutyl)piperidin-4-yl)-1,2,3,4-tetrahydroisoquinoline

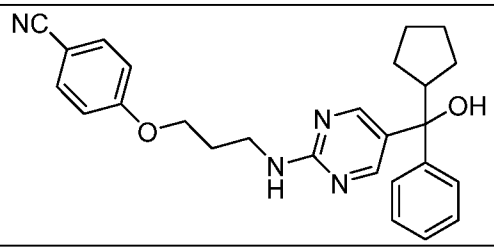
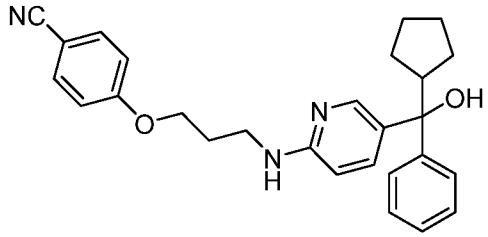
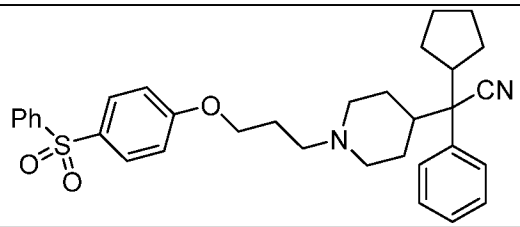
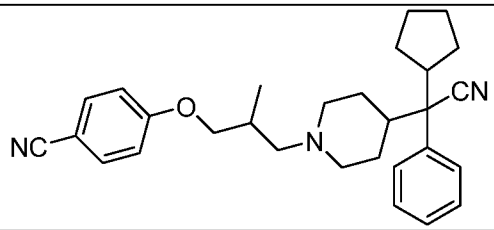
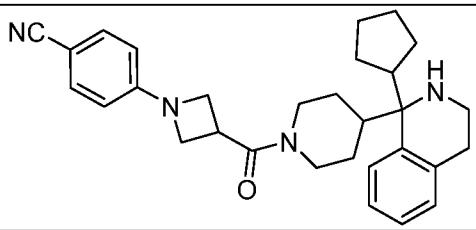
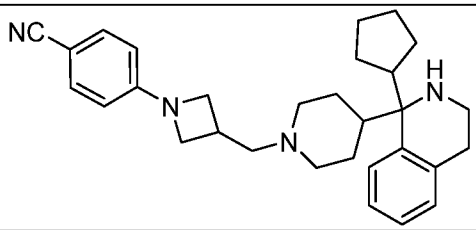
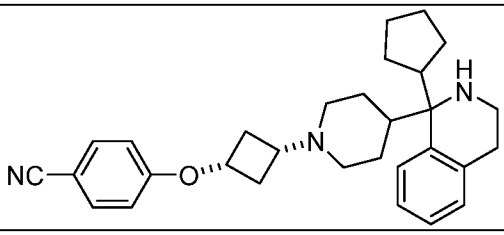
Cpd. No.	Chemical Structure	Chemical Name
90		1-cyclopentyl-1-(1-((1r,3r)-3-(4-(cyclopropylsulfonyl)phenoxy)cyclobutyl)piperidin-4-yl)-1,2,3,4-tetrahydroisoquinoline
91		1-cyclopentyl-1-(1-((1-(4-((cyclopentylmethyl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1,2,3,4-tetrahydroisoquinoline
92		1-(1-((1-(4-(cyclohexylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1-cyclopentyl-1,2,3,4-tetrahydroisoquinoline
93		1-(1-((1-(4-((cyclohexylmethyl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1-cyclopentyl-1,2,3,4-tetrahydroisoquinoline
94		4-cyclopentyl-4-(1-((1-(4-(cyclopropylsulfonyl)phenyl)azetidin-3-yl)methyl)-2-methylpiperidin-4-yl)-2-ethyl-1,2,3,4-tetrahydroisoquinoline
95		4-cyclopentyl-4-(1-((1-(4-(cyclopropylsulfonyl)phenyl)azetidin-3-yl)methyl)-2-methylpiperidin-4-yl)-2-ethyl-1,2,3,4-tetrahydroisoquinoline

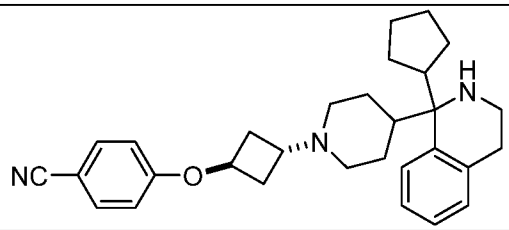
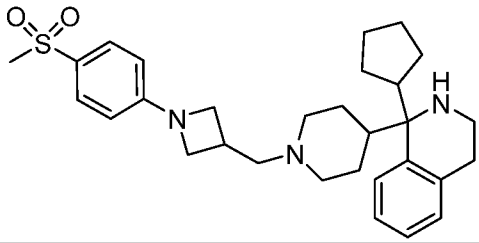
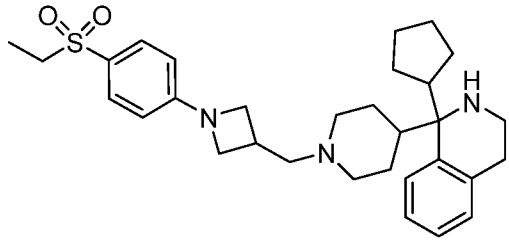
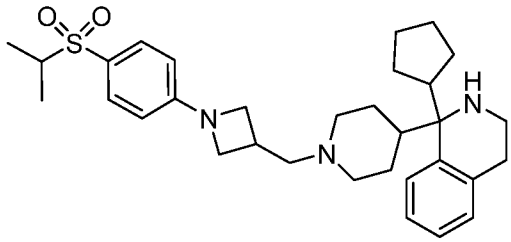
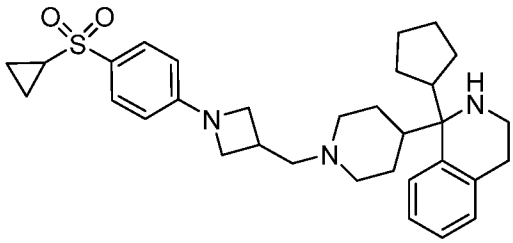
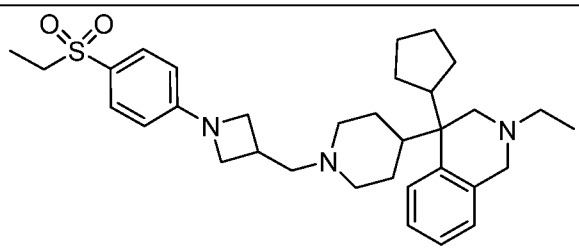
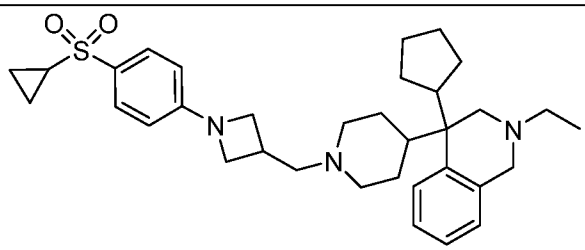
Cpd. No.	Chemical Structure	Chemical Name
96		4-cyclopentyl-4-(1-((1-(4-(cyclopropylsulfonyl)-2-methylphenyl)azetidin-3-yl)methyl)piperidin-4-yl)-2-ethyl-1,2,3,4-tetrahydroisoquinoline
97		1-cyclopentyl-1-(1-((1-(4-((tetrahydro-2H-pyran-4-yl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1,2,3,4-tetrahydroisoquinoline
98		1-cyclopentyl-1-(1-((1-(4-((1-methyl-1H-pyrrol-2-yl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1,2,3,4-tetrahydroisoquinoline
99		1-cyclopentyl-2'-(4-(cyclopropylsulfonyl)phenethyl)-1,1',2,2',3,3',4,4'-octahydro-1,6'-biisoquinoline
100		1-(1-cyclopentyl-1,2,3,3',4,4'-hexahydro-[1,6'-biisoquinolin]-2'(1'H)-yl)-2-(4-(cyclopropylsulfonyl)phenyl)ethan-1-one
101		4-cyclopentyl-2-ethyl-4-(1-((1-(4-((1-methyl-1H-pyrrol-3-yl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1,2,3,4-tetrahydroisoquinoline
102		4-cyclopentyl-2-ethyl-4-(1-((1-(4-((1-methyl-1H-pyrazol-4-yl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1,2,3,4-tetrahydroisoquinoline

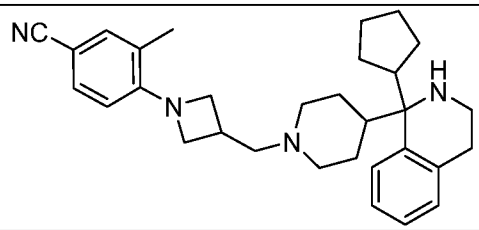
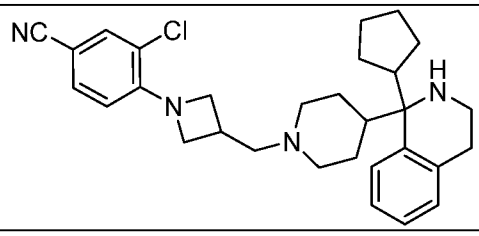
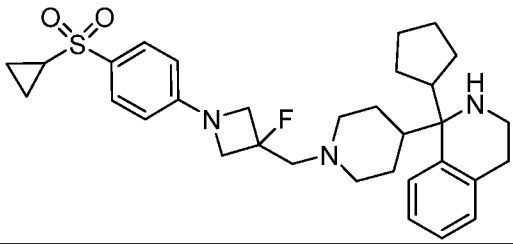
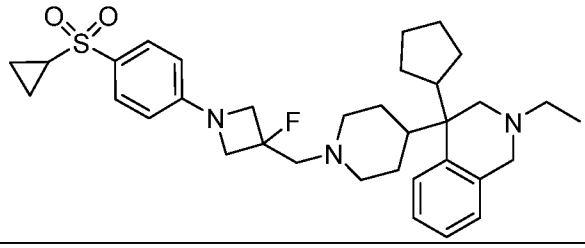
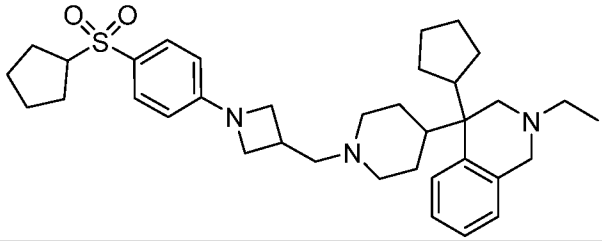
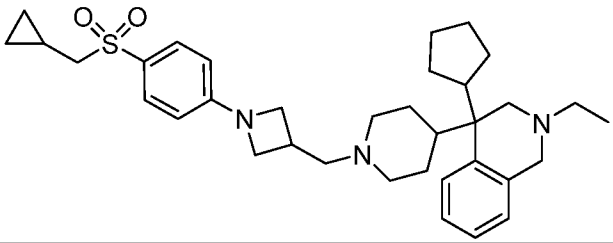
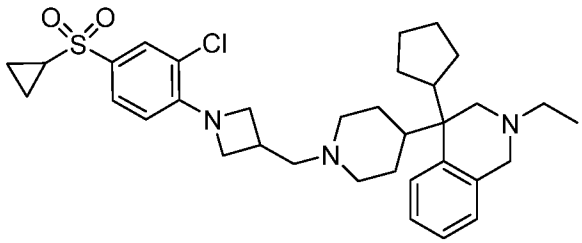
Cpd. No.	Chemical Structure	Chemical Name
103		4-cyclopentyl-2-ethyl-4-(1-((1-(4-((1-ethyl-1H-pyrazol-4-yl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1,2,3,4-tetrahydroisoquinoline
104		4-(3-(4-((1-cyclopentyl-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)piperidin-1-yl)propoxy)benzonitrile
105		4-(2-(4-((1-cyclopentyl-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)piperidin-1-yl)ethoxy)benzonitrile
106		1-((1-benzylpiperidin-4-yl)methyl)-1-cyclopentyl-1,2,3,4-tetrahydroisoquinoline
107		1-cyclopentyl-1-(piperidin-4-ylmethyl)-1,2,3,4-tetrahydroisoquinoline
108		4-(3-(3-(1-cyclopentyl-1,2,3,4-tetrahydroisoquinolin-1-yl)pyrrolidin-1-yl)propoxy)benzonitrile
109		5-(3-((4-(1-cyclopentyl-1,2,3,4-tetrahydroisoquinolin-1-yl)piperidin-1-yl)methyl)azetidin-1-yl)picolinonitrile

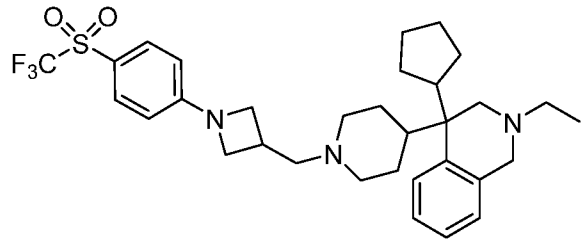
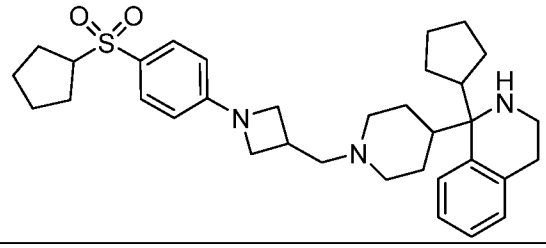
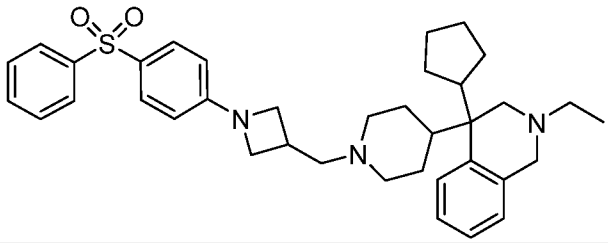
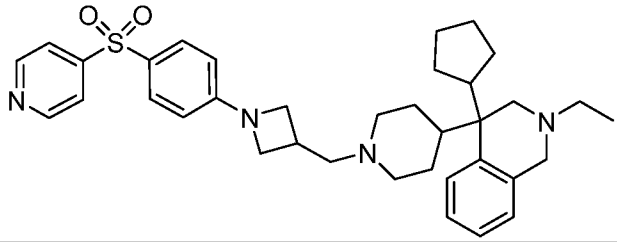
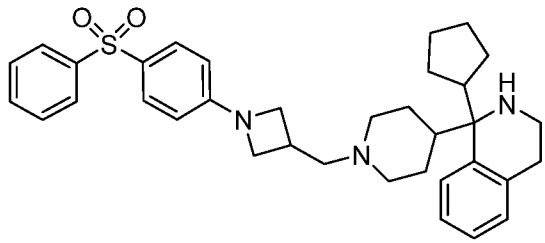
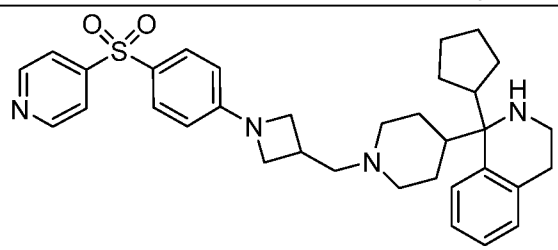
Cpd. No.	Chemical Structure	Chemical Name
110		6-(3-((4-(1-cyclopentyl-1,2,3,4-tetrahydroisoquinolin-1-yl)piperidin-1-yl)methyl)azetidin-1-yl)nicotinonitrile
111		1-cyclopentyl-1-(1-((1-(pyrimidin-2-yl)azetidin-3-yl)methyl)piperidin-4-yl)-1,2,3,4-tetrahydroisoquinoline
112		5-((4-((1-cyclopentyl-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)piperidin-1-yl)methyl)-1H-indole-2-carbonitrile
113		4-(3-((4-(1-cyclopentyl-1,2,3,4-tetrahydroisoquinolin-1-yl)piperidin-1-yl)methyl)pyrrolidin-1-yl)benzonitrile
114		5-((4-(1-cyclopentyl-1,2,3,4-tetrahydroisoquinolin-1-yl)piperidin-1-yl)methyl)-1H-indole-2-carbonitrile
115		4-(3-((4-(1-cyclopentyl-1,2,3,4-tetrahydroisoquinolin-1-yl)piperidin-1-yl)methyl)piperidin-1-yl)benzonitrile
116		(4-(1-cyclopentyl-5-fluoro-1,2,3,4-tetrahydroisoquinolin-1-yl)piperidin-1-yl)(1-(4-(ethylsulfonyl)phenyl)azetidin-3-yl)methanone

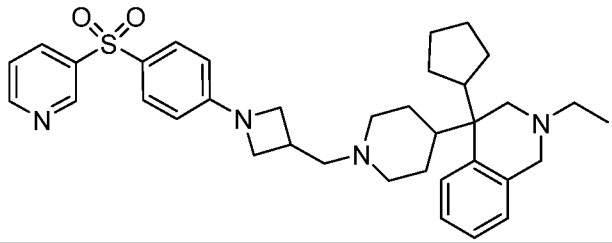
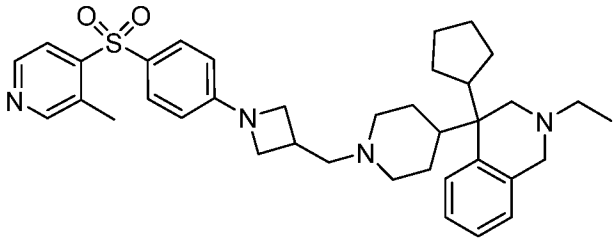
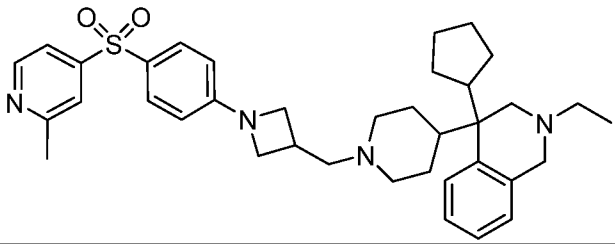
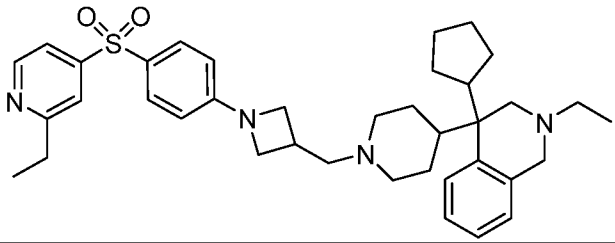
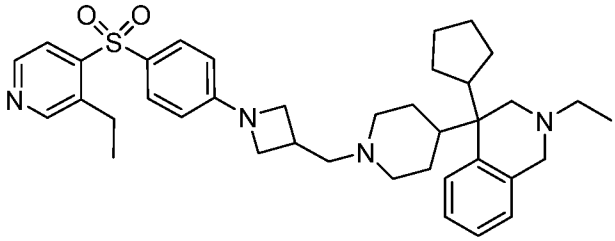
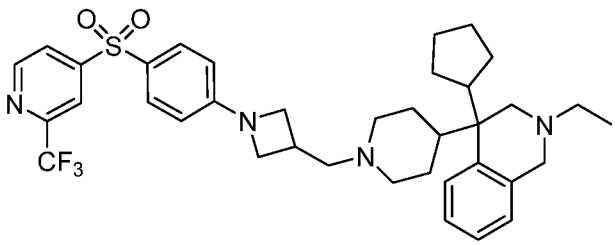
Cpd. No.	Chemical Structure	Chemical Name
117		(4-(1-cyclopentyl-5-fluoro-1,2,3,4-tetrahydroisoquinolin-1-yl)piperidin-1-yl)(1-(4-(ethylsulfonyl)phenyl)piperidin-4-yl)methanone
118		6-(4-((1-cyclopentyl-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)piperidine-1-carbonyl)-1H-indole-2-carbonitrile
119		4-(3-((4-(1-cyclopentyl-5-fluoro-1,2,3,4-tetrahydroisoquinolin-1-yl)piperidin-1-yl)methyl)azetidin-1-yl)-N-methylbenzenesulfonamide
120		4-(3-(4-(cyano(cyclopentyl)(phenyl)methyl)-3-methylpiperidin-1-yl)propoxy)benzonitrile
121		4-(3-((2S,6R)-4-(cyano(cyclopentyl)(phenyl)methyl)-2,6-dimethylpiperidin-1-yl)propoxy)benzonitrile
122		(4-(1-cyclopentyl-1,2,3,4-tetrahydroisoquinolin-1-yl)piperidin-1-yl)(1-(4-(cyclopropylsulfonyl)phenyl)-1H-pyrrol-3-yl)methanone
123		1-cyclopentyl-1-(1-((1-(4-(cyclopropylsulfonyl)phenyl)-1H-pyrrol-3-yl)methyl)piperidin-4-yl)-5-fluoro-1,2,3,4-tetrahydroisoquinoline

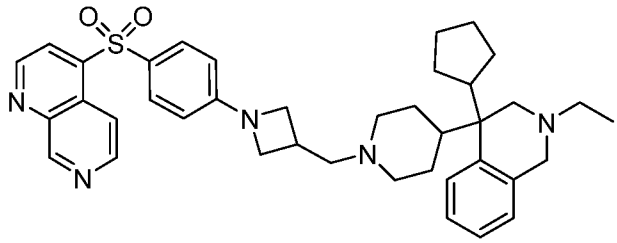
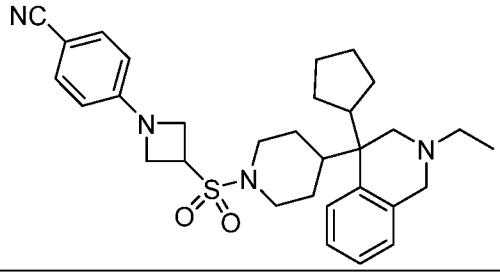
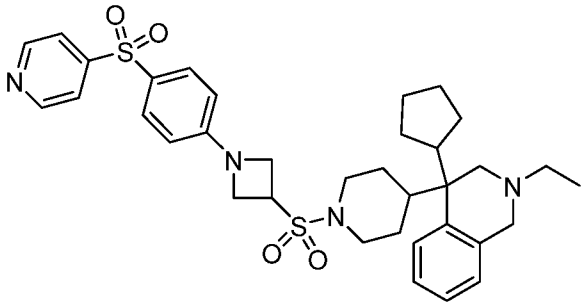
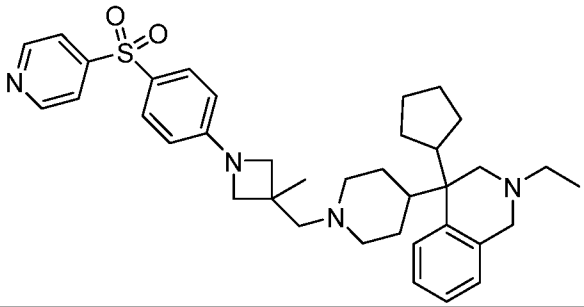
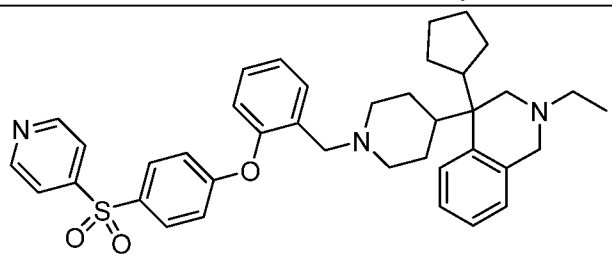
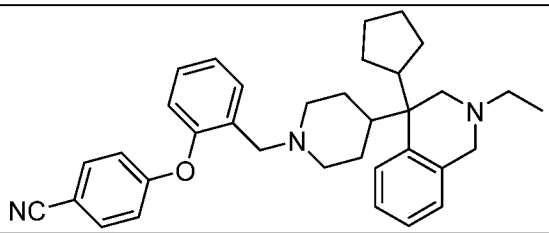
Cpd. No.	Chemical Structure	Chemical Name
124		4-(3-((5-(cyclopentyl(hydroxy)(phenyl)methyl)pyrimidin-2-yl)amino)propoxy)benzonitrile
125		4-(3-((5-(cyclopentyl(hydroxy)(phenyl)methyl)pyridin-2-yl)amino)propoxy)benzonitrile
126		2-cyclopentyl-2-phenyl-2-(1-(3-(4-(phenylsulfonyl)phenoxy)propyl)piperidin-4-yl)acetonitrile
127		4-(3-(4-(cyano(cyclopentyl)(phenyl)methyl)piperidin-1-yl)-2-methylpropoxy)benzonitrile
128		4-(3-(4-(1-cyclopentyl-1,2,3,4-tetrahydroisoquinolin-1-yl)piperidine-1-carbonyl)azetidin-1-yl)benzonitrile
129		4-(3-((4-(1-cyclopentyl-1,2,3,4-tetrahydroisoquinolin-1-yl)piperidin-1-yl)methyl)azetidin-1-yl)benzonitrile
130		4-((1s,3s)-3-(4-(1-cyclopentyl-1,2,3,4-tetrahydroisoquinolin-1-yl)piperidin-1-yl)cyclobutoxy)benzonitrile

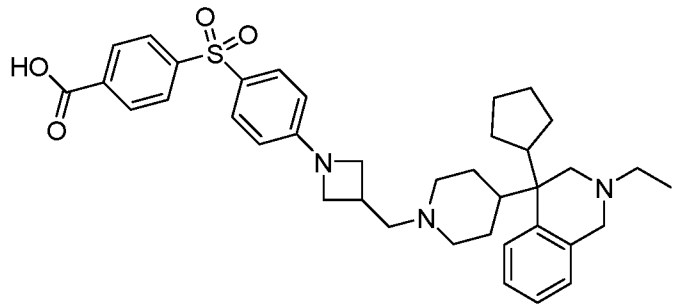
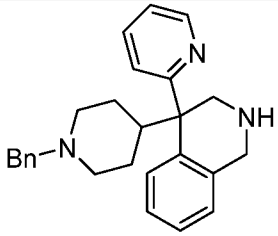
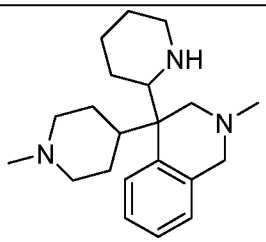
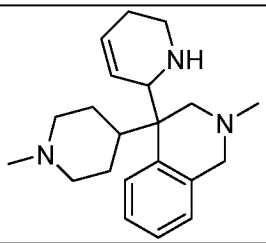
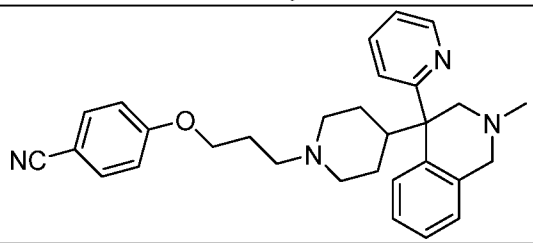
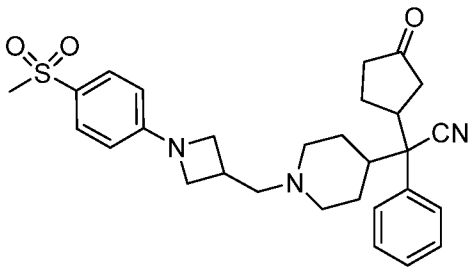
Cpd. No.	Chemical Structure	Chemical Name
131		4-((1r,3r)-3-(4-(1-cyclopentyl-1,2,3,4-tetrahydroisoquinolin-1-yl)piperidin-1-yl)cyclobutoxy)benzonitrile
132		1-cyclopentyl-1-(1-((1-(4-(methylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1,2,3,4-tetrahydroisoquinoline
133		1-cyclopentyl-1-(1-((1-(4-(ethylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1,2,3,4-tetrahydroisoquinoline
134		1-cyclopentyl-1-(1-((1-(4-(isopropylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1,2,3,4-tetrahydroisoquinoline
135		1-cyclopentyl-1-(1-((1-(4-(cyclopropylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1,2,3,4-tetrahydroisoquinoline
136		4-cyclopentyl-2-ethyl-4-(1-((1-(4-(ethylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1,2,3,4-tetrahydroisoquinoline
137		4-cyclopentyl-4-(1-((1-(4-(cyclopropylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-2-ethyl-1,2,3,4-tetrahydroisoquinoline

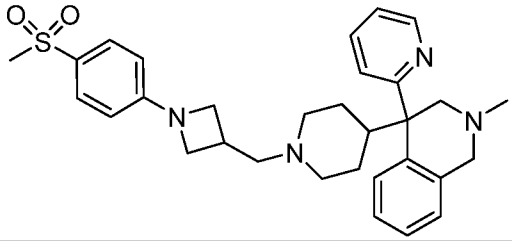
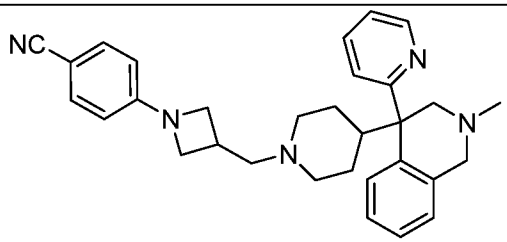
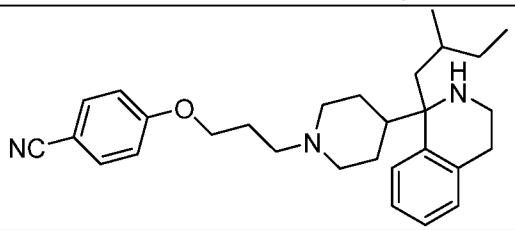
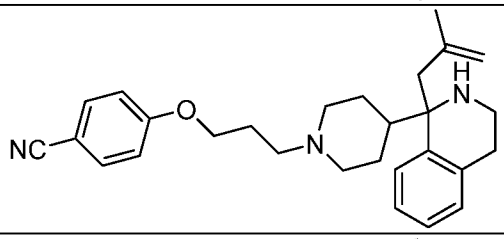
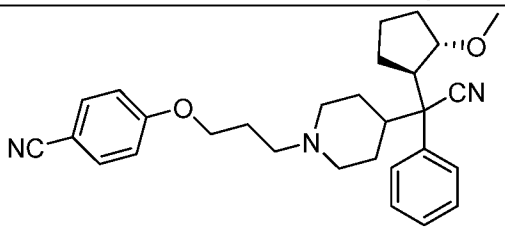
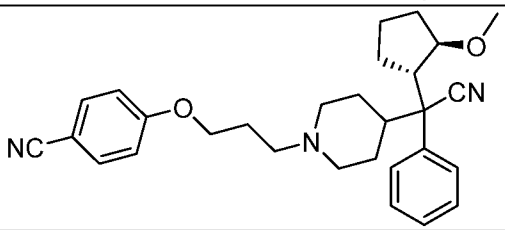
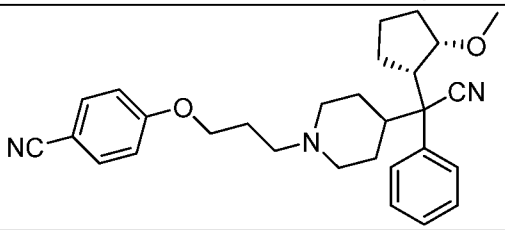
Cpd. No.	Chemical Structure	Chemical Name
138		4-(3-((4-(1-cyclopentyl-1,2,3,4-tetrahydroisoquinolin-1-yl)piperidin-1-yl)methyl)azetidin-1-yl)-3-methylbenzonitrile
139		3-chloro-4-(3-((4-(1-cyclopentyl-1,2,3,4-tetrahydroisoquinolin-1-yl)piperidin-1-yl)methyl)azetidin-1-yl)benzonitrile
140		1-cyclopentyl-1-(1-((1-(4-(cyclopropylsulfonyl)phenyl)-3-fluoroazetidin-3-yl)methyl)piperidin-4-yl)-1,2,3,4-tetrahydroisoquinoline
141		4-cyclopentyl-4-(1-((1-(4-(cyclopropylsulfonyl)phenyl)-3-fluoroazetidin-3-yl)methyl)piperidin-4-yl)-2-ethyl-1,2,3,4-tetrahy36droisoquinoline
142		4-cyclopentyl-4-(1-((1-(4-(cyclopentylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-2-ethyl-1,2,3,4-tetrahydroisoquinoline
143		4-cyclopentyl-4-(1-((1-(4-((cyclopropylmethyl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-2-ethyl-1,2,3,4-tetrahydroisoquinoline
144		4-(1-((1-(2-chloro-4-(cyclopropylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-4-cyclopentyl-2-ethyl-1,2,3,4-tetrahydroisoquinoline

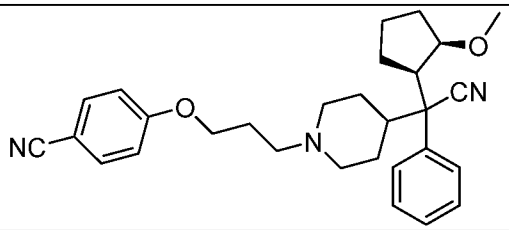
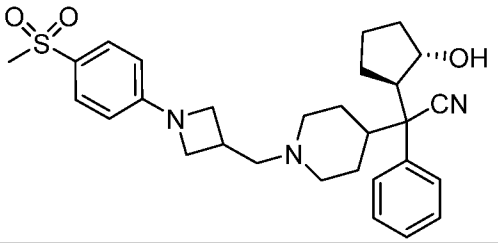
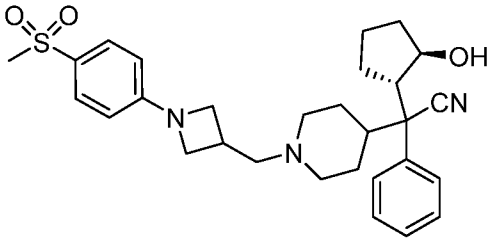
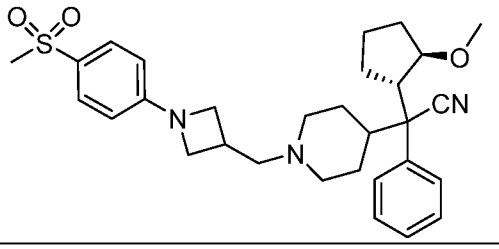
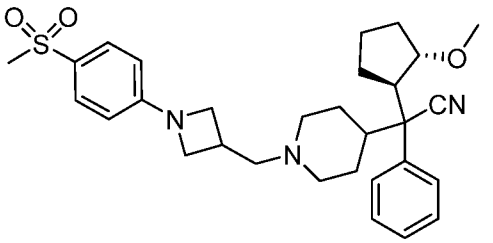
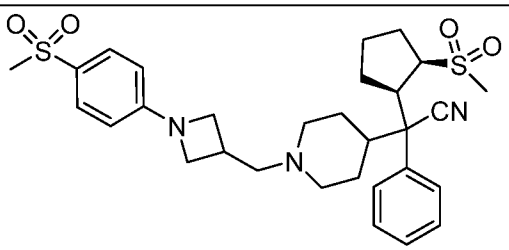
Cpd. No.	Chemical Structure	Chemical Name
145		4-cyclopentyl-2-ethyl-4-(1-((1-(4-((trifluoromethyl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1,2,3,4-tetrahydroisoquinoline
146		1-cyclopentyl-1-(1-((1-(4-(cyclopentylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1,2,3,4-tetrahydroisoquinoline
147		4-cyclopentyl-2-ethyl-4-(1-((1-(4-(phenylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1,2,3,4-tetrahydroisoquinoline
148		4-cyclopentyl-2-ethyl-4-(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1,2,3,4-tetrahydroisoquinoline
149		1-cyclopentyl-1-(1-((1-(4-(phenylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1,2,3,4-tetrahydroisoquinoline
151		1-cyclopentyl-1-(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1,2,3,4-tetrahydroisoquinoline

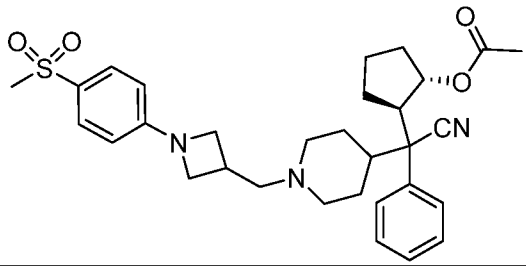
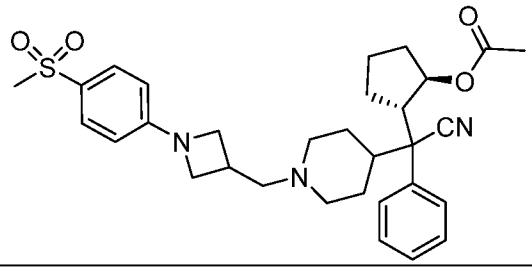
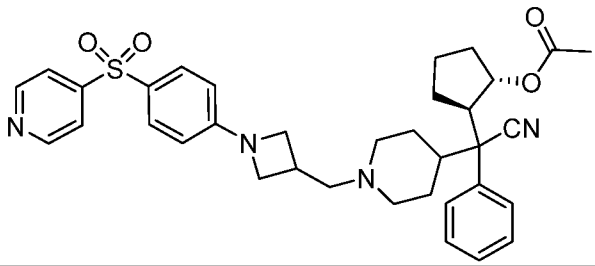
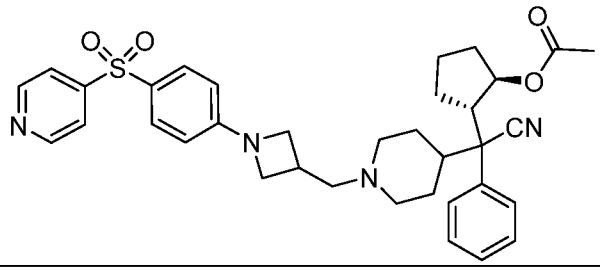
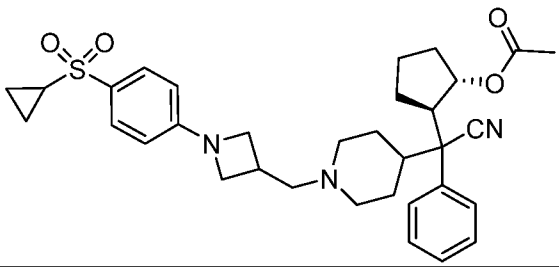
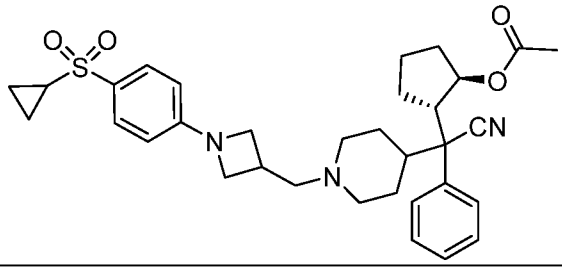
Cpd. No.	Chemical Structure	Chemical Name
152		4-cyclopentyl-2-ethyl-4-(1-((1-(4-(pyridin-3-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1,2,3,4-tetrahydroisoquinoline
153		4-cyclopentyl-2-ethyl-4-(1-((1-(4-((3-methylpyridin-4-yl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1,2,3,4-tetrahydroisoquinoline
154		4-cyclopentyl-2-ethyl-4-(1-((1-(4-((2-methylpyridin-4-yl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1,2,3,4-tetrahydroisoquinoline
155		4-cyclopentyl-2-ethyl-4-(1-((1-(4-((2-ethylpyridin-4-yl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1,2,3,4-tetrahydroisoquinoline
156		4-cyclopentyl-2-ethyl-4-(1-((1-(4-((3-ethylpyridin-4-yl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1,2,3,4-tetrahydroisoquinoline
157		4-cyclopentyl-2-ethyl-4-(1-((1-(4-((2-(trifluoromethyl)pyridin-4-yl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1,2,3,4-tetrahydroisoquinoline

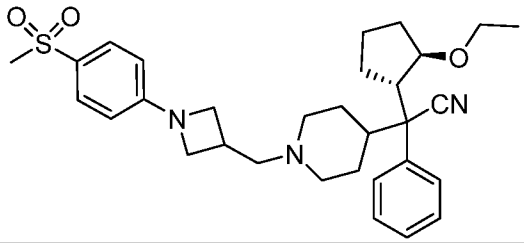
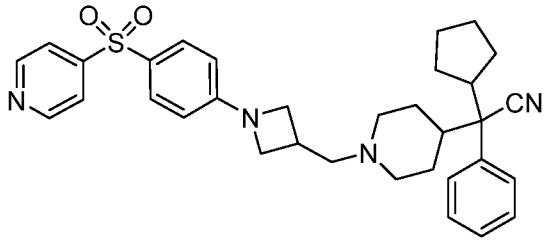
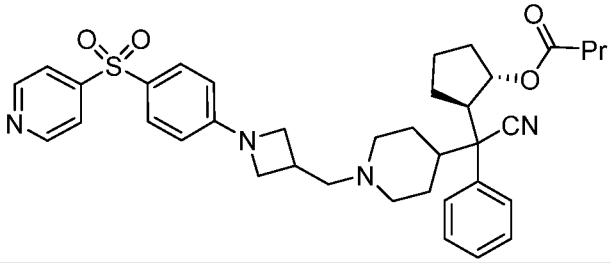
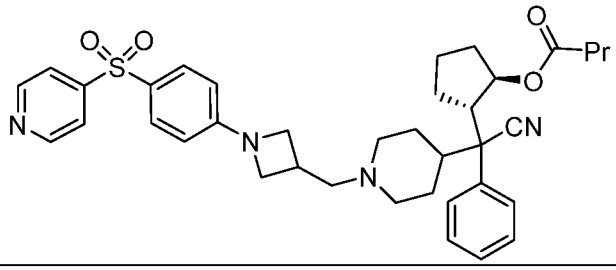
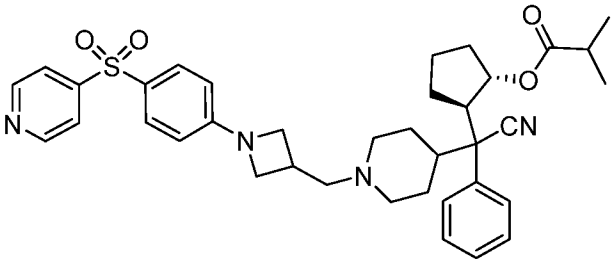
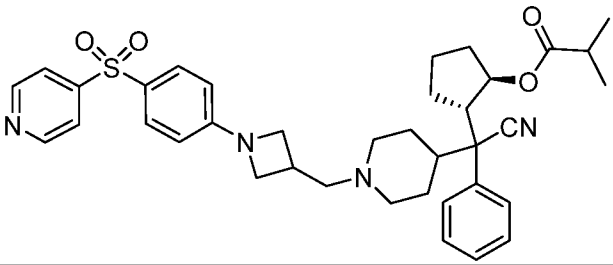
Cpd. No.	Chemical Structure	Chemical Name
158		4-((4-(3-((4-(4-cyclopentyl-2-ethyl-1,2,3,4-tetrahydroisoquinolin-4-yl)piperidin-1-yl)methyl)azetidin-1-yl)phenyl)sulfonyl)-1,7-naphthyridine
159		4-(3-((4-(4-cyclopentyl-2-ethyl-1,2,3,4-tetrahydroisoquinolin-4-yl)piperidin-1-yl)sulfonyl)azetidin-1-yl)benzonitrile
160		4-cyclopentyl-2-ethyl-4-(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)sulfonyl)piperidin-4-yl)-1,2,3,4-tetrahydroisoquinoline
161		4-cyclopentyl-2-ethyl-4-(1-((3-methyl-1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1,2,3,4-tetrahydroisoquinoline
162		4-cyclopentyl-2-ethyl-4-(1-(2-(4-(pyridin-4-ylsulfonyl)phenoxy)benzyl)piperidin-4-yl)-1,2,3,4-tetrahydroisoquinoline
163		4-(2-((4-(4-cyclopentyl-2-ethyl-1,2,3,4-tetrahydroisoquinolin-4-yl)piperidin-1-yl)methyl)phenoxy)benzonitrile

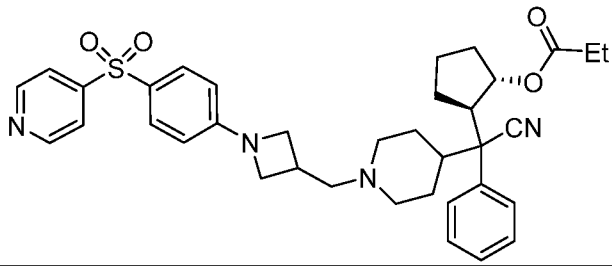
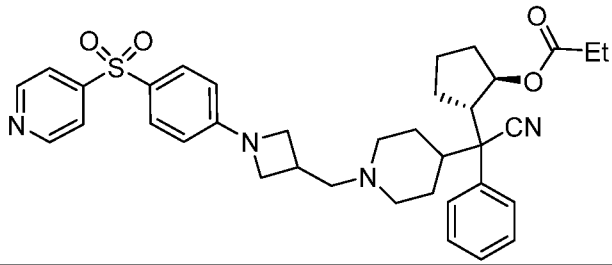
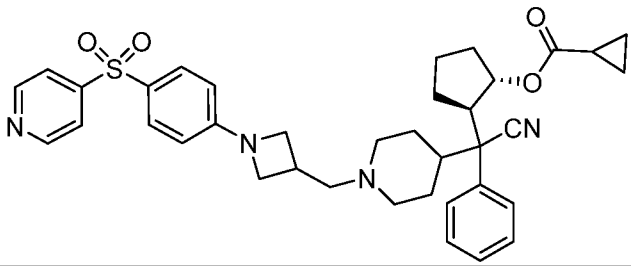
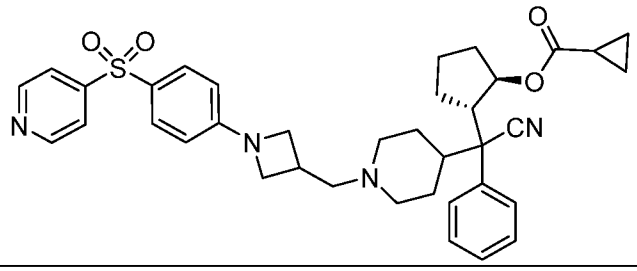
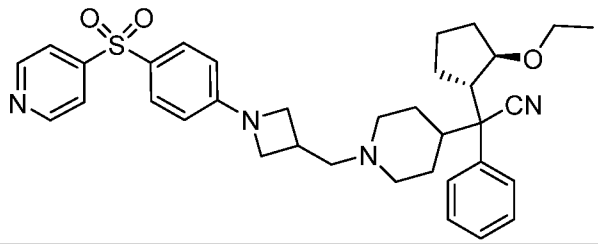
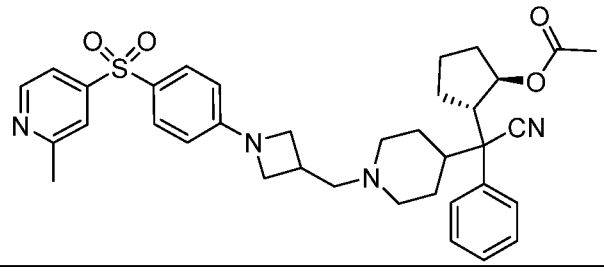
Cpd. No.	Chemical Structure	Chemical Name
164		4-((4-(3-((4-(4-cyclopentyl-2-ethyl-1,2,3,4-tetrahydroisoquinolin-4-yl)piperidin-1-yl)methyl)azetidin-1-yl)phenyl)sulfonyl)benzoic acid
165		4-(1-benzylpiperidin-4-yl)-4-(pyridin-2-yl)-1,2,3,4-tetrahydroisoquinoline
166		2-methyl-4-(1-methylpiperidin-4-yl)-4-(piperidin-2-yl)-1,2,3,4-tetrahydroisoquinoline
167		2-methyl-4-(1-methylpiperidin-4-yl)-4-(1,2,5,6-tetrahydropyridin-2-yl)-1,2,3,4-tetrahydroisoquinoline
168		4-(3-(4-(2-methyl-4-(pyridin-2-yl)-1,2,3,4-tetrahydroisoquinolin-4-yl)piperidin-1-yl)propoxy)benzonitrile
169		2-(1-((1-(4-(methylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-2-(3-oxocyclopentyl)-2-phenylacetonitrile

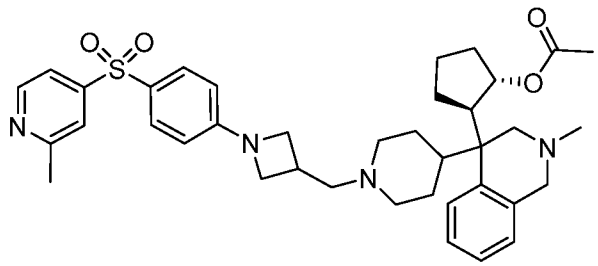
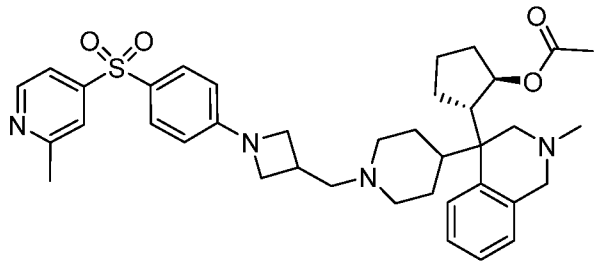
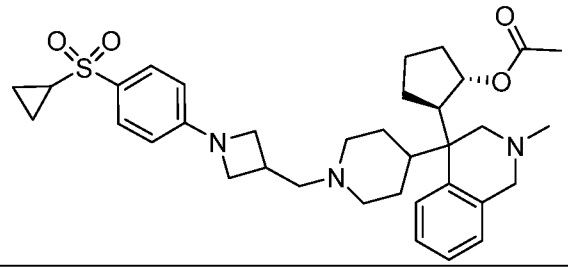
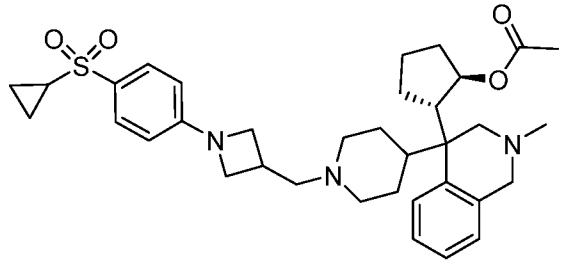
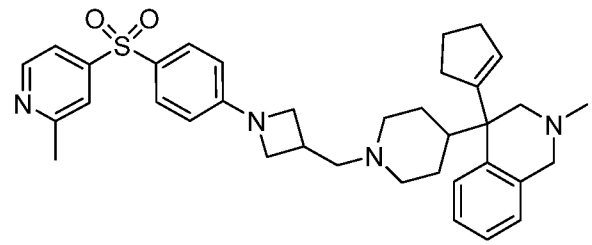
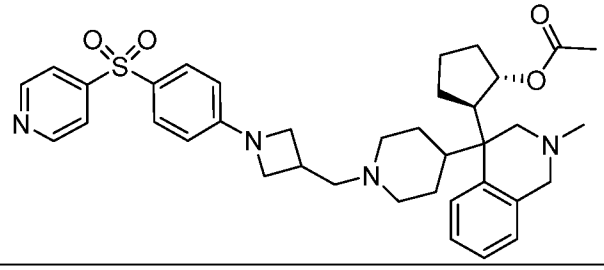
Cpd. No.	Chemical Structure	Chemical Name
170		2-methyl-4-(1-((1-(4-(methylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-4-(pyridin-2-yl)-1,2,3,4-tetrahydroisoquinoline
171		4-(3-((4-(2-methyl-4-(pyridin-2-yl)-1,2,3,4-tetrahydroisoquinolin-4-yl)piperidin-1-yl)methyl)azetidin-1-yl)benzonitrile
172		4-(3-(4-(1-(2-methylbutyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)piperidin-1-yl)propoxy)benzonitrile
173		4-(3-(4-(1-(2-methylallyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)piperidin-1-yl)propoxy)benzonitrile
174		4-(3-(4-(cyano((1R,2S)-2-methoxycyclopentyl)(phenyl)methyl)piperidin-1-yl)propoxy)benzonitrile
175		rac-4-(3-(4-(cyano((1S,2R)-2-methoxycyclopentyl)(phenyl)methyl)piperidin-1-yl)propoxy)benzonitrile
176		rac-4-(3-(4-(cyano((1S,2S)-2-methoxycyclopentyl)(phenyl)methyl)piperidin-1-yl)propoxy)benzonitrile

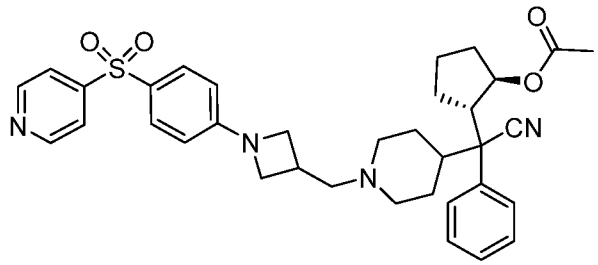
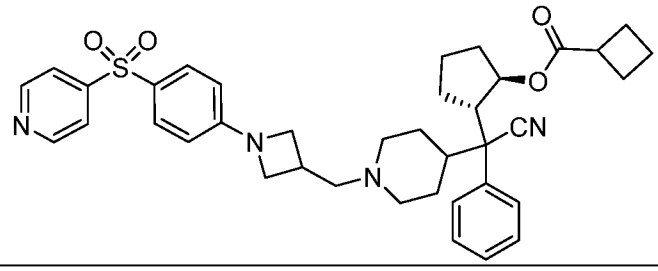
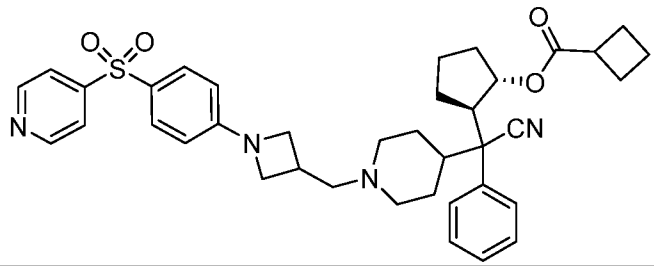
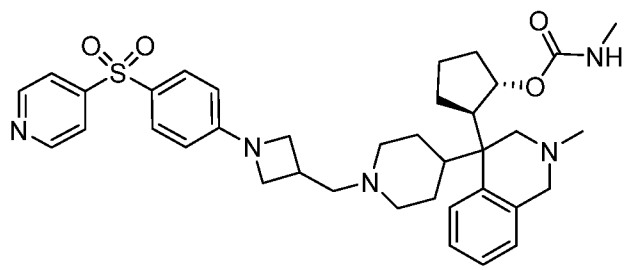
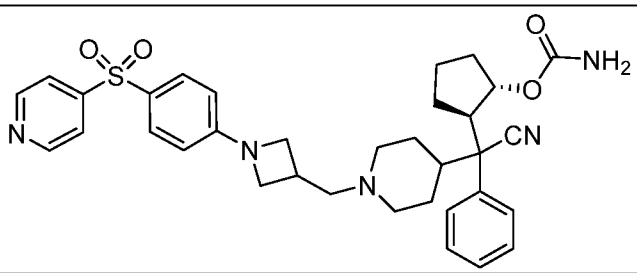
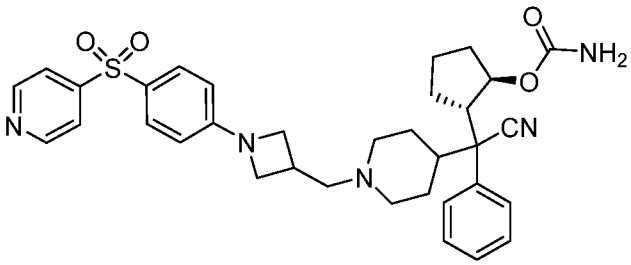
Cpd. No.	Chemical Structure	Chemical Name
177		rac-4-(3-(4-(cyano((1R,2R)-2-methoxycyclopentyl)(phenyl)methyl)piperidin-1-yl)propoxy)benzonitrile
178		rac-2-((1R,2S)-2-hydroxycyclopentyl)-2-(1-((1-(4-(methylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-2-phenylacetonitrile
179		rac-2-((1S,2R)-2-hydroxycyclopentyl)-2-(1-((1-(4-(methylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-2-phenylacetonitrile
180		rac-2-((1S,2R)-2-methoxycyclopentyl)-2-(1-((1-(4-(methylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-2-phenylacetonitrile
181		rac-2-((1R,2S)-2-methoxycyclopentyl)-2-(1-((1-(4-(methylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-2-phenylacetonitrile
182		rac-2-((1R,2R)-2-(methylsulfonyl)cyclopentyl)-2-(1-((1-(4-(methylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-2-phenylacetonitrile

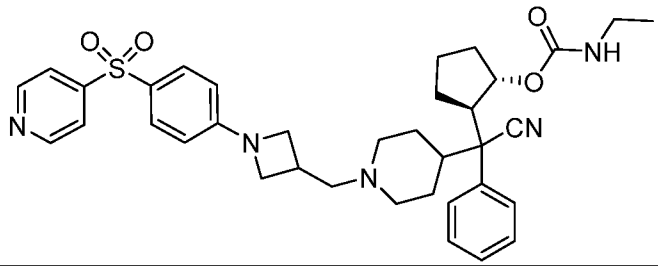
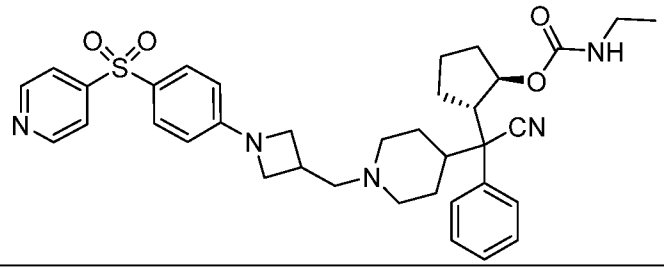
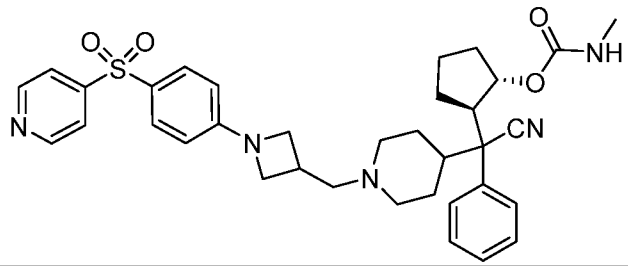
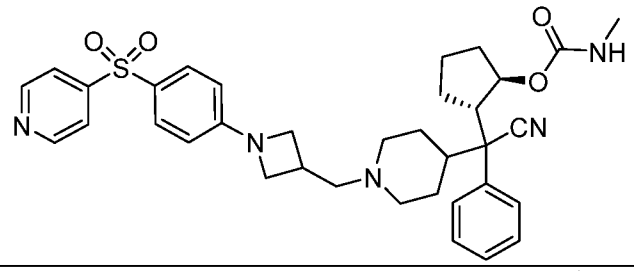
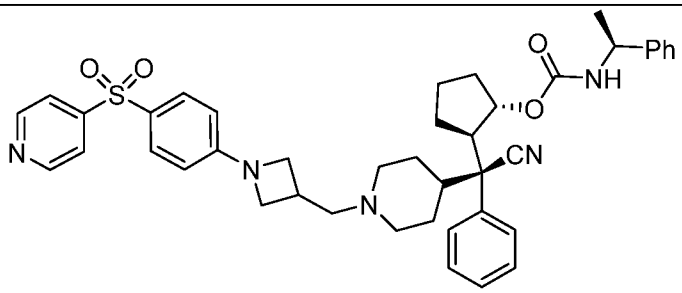
Cpd. No.	Chemical Structure	Chemical Name
183		rac-(1S,2R)-2-(cyano(1-((1-(4-(methylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)(phenyl)methyl)cyclopentyl acetate
184		rac-(1R,2S)-2-(cyano(1-((1-(4-(methylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)(phenyl)methyl)cyclopentyl acetate
185		rac-(1S,2R)-2-(cyano(phenyl)(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)methyl)cyclopentyl acetate
186		rac-(1R,2S)-2-(cyano(phenyl)(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)methyl)cyclopentyl acetate
187		rac-(1S,2R)-2-(cyano(1-((1-(4-(cyclopropylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)(phenyl)methyl)cyclopentyl acetate
188		rac-((1R,2S)-2-(cyano(1-((1-(4-(cyclopropylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)(phenyl)methyl)cyclopentyl acetate

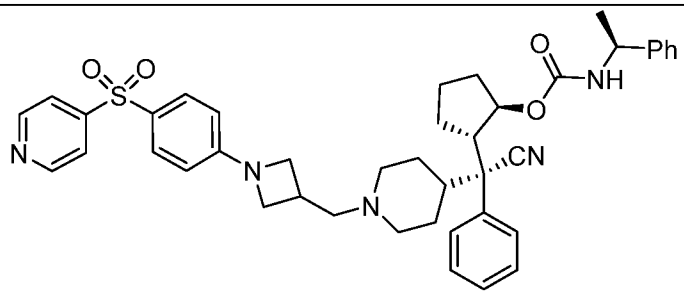
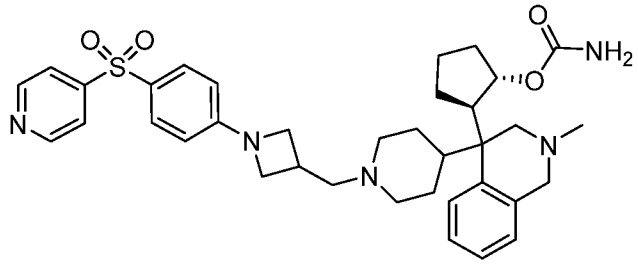
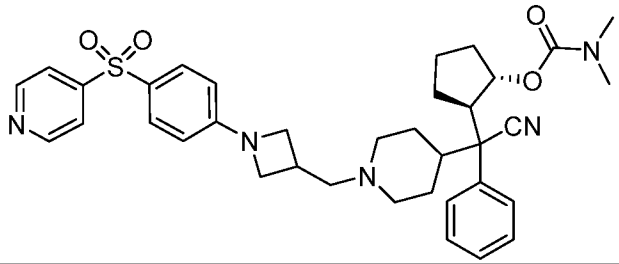
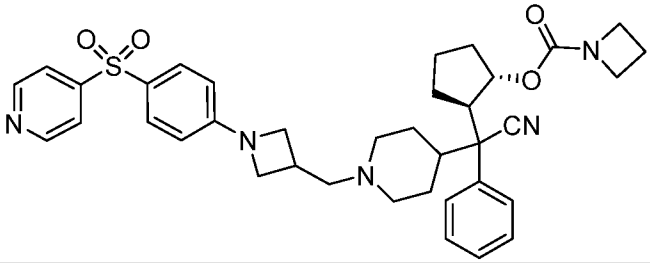
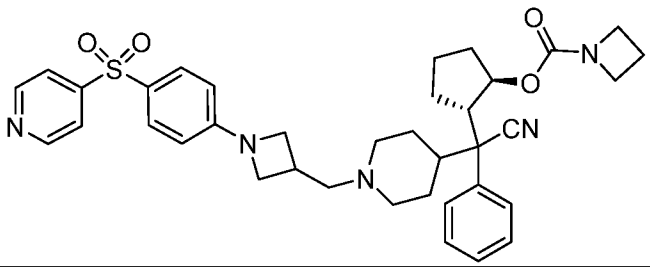
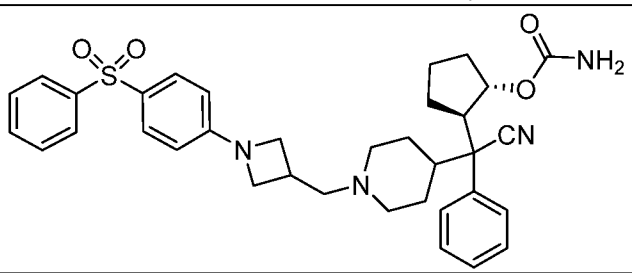
Cpd. No.	Chemical Structure	Chemical Name
189		rac-2-((1S,2R)-2-ethoxycyclopentyl)-2-(1-((1-(4-(methylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-2-phenylacetonitrile
190		2-cyclopentyl-2-phenyl-2-(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)acetonitrile
191		rac- (1S,2R)-2-(cyano(phenyl)(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)methyl)cyclopentyl butyrate
192		rac-(1R,2S)-2-(cyano(phenyl)(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)methyl)cyclopentyl butyrate
193		rac-(1S,2R)-2-(cyano(phenyl)(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)methyl)cyclopentyl isobutyrate
194		rac-(1R,2S)-2-(cyano(phenyl)(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)methyl)cyclopentyl isobutyrate

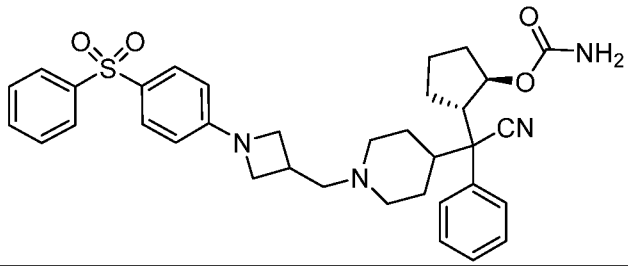
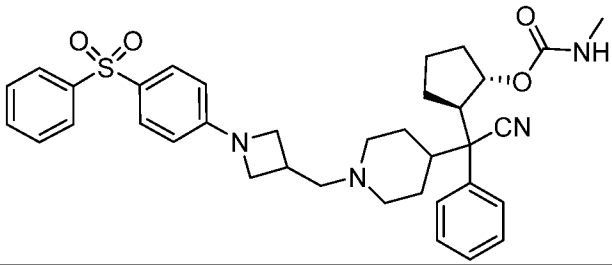
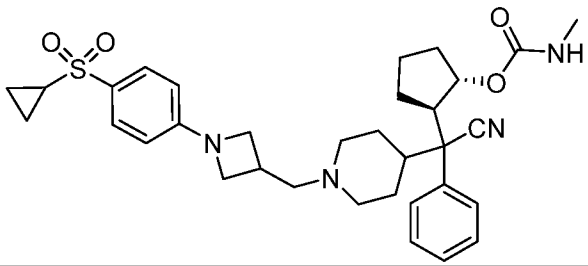
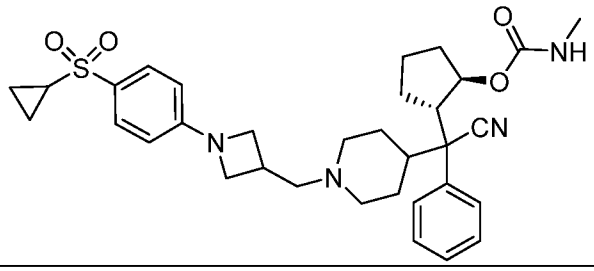
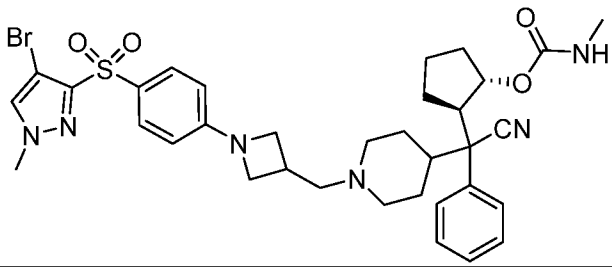
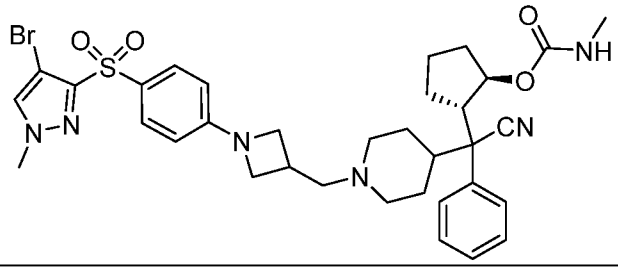
Cpd. No.	Chemical Structure	Chemical Name
195		rac-(1S,2R)-2-(cyano(phenyl)(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)methyl)cyclopentyl propionate
196		rac-(1R,2S)-2-(cyano(phenyl)(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)methyl)cyclopentyl propionate
197		rac-(1S,2R)-2-(cyano(phenyl)(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)methyl)cyclopentyl cyclopropanecarboxylate
198		rac-(1R,2S)-2-(cyano(phenyl)(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)methyl)cyclopentyl cyclopropanecarboxylate
199		rac-2-((1S,2R)-2-ethoxycyclopentyl)-2-phenyl-2-(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)acetonitrile
200		rac-(1R,2S)-2-(cyano(1-((1-(4-((2-methylpyridin-4-yl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)(phenyl)methyl)cyclopentyl acetate

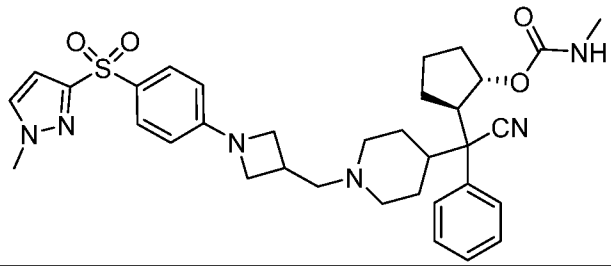
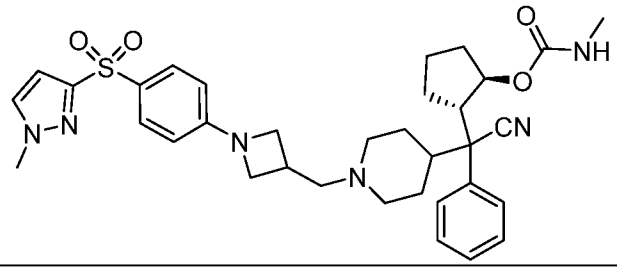
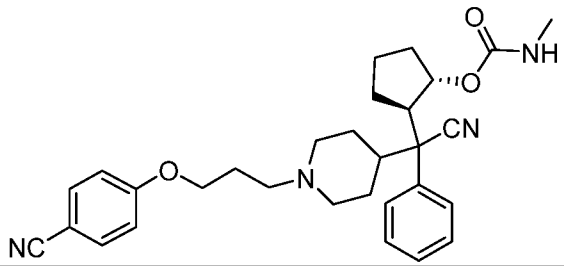
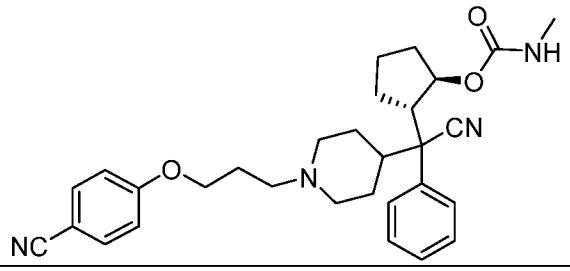
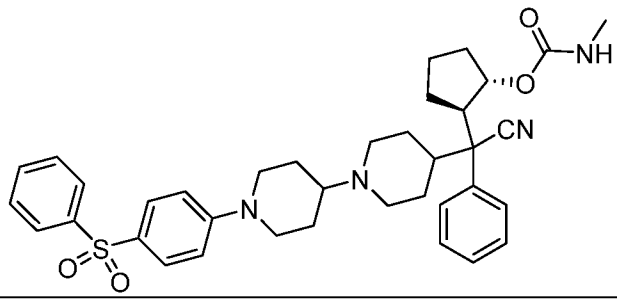
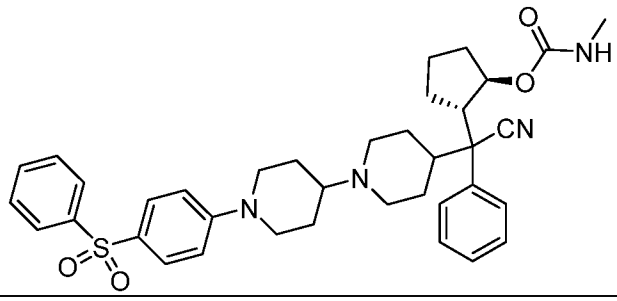
Cpd. No.	Chemical Structure	Chemical Name
201		rac-(1S,2R)-2-(2-methyl-4-(1-((1-(4-((2-methylpyridin-4-yl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1,2,3,4-tetrahydroisoquinolin-4-yl)cyclopentyl acetate
202		rac-(1R,2S)-2-(2-methyl-4-(1-((1-(4-((2-methylpyridin-4-yl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1,2,3,4-tetrahydroisoquinolin-4-yl)cyclopentyl acetate
203		rac-(1S,2R)-2-(4-(1-((1-(4-(cyclopropylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)cyclopentyl acetate
204		rac-(1R,2S)-2-(4-(1-((1-(4-(cyclopropylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)cyclopentyl acetate
205		4-(cyclopent-1-en-1-yl)-2-methyl-4-(1-((1-(4-((2-methylpyridin-4-yl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1,2,3,4-tetrahydroisoquinoline
206		rac-(1S,2R)-2-(2-methyl-4-(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1,2,3,4-tetrahydroisoquinolin-4-yl)cyclopentyl acetate

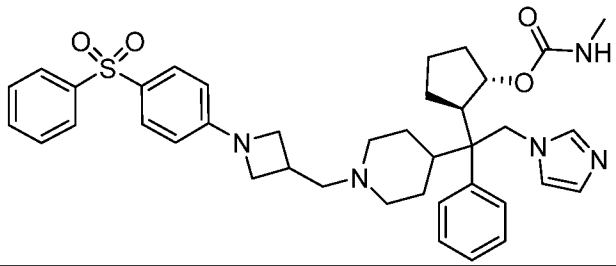
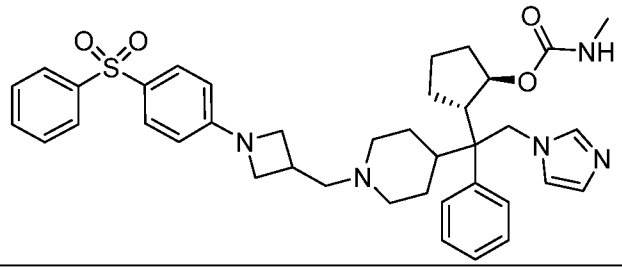
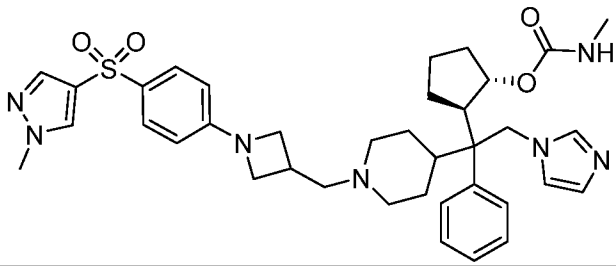
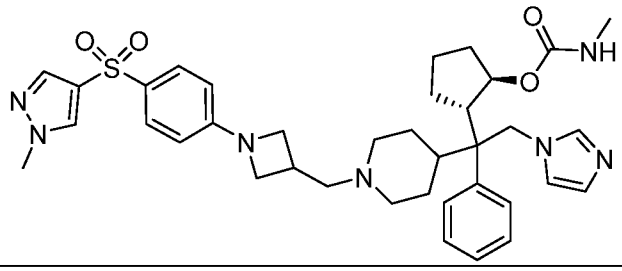
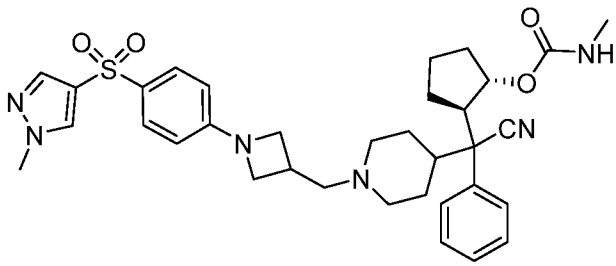
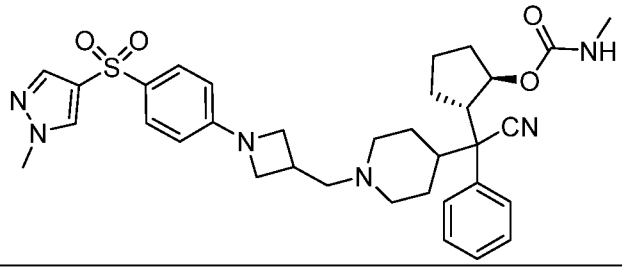
Cpd. No.	Chemical Structure	Chemical Name
207		rac-(1R,2S)-2-(cyano(phenyl)(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)methyl)cyclopentyl acetate
208		rac-(1R,2S)-2-(cyano(phenyl)(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)methyl)cyclopentyl cyclobutanecarboxylate
209		rac-(1S,2R)-2-(cyano(phenyl)(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)methyl)cyclopentyl cyclobutanecarboxylate
210		rac-(1S,2R)-2-(2-methyl-4-(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1,2,3,4-tetrahydroisoquinolin-4-yl)cyclopentyl methylcarbamate
211		rac-(1S,2R)-2-(cyano(phenyl)(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)methyl)cyclopentyl carbamate
212		rac-(1R,2S)-2-(cyano(phenyl)(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)methyl)cyclopentyl carbamate

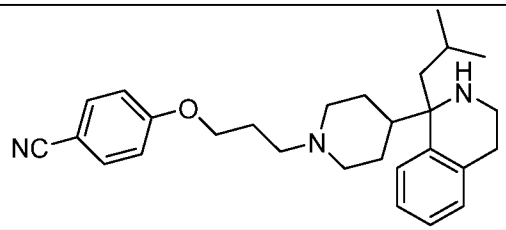
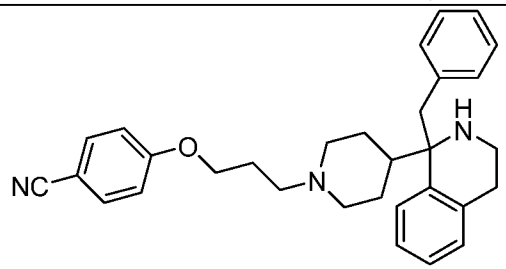
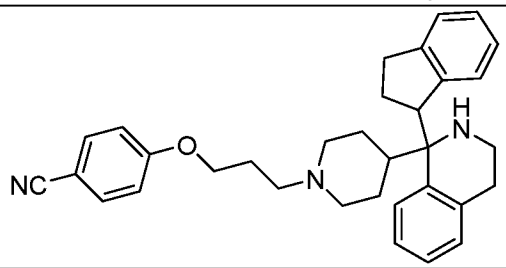
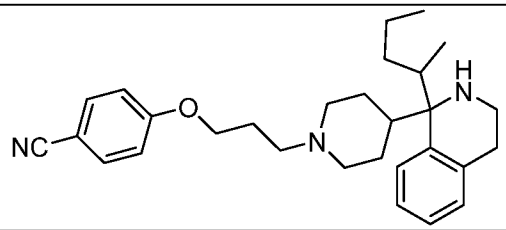
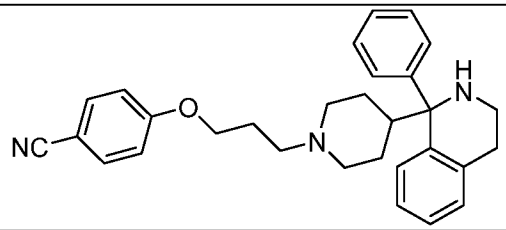
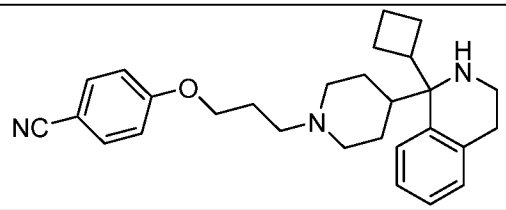
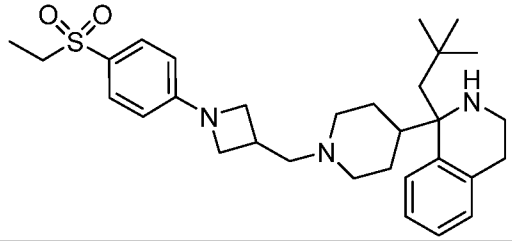
Cpd. No.	Chemical Structure	Chemical Name
213		rac-(1S,2R)-2-(cyano(phenyl)(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)methyl)cyclopentyl ethylcarbamate
214		rac-(1R,2S)-2-(cyano(phenyl)(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)methyl)cyclopentyl ethylcarbamate
215		rac-(1S,2R)-2-(cyano(phenyl)(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)methyl)cyclopentyl methylcarbamate
216		rac-(1R,2S)-2-(cyano(phenyl)(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)methyl)cyclopentyl methylcarbamate
217		(1S,2R)-2-((S)-cyano(phenyl)(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)methyl)cyclopentyl ((S)-1-phenylethyl)carbamate

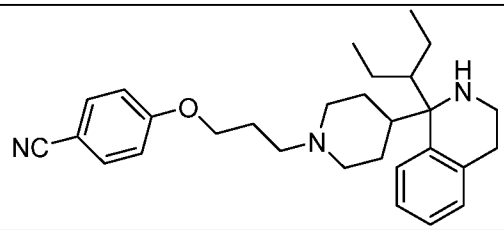
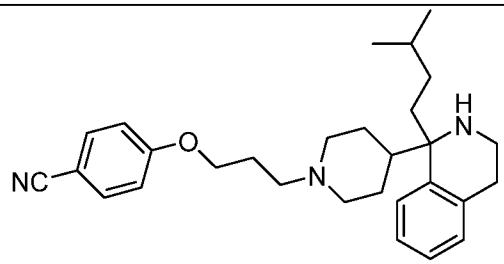
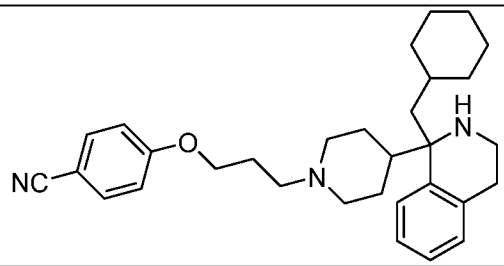
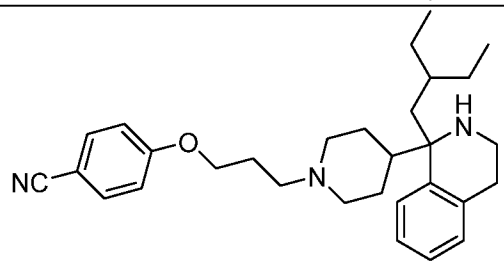
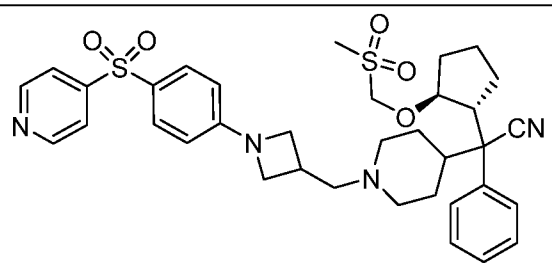
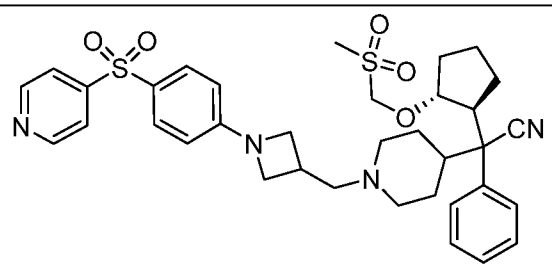
Cpd. No.	Chemical Structure	Chemical Name
218		(1R,2S)-2-((R)-cyano(phenyl)(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)methyl)cyclopentyl ((S)-1-phenylethyl)carbamate
219		rac-(1S,2R)-2-(2-methyl-4-(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1,2,3,4-tetrahydroisoquinolin-4-yl)cyclopentyl carbamate
220		rac-(1S,2R)-2-(cyano(phenyl)(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)methyl)cyclopentyl dimethylcarbamate
221		rac-(1S,2R)-2-(cyano(phenyl)(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)methyl)cyclopentyl azetidine-1-carboxylate
222		rac-(1R,2S)-2-(cyano(phenyl)(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)methyl)cyclopentyl azetidine-1-carboxylate
223		rac-(1S,2R)-2-(cyano(phenyl)(1-((1-(4-(phenylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)methyl)cyclopentyl carbamate

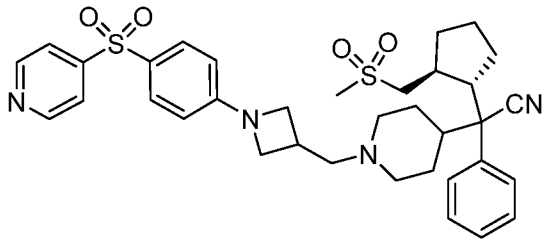
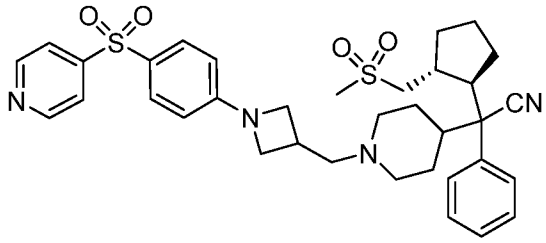
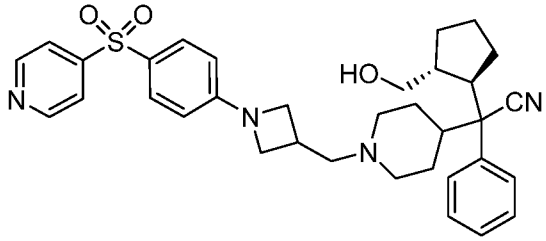
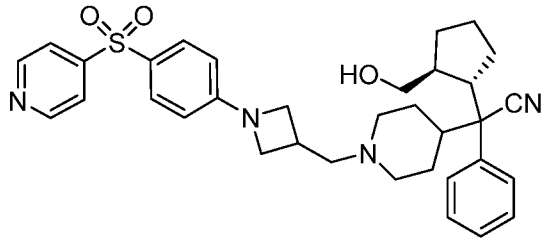
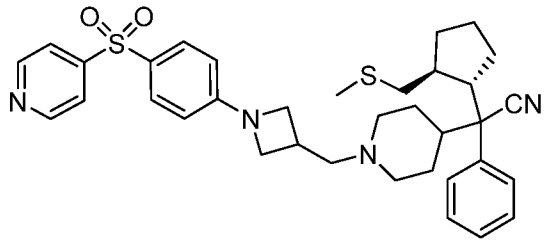
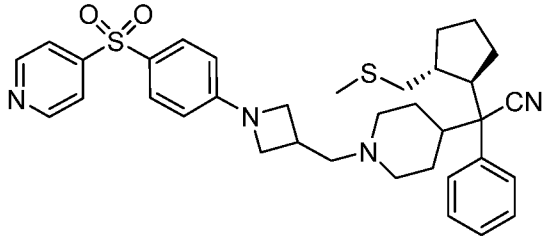
Cpd. No.	Chemical Structure	Chemical Name
224		rac-(1R,2S)-2-(cyano(phenyl)(1-((1-(4-(phenylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)methyl)cyclopentyl carbamate
225		rac-(1S,2R)-2-(cyano(phenyl)(1-((1-(4-(phenylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)methyl)cyclopentyl methylcarbamate
226		rac-(1S,2R)-2-(cyano(1-((1-(4-(cyclopropylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)(phenyl)methyl)cyclopentyl methylcarbamate
227		rac-(1R,2S)-2-(cyano(1-((1-(4-(cyclopropylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)(phenyl)methyl)cyclopentyl methylcarbamate
228		rac-(1S,2R)-2-((1-((1-(4-((4-bromo-1-methyl-1H-pyrazol-3-yl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)(cyano)(phenyl)methyl)cyclopentyl methylcarbamate
229		rac-(1R,2S)-2-((1-((1-(4-((4-bromo-1-methyl-1H-pyrazol-3-yl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)(cyano)(phenyl)methyl)cyclopentyl methylcarbamate

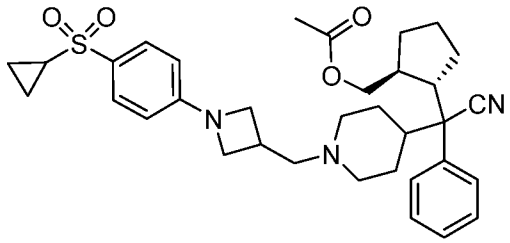
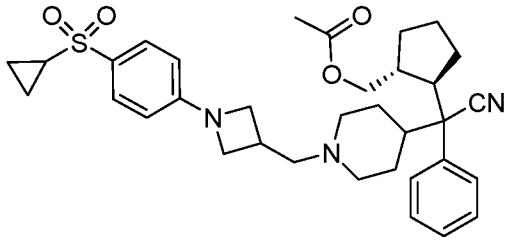
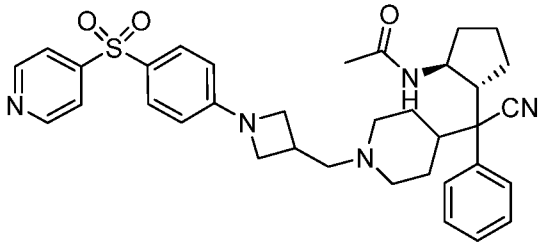
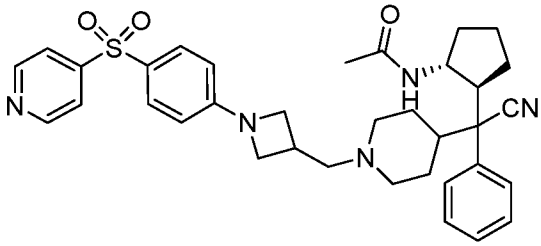
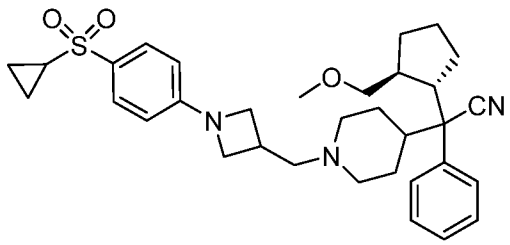
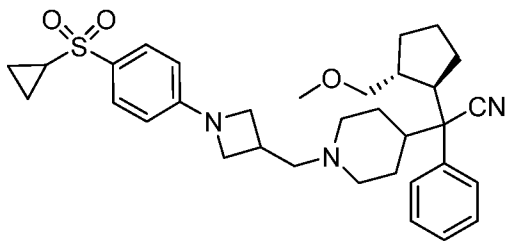
Cpd. No.	Chemical Structure	Chemical Name
230		rac-(1S,2R)-2-(cyano(1-((1-(4-((1-methyl-1H-pyrazol-3-yl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)(phenyl)methyl)cyclopentyl methylcarbamate
231		rac-(1R,2S)-2-((1-((1-(4-((4-bromo-1-methyl-1H-pyrazol-3-yl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)(cyano)(phenyl)methyl)cyclopentyl methylcarbamate
232		rac-(1S,2R)-2-(cyano(1-(3-(4-cyanophenoxy)propyl)piperidin-4-yl)(phenyl)methyl)cyclopentyl methylcarbamate
233		rac-(1R,2S)-2-(cyano(1-(3-(4-cyanophenoxy)propyl)piperidin-4-yl)(phenyl)methyl)cyclopentyl methylcarbamate
234		rac-(1S,2R)-2-(cyano(phenyl)(1'-(4-(phenylsulfonyl)phenyl)-[1,4'-bipiperidin]-4-yl)methyl)cyclopentyl methylcarbamate
235		rac-(1R,2S)-2-(cyano(phenyl)(1'-(4-(phenylsulfonyl)phenyl)-[1,4'-bipiperidin]-4-yl)methyl)cyclopentyl methylcarbamate

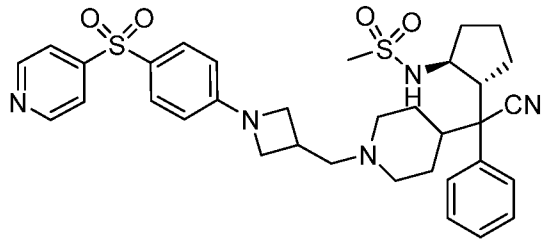
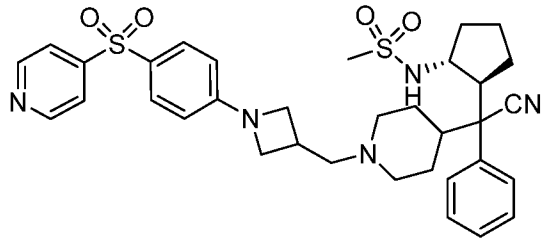
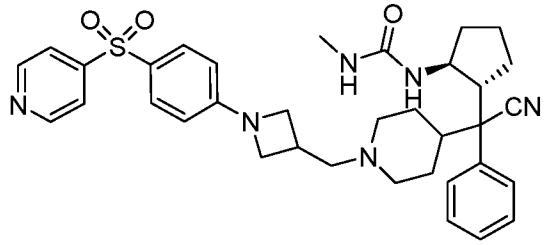
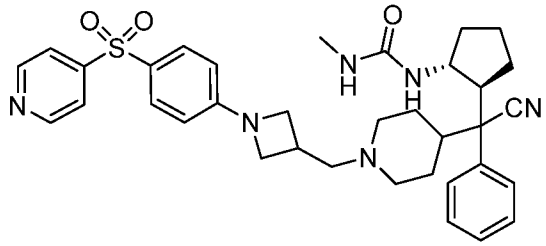
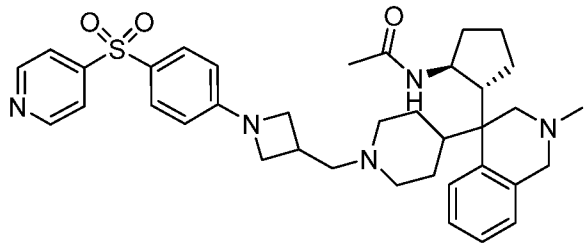
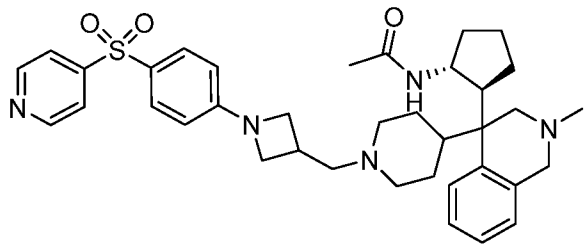
Cpd. No.	Chemical Structure	Chemical Name
236		rac-(1S,2R)-2-(2-(1H-imidazol-1-yl)-1-phenyl-1-(1-((1-(4-(phenylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)ethyl)cyclopentyl methylcarbamate
237		rac-(1R,2S)-2-(2-(1H-imidazol-1-yl)-1-phenyl-1-(1-((1-(4-(phenylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)ethyl)cyclopentyl methylcarbamate
238		rac-(1S,2R)-2-(2-(1H-imidazol-1-yl)-1-(1-((1-(4-((1-methyl-1H-pyrazol-4-yl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1-phenylethyl)cyclopentyl methylcarbamate
239		rac-(1R,2S)-2-(2-(1H-imidazol-1-yl)-1-(1-((1-(4-((1-methyl-1H-pyrazol-4-yl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1-phenylethyl)cyclopentyl methylcarbamate
240		rac-(1S,2R)-2-(cyano(1-((1-(4-((1-methyl-1H-pyrazol-4-yl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)(phenyl)methyl)cyclopentyl methylcarbamate
241		rac-(1R,2S)-2-(cyano(1-((1-(4-((1-methyl-1H-pyrazol-4-yl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)(phenyl)methyl)cyclopentyl methylcarbamate

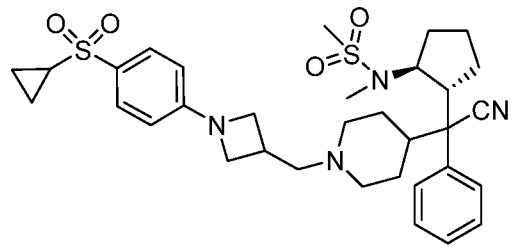
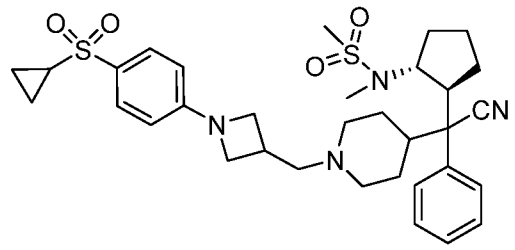
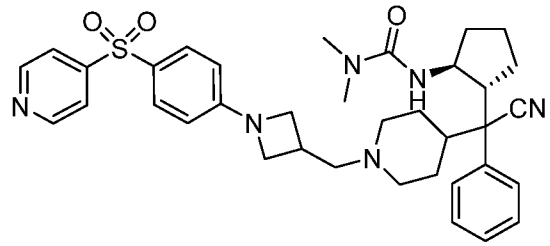
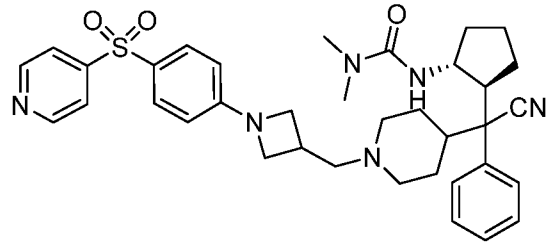
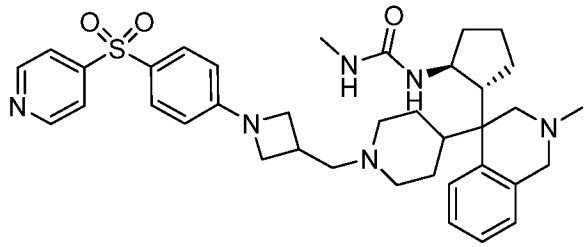
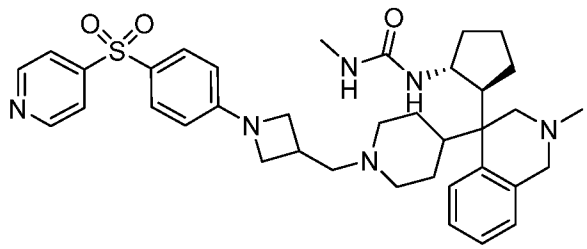
Cpd. No.	Chemical Structure	Chemical Name
242		4-(3-(4-(1-isobutyl-1,2,3,4-tetrahydroisoquinolin-1-yl)piperidin-1-yl)propoxy)benzonitrile
243		4-(3-(4-(1-benzyl-1,2,3,4-tetrahydroisoquinolin-1-yl)piperidin-1-yl)propoxy)benzonitrile
244		4-(3-(4-(1-(2,3-dihydro-1H-inden-1-yl)-1,2,3,4-tetrahydroisoquinolin-1-yl)piperidin-1-yl)propoxy)benzonitrile
245		4-(3-(4-(1-(pentan-2-yl)-1,2,3,4-tetrahydroisoquinolin-1-yl)piperidin-1-yl)propoxy)benzonitrile
246		4-(3-(4-(1-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)piperidin-1-yl)propoxy)benzonitrile
247		4-(3-(4-(1-cyclobutyl-1,2,3,4-tetrahydroisoquinolin-1-yl)piperidin-1-yl)propoxy)benzonitrile
248		1-(1-((1-(4-(ethylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1-neopentyl-1,2,3,4-tetrahydroisoquinoline

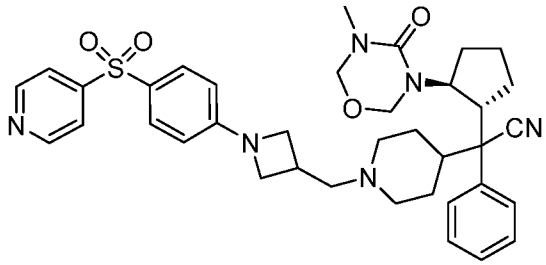
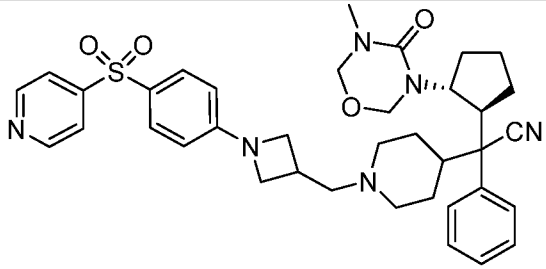
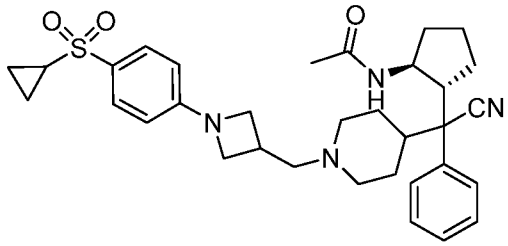
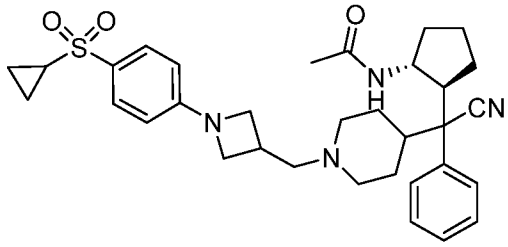
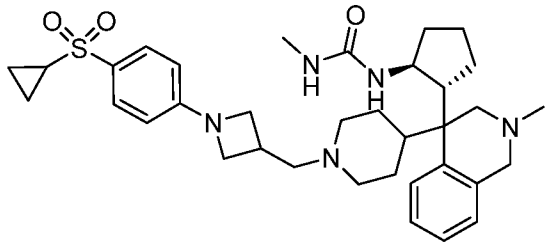
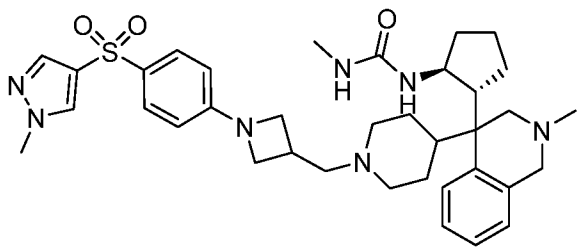
Cpd. No.	Chemical Structure	Chemical Name
249		4-(3-(4-(1-(pentan-3-yl)-1,2,3,4-tetrahydroisoquinolin-1-yl)piperidin-1-yl)propoxy)benzonitrile
250		4-(3-(4-(1-isopentyl-1,2,3,4-tetrahydroisoquinolin-1-yl)piperidin-1-yl)propoxy)benzonitrile
251		4-(3-(4-(1-(cyclohexylmethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)piperidin-1-yl)propoxy)benzonitrile
252		4-(3-(4-(1-(2-ethylbutyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)piperidin-1-yl)propoxy)benzonitrile
253		rac-2-((1R,2S)-2-((methylsulfonyl)methoxy)cyclopentyl)-2-phenyl-2-(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)acetonitrile
254		rac-2-((1S,2R)-2-((methylsulfonyl)methoxy)cyclopentyl)-2-phenyl-2-(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)acetonitrile

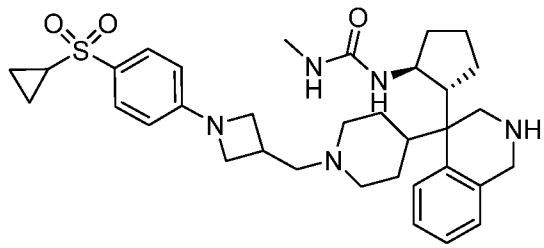
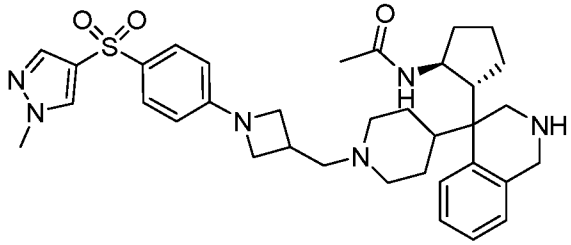
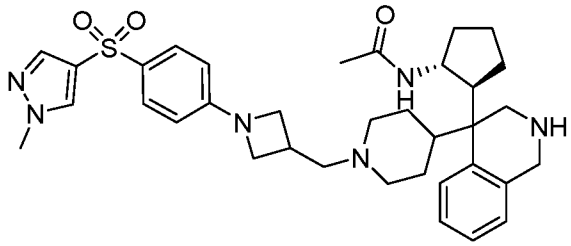
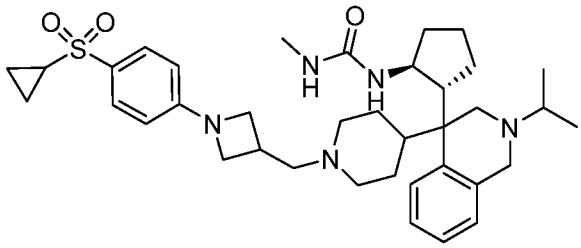
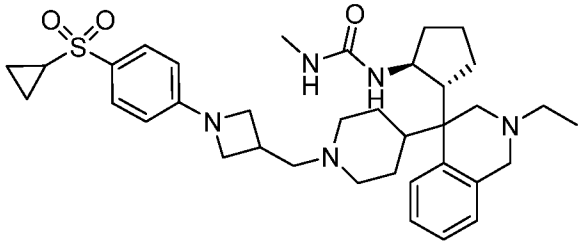
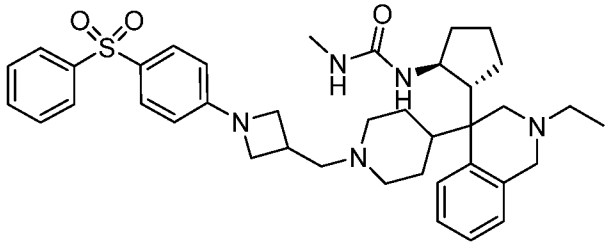
Cpd. No.	Chemical Structure	Chemical Name
255		rac-2-((1S,2S)-2-((methylsulfonyl)methyl)cyclopentyl)-2-phenyl-2-(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)acetonitrile
256		rac-2-((1R,2R)-2-((methylsulfonyl)methyl)cyclopentyl)-2-phenyl-2-(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)acetonitrile
257		rac-2-((1R,2R)-2-(hydroxymethyl)cyclopentyl)-2-phenyl-2-(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)acetonitrile
258		rac-2-((1S,2S)-2-(hydroxymethyl)cyclopentyl)-2-phenyl-2-(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)acetonitrile
259		rac-2-((1S,2S)-2-((methylthio)methyl)cyclopentyl)-2-phenyl-2-(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)acetonitrile
260		rac-2-((1R,2R)-2-((methylthio)methyl)cyclopentyl)-2-phenyl-2-(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)acetonitrile

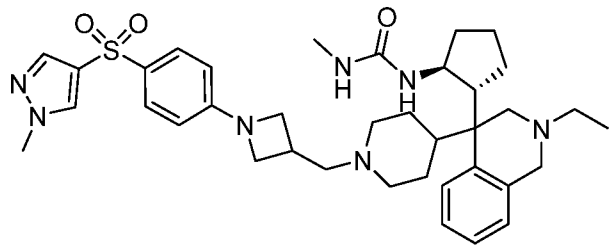
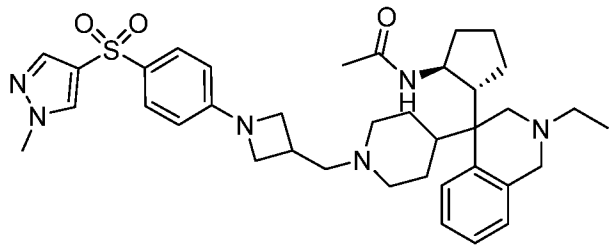
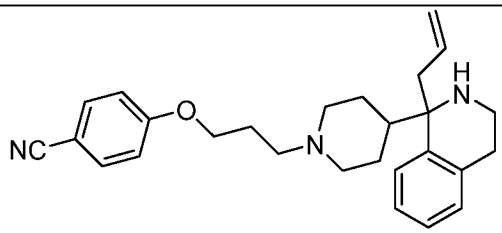
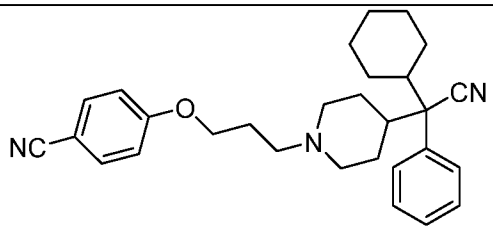
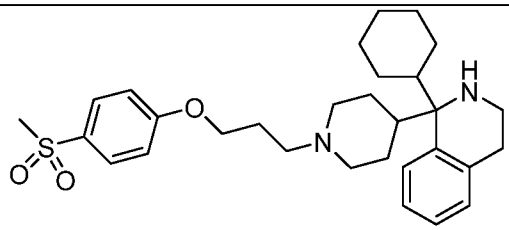
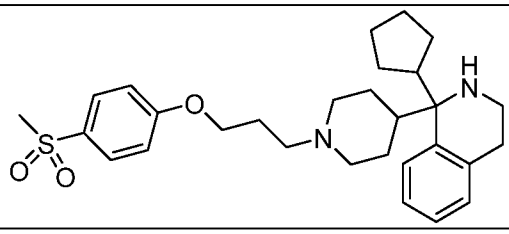
Cpd. No.	Chemical Structure	Chemical Name
261		rac-((1S,2S)-2-(cyano(1-((1-(4-(cyclopropylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)(phenyl)methyl)cyclopentyl)methyl acetate
262		rac-((1R,2R)-2-(cyano(1-((1-(4-(cyclopropylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)(phenyl)methyl)cyclopentyl)methyl acetate
263		rac-N-((1S,2R)-2-(cyano(phenyl)(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)methyl)cyclopentyl)acetamide
264		rac-N-((1R,2S)-2-(cyano(phenyl)(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)methyl)cyclopentyl)acetamide
265		rac-2-(1-((1-(4-(cyclopropylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-2-((1S,2S)-2-(methoxymethyl)cyclopentyl)-2-phenylacetonitrile
266		rac-2-(1-((1-(4-(cyclopropylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-2-((1R,2R)-2-(methoxymethyl)cyclopentyl)-2-phenylacetonitrile

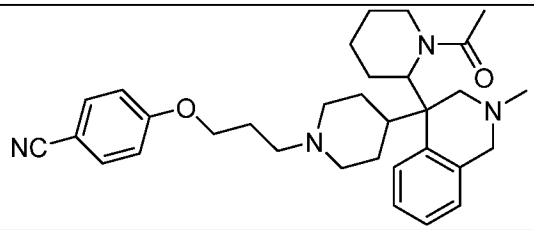
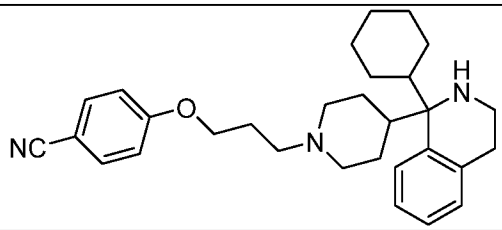
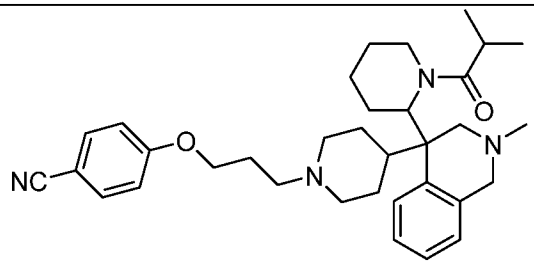
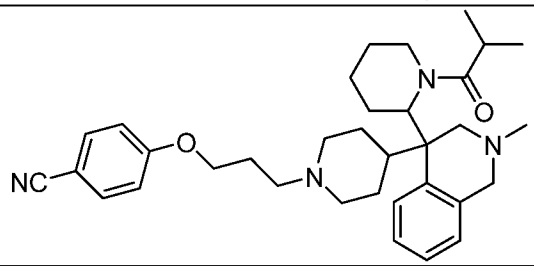
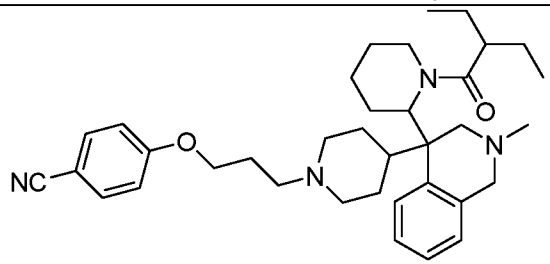
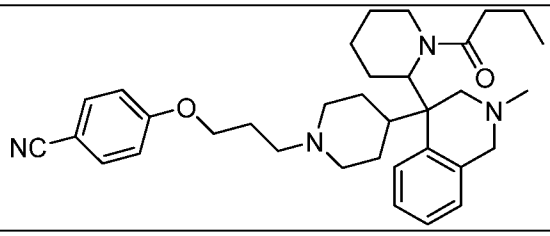
Cpd. No.	Chemical Structure	Chemical Name
267		rac-N-((1S,2R)-2-(cyano(phenyl)(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)methyl)cyclopentyl)methanesulfonamide
268		rac-N-((1R,2S)-2-(cyano(phenyl)(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)methyl)cyclopentyl)methanesulfonamide
269		rac-1-((1S,2R)-2-(cyano(phenyl)(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)methyl)cyclopentyl)-3-methylurea
270		rac-1-((1R,2S)-2-(cyano(phenyl)(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)methyl)cyclopentyl)-3-methylurea
271		rac-N-((1S,2R)-2-(2-methyl-4-(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1,2,3,4-tetrahydroisoquinolin-4-yl)cyclopentyl)acetamide
272		rac-N-((1R,2S)-2-(2-methyl-4-(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1,2,3,4-tetrahydroisoquinolin-4-yl)cyclopentyl)acetamide

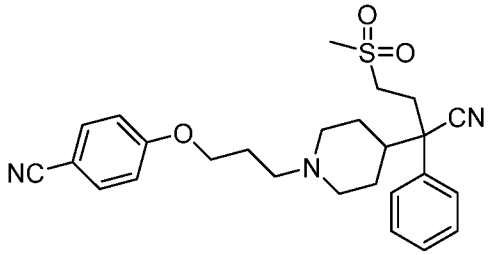
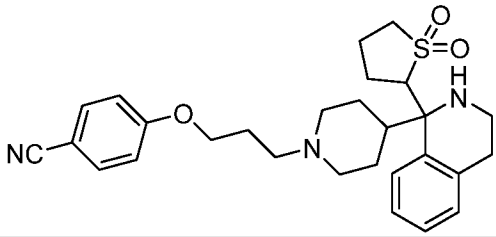
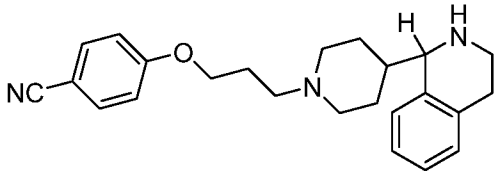
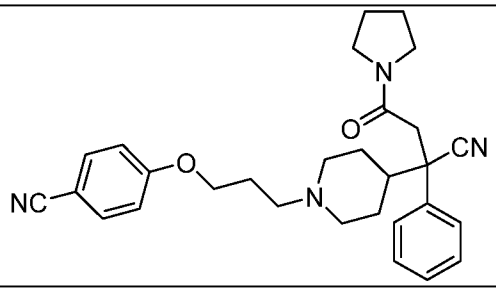
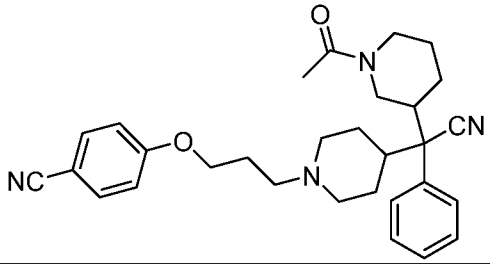
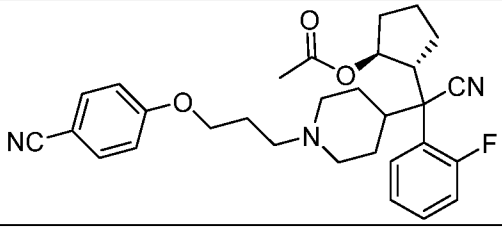
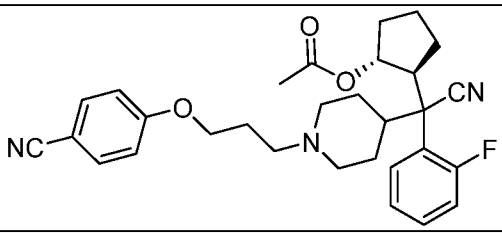
Cpd. No.	Chemical Structure	Chemical Name
273		rac-N-((1S,2R)-2-(cyano(1-((1-(4-(cyclopropylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)(phenyl)methyl)cyclopentyl)-N-methylmethanesulfonamide
274		rac-N-((1R,2S)-2-(cyano(1-((1-(4-(cyclopropylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)(phenyl)methyl)cyclopentyl)-N-methylmethanesulfonamide
275		rac-3-((1S,2R)-2-(cyano(phenyl)(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)methyl)cyclopentyl)-1,1-dimethylurea
276		rac-3-((1R,2S)-2-(cyano(phenyl)(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)methyl)cyclopentyl)-1,1-dimethylurea
277		rac-1-methyl-3-((1S,2R)-2-(2-methyl-4-(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1,2,3,4-tetrahydroisoquinolin-4-yl)cyclopentyl)urea
278		rac-1-methyl-3-((1R,2S)-2-(2-methyl-4-(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1,2,3,4-tetrahydroisoquinolin-4-yl)cyclopentyl)urea

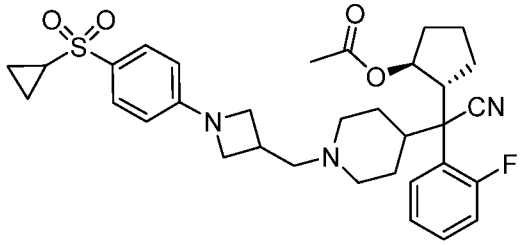
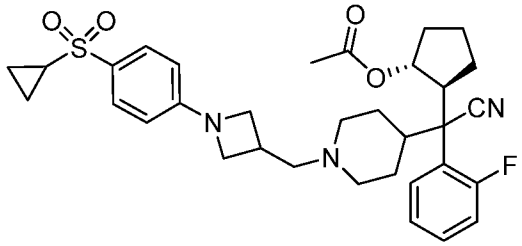
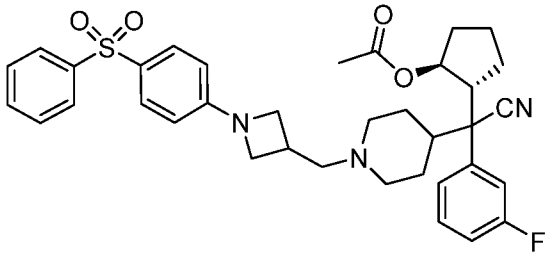
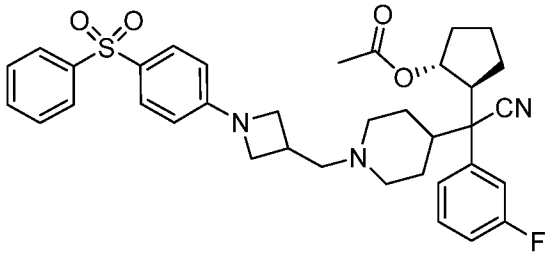
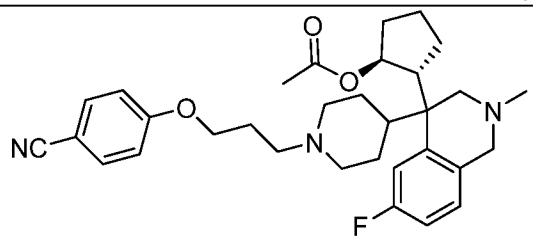
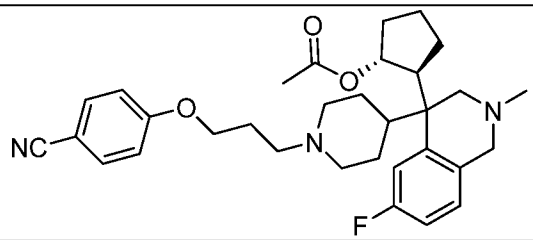
Cpd. No.	Chemical Structure	Chemical Name
279		rac-2-((1R,2S)-2-(5-methyl-4-oxo-1,3,5-oxadiazinan-3-yl)cyclopentyl)-2-phenyl-2-(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)acetonitrile
280		rac-2-((1S,2R)-2-(5-methyl-4-oxo-1,3,5-oxadiazinan-3-yl)cyclopentyl)-2-phenyl-2-(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)acetonitrile
281		rac-N-((1S,2R)-2-(cyano(1-((1-(4-(cyclopropylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)(phenyl)methyl)cyclopentyl)acetamide
282		rac-N-((1R,2S)-2-(cyano(1-((1-(4-(cyclopropylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)(phenyl)methyl)cyclopentyl)acetamide
283		rac-1-((1S,2R)-2-(4-(1-((1-(4-(cyclopropylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)cyclopentyl)-3-methylurea
284		rac-1-methyl-3-((1S,2R)-2-(2-methyl-4-(1-((1-(4-((1-methyl-1H-pyrazol-4-yl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1,2,3,4-tetrahydroisoquinolin-4-yl)cyclopentyl)urea

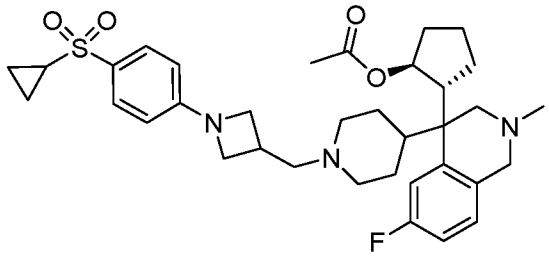
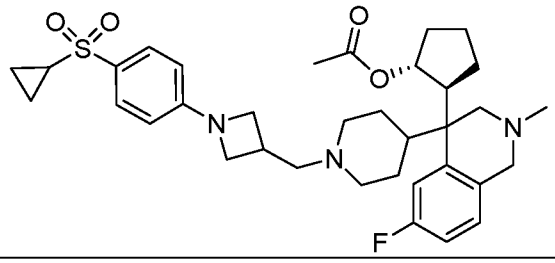
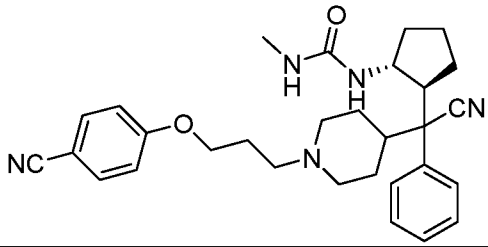
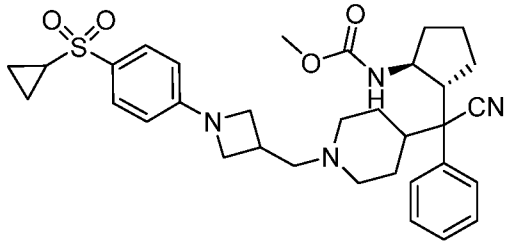
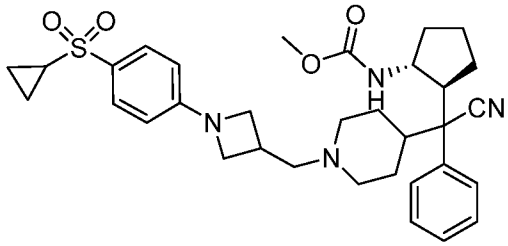
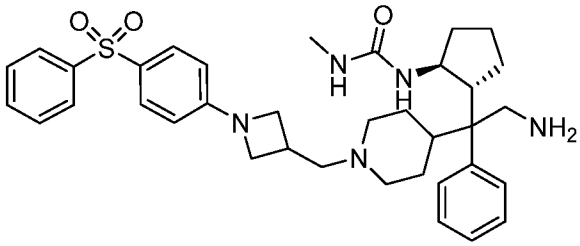
Cpd. No.	Chemical Structure	Chemical Name
285		rac-1-((1S,2R)-2-(4-(1-((1-(4-(cyclopropylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1,2,3,4-tetrahydroisoquinolin-4-yl)cyclopentyl)-3-methylurea
286		rac-N-((1S,2R)-2-(4-(1-((1-(4-((1-methyl-1H-pyrazol-4-yl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1,2,3,4-tetrahydroisoquinolin-4-yl)cyclopentyl)acetamide
287		rac-N-((1R,2S)-2-(4-(1-((1-(4-((1-methyl-1H-pyrazol-4-yl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1,2,3,4-tetrahydroisoquinolin-4-yl)cyclopentyl)acetamide
288		rac-1-((1S,2R)-2-(4-(1-((1-(4-(cyclopropylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-2-isopropyl-1,2,3,4-tetrahydroisoquinolin-4-yl)cyclopentyl)-3-methylurea
289		rac-1-((1S,2R)-2-(4-(1-((1-(4-(cyclopropylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-2-ethyl-1,2,3,4-tetrahydroisoquinolin-4-yl)cyclopentyl)-3-methylurea
290		rac-1-((1S,2R)-2-(2-ethyl-4-(1-((1-(4-(phenylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1,2,3,4-tetrahydroisoquinolin-4-yl)cyclopentyl)-3-methylurea

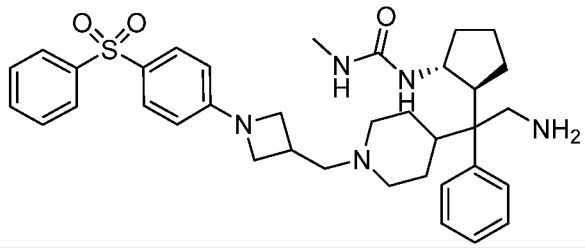
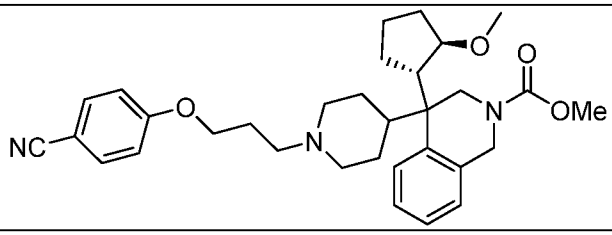
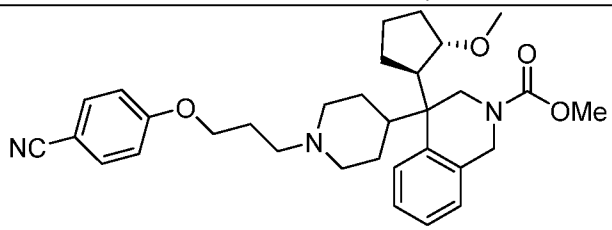
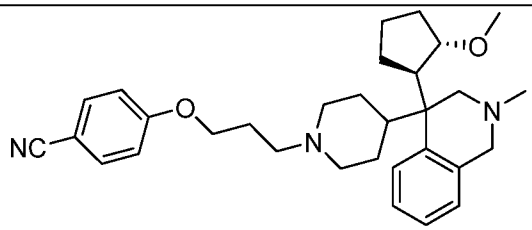
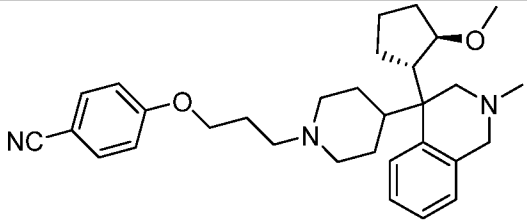
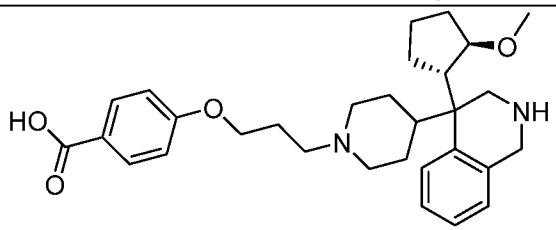
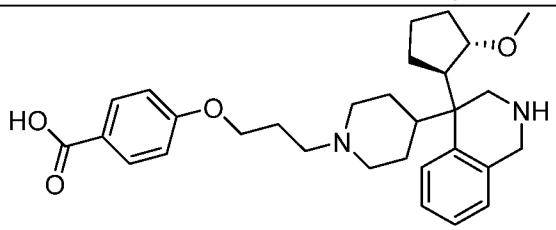
Cpd. No.	Chemical Structure	Chemical Name
291		rac-1-((1S,2R)-2-(2-ethyl-4-(1-((1-(4-((1-methyl-1H-pyrazol-4-yl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1,2,3,4-tetrahydroisoquinolin-4-yl)cyclopentyl)-3-methylurea
292		rac-N-((1S,2R)-2-(2-ethyl-4-(1-((1-(4-((1-methyl-1H-pyrazol-4-yl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1,2,3,4-tetrahydroisoquinolin-4-yl)cyclopentyl)acetamide
293		4-(3-(4-(1-allyl-1,2,3,4-tetrahydroisoquinolin-1-yl)piperidin-1-yl)propoxy)benzonitrile
294		4-(3-(4-(cyano(cyclohexyl)(phenyl)methyl)piperidin-1-yl)propoxy)benzonitrile
295		1-cyclohexyl-1-(1-(3-(4-(methylsulfonyl)phenoxy)propyl)piperidin-4-yl)-1,2,3,4-tetrahydroisoquinoline
296		1-cyclopentyl-1-(1-(3-(4-(methylsulfonyl)phenoxy)propyl)piperidin-4-yl)-1,2,3,4-tetrahydroisoquinoline

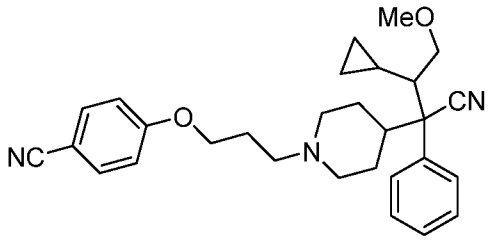
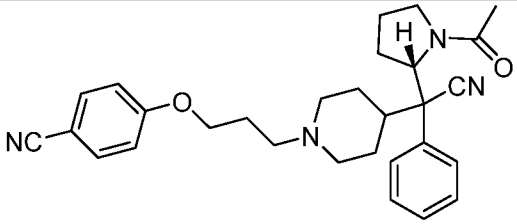
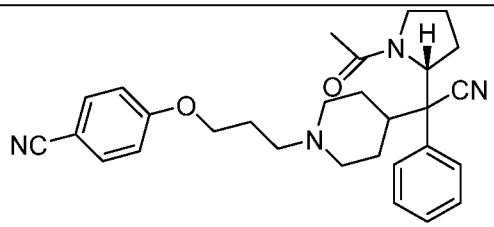
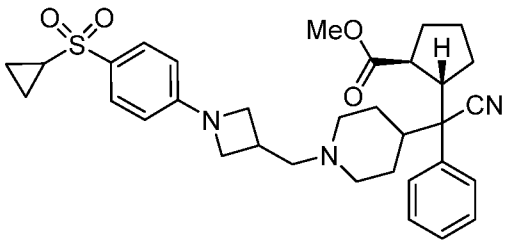
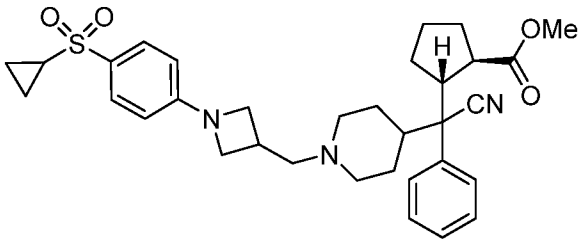
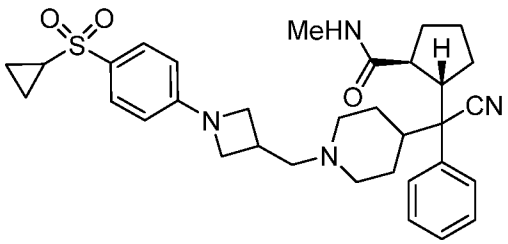
Cpd. No.	Chemical Structure	Chemical Name
297		4-(3-(4-(4-(1-acetylpiperidin-2-yl)-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)piperidin-1-yl)propoxy)benzonitrile
298		4-(3-(4-(1-cyclohexyl-1,2,3,4-tetrahydroisoquinolin-1-yl)piperidin-1-yl)propoxy)benzonitrile
299		4-(3-(4-(4-(1-isobutyrylpiperidin-2-yl)-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)piperidin-1-yl)propoxy)benzonitrile
300		4-(3-(4-(4-(1-isobutyrylpiperidin-2-yl)-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)piperidin-1-yl)propoxy)benzonitrile
301		4-(3-(4-(4-(1-(2-ethylbutanoyl)piperidin-2-yl)-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)piperidin-1-yl)propoxy)benzonitrile
302		4-(3-(4-(4-(1-butyrylpiperidin-2-yl)-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)piperidin-1-yl)propoxy)benzonitrile

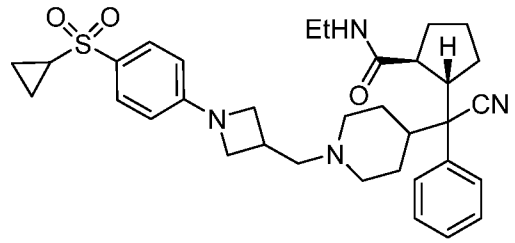
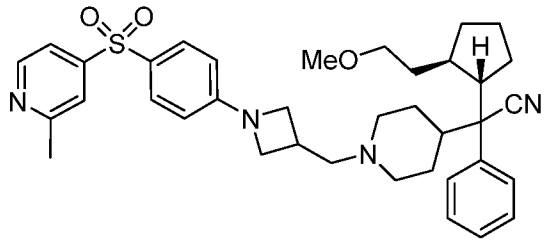
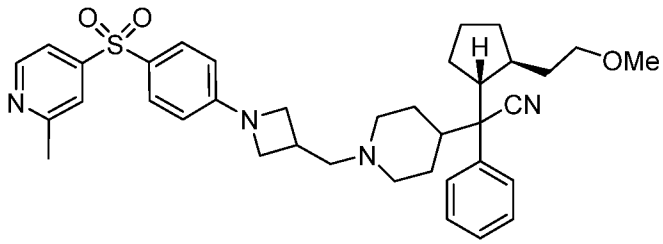
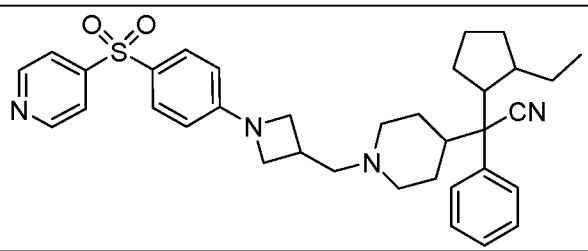
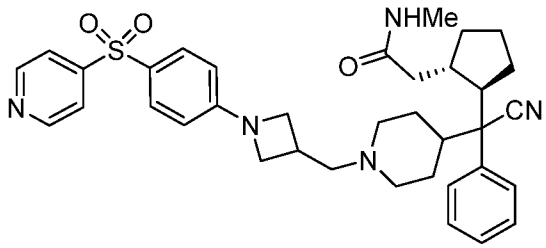
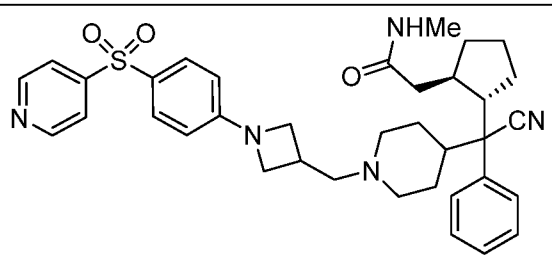
Cpd. No.	Chemical Structure	Chemical Name
303		4-(3-(4-(1-cyano-3-(methylsulfonyl)-1-phenylpropyl)piperidin-1-yl)propoxy)benzonitrile
304		4-(3-(4-(1-(1,1-dioxidotetrahydrothiophen-2-yl)-1,2,3,4-tetrahydroisoquinolin-1-yl)piperidin-1-yl)propoxy)benzonitrile
305		4-(3-(4-(1,2,3,4-tetrahydroisoquinolin-1-yl)piperidin-1-yl)propoxy)benzonitrile
306		4-(3-(4-(1-cyano-3-oxo-1-phenyl-3-(pyrrolidin-1-yl)propyl)piperidin-1-yl)propoxy)benzonitrile
307		4-(3-(4-((1-acetylpiperidin-3-yl)(cyano)(phenyl)methyl)piperidin-1-yl)propoxy)benzonitrile
308		rac-(1S,2R)-2-(cyano(1-(3-(4-cyanophenoxy)propyl)piperidin-4-yl)(2-fluorophenyl)methyl)cyclopentyl acetate
309		rac-(1R,2S)-2-(cyano(1-(3-(4-cyanophenoxy)propyl)piperidin-4-yl)(2-fluorophenyl)methyl)cyclopentyl acetate

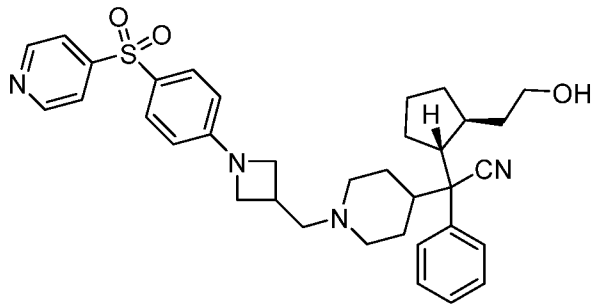
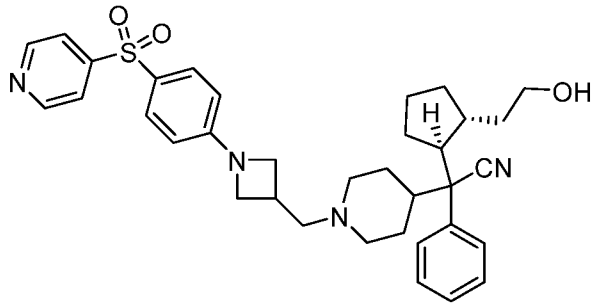
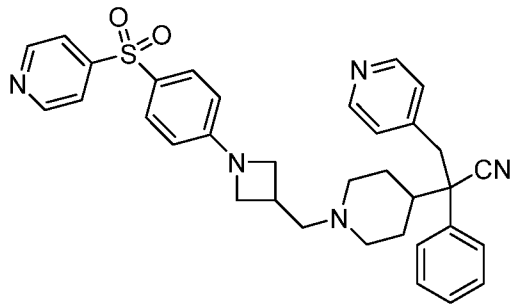
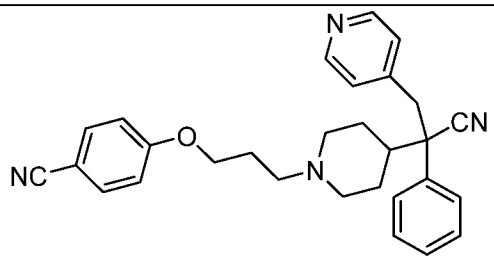
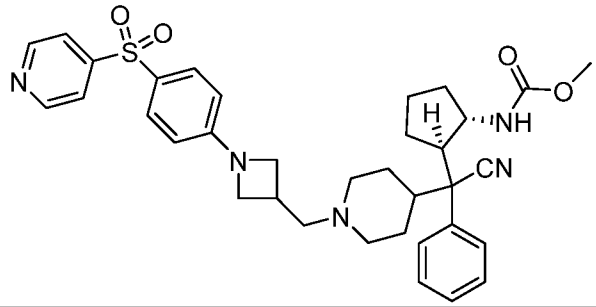
Cpd. No.	Chemical Structure	Chemical Name
310		rac-(1S,2R)-2-(cyano(1-((1-(4-(cyclopropylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)(2-fluorophenyl)methyl)cyclopentyl acetate
311		rac-(1R,2S)-2-(cyano(1-((1-(4-(cyclopropylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)(2-fluorophenyl)methyl)cyclopentyl acetate
312		rac-(1S,2R)-2-(cyano(3-fluorophenyl)(1-((1-(4-(phenylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)methyl)cyclopentyl acetate
313		rac-(1R,2S)-2-(cyano(3-fluorophenyl)(1-((1-(4-(phenylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)methyl)cyclopentyl acetate
314		rac-(1S,2R)-2-(4-(1-(3-(4-cyanophenoxy)propyl)piperidin-4-yl)-6-fluoro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)cyclopentyl acetate
315		rac-(1R,2S)-2-(4-(1-(3-(4-cyanophenoxy)propyl)piperidin-4-yl)-6-fluoro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)cyclopentyl acetate

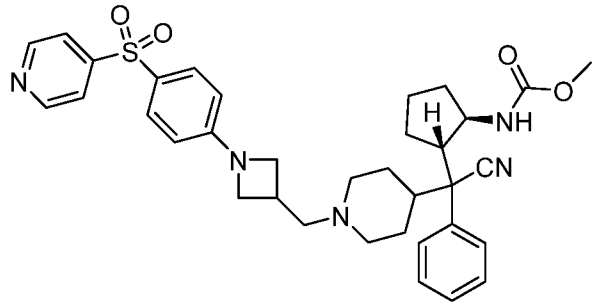
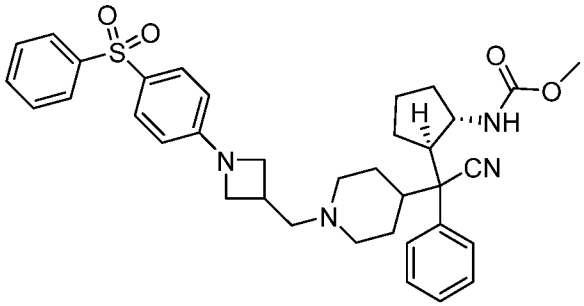
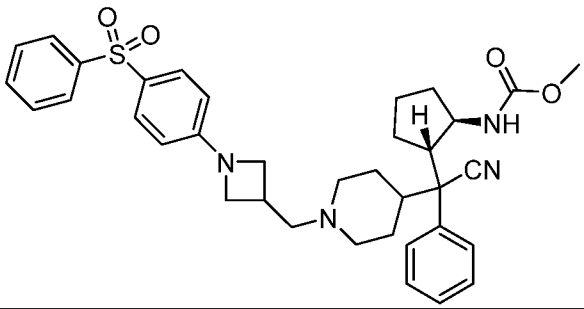
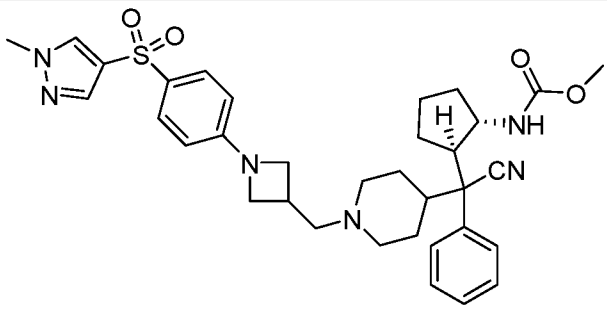
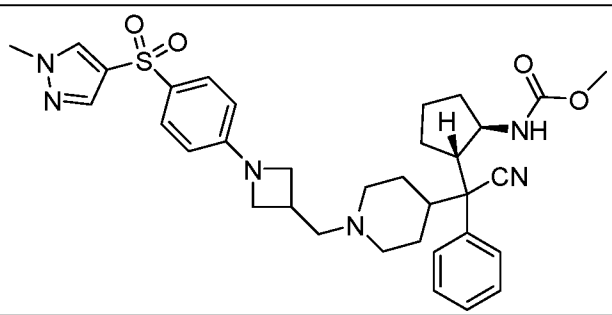
Cpd. No.	Chemical Structure	Chemical Name
316		rac-(1S,2R)-2-(4-(1-((1-(4-(cyclopropylsulfonyl)phenyl) azetidin-3-yl)methyl)piperidin-4-yl)-6-fluoro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)cyclopentyl acetate
317		rac-(1R,2S)-2-(4-(1-((1-(4-(cyclopropylsulfonyl)phenyl) azetidin-3-yl)methyl)piperidin-4-yl)-6-fluoro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)cyclopentyl acetate
318		rac-1-((1R,2S)-2-(cyano(1-(3-(4-cyanophenoxy)propyl)piperidin-4-yl)(phenyl)methyl)cyclopentyl)-3-methylurea
319		rac-methyl ((1S,2R)-2-(cyano(1-((1-(4-(cyclopropylsulfonyl)phenyl) azetidin-3-yl)methyl)piperidin-4-yl)(phenyl)methyl)cyclopentyl)carbamate
320		rac-methyl ((1R,2S)-2-(cyano(1-((1-(4-(cyclopropylsulfonyl)phenyl) azetidin-3-yl)methyl)piperidin-4-yl)(phenyl)methyl)cyclopentyl)carbamate
321		rac-1-((1S,2R)-2-(2-amino-1-phenyl-1-(1-((1-(4-(phenylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)ethyl)cyclopentyl)-3-methylurea

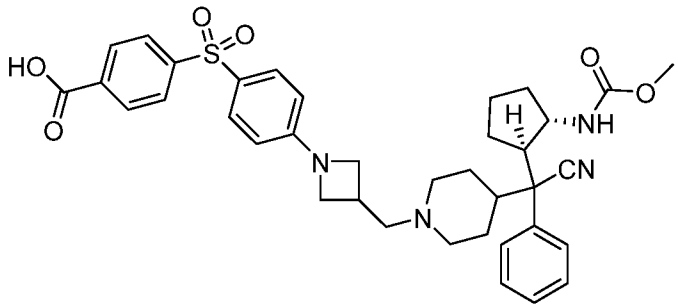
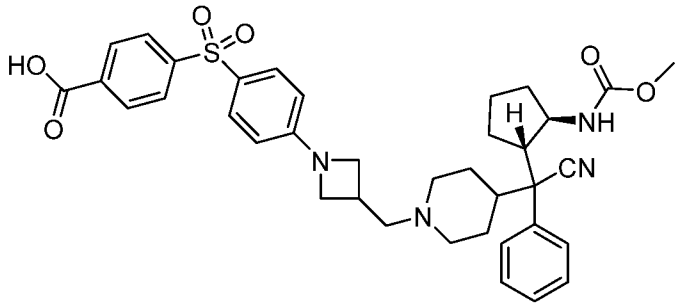
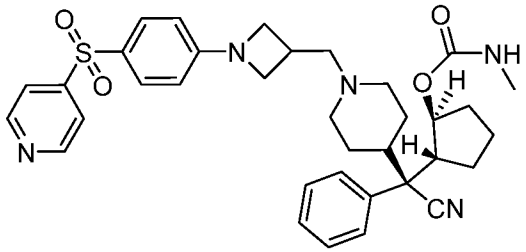
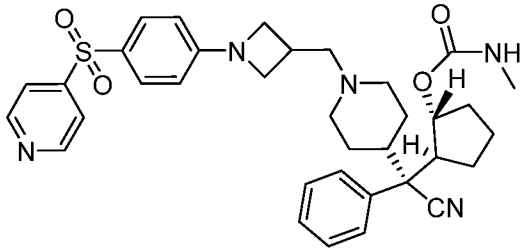
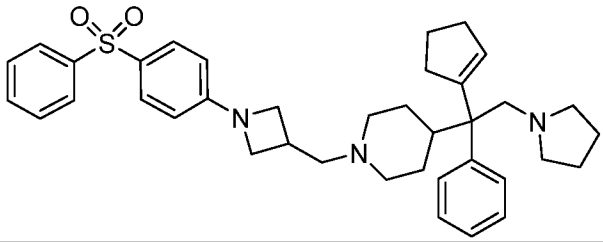
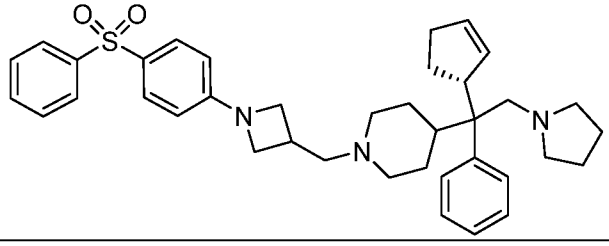
Cpd. No.	Chemical Structure	Chemical Name
322		rac-1-((1R,2S)-2-(2-amino-1-phenyl-1-(1-((1-(4-(phenylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)ethyl)cyclopentyl)-3-methylurea
323		methyl rac-4-(1-(3-(4-cyanophenoxy)propyl)piperidin-4-yl)-4-((1S,2R)-2-methoxycyclopentyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate
324		methyl rac-4-(1-(3-(4-cyanophenoxy)propyl)piperidin-4-yl)-4-((1R,2S)-2-methoxycyclopentyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate
325		rac-4-(3-(4-(4-((1R,2S)-2-methoxycyclopentyl)-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)piperidin-1-yl)propoxy)benzonitrile
326		rac-4-(3-(4-(4-((1S,2R)-2-methoxycyclopentyl)-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)piperidin-1-yl)propoxy)benzonitrile
327		rac-4-(3-(4-(4-((1S,2R)-2-methoxycyclopentyl)-1,2,3,4-tetrahydroisoquinolin-4-yl)piperidin-1-yl)propoxy)benzoic acid
328		rac-4-(3-(4-(4-((1R,2S)-2-methoxycyclopentyl)-1,2,3,4-tetrahydroisoquinolin-4-yl)piperidin-1-yl)propoxy)benzoic acid

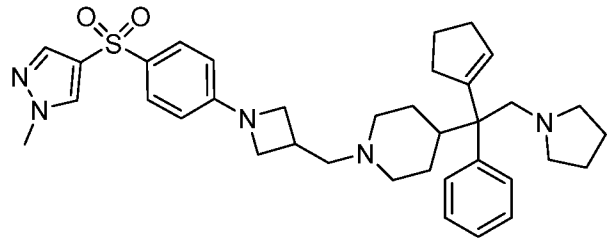
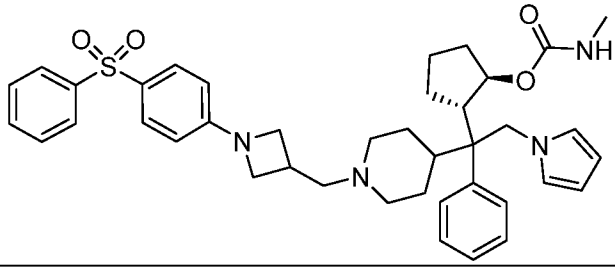
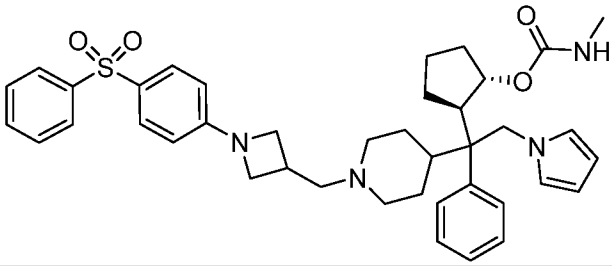
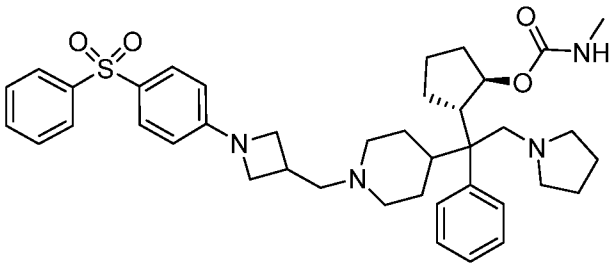
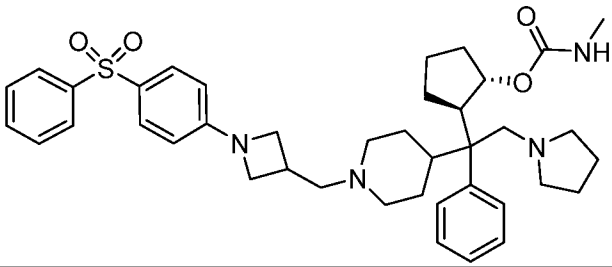
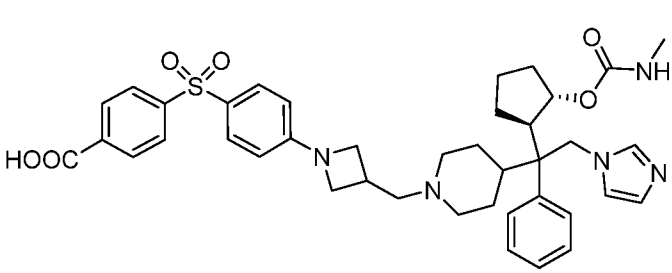
Cpd. No.	Chemical Structure	Chemical Name
329		4-(3-(4-(1-cyano-2-cyclopropyl-3-methoxy-1-phenylpropyl)piperidin-1-yl)propoxy)benzonitrile
330		4-(3-(4-(((S)-1-acetylpyrrolidin-2-yl)(cyano)(phenyl)methyl)piperidin-1-yl)propoxy)benzonitrile
331		4-(3-(4-(((R)-1-acetylpyrrolidin-2-yl)(cyano)(phenyl)methyl)piperidin-1-yl)propoxy)benzonitrile
332		methyl rac-(1S,2S)-2-(cyano(1-((1-(4-(cyclopropylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)(phenyl)methyl)cyclopentane-1-carboxylate
333		methyl rac-(1R,2R)-2-(cyano(1-((1-(4-(cyclopropylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)(phenyl)methyl)cyclopentane-1-carboxylate
334		rac-(1S,2S)-2-(cyano(1-((1-(4-(cyclopropylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)(phenyl)methyl)-N-methylcyclopentane-1-carboxamide

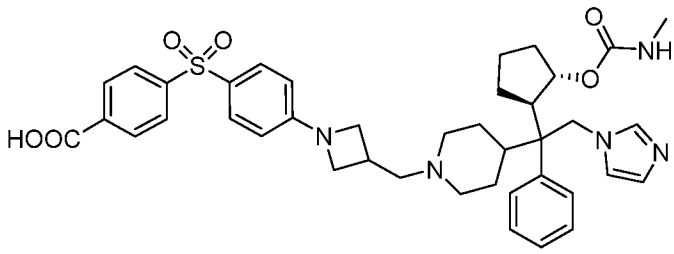
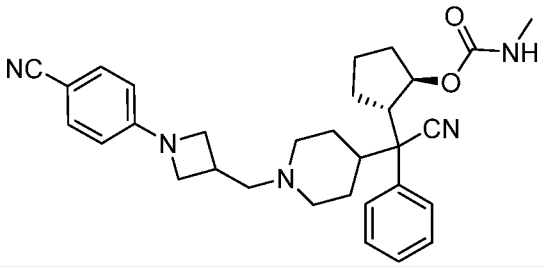
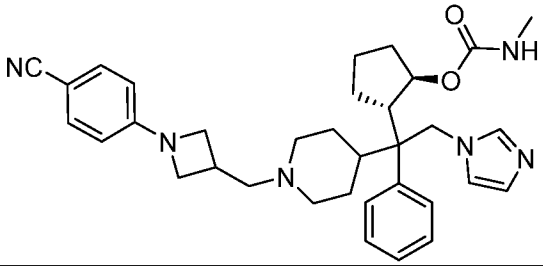
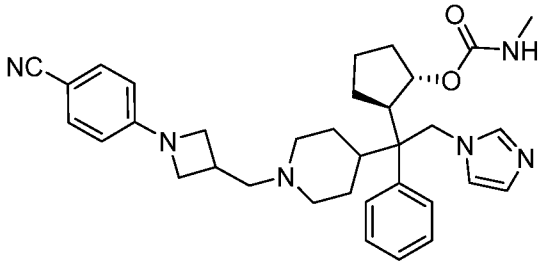
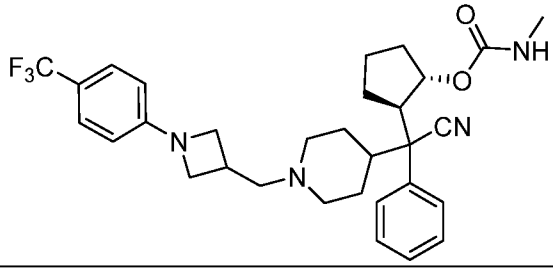
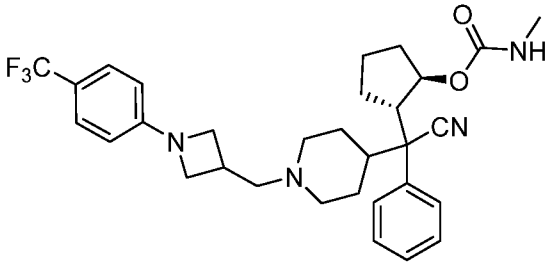
Cpd. No.	Chemical Structure	Chemical Name
335		rac-(1S,2S)-2-(cyano(1-((1-(4-(cyclopropylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)(phenyl)methyl)-N-ethylcyclopentane-1-carboxamide
336		rac-2-((1S,2R)-2-(2-methoxyethyl)cyclopentyl)-2-(1-((1-(4-((2-methylpyridin-4-yl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-2-phenylacetonitrile
337		rac-2-((1R,2S)-2-(2-methoxyethyl)cyclopentyl)-2-(1-((1-(4-((2-methylpyridin-4-yl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-2-phenylacetonitrile
338		2-(2-ethylcyclopentyl)-2-phenyl-2-(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)acetonitrile
339		rac-2-((1S,2R)-2-(cyano(phenyl)(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)methyl)cyclopentyl)-N-methylacetamide
340		rac-2-((1R,2S)-2-(cyano(phenyl)(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)methyl)cyclopentyl)-N-methylacetamide

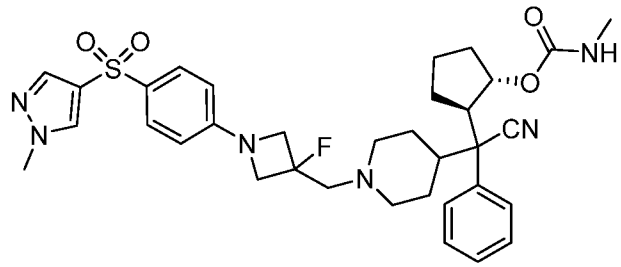
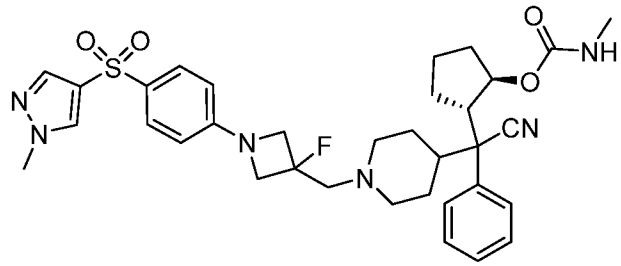
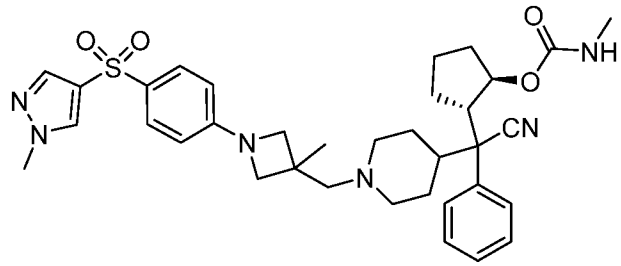
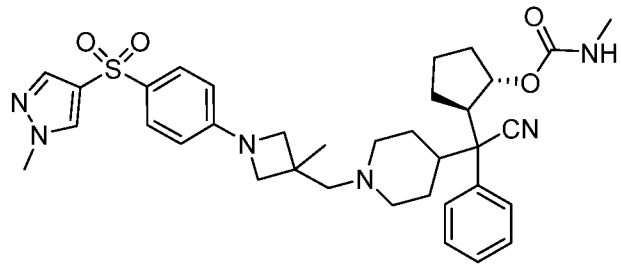
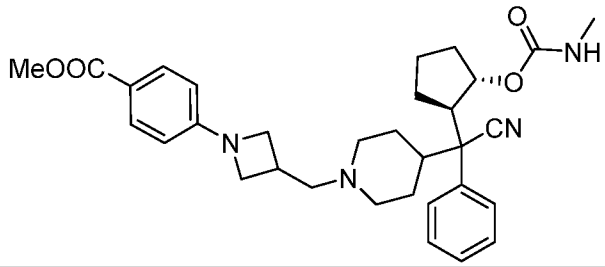
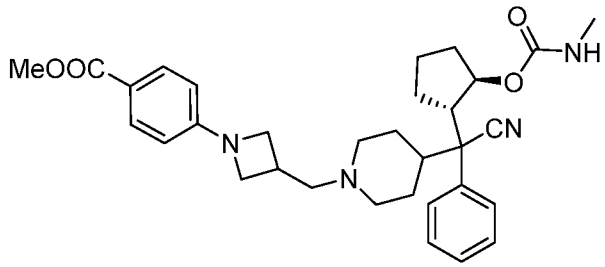
Cpd. No.	Chemical Structure	Chemical Name
341		rac-2-((1R,2S)-2-(2-hydroxyethyl)cyclopentyl)-2-phenyl-2-(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)acetonitrile
342		rac-2-((1S,2R)-2-(2-hydroxyethyl)cyclopentyl)-2-phenyl-2-(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)acetonitrile
343		2-phenyl-3-(pyridin-4-yl)-2-(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)propanenitrile
344		4-(3-(4-(1-cyano-1-phenyl-2-(pyridin-4-yl)ethyl)piperidin-1-yl)propoxy)benzonitrile
345		methyl (rac-(1S,2R)-2-(cyano(phenyl)(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)methyl)cyclopentyl)carbamate

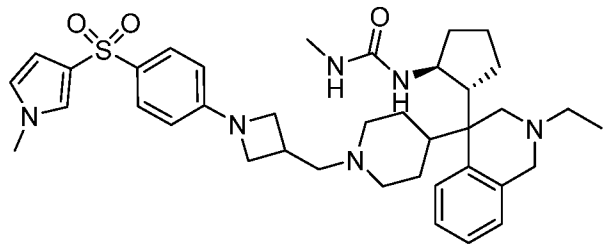
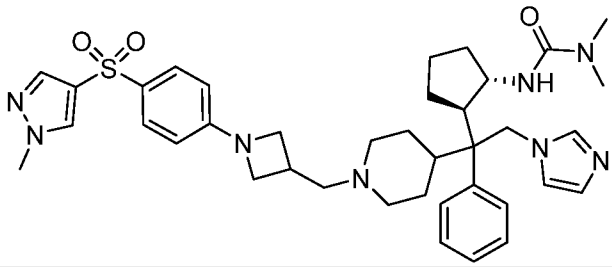
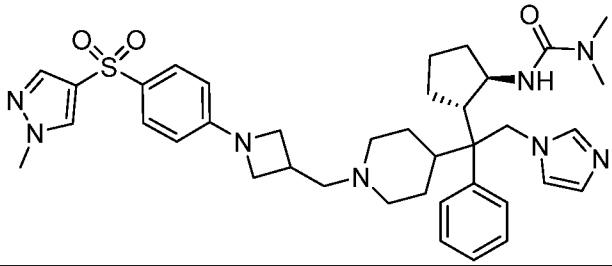
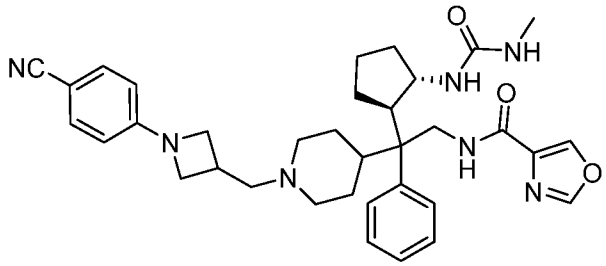
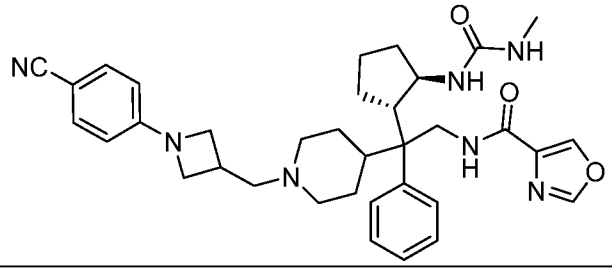
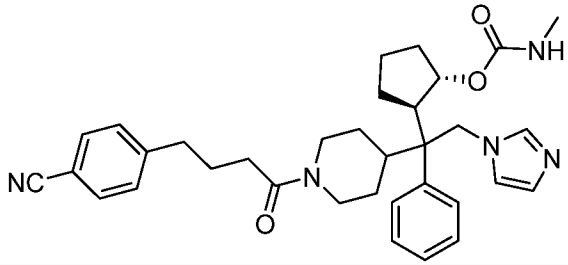
Cpd. No.	Chemical Structure	Chemical Name
346		methyl (rac-(1R,2S)-2-(cyano(phenyl)(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)methyl)cyclopentyl)carbamate
347		methyl (rac-(1S,2R)-2-(cyano(phenyl)(1-((1-(4-(phenylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)methyl)cyclopentyl)carbamate
348		methyl (rac-(1R,2S)-2-(cyano(phenyl)(1-((1-(4-(phenylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)methyl)cyclopentyl)carbamate
349		methyl (rac-(1S,2R)-2-(cyano(1-((1-(4-((1-methyl-1H-pyrazol-4-yl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)(phenyl)methyl)cyclopentyl)carbamate
350		methyl (rac-(1R,2S)-2-(cyano(1-((1-(4-((1-methyl-1H-pyrazol-4-yl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)(phenyl)methyl)cyclopentyl)carbamate

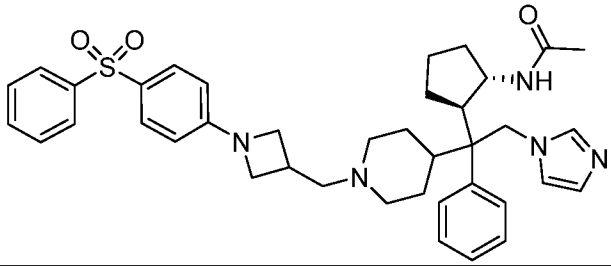
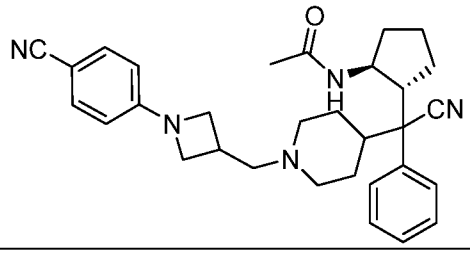
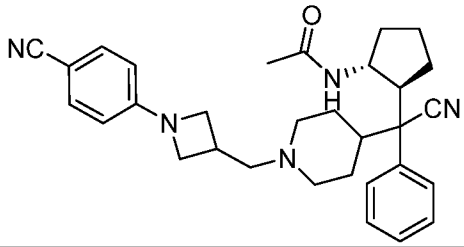
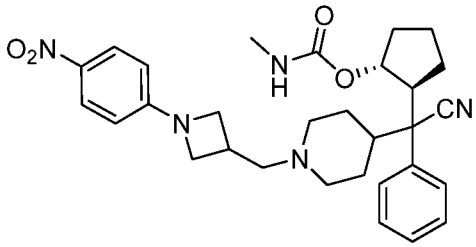
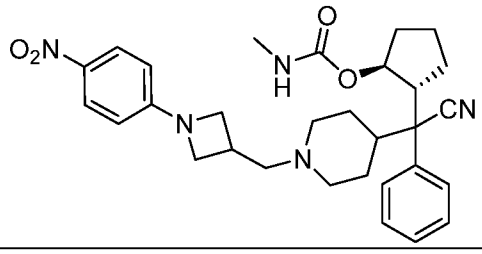
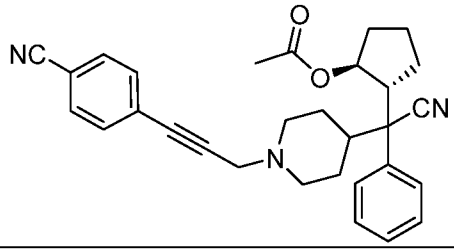
Cpd. No.	Chemical Structure	Chemical Name
351		rac-4-((4-(3-((4-(cyano((1R,2S)-2-((methoxycarbonyl)amino)cyclopentyl)(phenyl)methyl)piperidin-1-yl)methyl)azetidin-1-yl)phenyl)sulfonyl)benzoic acid
352		rac-4-((4-(3-((4-(cyano((1S,2R)-2-((methoxycarbonyl)amino)cyclopentyl)(phenyl)methyl)piperidin-1-yl)methyl)azetidin-1-yl)phenyl)sulfonyl)benzoic acid
353		rac-(1S,2R)-2-((S)-cyano(phenyl)(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)methyl)cyclopentyl methylcarbamate
354		rac-(1R,2S)-2-((R)-cyano(phenyl)(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)methyl)cyclopentyl methylcarbamate
355		4-(1-(cyclopent-1-en-1-yl)-1-phenyl-2-(pyrrolidin-1-yl)ethyl)-1-((1-(4-(phenylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidine
356		4-(1-((R)-cyclopent-2-en-1-yl)-1-phenyl-2-(pyrrolidin-1-yl)ethyl)-1-((1-(4-(phenylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidine

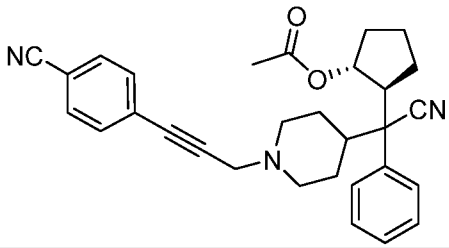
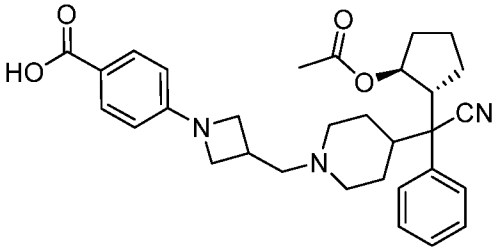
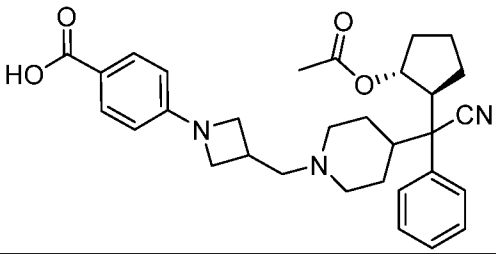
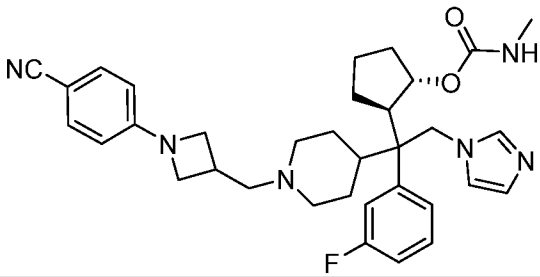
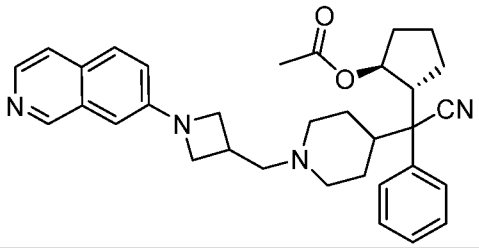
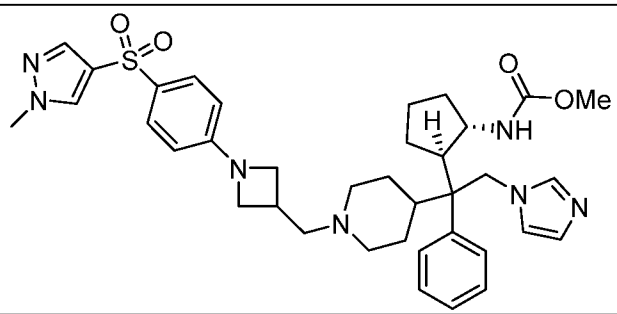
Cpd. No.	Chemical Structure	Chemical Name
357		4-(1-(cyclopent-1-en-1-yl)-1-phenyl-2-(pyrrolidin-1-yl)ethyl)-1-((1-(4-((1-methyl-1H-pyrazol-4-yl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidine
358		rac-(1R,2S)-2-(1-phenyl-1-(1-((1-(4-(phenylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-2-(1H-pyrrol-1-yl)ethyl)cyclopentyl methylcarbamate
359		rac-(1S,2R)-2-(1-phenyl-1-(1-((1-(4-(phenylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-2-(1H-pyrrol-1-yl)ethyl)cyclopentyl methylcarbamate
360		rac-(1R,2S)-2-(1-phenyl-1-(1-((1-(4-(phenylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-2-(pyrrolidin-1-yl)ethyl)cyclopentyl methylcarbamate
361		rac-(1S,2R)-2-(1-phenyl-1-(1-((1-(4-(phenylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-2-(pyrrolidin-1-yl)ethyl)cyclopentyl methylcarbamate
362		rac-4-((4-(3-((4-(2-(1H-imidazol-1-yl)-1-((1R,2S)-2-((methylcarbamoyl)oxy)cyclopentyl)-1-phenylethyl)piperidin-1-yl)methyl)azetidin-1-yl)phenyl)sulfonyl)benzoic acid

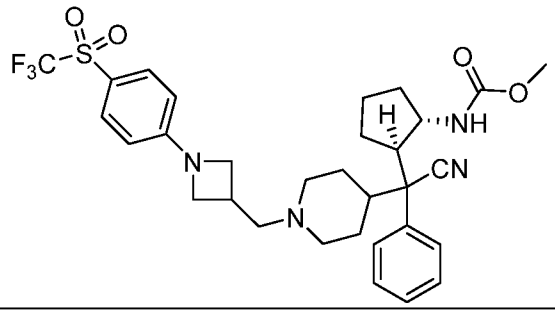
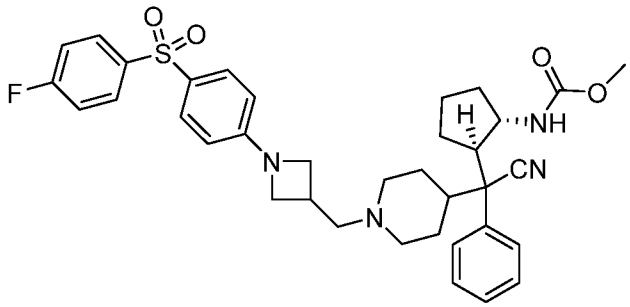
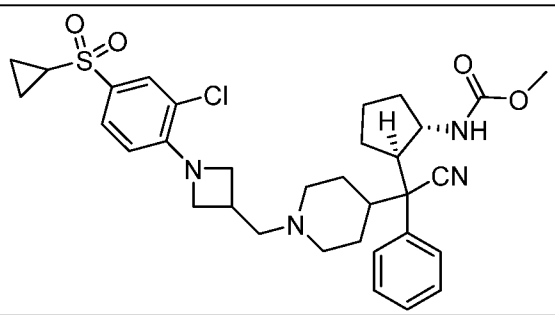
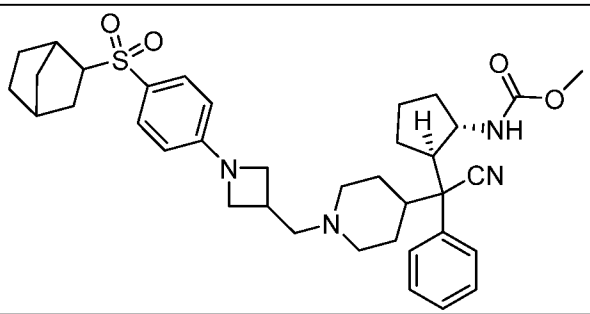
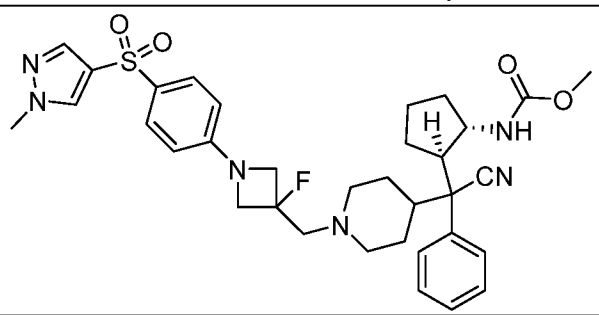
Cpd. No.	Chemical Structure	Chemical Name
363		rac-4-((4-(3-((4-(2-(1H-imidazol-1-yl)-1-((1R,2S)-2-((methylcarbamoyl)oxy)cyclopentyl)-1-phenylethyl)piperidin-1-yl)methyl)azetidin-1-yl)phenyl)sulfonyl)benzoic acid
364		rac-(1R,2S)-2-(cyano(1-((1-(4-cyanophenyl)azetidin-3-yl)methyl)piperidin-4-yl)(phenyl)methyl)cyclopentyl methylcarbamate
365		rac-(1R,2S)-2-(1-(1-((1-(4-cyanophenyl)azetidin-3-yl)methyl)piperidin-4-yl)-2-(1H-imidazol-1-yl)-1-phenylethyl)cyclopentyl methylcarbamate
366		rac-(1S,2R)-2-(1-(1-((1-(4-cyanophenyl)azetidin-3-yl)methyl)piperidin-4-yl)-2-(1H-imidazol-1-yl)-1-phenylethyl)cyclopentyl methylcarbamate
367		rac-(1S,2R)-2-(cyano(phenyl)(1-((1-(4-(trifluoromethyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)methyl)cyclopentyl methylcarbamate
368		rac-(1R,2S)-2-(cyano(phenyl)(1-((1-(4-(trifluoromethyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)methyl)cyclopentyl methylcarbamate

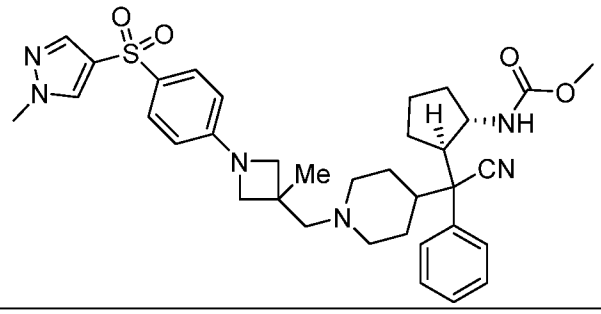
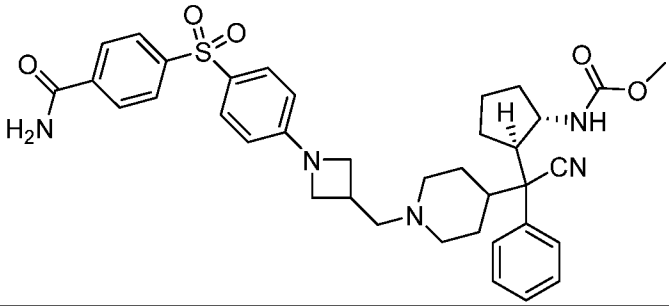
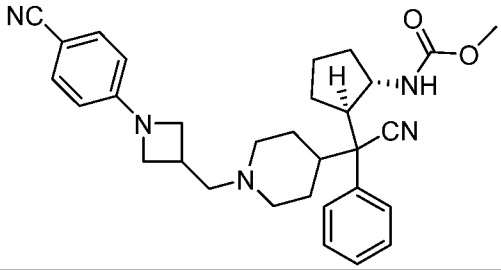
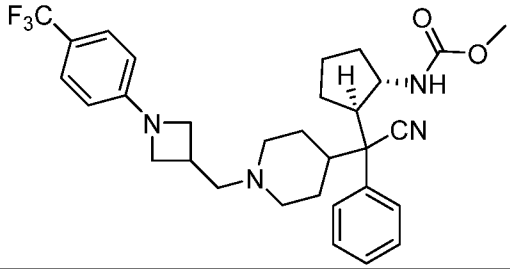
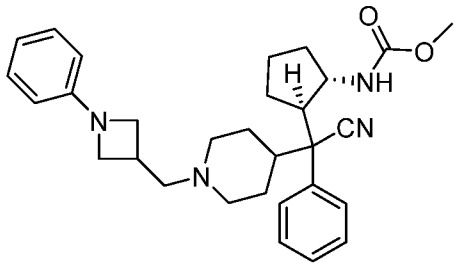
Cpd. No.	Chemical Structure	Chemical Name
369		rac-(1S,2R)-2-(cyano(1-((3-fluoro-1-(4-((1-methyl-1H-pyrazol-4-yl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)(phenyl)methyl)cyclopentyl methylcarbamate
370		rac-(1R,2S)-2-(cyano(1-((3-fluoro-1-(4-((1-methyl-1H-pyrazol-4-yl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)(phenyl)methyl)cyclopentyl methylcarbamate
371		rac-(1R,2S)-2-(cyano(1-((3-methyl-1-(4-((1-methyl-1H-pyrazol-4-yl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)(phenyl)methyl)cyclopentyl methylcarbamate
372		rac-(1S,2R)-2-(cyano(1-((3-methyl-1-(4-((1-methyl-1H-pyrazol-4-yl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)(phenyl)methyl)cyclopentyl methylcarbamate
373		methyl rac-4-(3-((4-(cyano((1R,2S)-2-((methylcarbamoyl)oxy)cyclopentyl)(phenyl)methyl)piperidin-1-yl)methyl)azetidin-1-yl)benzoate
374		methyl rac-4-(3-((4-(cyano((1S,2R)-2-((methylcarbamoyl)oxy)cyclopentyl)(phenyl)methyl)piperidin-1-yl)methyl)azetidin-1-yl)benzoate

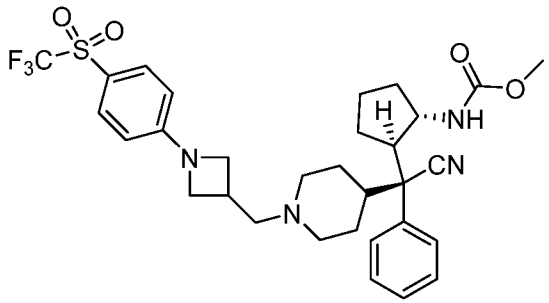
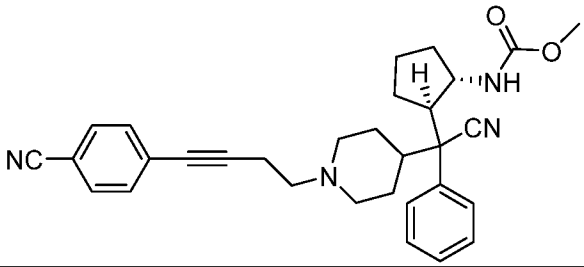
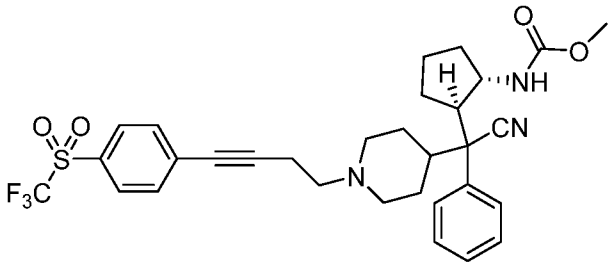
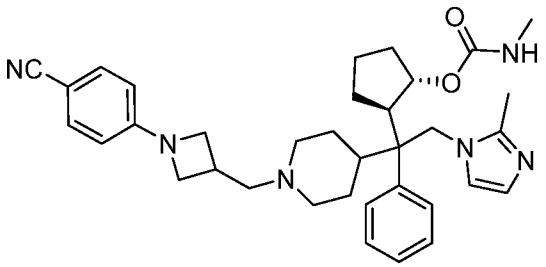
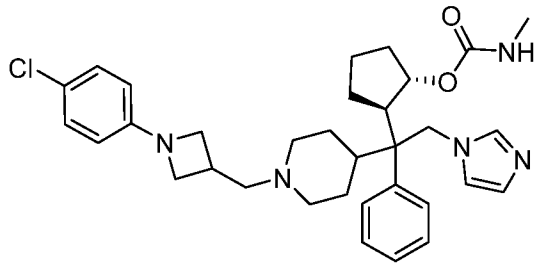
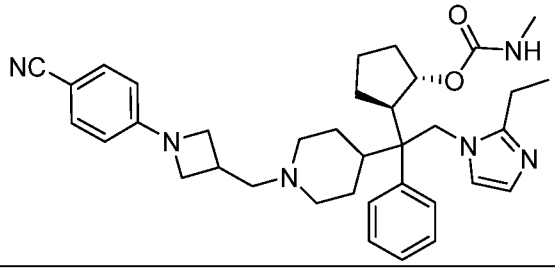
Cpd. No.	Chemical Structure	Chemical Name
375		rac-1-((1S,2R)-2-(2-ethyl-4-(1-((1-(4-((1-methyl-1H-pyrrol-3-yl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1,2,3,4-tetrahydroisoquinolin-4-yl)cyclopentyl)-3-methylurea
376		rac-3-((1S,2R)-2-(2-(1H-imidazol-1-yl)-1-(1-((1-(4-((1-methyl-1H-pyrazol-4-yl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1-phenylethyl)cyclopentyl)-1,1-dimethylurea
377		rac-3-((1R,2S)-2-(2-(1H-imidazol-1-yl)-1-(1-((1-(4-((1-methyl-1H-pyrazol-4-yl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1-phenylethyl)cyclopentyl)-1,1-dimethylurea
378		rac-N-(2-(1-((1-(4-cyanophenyl)azetidin-3-yl)methyl)piperidin-4-yl)-2-((1R,2S)-2-(3-methylureido)cyclopentyl)-2-phenylethyl)oxazole-4-carboxamide
379		rac-N-(2-(1-((1-(4-cyanophenyl)azetidin-3-yl)methyl)piperidin-4-yl)-2-((1S,2R)-2-(3-methylureido)cyclopentyl)-2-phenylethyl)oxazole-4-carboxamide
380		rac- (1S,2R)-2-(1-(1-(4-(4-cyanophenyl)butanoyl)piperidin-4-yl)-2-(1H-imidazol-1-yl)-1-phenylethyl)cyclopentyl methylcarbamate

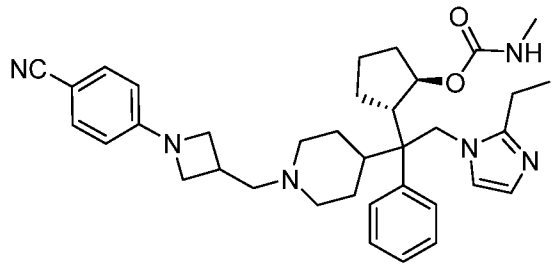
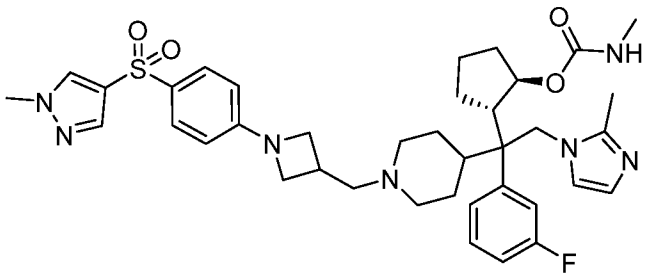
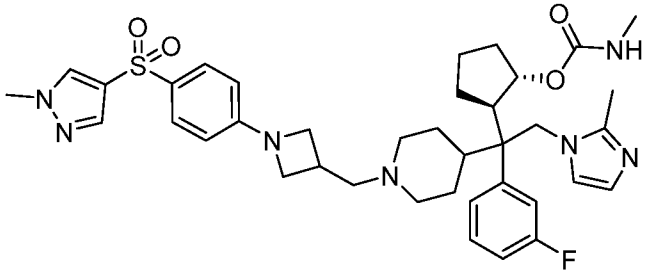
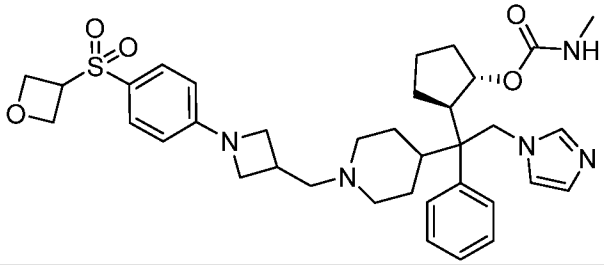
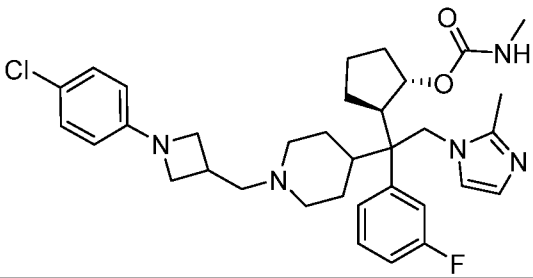
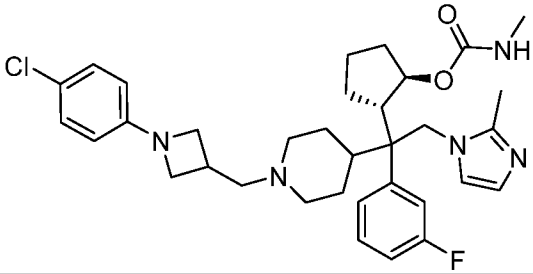
Cpd. No.	Chemical Structure	Chemical Name
381		rac-N-((1S,2R)-2-(2-(1H-imidazol-1-yl)-1-phenyl-1-(1-((1-(4-(phenylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)ethyl)cyclopentyl)acetamide
382		rac-N-((1S,2R)-2-(cyano(1-((1-(4-cyanophenyl)azetidin-3-yl)methyl)piperidin-4-yl)(phenyl)methyl)cyclopentyl)acetamide
383		rac-N-((1R,2S)-2-(cyano(1-((1-(4-cyanophenyl)azetidin-3-yl)methyl)piperidin-4-yl)(phenyl)methyl)cyclopentyl)acetamide
384		rac- (1R,2S)-2-(cyano(1-((1-(4-nitrophenyl)azetidin-3-yl)methyl)piperidin-4-yl)(phenyl)methyl)cyclopentyl methylcarbamate
385		rac- (1S,2R)-2-(cyano(1-((1-(4-nitrophenyl)azetidin-3-yl)methyl)piperidin-4-yl)(phenyl)methyl)cyclopentyl methylcarbamate
386		rac- (1S,2R)-2-(cyano(1-(3-(4-cyanophenyl)prop-2-yn-1-yl)piperidin-4-yl)(phenyl)methyl)cyclopentyl acetate

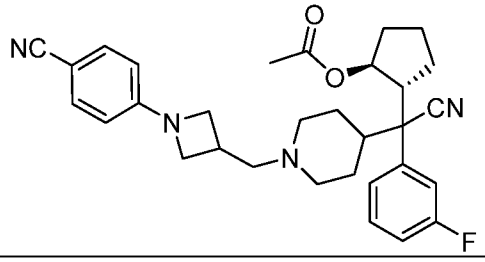
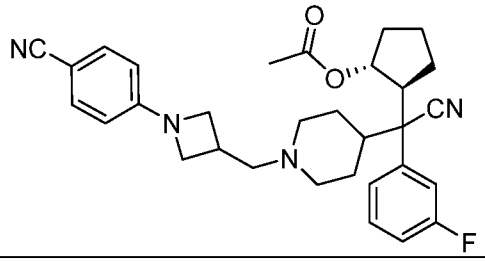
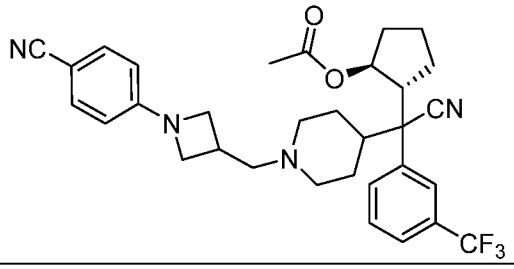
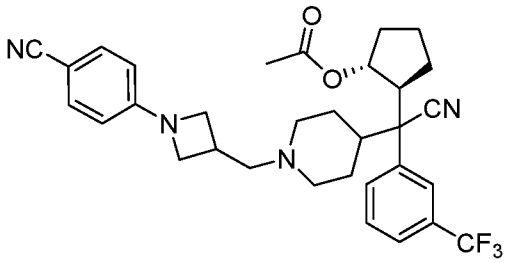
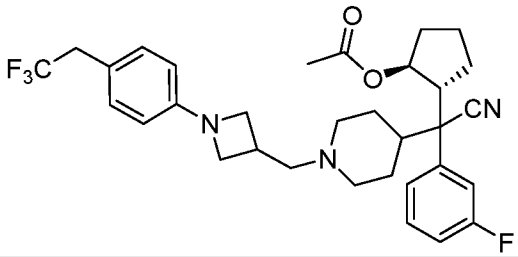
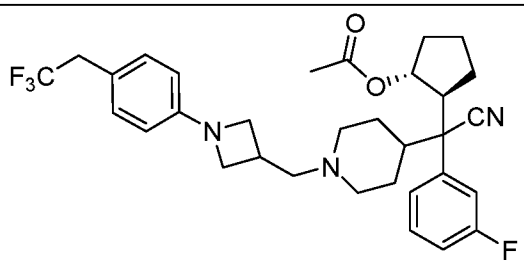
Cpd. No.	Chemical Structure	Chemical Name
387		rac- (1R,2S)-2-(cyano(1-(3-(4-cyanophenyl)prop-2-yn-1-yl)piperidin-4-yl)(phenyl)methyl)cyclopentyl acetate
388		rac-4-(3-((4-(((1R,2S)-2-acetoxycyclopentyl)(cyano)(phenyl)methyl)piperidin-1-yl)methyl)azetidin-1-yl)benzoic acid
389		rac-4-(3-((4-(((1S,2R)-2-acetoxycyclopentyl)(cyano)(phenyl)methyl)piperidin-1-yl)methyl)azetidin-1-yl)benzoic acid
390		rac-(1S,2R)-2-(1-(1-((1-(4-cyanophenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1-(3-fluorophenyl)-2-(1H-imidazol-1-yl)ethyl)cyclopentyl methylcarbamate
391		rac-(1S,2R)-2-(cyano(1-((1-(isoquinolin-7-yl)azetidin-3-yl)methyl)piperidin-4-yl)(phenyl)methyl)cyclopentyl acetate
392		methyl rac-((1S,2R)-2-(2-(1H-imidazol-1-yl)-1-(1-((1-(4-((1-methyl-1H-pyrazol-4-yl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1-phenylethyl)cyclopentyl)carbamate

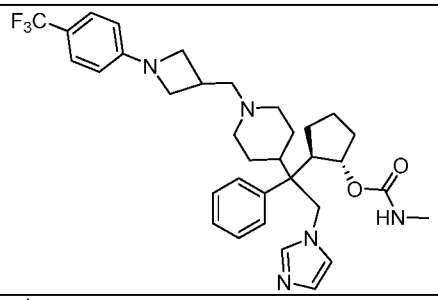
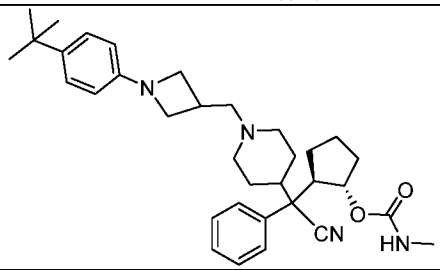
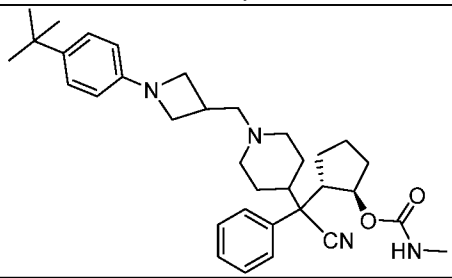
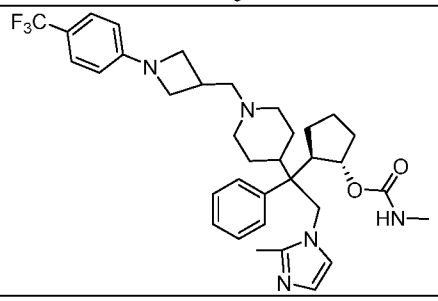
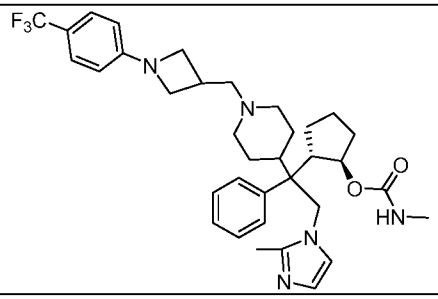
Cpd. No.	Chemical Structure	Chemical Name
393		methyl rac-((1S,2R)-2-(cyano(phenyl)(1-((1-(4-((trifluoromethyl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)methyl)cyclopentyl)carbamate
394		methyl rac((1S,2R)-2-(cyano(1-((1-(4-((4-fluorophenyl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)(phenyl)methyl)cyclopentyl)carbamate
395		methyl rac-((1S,2R)-2-((1-((1-(2-chloro-4-(cyclopropylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)(cyano)(phenyl)methyl)cyclopentyl)carbamate
396		methyl rac-((1S,2R)-2-((1-((1-(4-(bicyclo[2.2.1]heptan-2-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)(cyano)(phenyl)methyl)cyclopentyl)carbamate
397		methyl rac-((1S,2R)-2-(cyano(1-((3-fluoro-1-(4-((1-methyl-1H-pyrazol-4-yl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)(phenyl)methyl)cyclopentyl)carbamate

Cpd. No.	Chemical Structure	Chemical Name
398		methyl rac-((1S,2R)-2-(cyano(1-((3-methyl-1-(4-((1-methyl-1H-pyrazol-4-yl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)(phenyl)methyl)cyclopentyl)carbamate
399		methyl rac-((1S,2R)-2-((1-((1-(4-((4-carbamoylphenyl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)(cyano)(phenyl)methyl)cyclopentyl)carbamate
400		methyl rac-((1S,2R)-2-(cyano(1-((1-(4-cyanophenyl)azetidin-3-yl)methyl)piperidin-4-yl)(phenyl)methyl)cyclopentyl)carbamate
401		methyl rac-((1S,2R)-2-(cyano(phenyl)(1-((1-(4-(trifluoromethyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)methyl)cyclopentyl)carbamate
402		methyl rac-((1S,2R)-2-(cyano(phenyl)(1-((1-phenylazetidin-3-yl)methyl)piperidin-4-yl)methyl)cyclopentyl)carbamate

Cpd. No.	Chemical Structure	Chemical Name
403		methyl ((1S,2R)-2-((S)-cyano(phenyl)(1-((1-(4-((trifluoromethyl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)methyl)cyclopentyl)carbamate
404		methyl rac-((1S,2R)-2-(cyano(1-(4-(4-cyanophenyl)but-3-yn-1-yl)piperidin-4-yl)(phenyl)methyl)cyclopentyl)carbamate
405		methyl rac-((1S,2R)-2-(cyano(phenyl)(1-(4-(4-((trifluoromethyl)sulfonyl)phenyl)but-3-yn-1-yl)piperidin-4-yl)methyl)cyclopentyl)carbamate
406		rac-(1S,2R)-2-(1-(1-((1-(4-cyanophenyl)azetidin-3-yl)methyl)piperidin-4-yl)-2-(2-methyl-1H-imidazol-1-yl)-1-phenylethyl)cyclopentyl methylcarbamate
407		rac-(1S,2R)-2-(1-(1-((1-(4-chlorophenyl)azetidin-3-yl)methyl)piperidin-4-yl)-2-(1H-imidazol-1-yl)-1-phenylethyl)cyclopentyl methylcarbamate
408		rac-(1S,2R)-2-(1-(1-((1-(4-cyanophenyl)azetidin-3-yl)methyl)piperidin-4-yl)-2-(2-ethyl-1H-imidazol-1-yl)-1-phenylethyl)cyclopentyl methylcarbamate

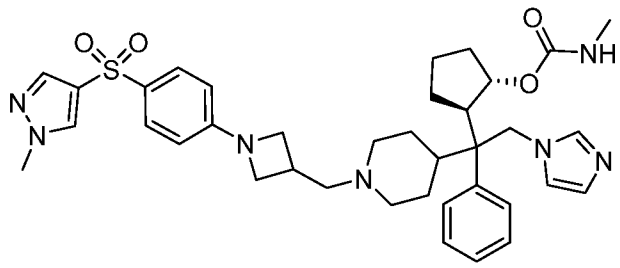
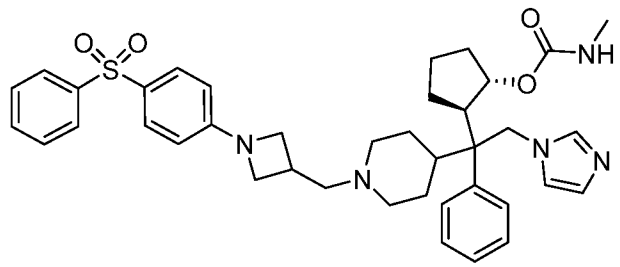
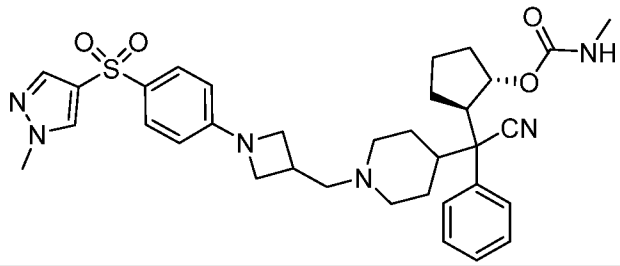
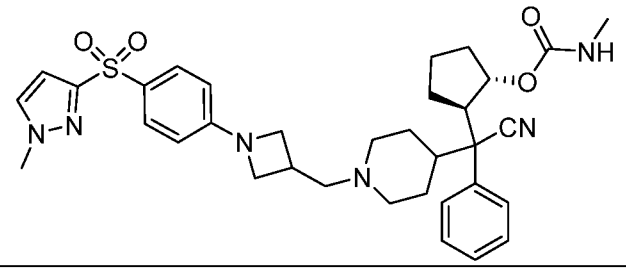
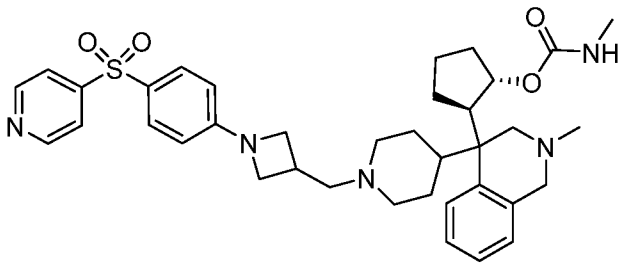
Cpd. No.	Chemical Structure	Chemical Name
409		rac-(1R,2S)-2-(1-(1-((1-(4-cyanophenyl)azetidin-3-yl)methyl)piperidin-4-yl)-2-(2-ethyl-1H-imidazol-1-yl)-1-phenylethyl)cyclopentyl methylcarbamate
410		rac-(1R,2S)-2-(1-(3-fluorophenyl)-2-(2-methyl-1H-imidazol-1-yl)-1-(1-((1-(4-((1-methyl-1H-pyrazol-4-yl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)ethyl)cyclopentyl methylcarbamate
411		rac-(1S,2R)-2-(1-(3-fluorophenyl)-2-(2-methyl-1H-imidazol-1-yl)-1-(1-((1-(4-((1-methyl-1H-pyrazol-4-yl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)ethyl)cyclopentyl methylcarbamate
412		rac-(1S,2R)-2-(2-(1H-imidazol-1-yl)-1-(1-((1-(4-(oxetan-3-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1-phenylethyl)cyclopentyl methylcarbamate
413		rac-(1S,2R)-2-(1-(1-((1-(4-chlorophenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1-(3-fluorophenyl)-2-(2-methyl-1H-imidazol-1-yl)ethyl)cyclopentyl methylcarbamate
414		rac-(1R,2S)-2-(1-(1-((1-(4-chlorophenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1-(3-fluorophenyl)-2-(2-methyl-1H-imidazol-1-yl)ethyl)cyclopentyl methylcarbamate

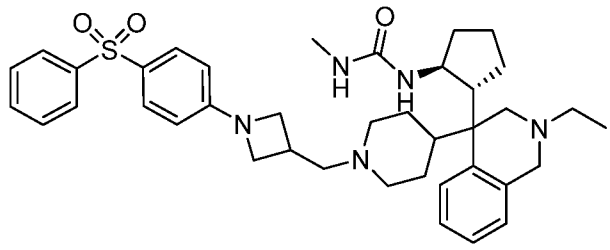
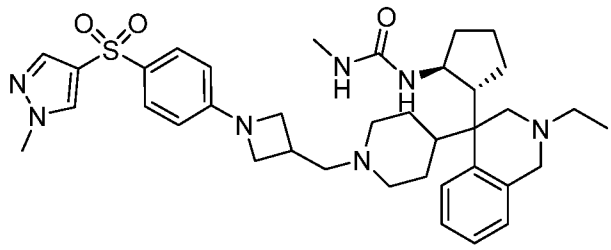
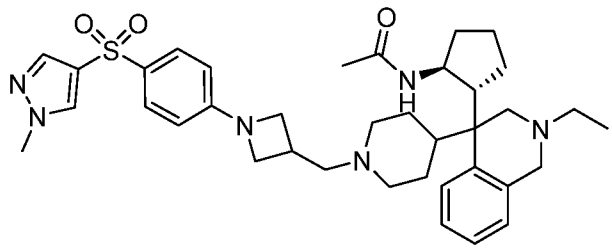
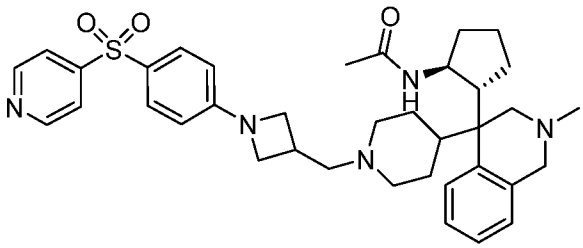
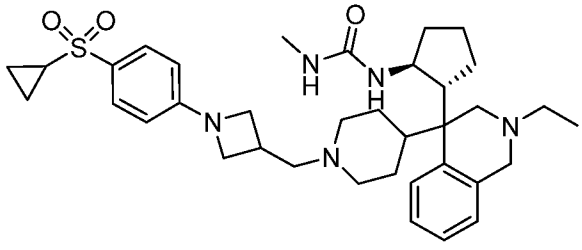
Cpd. No.	Chemical Structure	Chemical Name
415		rac-(1S,2R)-2-(cyano(1-((1-(4-cyanophenyl)azetidin-3-yl)methyl)piperidin-4-yl)(3-fluorophenyl)methyl)cyclopentyl acetate
416		rac-(1R,2S)-2-(cyano(1-((1-(4-cyanophenyl)azetidin-3-yl)methyl)piperidin-4-yl)(3-fluorophenyl)methyl)cyclopentyl acetate
417		rac-(1S,2R)-2-(cyano(1-((1-(4-cyanophenyl)azetidin-3-yl)methyl)piperidin-4-yl)(3-(trifluoromethyl)phenyl)methyl)cyclopentyl acetate
418		rac-(1R,2S)-2-(cyano(1-((1-(4-cyanophenyl)azetidin-3-yl)methyl)piperidin-4-yl)(3-(trifluoromethyl)phenyl)methyl)cyclopentyl acetate
419		rac-(1S,2R)-2-(cyano(3-fluorophenyl)(1-((1-(4-(2,2,2-trifluoroethyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)methyl)cyclopentyl acetate
420		rac-(1R,2S)-2-(cyano(3-fluorophenyl)(1-((1-(4-(2,2,2-trifluoroethyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)methyl)cyclopentyl acetate

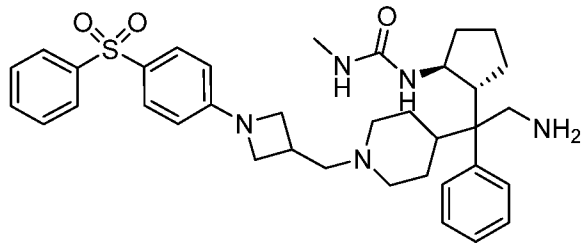
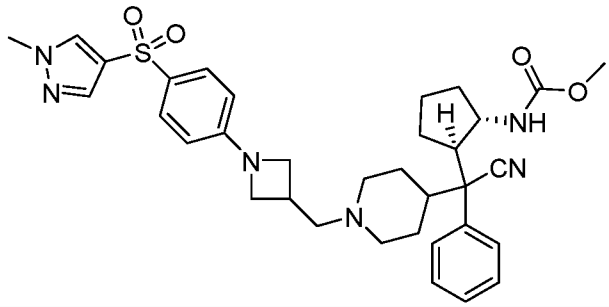
Cpd. No.	Chemical Structure	Chemical Name
421		rac-(1S,2R)-2-(2-(1H-imidazol-1-yl)-1-phenyl-1-(1-((1-(4-(trifluoromethyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)ethyl)cyclopentyl methylcarbamate
422		rac-(1S,2R)-2-((1-((1-(4-(tert-butyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)(cyano)(phenyl)methyl)cyclopentyl methylcarbamate
423		rac-(1R,2S)-2-((1-((1-(4-(tert-butyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)(cyano)(phenyl)methyl)cyclopentyl methylcarbamate
424		rac-(1S,2R)-2-(2-(2-methyl-1H-imidazol-1-yl)-1-phenyl-1-(1-((1-(4-(trifluoromethyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)ethyl)cyclopentyl methylcarbamate
425		rac-(1R,2S)-2-(2-(2-methyl-1H-imidazol-1-yl)-1-phenyl-1-(1-((1-(4-(trifluoromethyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)ethyl)cyclopentyl methylcarbamate

[0103] In another embodiment, Compounds of the Disclosure are one or more of the compounds of Table 2, and the pharmaceutically acceptable salts, hydrates, and solvates thereof.

Table 2

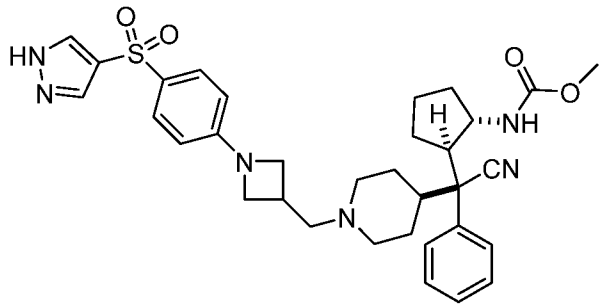
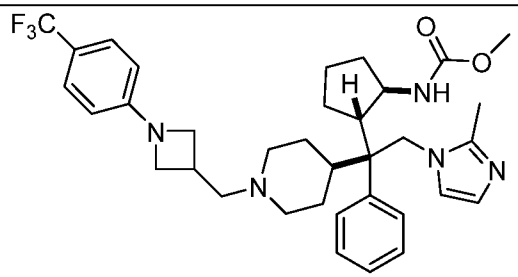
Cpd No.	Chemical Structure	Chemical Name
238		rac-(1S,2R)-2-(2-(1H-imidazol-1-yl)-1-(1-((1-(4-((1-methyl-1H-pyrazol-4-yl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1-phenylethyl)cyclopentyl methylcarbamate
236		rac-(1S,2R)-2-(2-(1H-imidazol-1-yl)-1-phenyl-1-(1-((1-(4-(phenylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)ethyl)cyclopentyl methylcarbamate
240		rac-(1S,2R)-2-(cyano(1-((1-(4-((1-methyl-1H-pyrazol-4-yl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)(phenyl)methyl)cyclopentyl methylcarbamate
230		rac-(1S,2R)-2-(cyano(1-((1-(4-((1-methyl-1H-pyrazol-3-yl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)(phenyl)methyl)cyclopentyl methylcarbamate
210		rac-(1S,2R)-2-(2-methyl-4-(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1,2,3,4-tetrahydroisoquinolin-4-yl)cyclopentyl methylcarbamate

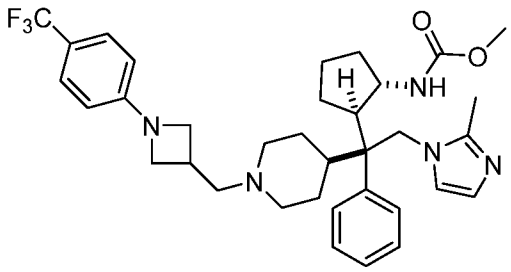
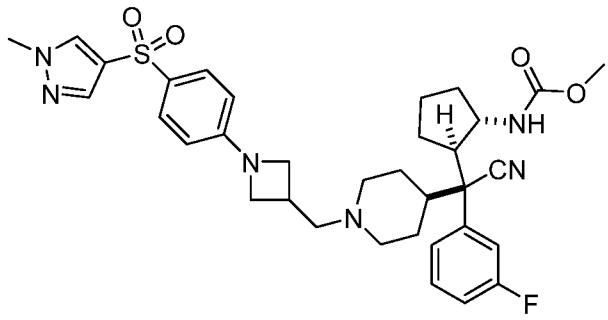
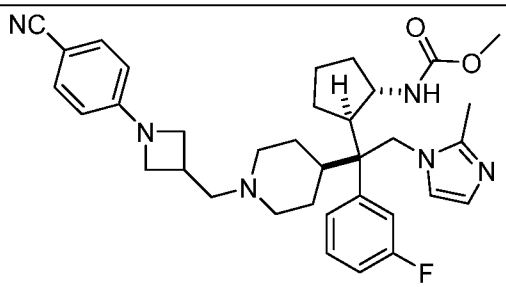
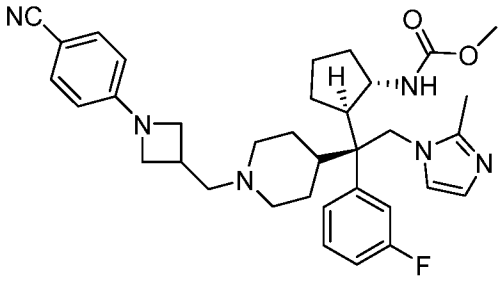
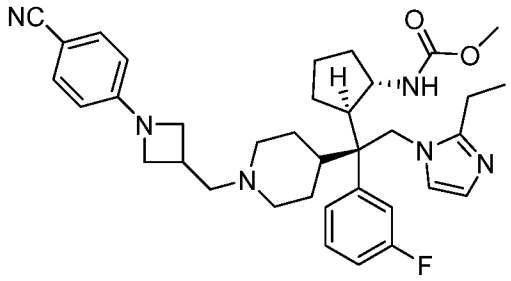
290		rac-1-((1S,2R)-2-(2-ethyl-4-(1-((1-(4-(phenylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1,2,3,4-tetrahydroisoquinolin-4-yl)cyclopentyl)-3-methylurea
291		rac-1-((1S,2R)-2-(2-ethyl-4-(1-((1-(4-((1-methyl-1H-pyrazol-4-yl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1,2,3,4-tetrahydroisoquinolin-4-yl)cyclopentyl)-3-methylurea
292		rac-N-((1S,2R)-2-(2-ethyl-4-(1-((1-(4-((1-methyl-1H-pyrazol-4-yl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1,2,3,4-tetrahydroisoquinolin-4-yl)cyclopentyl)acetamide
271		rac-N-((1S,2R)-2-(2-methyl-4-(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1,2,3,4-tetrahydroisoquinolin-4-yl)cyclopentyl)acetamide
289		rac-1-((1S,2R)-2-(4-(1-((1-(4-(cyclopropylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-2-ethyl-1,2,3,4-tetrahydroisoquinolin-4-yl)cyclopentyl)-3-methylurea

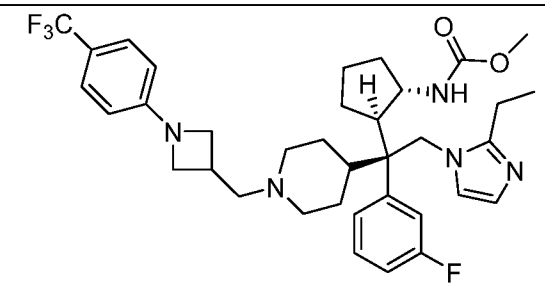
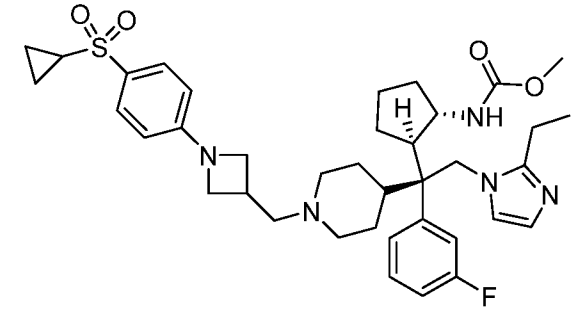
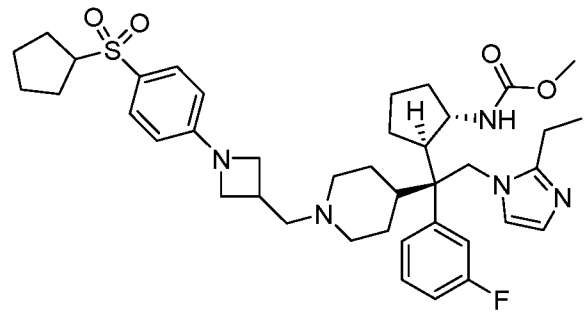
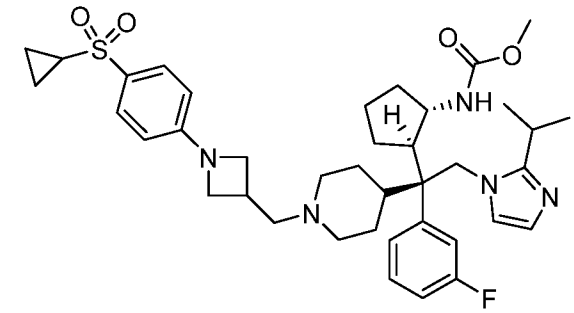
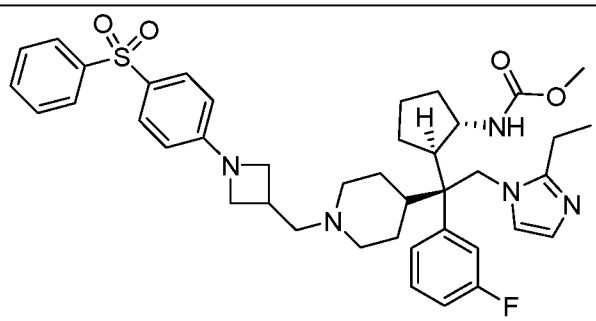
321		rac-1-((1S,2R)-2-(2-amino-1-phenyl-1-(1-((1-(4-(phenylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)ethyl)cyclopentyl)-3-methylurea
349		methyl (rac-(1S,2R)-2-(cyano(1-((1-(4-((1-methyl-1H-pyrazol-4-yl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)(phenyl)methyl)cyclopentyl)carbamate

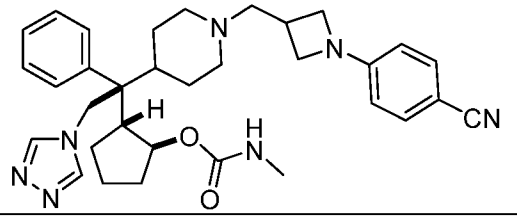
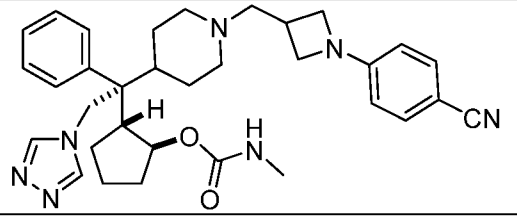
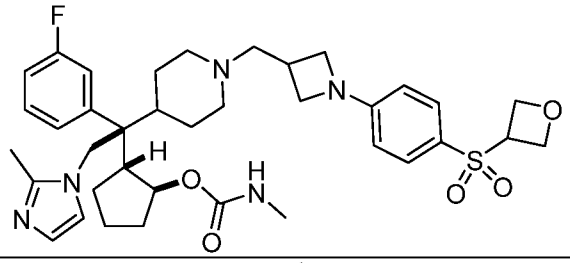
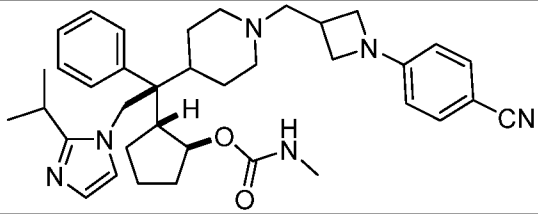
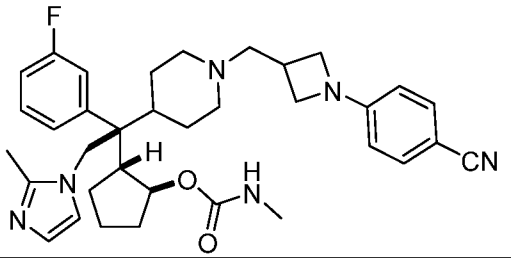
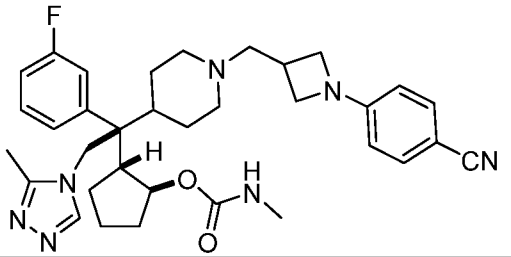
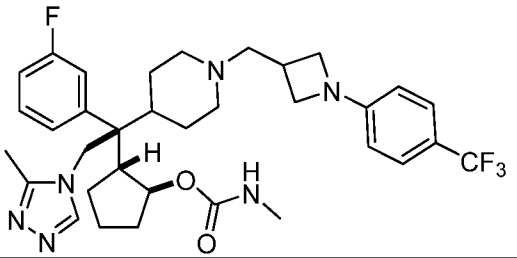
[0104] In another embodiment, Compounds of the Disclosure are one or more of the compounds of Table 5, and the pharmaceutically acceptable salts, hydrates, and solvates thereof.

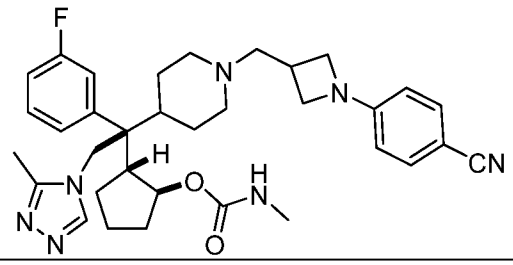
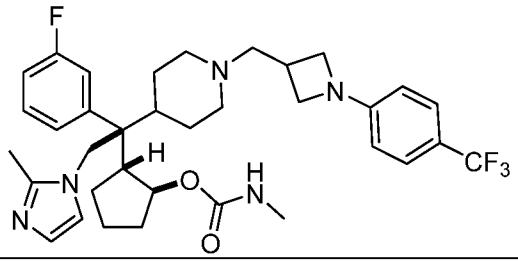
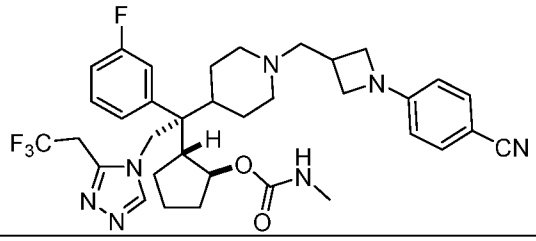
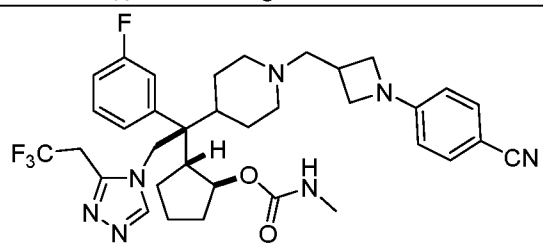
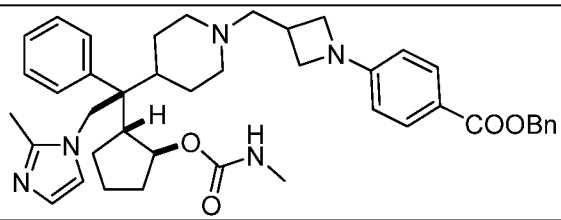
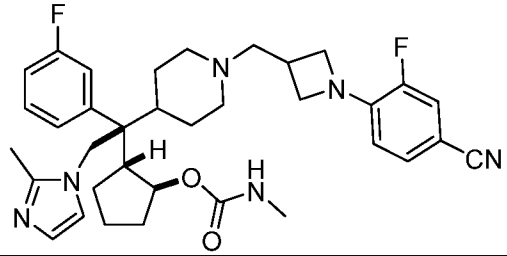
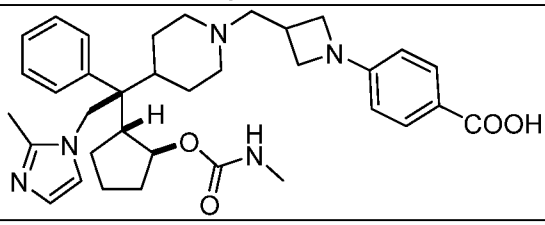
Table 5

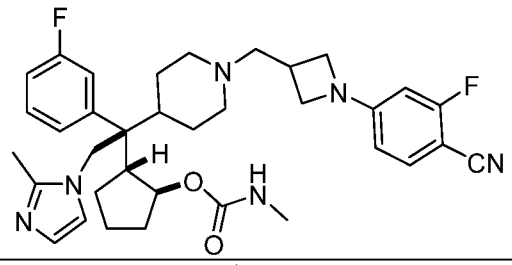
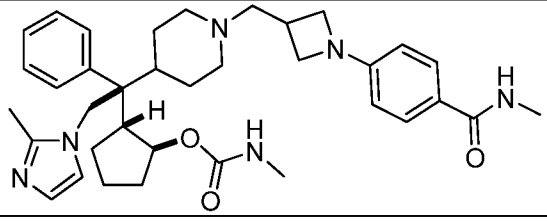
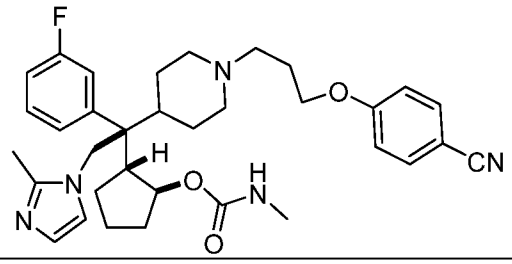
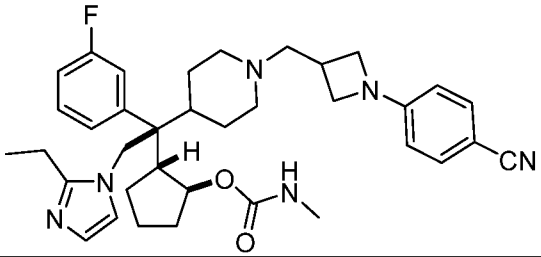
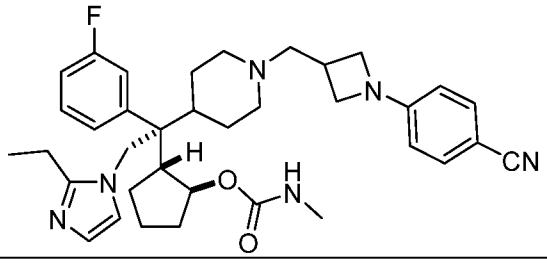
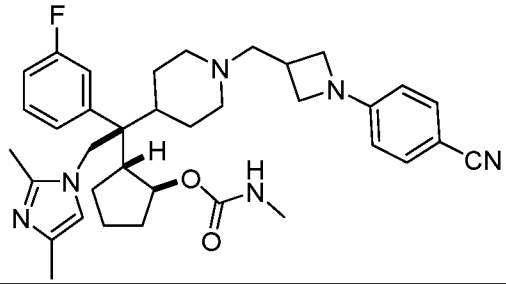
Cpd. No.	Chemical Structure
426	
427	

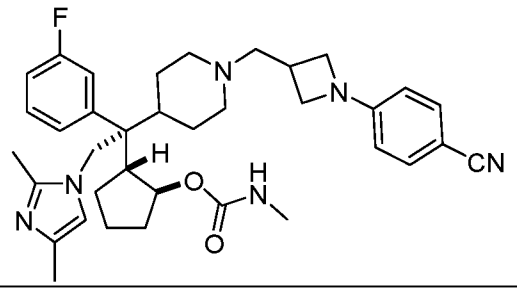
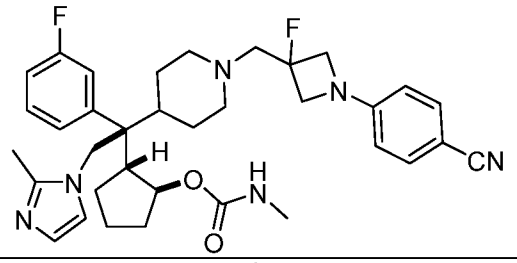
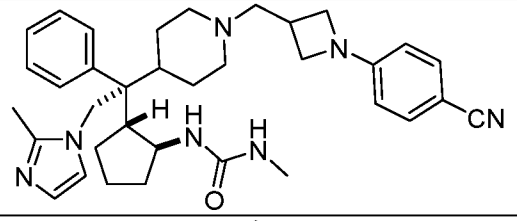
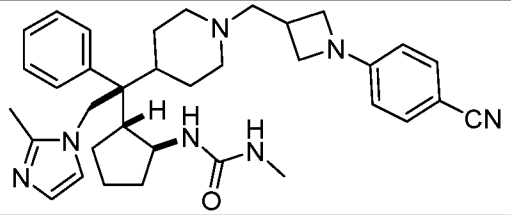
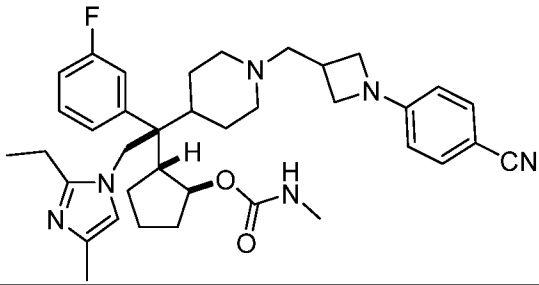
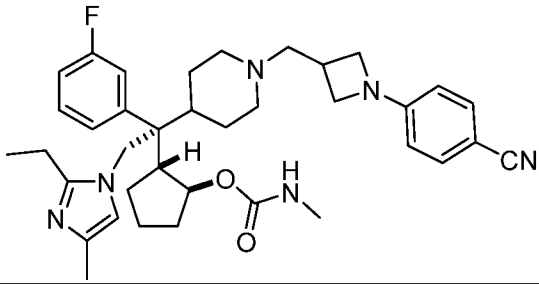
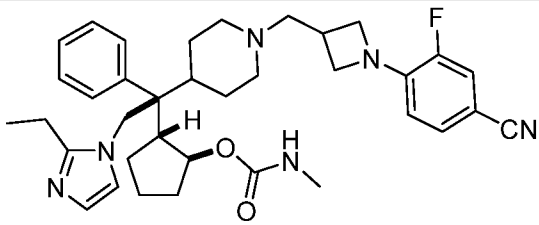
428	
429	
430	
431	
432	

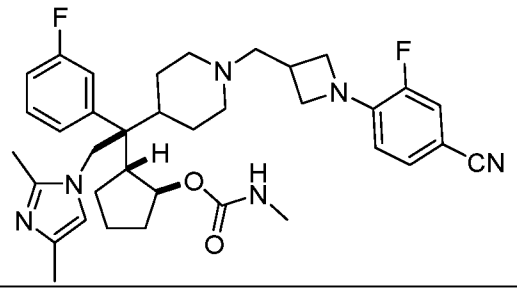
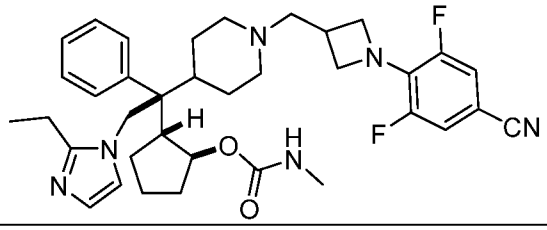
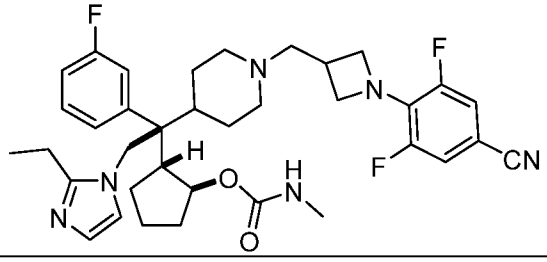
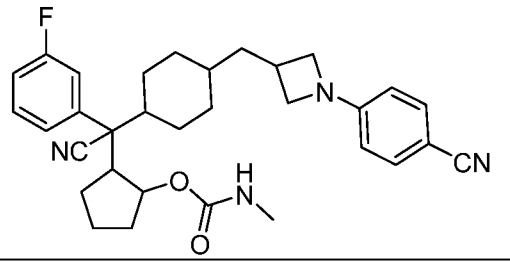
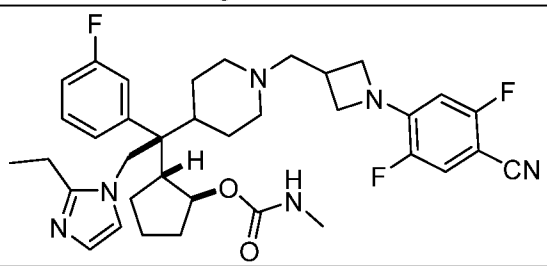
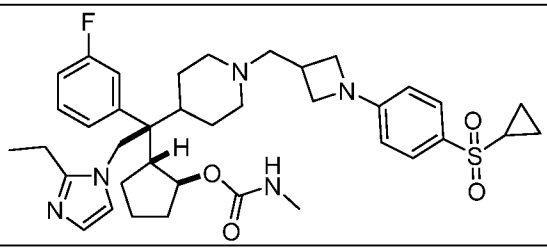
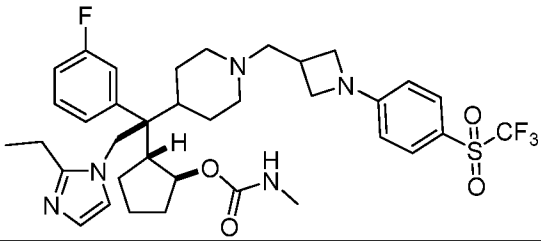
433	
434	
435	
436	
437	

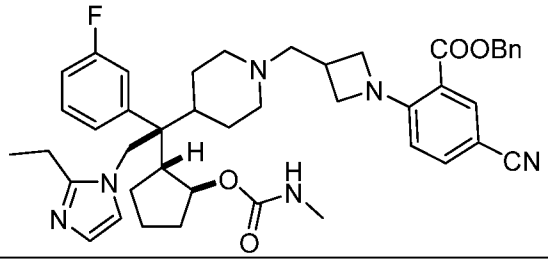
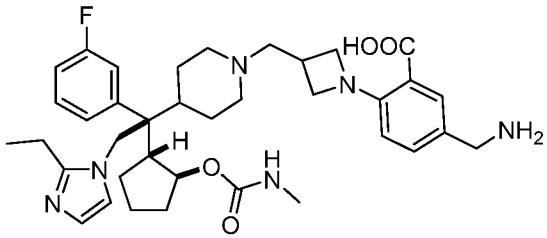
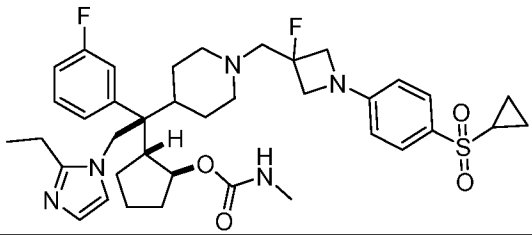
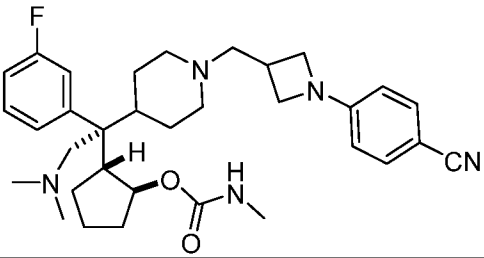
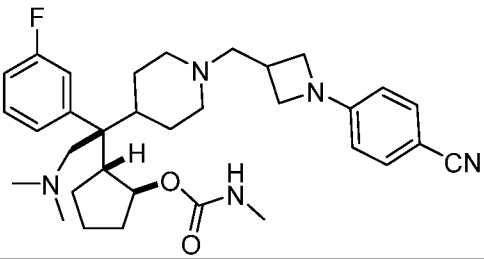
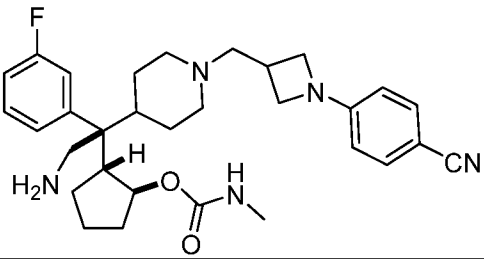
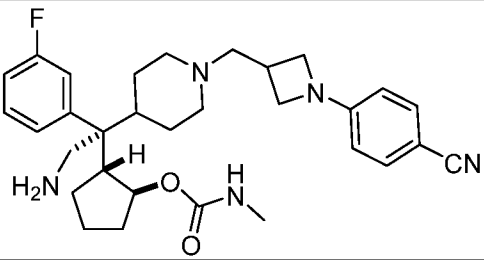
438	
439	
440	
441	
442	
443	
444	

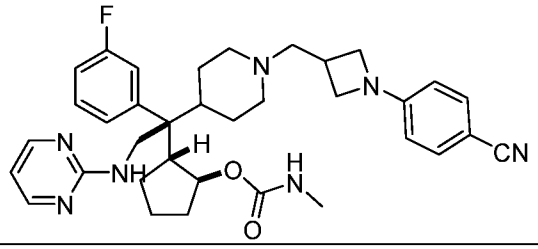
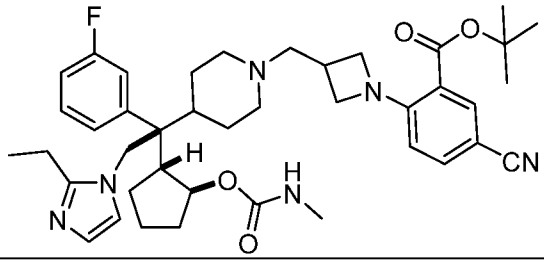
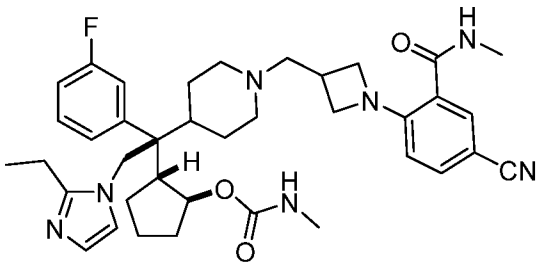
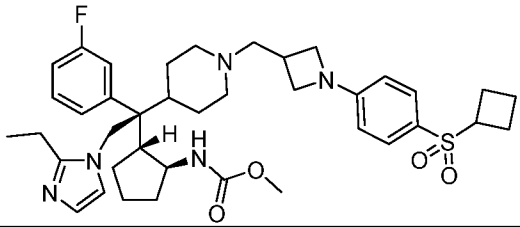
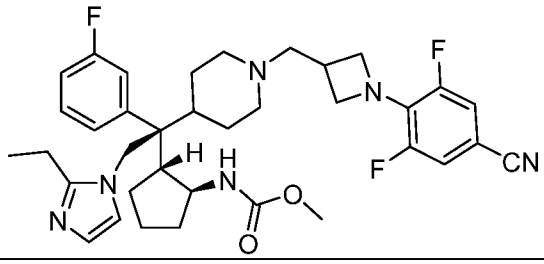
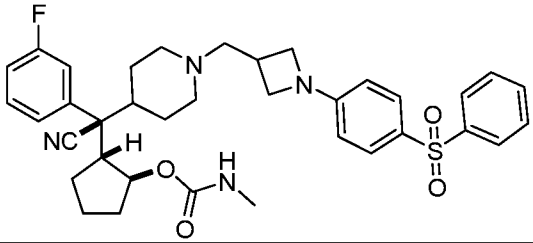
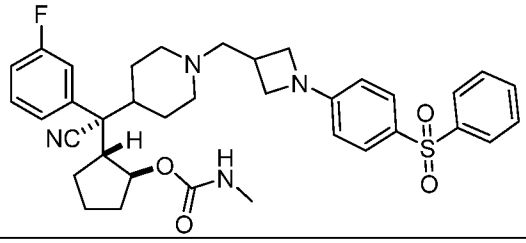
445	
446	
447	
448	
449	
450	
451	

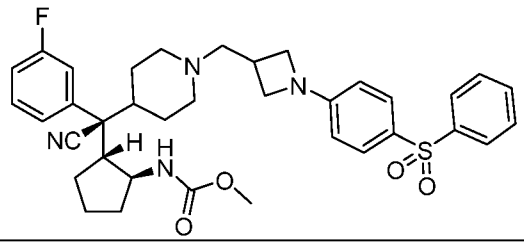
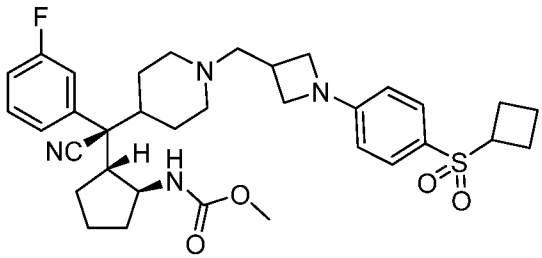
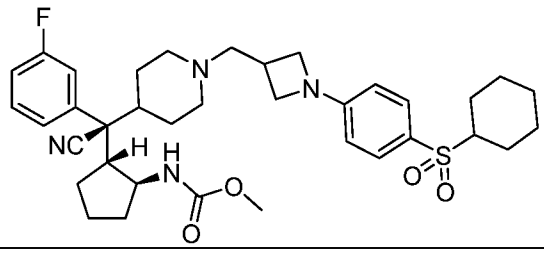
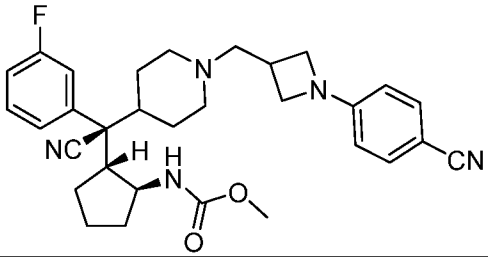
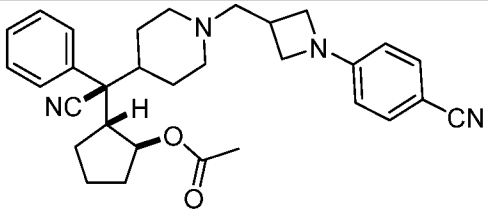
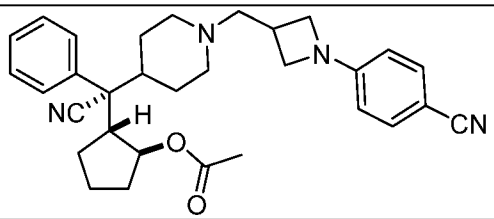
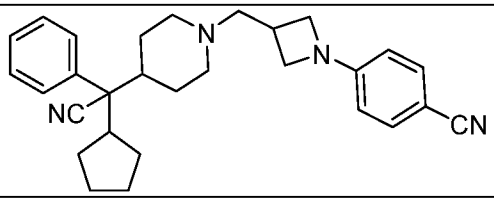
452	
453	
454	
455	
456	
457	

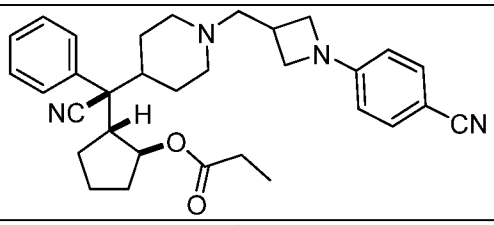
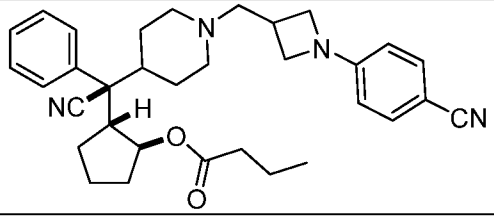
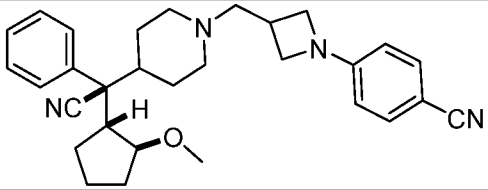
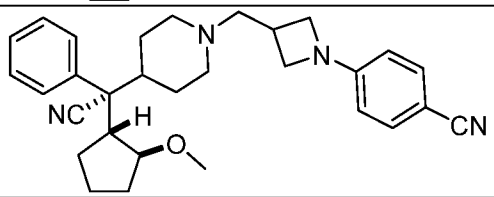
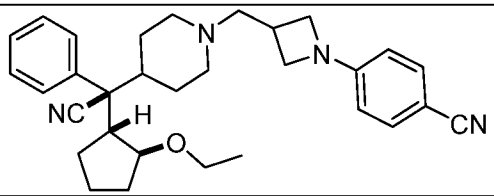
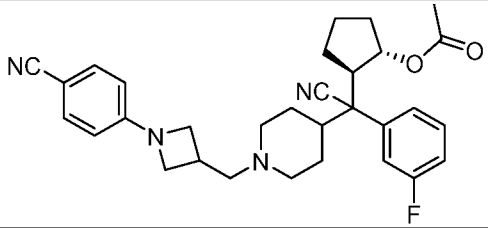
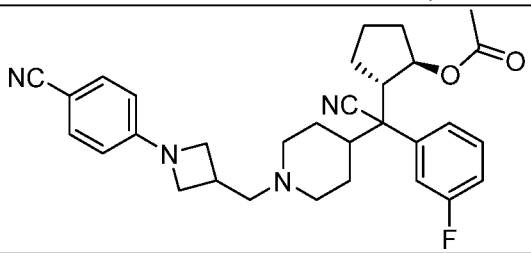
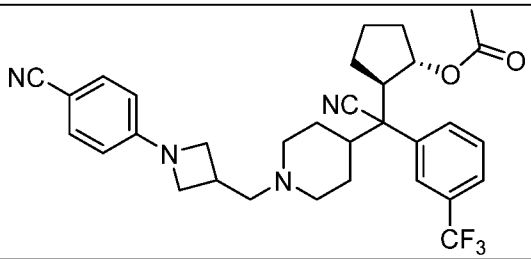
458	
459	
460	
461	
462	
463	
464	

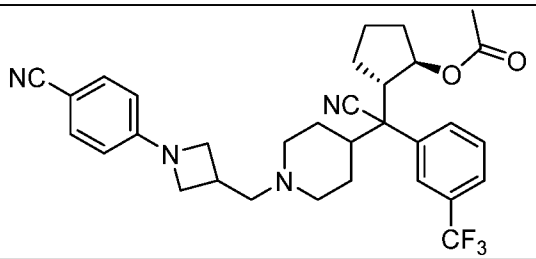
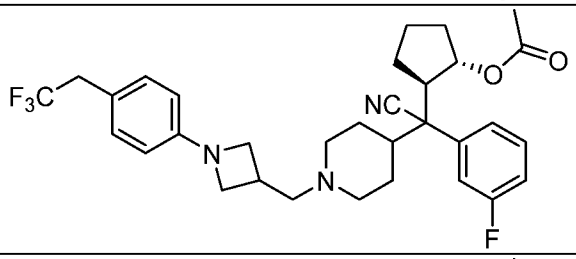
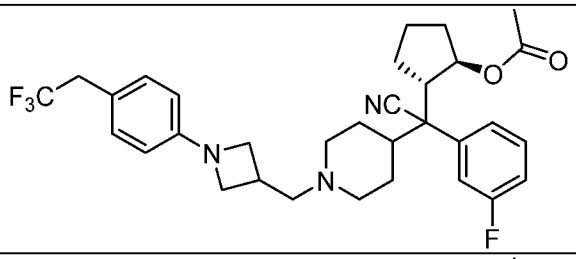
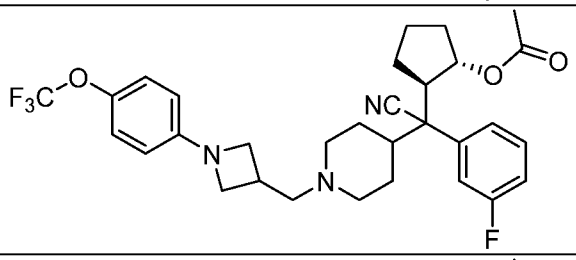
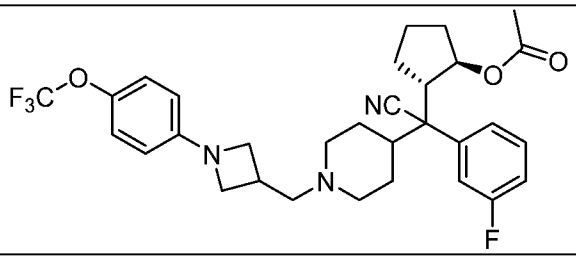
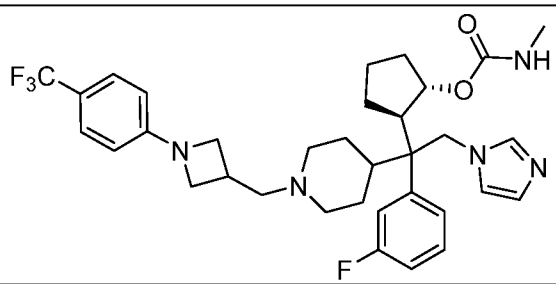
465	
466	
467	
468	
469	
470	
471	

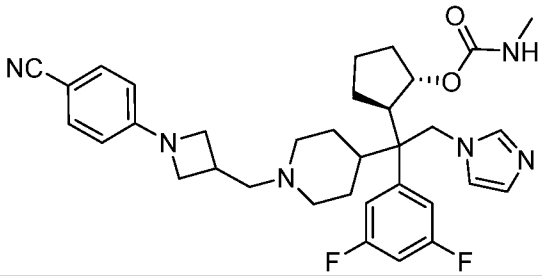
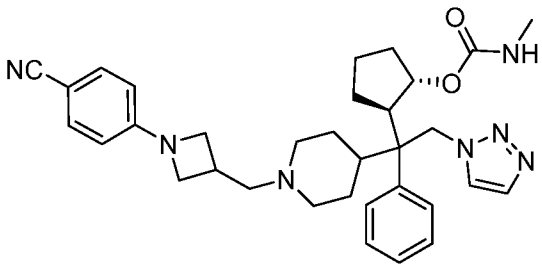
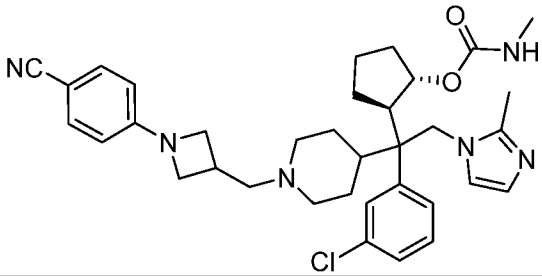
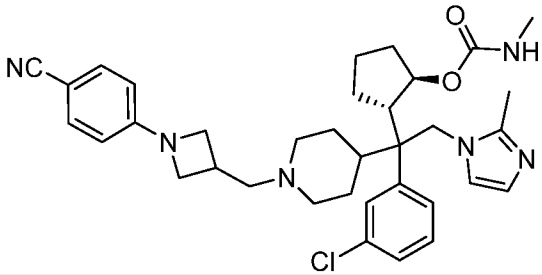
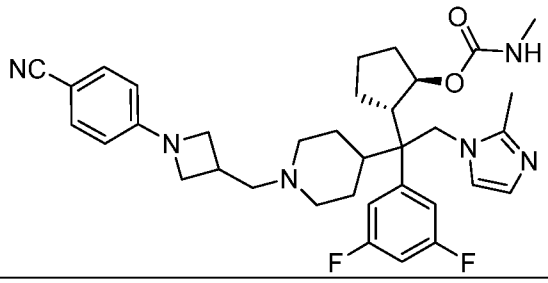
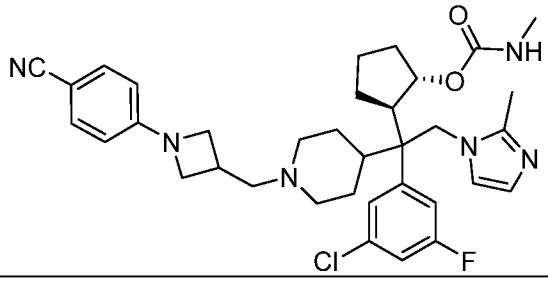
472	
473	
474	
475	
476	
477	
478	

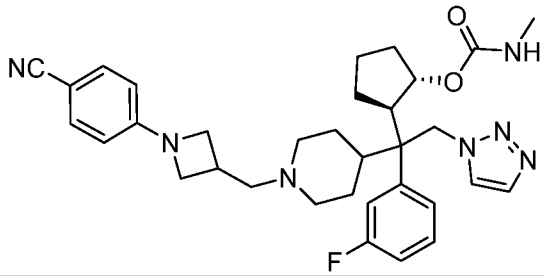
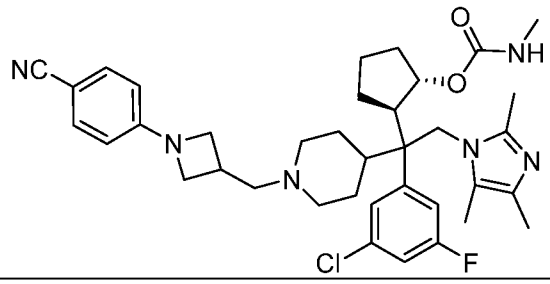
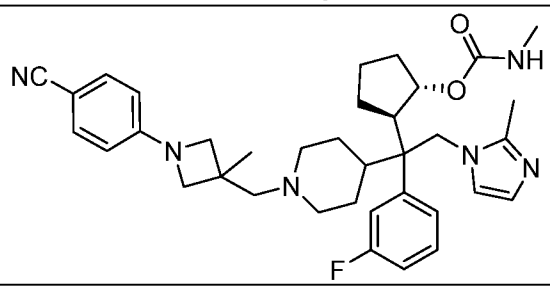
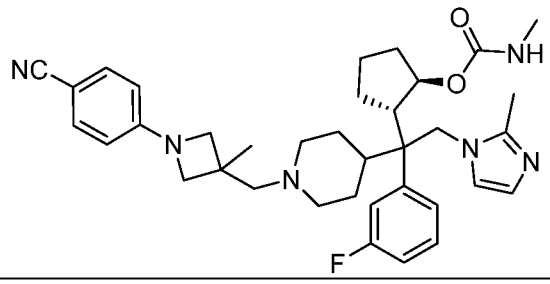
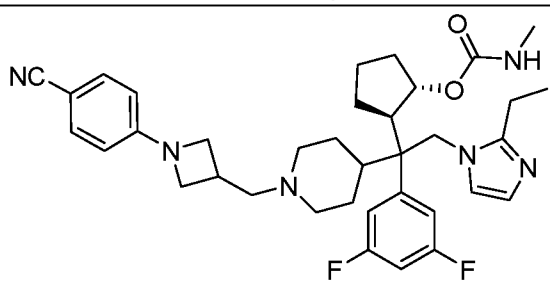
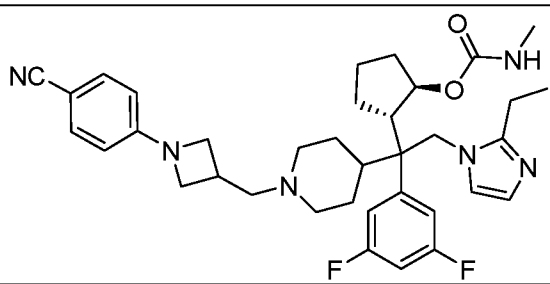
479	
480	
481	
482	
483	
484	
485	

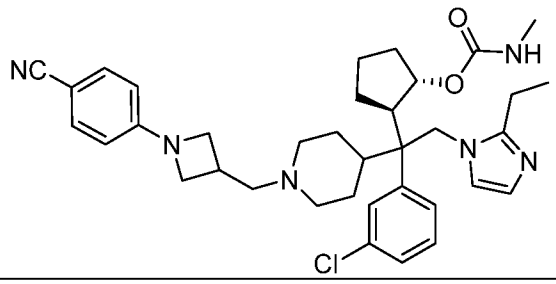
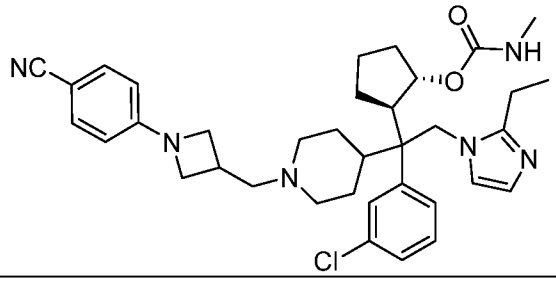
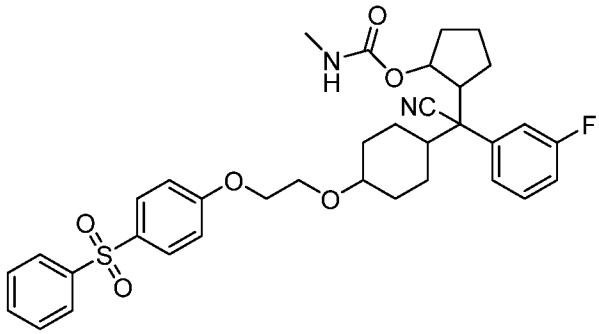
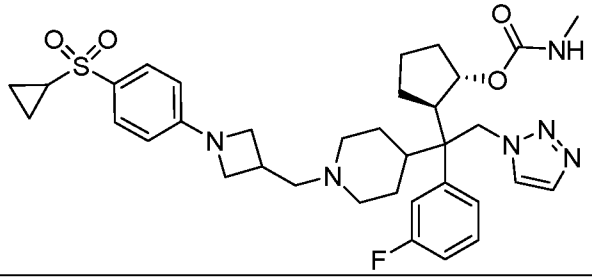
486	
487	
488	
489	
490	
491	
492	

493	
494	
495	
496	
497	
498	
499	
500	

501	
502	
503	
504	
505	
506	

507	
508	
509	
510	
511	
512	

513	
514	
515	
516	
517	
518	

519	
520	
521	
522	

[0105] Compounds of the Disclosure inhibit menin and are useful in the treatment of a variety of diseases and conditions. In particular, Compounds of the Disclosure are useful in methods of treating a disease or condition wherein inhibition of menin provides a benefit, for example, cancers and proliferative diseases. Methods of the disclosure comprise administering a therapeutically effective amount of a Compound of the Disclosure to an individual in need thereof. The present methods also encompass administering a second therapeutic agent to the individual in addition to the Compound of the Disclosure. The second therapeutic agent is selected from drugs known as useful in treating the disease or condition afflicting the individual in need thereof,

e.g., a chemotherapeutic agent and/or radiation known as useful in treating a particular cancer.

[0106] Salts, hydrates, and solvates of the Compounds of the Disclosure can also be used in the methods disclosed herein. The present disclosure further includes all possible stereoisomers and geometric isomers of Compounds of the Disclosure to include both racemic compounds and optically active isomers. When a Compound of the Disclosure is desired as a single enantiomer, it can be obtained either by resolution of the final product or by stereospecific synthesis from either isomerically pure starting material or use of a chiral auxiliary reagent, for example, see Z. Ma et al., *Tetrahedron: Asymmetry, 8(6)*, pages 883-888 (1997). Resolution of the final product, an intermediate, or a starting material can be achieved by any suitable method known in the art. Additionally, in situations where tautomers of the Compounds of the Disclosure are possible, the present disclosure is intended to include all tautomeric forms of the compounds.

[0107] The present disclosure encompasses the preparation and use of salts of Compounds of the Disclosure. As used herein, the pharmaceutical "pharmaceutically acceptable salt" refers to salts or zwitterionic forms of Compounds of the Disclosure. Salts of Compounds of the Disclosure can be prepared during the final isolation and purification of the compounds or separately by reacting the compound with an acid having a suitable cation. The pharmaceutically acceptable salts of Compounds of the Disclosure can be acid addition salts formed with pharmaceutically acceptable acids. Examples of acids which can be employed to form pharmaceutically acceptable salts include inorganic acids such as nitric, boric, hydrochloric, hydrobromic, sulfuric, and phosphoric, and organic acids such as oxalic, maleic, succinic, and citric. Nonlimiting examples of salts of compounds of the disclosure include, but are not limited to, the hydrochloride, hydrobromide, hydroiodide, sulfate, bisulfate, 2-hydroxyethansulfonate, phosphate, hydrogen phosphate, acetate, adipate, alginate, aspartate, benzoate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, glycerolphsphate, hemisulfate, heptanoate, hexanoate, formate, succinate, fumarate, maleate, ascorbate, isethionate, salicylate, methanesulfonate, mesitylenesulfonate, naphthylenesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, pamoate, pectinate, persulfate, 3-phenylproprionate, picrate, pivalate, propionate, trichloroacetate, trifluoroacetate,

phosphate, glutamate, bicarbonate, paratoluenesulfonate, undecanoate, lactate, citrate, tartrate, gluconate, methanesulfonate, ethanedisulfonate, benzene sulfonate, and p-toluenesulfonate salts. In addition, available amino groups present in the compounds of the disclosure can be quaternized with methyl, ethyl, propyl, and butyl chlorides, bromides, and iodides; dimethyl, diethyl, dibutyl, and diamyl sulfates; decyl, lauryl, myristyl, and steryl chlorides, bromides, and iodides; and benzyl and phenethyl bromides. In light of the foregoing, any reference Compounds of the Disclosure appearing herein is intended to include compounds of Compounds of the Disclosure as well as pharmaceutically acceptable salts, hydrates, or solvates thereof.

[0108] The present disclosure encompasses the preparation and use of solvates of Compounds of the Disclosure. Solvates typically do not significantly alter the physiological activity or toxicity of the compounds, and as such may function as pharmacological equivalents. The term "solvate" as used herein is a combination, physical association and/or solvation of a compound of the present disclosure with a solvent molecule such as, e.g. a disolvate, monosolvate, or hemisolvate, where the ratio of solvent molecule to compound of the present disclosure is about 2:1, about 1:1 or about 1:2, respectively. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances, the solvate can be isolated, such as when one or more solvent molecules are incorporated into the crystal lattice of a crystalline solid. Thus, "solvate" encompasses both solution-phase and isolatable solvates. Compounds of the Disclosure can be present as solvated forms with a pharmaceutically acceptable solvent, such as water, methanol, ethanol, and the like, and it is intended that the disclosure includes both solvated and unsolvated forms of Compounds of the Disclosure. One type of solvate is a hydrate. A "hydrate" relates to a particular subgroup of solvates where the solvent molecule is water. Solvates typically can function as pharmacological equivalents. Preparation of solvates is known in the art. See, for example, M. Caira *et al*, *J. Pharmaceut. Sci., 93(3)*:601-611 (2004), which describes the preparation of solvates of fluconazole with ethyl acetate and with water. Similar preparation of solvates, hemisolvates, hydrates, and the like are described by E.C. van Tonder *et al.*, *AAPS Pharm. Sci. Tech., 5(1)*:Article 12 (2004), and A.L. Bingham *et al.*, *Chem. Commun.* 603-604 (2001). A typical, non-limiting, process of preparing a solvate would involve dissolving a Compound of the

Disclosure in a desired solvent (organic, water, or a mixture thereof) at temperatures above 20°C to about 25°C, then cooling the solution at a rate sufficient to form crystals, and isolating the crystals by known methods, e.g., filtration. Analytical techniques such as infrared spectroscopy can be used to confirm the presence of the solvent in a crystal of the solvate.

[0109] The present disclosure provides Compounds of the Disclosure as menin inhibitors for the treatment of diseases and conditions wherein inhibition of menin has a beneficial effect. Compounds of the Disclosure typically have a binding affinity (IC_{50}) to menin of less than 100 μM, e.g., less than 50 μM, less than 25 μM, and less than 5 μM, less than about 1 μM, less than about 0.5 μM, less than about 0.1 μM, less than about 0.05 μM, or less than about 0.01 μM. In one embodiment, the present disclosure relates to a method of treating an individual suffering from a disease or condition wherein inhibition of menin provides a benefit comprising administering a therapeutically effective amount of a Compound of the Disclosure to an individual in need thereof.

[0110] Diseases and conditions mediated by menin can be treated by administering Compounds of the Disclosure because these compounds are inhibitors of menin. The present disclosure is thus directed generally to a method for treating a condition or disorder responsive to inhibition of menin, in an animal, e.g., a human, suffering from, or at risk of suffering from, the condition or disorder, the method comprising administering to the animal an effective amount of one or more Compounds of the Disclosure.

[0111] The present disclosure is further directed to a method of inhibiting menin in an animal in need thereof, said method comprising administering to the animal an effective amount of at least one Compound of the Disclosure.

[0112] The methods of the present disclosure can be accomplished by administering a Compound of the Disclosure as the neat compound or as a pharmaceutical composition. Administration of a pharmaceutical composition, or neat compound of a Compound of the Disclosure, can be performed during or after the onset of the disease or condition of interest. Typically, the pharmaceutical compositions are sterile, and contain no toxic, carcinogenic, or mutagenic compounds that would cause an adverse reaction when administered. Further provided are kits comprising a Compound of the Disclosure and,

optionally, a second therapeutic agent, packaged separately or together, and an insert having instructions for using these active agents.

[0113] In one embodiment, a Compound of the Disclosure is administered in conjunction with a second therapeutic agent useful in the treatment of a disease or condition wherein inhibition of menin provides a benefit. The second therapeutic agent is different from the Compound of the Disclosure. A Compound of the Disclosure and the second therapeutic agent can be administered simultaneously or sequentially to achieve the desired effect. In addition, the Compound of the Disclosure and second therapeutic agent can be administered from a single composition or two separate compositions.

[0114] The second therapeutic agent is administered in an amount to provide its desired therapeutic effect. The effective dosage range for each second therapeutic agent is known in the art, and the second therapeutic agent is administered to an individual in need thereof within such established ranges.

[0115] A Compound of the Disclosure and the second therapeutic agent can be administered together as a single-unit dose or separately as multi-unit doses, wherein the Compound of the Disclosure is administered before the second therapeutic agent or vice versa. One or more doses of the Compound of the Disclosure and/or one or more dose of the second therapeutic agent can be administered. The Compound of the Disclosure therefore can be used in conjunction with one or more second therapeutic agents, for example, but not limited to, anticancer agents.

[0116] Diseases and conditions treatable by the methods of the present disclosure include, but are not limited to, cancer and other proliferative disorders, inflammatory diseases, sepsis, autoimmune disease, and viral infection. In one embodiment, a human patient is treated with a Compound of the Disclosure, or a pharmaceutical composition comprising a Compound of the Disclosure, wherein the compound is administered in an amount sufficient to inhibit menin activity in the patient.

[0117] In one embodiment, the disease to be treated by the Compound of the Disclosure is cancer. Examples of treatable cancers include, but are not limited to, adrenal cancer, acinic cell carcinoma, acoustic neuroma, acral lentigious melanoma, acrospiroma, acute eosinophilic leukemia, acute erythroid leukemia, acute lymphoblastic leukemia, acute megakaryoblastic leukemia, acute monocytic leukemia,

acute promyelocytic leukemia, adenocarcinoma, adenoid cystic carcinoma, adenoma, adenomatoid odontogenic tumor, adenosquamous carcinoma, adipose tissue neoplasm, adrenocortical carcinoma, adult T-cell leukemia/lymphoma, aggressive NK-cell leukemia, AIDS-related lymphoma, alveolar rhabdomyosarcoma, alveolar soft part sarcoma, ameloblastic fibroma, anaplastic large cell lymphoma, anaplastic thyroid cancer, angioimmunoblastic T-cell lymphoma, angiomyolipoma, angiosarcoma, astrocytoma, atypical teratoid rhabdoid tumor, B-cell chronic lymphocytic leukemia, B-cell prolymphocytic leukemia, B-cell lymphoma, basal cell carcinoma, biliary tract cancer, bladder cancer, blastoma, bone cancer, Brenner tumor, Brown tumor, Burkitt's lymphoma, breast cancer, brain cancer, carcinoma, carcinoma in situ, carcinosarcoma, cartilage tumor, cementoma, myeloid sarcoma, chondroma, chordoma, choriocarcinoma, choroid plexus papilloma, clear-cell sarcoma of the kidney, craniopharyngioma, cutaneous T-cell lymphoma, cervical cancer, colorectal cancer, Degos disease, desmoplastic small round cell tumor, diffuse large B-cell lymphoma, dysembryoplastic neuroepithelial tumor, dysgerminoma, embryonal carcinoma, endocrine gland neoplasm, endodermal sinus tumor, enteropathy-associated T-cell lymphoma, esophageal cancer, fetus in fetu, fibroma, fibrosarcoma, follicular lymphoma, follicular thyroid cancer, ganglioneuroma, gastrointestinal cancer, germ cell tumor, gestational choriocarcinoma, giant cell fibroblastoma, giant cell tumor of the bone, glial tumor, glioblastoma multiforme, glioma, gliomatosis cerebri, glucagonoma, gonadoblastoma, granulosa cell tumor, gynandroblastoma, gallbladder cancer, gastric cancer, hairy cell leukemia, hemangioblastoma, head and neck cancer, hemangiopericytoma, hematological malignancy, hepatoblastoma, hepatosplenic T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, invasive lobular carcinoma, intestinal cancer, kidney cancer, laryngeal cancer, lentigo maligna, lethal midline carcinoma, leukemia, leydig cell tumor, liposarcoma, lung cancer, lymphangioma, lymphangiosarcoma, lymphoepithelioma, lymphoma, acute lymphocytic leukemia, acute myelogeous leukemia, chronic lymphocytic leukemia, liver cancer, small cell lung cancer, non-small cell lung cancer, MALT lymphoma, malignant fibrous histiocytoma, malignant peripheral nerve sheath tumor, malignant triton tumor, mantle cell lymphoma, marginal zone B-cell lymphoma, mast cell leukemia, mediastinal germ cell tumor, medullary carcinoma of the breast, medullary

thyroid cancer, medulloblastoma, melanoma, meningioma, merkel cell cancer, mesothelioma, metastatic urothelial carcinoma, mixed Mullerian tumor, mucinous tumor, multiple myeloma, muscle tissue neoplasm, mycosis fungoides, myxoid liposarcoma, myxoma, myxosarcoma, nasopharyngeal carcinoma, neurinoma, neuroblastoma, neurofibroma, neuroma, nodular melanoma, ocular cancer, oligoastrocytoma, oligodendroglioma, oncocytoma, optic nerve sheath meningioma, optic nerve tumor, oral cancer, osteosarcoma, ovarian cancer, Pancoast tumor, papillary thyroid cancer, paraganglioma, pinealoblastoma, pineocytoma, pituicytoma, pituitary adenoma, pituitary tumor, plasmacytoma, polyembryoma, precursor T-lymphoblastic lymphoma, primary central nervous system lymphoma, primary effusion lymphoma, preimary peritoneal cancer, prostate cancer, pancreatic cancer, pharyngeal cancer, pseudomyxoma periotonei, renal cell carcinoma, renal medullary carcinoma, retinoblastoma, rhabdomyoma, rhabdomyosarcoma, Richter's transformation, rectal cancer, sarcoma, Schwannomatosis, seminoma, Sertoli cell tumor, sex cord-gonadal stromal tumor, signet ring cell carcinoma, skin cancer, small blue round cell tumors, small cell carcinoma, soft tissue sarcoma, somatostatinoma, soot wart, spinal tumor, splenic marginal zone lymphoma, squamous cell carcinoma, synovial sarcoma, Sezary's disease, small intestine cancer, squamous carcinoma, stomach cancer, T-cell lymphoma, testicular cancer, thecoma, thyroid cancer, transitional cell carcinoma, throat cancer, urachal cancer, urogenital cancer, urothelial carcinoma, uveal melanoma, uterine cancer, verrucous carcinoma, visual pathway glioma, vulvar cancer, vaginal cancer, Waldenstrom's macroglobulinemia, Warthin's tumor, and Wilms' tumor.

[0118] In another embodiment, the cancer is a leukaemia, for example a leukaemia selected from acute monocytic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia and mixed lineage leukaemia (MLL). In another embodiment the cancer is NUT-midline carcinoma. In another embodiment the cancer is multiple myeloma. In another embodiment the cancer is a lung cancer such as small cell lung cancer (SCLC). In another embodiment the cancer is a neuroblastoma. In another embodiment the cancer is Burkitt's lymphoma. In another embodiment the cancer is cervical cancer. In another embodiment the cancer is esophageal cancer. In another embodiment the cancer is ovarian cancer. In another

embodiment the cancer is colorectal cancer. In another embodiment, the cancer is prostate cancer. In another embodiment, the cancer is breast cancer.

[0119] In another embodiment, the present disclosure provides a method of treating a benign proliferative disorder, such as, but are not limited to, benign soft tissue tumors, bone tumors, brain and spinal tumors, eyelid and orbital tumors, granuloma, lipoma, meningioma, multiple endocrine neoplasia, nasal polyps, pituitary tumors, prolactinoma, pseudotumor cerebri, seborrheic keratoses, stomach polyps, thyroid nodules, cystic neoplasms of the pancreas, hemangiomas, vocal cord nodules, polyps, and cysts, Castleman disease, chronic pilonidal disease, dermatofibroma, pilar cyst, pyogenic granuloma, and juvenile polyposis syndrome.

[0120] Compounds of the Disclosure can also treat infectious and noninfectious inflammatory events and autoimmune and other inflammatory diseases by administration of an effective amount of a present compound to a mammal, in particular a human in need of such treatment. Examples of autoimmune and inflammatory diseases, disorders, and syndromes treated using the compounds and methods described herein include inflammatory pelvic disease, urethritis, skin sunburn, sinusitis, pneumonitis, encephalitis, meningitis, myocarditis, nephritis, osteomyelitis, myositis, hepatitis, gastritis, enteritis, dermatitis, gingivitis, appendictitis, pancreatitis, cholocystitus, agammaglobulinemia, psoriasis, allergy, Crohn's disease, irritable bowel syndrome, ulcerative colitis, Sjogren's disease, tissue graft rejection, hyperacute rejection of transplanted organs, asthma, allergic rhinitis, chronic obstructive pulmonary disease (COPD), autoimmune polyglandular disease (also known as autoimmune polyglandular syndrome), autoimmune alopecia, pernicious anemia, glomerulonephritis, dermatomyositis, multiple sclerosis, scleroderma, vasculitis, autoimmune hemolytic and thrombocytopenic states, Goodpasture's syndrome, atherosclerosis, Addison's disease, Parkinson's disease, Alzheimer's disease, Type I diabetes, septic shock, systemic lupus erythematosus (SLE), rheumatoid arthritis, psoriatic arthritis, juvenile arthritis, osteoarthritis, chronic idiopathic thrombocytopenic purpura, Waldenstrom macroglobulinemia, myasthenia gravis, Hashimoto's thyroiditis, atopic dermatitis, degenerative joint disease, vitiligo, autoimmune hypopituatarism, Guillain-Barre syndrome, Behcet's disease, scleracierma, mycosis fungoides, acute

inflammatory responses (such as acute respiratory distress syndrome and ischemia/reperfusion injury), and Graves' disease.

[0121] In another embodiment, the present disclosure provides a method of treating systemic inflammatory response syndromes, such as LPS-induced endotoxic shock and/or bacteria-induced sepsis by administration of an effective amount of a Compound of the Disclosure to a mammal, in particular a human in need of such treatment.

[0122] In another embodiment, the present disclosure provides a method for treating viral infections and diseases. Examples of viral infections and diseases treated using the compounds and methods described herein include episome-based DNA viruses including, but not limited to, human papillomavirus, Herpesvirus, Epstein-Barr virus, human immunodeficiency virus, hepatis B virus, and hepatitis C virus.

[0123] In another embodiment, the present disclosure provides therapeutic method of modulating protein methylation, gene expression, cell proliferation, cell differentiation and/or apoptosis *in vivo* in diseases mentioned above, in particular cancer, inflammatory disease, and/or viral disease is provided by administering a therapeutically effective amount of a Compound of the Disclosure to a subject in need of such therapy.

[0124] In another embodiment, the present disclosure provides a method of regulating endogenous or heterologous promoter activity by contacting a cell with a Compound of the Disclosure.

[0125] In methods of the present disclosure, a therapeutically effective amount of a Compound of the Disclosure, typically formulated in accordance with pharmaceutical practice, is administered to a human being in need thereof. Whether such a treatment is indicated depends on the individual case and is subject to medical assessment (diagnosis) that takes into consideration signs, symptoms, and/or malfunctions that are present, the risks of developing particular signs, symptoms and/or malfunctions, and other factors.

[0126] A Compound of the Disclosure can be administered by any suitable route, for example by oral, buccal, inhalation, sublingual, rectal, vaginal, intracisternal or intrathecal through lumbar puncture, transurethral, nasal, percutaneous, i.e., transdermal, or parenteral (including intravenous, intramuscular, subcutaneous, intracoronary, intradermal, intramammary, intraperitoneal, intraarticular, intrathecal,

retrobulbar, intrapulmonary injection and/or surgical implantation at a particular site) administration. Parenteral administration can be accomplished using a needle and syringe or using a high pressure technique.

[0127] Pharmaceutical compositions include those wherein a Compound of the Disclosure is administered in an effective amount to achieve its intended purpose. The exact formulation, route of administration, and dosage is determined by an individual physician in view of the diagnosed condition or disease. Dosage amount and interval can be adjusted individually to provide levels of a Compound of the Disclosure that is sufficient to maintain therapeutic effects.

[0128] Toxicity and therapeutic efficacy of the Compounds of the Disclosure can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the maximum tolerated dose (MTD) of a compound, which defines as the highest dose that causes no toxicity in animals. The dose ratio between the maximum tolerated dose and therapeutic effects (e.g. inhibiting of tumor growth) is the therapeutic index. The dosage can vary within this range depending upon the dosage form employed, and the route of administration utilized. Determination of a therapeutically effective amount is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein.

[0129] A therapeutically effective amount of a Compound of the Disclosure required for use in therapy varies with the nature of the condition being treated, the length of time that activity is desired, and the age and the condition of the patient, and ultimately is determined by the attendant physician. Dosage amounts and intervals can be adjusted individually to provide plasma levels of the menin inhibitor that are sufficient to maintain the desired therapeutic effects. The desired dose conveniently can be administered in a single dose, or as multiple doses administered at appropriate intervals, for example as one, two, three, four or more subdoses per day. Multiple doses often are desired, or required. For example, a Compound of the Disclosure can be administered at a frequency of: four doses delivered as one dose per day at four-day intervals (q4d x 4); four doses delivered as one dose per day at three-day intervals (q3d x 4); one dose delivered per day at five-day intervals (qd x 5); one dose per week for three weeks (qwk3); five daily doses, with two days rest, and another five daily doses (5/2/5); or, any dose regimen determined to be appropriate for the circumstance.

[0130] A Compound of the Disclosure used in a method of the present disclosure can be administered in an amount of about 0.005 to about 500 milligrams per dose, about 0.05 to about 250 milligrams per dose, or about 0.5 to about 100 milligrams per dose. For example, a Compound of the Disclosure can be administered, per dose, in an amount of about 0.005, about 0.05, about 0.5, about 5, about 10, about 20, about 30, about 40, about 50, about 100, about 150, about 200, about 250, about 300, about 350, about 400, about 450, or about 500 milligrams, including all doses between 0.005 and 500 milligrams.

[0131] The dosage of a composition containing a Compound of the Disclosure, or a composition containing the same, can be from about 1 ng/kg to about 200 mg/kg, about 1 μg/kg to about 100 mg/kg, or about 1 mg/kg to about 50 mg/kg. The dosage of a composition can be at any dosage including, but not limited to, about 1 μg/kg. The dosage of a composition may be at any dosage including, but not limited to, about 1 μg/kg, about 10 μg/kg, about 25 μg/kg, about 50 μg/kg, about 75 μg/kg, about 100 μg/kg, about 125 μg/kg, about 150 μg/kg, about 175 μg/kg, about 200 μg/kg, about 225 μg/kg, about 250 μg/kg, about 275 μg/kg, about 300 μg/kg, about 325 μg/kg, about 350 μg/kg, about 375 μg/kg, about 400 μg/kg, about 425 μg/kg, about 450 μg/kg, about 475 μg/kg, about 500 μg/kg, about 525 μg/kg, about 550 μg/kg, about 575 μg/kg, about 600 μg/kg, about 625 μg/kg, about 650 μg/kg, about 675 μg/kg, about 700 μg/kg, about 725 μg/kg, about 750 μg/kg, about 775 μg/kg, about 800 μg/kg, about 825 μg/kg, about 850 μg/kg, about 875 μg/kg, about 900 μg/kg, about 925 μg/kg, about 950 μg/kg, about 975 μg/kg, about 1 mg/kg, about 5 mg/kg, about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, about 25 mg/kg, about 30 mg/kg, about 35 mg/kg, about 40 mg/kg, about 45 mg/kg, about 50 mg/kg, about 60 mg/kg, about 70 mg/kg, about 80 mg/kg, about 90 mg/kg, about 100 mg/kg, about 125 mg/kg, about 150 mg/kg, about 175 mg/kg, about 200 mg/kg, or more. The above dosages are exemplary of the average case, but there can be individual instances in which higher or lower dosages are merited, and such are within the scope of this disclosure. In practice, the physician determines the actual dosing regimen that is most suitable for an individual patient, which can vary with the age, weight, and response of the particular patient.

[0132] As stated above, a Compound of the Disclosure can be administered in combination with a second therapeutically active agent. In some embodiments, the

second therapeutic agent is an epigenetic drug. As used herein, the term "epigenetic drug" refers to a therapeutic agent that targets an epigenetic regulator. Examples of epigenetic regulators include the histone lysine methyltransferases, histone arginine methyl transferases, histone demethylases, histone deacetylases, histone acetylases, and DNA methyltransferases. Histone deacetylase inhibitors include, but are not limited to, vorinostat.

[0133] In another embodiment, chemotherapeutic agents or other anti-proliferative agents can be combined with Compound of the Disclosure to treat proliferative diseases and cancer. Examples of therapies and anticancer agents that can be used in combination with Compounds of the Disclosure include surgery, radiotherapy (e.g., gamma-radiation, neutron beam radiotherapy, electron beam radiotherapy, proton therapy, brachytherapy, and systemic radioactive isotopes), endocrine therapy, a biologic response modifier (e.g., an interferon, an interleukin, tumor necrosis factor (TNF), hyperthermia and cryotherapy, an agent to attenuate any adverse effect (e.g., an antiemetic), and any other approved chemotherapeutic drug.

[0134] Examples of antiproliferative compounds include, but are not limited to, an aromatase inhibitor; an anti-estrogen; an anti-androgen; a gonadorelin agonist; a topoisomerase I inhibitor; a topoisomerase II inhibitor; a microtubule active agent; an alkylating agent; a retinoid, a carontenoid, or a tocopherol; a cyclooxygenase inhibitor; an MMP inhibitor; an mTOR inhibitor; an antimetabolite; a platin compound; a methionine aminopeptidase inhibitor; a bisphosphonate; an antiproliferative antibody; a heparanase inhibitor; an inhibitor of Ras oncogenic isoforms; a telomerase inhibitor; a proteasome inhibitor; a compound used in the treatment of hematologic malignancies; a Flt-3 inhibitor; an Hsp90 inhibitor; a kinesin spindle protein inhibitor; a MEK inhibitor; an antitumor antibiotic; a nitrosourea; a compound targeting/decreasing protein or lipid kinase activity, a compound targeting/decreasing protein or lipid phosphatase activity, or any further anti-angiogenic compound.

[0135] Nonlimiting exemplary aromatase inhibitors include, but are not limited to, steroids, such as atamestane, exemestane, and formestane, and non-steroids, such as aminoglutethimide, roglethimide, pyridoglutethimide, trilostane, testolactone, ketokonazole, vorozole, fadrozole, anastrozole, and letrozole.

[0136] Nonlimiting anti-estrogens include, but are not limited to, tamoxifen, fulvestrant, raloxifene, and raloxifene hydrochloride. Anti-androgens include, but are not limited to, bicalutamide. Gonadorelin agonists include, but are not limited to, abarelix, goserelin, and goserelin acetate.

[0137] Exemplary topoisomerase I inhibitors include, but are not limited to, topotecan, gimatecan, irinotecan, camptothecin and its analogues, 9-nitrocamptothecin, and the macromolecular camptothecin conjugate PNU-166148. Topoisomerase II inhibitors include, but are not limited to, anthracyclines, such as doxorubicin, daunorubicin, epirubicin, idarubicin, and nemorubicin; anthraquinones, such as mitoxantrone and losoxantrone; and podophillotoxines, such as etoposide and teniposide.

[0138] Microtubule active agents include microtubule stabilizing, microtubule destabilizing compounds, and microtubulin polymerization inhibitors including, but not limited to, taxanes, such as paclitaxel and docetaxel; vinca alkaloids, such as vinblastine, vinblastine sulfate, vincristine, and vincristine sulfate, and vinorelbine; discodermolides; cochicine and epothilones and derivatives thereof.

[0139] Exemplary nonlimiting alkylating agents include cyclophosphamide, ifosfamide, melphalan, and nitrosoureas, such as carmustine and lomustine.

[0140] Exemplary nonlimiting cyclooxygenase inhibitors include Cox-2 inhibitors, 5-alkyl substituted 2-arylaminophenylacetic acid and derivatives, such as celecoxib, rofecoxib, etoricoxib, valdecoxib, or a 5-alkyl-2-arylaminophenylacetic acid, such as lumiracoxib.

[0141] Exemplary nonlimiting matrix metalloproteinase inhibitors ("MMP inhibitors") include collagen peptidomimetic and nonpeptidomimetic inhibitors, tetracycline derivatives, batimastat, marimastat, prinomastat, metastat, BMS-279251, BAY 12-9566, TAA211, MMI270B, and AAJ996.

[0142] Exemplary nonlimiting mTOR inhibitors include compounds that inhibit the mammalian target of rapamycin (mTOR) and possess antiproliferative activity such as sirolimus, everolimus, CCI-779, and ABT578.

[0143] Exemplary nonlimiting antimetabolites include 5-fluorouracil (5-FU), capecitabine, gemcitabine, DNA demethylating compounds, such as 5-azacytidine and decitabine, methotrexate and edatrexate, and folic acid antagonists, such as pemetrexed.

[0144] Exemplary nonlimiting platin compounds include carboplatin, cis-platin, cisplatinum, and oxaliplatin.

[0145] Exemplary nonlimiting methionine aminopeptidase inhibitors include bengamide or a derivative thereof and PPI-2458.

[0146] Exemplary nonlimiting bisphosphonates include etridonic acid, clodronic acid, tiludronic acid, pamidronic acid, alendronic acid, ibandronic acid, risedronic acid, and zoledronic acid.

[0147] Exemplary nonlimiting antiproliferative antibodies include trastuzumab, trastuzumab-DMl, cetuximab, bevacizumab, rituximab, PR064553, and 2C4. The term “antibody" is meant to include intact monoclonal antibodies, polyclonal antibodies, multispecific antibodies formed from at least two intact antibodies, and antibody fragments, so long as they exhibit the desired biological activity.

[0148] Exemplary nonlimiting heparanase inhibitors include compounds that target, decrease, or inhibit heparin sulfate degradation, such as PI-88 and OGT2115.

[0149] The term "an inhibitor of Ras oncogenic isoforms," such as H-Ras, K-Ras, or N-Ras, as used herein refers to a compound which targets, decreases, or inhibits the oncogenic activity of Ras, for example, a farnesyl transferase inhibitor, such as L-744832, DK8G557, tipifarnib, and lonafarnib.

[0150] Exemplary nonlimiting telomerase inhibitors include compounds that target, decrease, or inhibit the activity of telomerase, such as compounds that inhibit the telomerase receptor, such as telomestatin.

[0151] Exemplary nonlimiting proteasome inhibitors include compounds that target, decrease, or inhibit the activity of the proteasome including, but not limited to, bortezomid.

[0152] The phrase "compounds used in the treatment of hematologic malignancies" as used herein includes FMS-like tyrosine kinase inhibitors, which are compounds targeting, decreasing or inhibiting the activity of FMS-like tyrosine kinase receptors (Flt-3R); interferon, I-β-D-arabinofuransylcytosine (ara-c), and bisulfan; and ALK inhibitors, which are compounds which target, decrease, or inhibit anaplastic lymphoma kinase.

[0153] Exemplary nonlimiting Flt-3 inhibitors include PKC412, midostaurin, a staurosporine derivative, SU11248, and MLN518.

[0154] Exemplary nonlimiting HSP90 inhibitors include compounds targeting, decreasing, or inhibiting the intrinsic ATPase activity of HSP90; or degrading, targeting, decreasing or inhibiting the HSP90 client proteins via the ubiquitin proteosome pathway. Compounds targeting, decreasing or inhibiting the intrinsic ATPase activity of HSP90 are especially compounds, proteins, or antibodies that inhibit the ATPase activity of HSP90, such as 17-allylamino,17-demethoxygeldanamycin (17AAG), a geldanamycin derivative; other geldanamycin related compounds; radicicol and HDAC inhibitors.

[0155] The phrase "a compound targeting/decreasing a protein or lipid kinase activity; or a protein or lipid phosphatase activity; or any further anti-angiogenic compound" as used herein includes a protein tyrosine kinase and/or serine and/or threonine kinase inhibitor or lipid kinase inhibitor, such as a) a compound targeting, decreasing, or inhibiting the activity of the platelet- derived growth factor-receptors (PDGFR), such as a compound that targets, decreases, or inhibits the activity of PDGFR, such as an N-phenyl-2-pyrimidine-amine derivatives, such as imatinib, SUlOl, SU6668, and GFB-111; b) a compound targeting, decreasing, or inhibiting the activity of the fibroblast growth factor-receptors (FGFR); c) a compound targeting, decreasing, or inhibiting the activity of the insulin-like growth factor receptor I (IGF-IR), such as a compound that targets, decreases, or inhibits the activity of IGF-IR; d) a compound targeting, decreasing, or inhibiting the activity of the Trk receptor tyrosine kinase family, or ephrin B4 inhibitors; e) a compound targeting, decreasing, or inhibiting the activity of the Axl receptor tyrosine kinase family; f) a compound targeting, decreasing, or inhibiting the activity of the Ret receptor tyrosine kinase; g) a compound targeting, decreasing, or inhibiting the activity of the Kit/SCFR receptor tyrosine kinase, such as imatinib; h) a compound targeting, decreasing, or inhibiting the activity of the c-Kit receptor tyrosine kinases, such as imatinib; i) a compound targeting, decreasing, or inhibiting the activity of members of the c-Abl family, their gene-fusion products (e.g. Bcr-Abl kinase) and mutants, such as an N-phenyl-2-pyrimidine-amine derivative, such as imatinib or nilotinib; PD180970; AG957; NSC 680410; PD173955; or dasatinib; j) a compound targeting, decreasing, or inhibiting the activity of members of the protein kinase C (PKC) and Raf family of serine/threonine kinases, members of the MEK, SRC, JAK, FAK, PDK1, PKB/Akt, and Ras/MAPK family members, and/or members

of the cyclin-dependent kinase family (CDK), such as a staurosporine derivative disclosed in U.S. Patent No. 5,093,330, such as midostaurin; examples of further compounds include UCN-01, safingol, BAY 43-9006, bryostatin 1, perifosine; ilmofosine; RO 318220 and RO 320432; GO 6976; Isis 3521 ; LY333531/LY379196; a isochinoline compound; a farnesyl transferase inhibitor; PD184352 or QAN697, or AT7519; k) a compound targeting, decreasing or inhibiting the activity of a protein-tyrosine kinase, such as imatinib mesylate or a tyrphostin, such as Tyrphostin A23/RG-50810; AG 99; Tyrphostin AG 213; Tyrphostin AG 1748; Tyrphostin AG 490; Tyrphostin B44; Tyrphostin B44 (+) enantiomer; Tyrphostin AG 555; AG 494; Tyrphostin AG 556, AG957 and adaphostin (4-{[(2,5-dihydroxyphenyl)methyl]amino}-benzoic acid adamantyl ester; NSC 680410, adaphostin); 1) a compound targeting, decreasing, or inhibiting the activity of the epidermal growth factor family of receptor tyrosine kinases (EGFR, ErbB2, ErbB3, ErbB4 as homo- or heterodimers) and their mutants, such as CP 358774, ZD 1839, ZM 105180; trastuzumab, cetuximab, gefitinib, erlotinib, OSI-774, Cl-1033, EKB-569, GW-2016, antibodies El.l, E2.4, E2.5, E6.2, E6.4, E2.11, E6.3 and E7.6.3, and 7H-pyrrolo-[2,3-d]pyrimidine derivatives; and m) a compound targeting, decreasing, or inhibiting the activity of the c-Met receptor.

[0156] Exemplary compounds that target, decrease, or inhibit the activity of a protein or lipid phosphatase include inhibitors of phosphatase 1, phosphatase 2A, or CDC25, such as okadaic acid or a derivative thereof.

[0157] Further anti-angiogenic compounds include compounds having another mechanism for their activity unrelated to protein or lipid kinase inhibition, e.g., thalidomide and TNP-470.

[0158] Additional, nonlimiting, exemplary chemotherapeutic compounds, one or more of which may be used in combination with a Compound of the Disclosure, include: daunorubicin, adriamycin, Ara-C, VP-16, teniposide, mitoxantrone, idarubicin, carboplatinum, PKC412, 6-mercaptopurine (6-MP), fludarabine phosphate, octreotide, SOM230, FTY720, 6-thioguanine, cladribine, 6-mercaptopurine, pentostatin, hydroxyurea, 2-hydroxy-lH-isoindole-l,3-dione derivatives, l-(4-chloroanilino)-4-(4-pyridylmethyl)phthalazine or a pharmaceutically acceptable salt thereof, 1-(4-chloroanilino)-4-(4-pyridylmethyl)phthalazine succinate, angiostatin, endostatin,

anthranilic acid amides, ZD4190, ZD6474, SU5416, SU6668, bevacizumab, rhuMAb, rhuFab, macugon; FLT-4 inhibitors, FLT-3 inhibitors, VEGFR-2 IgGI antibody, RPI 4610, bevacizumab, porfimer sodium, anecortave, triamcinolone, hydrocortisone, 11-a-epihydrocotisol, cortex olone, 17a-hydroxyprogesterone, corticosterone, desoxycorticosterone, testosterone, estrone, dexamethasone, fluocinolone, a plant alkaloid, a hormonal compound and/or antagonist, a biological response modifier, such as a lymphokine or interferon, an antisense oligonucleotide or oligonucleotide derivative, shRNA, and siRNA.

[0159] Other examples of second therapeutic agents, one or more of which a Compound of the Disclosure also can be combined, include, but are not limited to: a treatment for Alzheimer's Disease, such as donepezil and rivastigmine; a treatment for Parkinson's Disease, such as L-DOPA/carbidopa, entacapone, ropinrole, pramipexole, bromocriptine, pergolide, trihexephendyl, and amantadine; an agent for treating multiple sclerosis (MS) such as beta interferon (e.g., AVONEX® and REBIF®), glatiramer acetate, and mitoxantrone; a treatment for asthma, such as albuterol and montelukast; an agent for treating schizophrenia, such as zyprexa, risperdal, seroquel, and haloperidol; an anti-inflammatory agent, such as a corticosteroid, a TNF blocker, IL-1 RA, azathioprine, cyclophosphamide, and sulfasalazine; an immunomodulatory agent, including immunosuppressive agents, such as cyclosporin, tacrolimus, rapamycin, mycophenolate mofetil, an interferon, a corticosteroid, cyclophosphamide, azathioprine, and sulfasalazine; a neurotrophic factor, such as an acetylcholinesterase inhibitor, an MAO inhibitor, an interferon, an anti-convulsant, an ion channel blocker, riluzole, or an anti-Parkinson's agent; an agent for treating cardiovascular disease, such as a beta-blocker, an ACE inhibitor, a diuretic, a nitrate, a calcium channel blocker, or a statin; an agent for treating liver disease, such as a corticosteroid, cholestyramine, an interferon, and an anti-viral agent; an agent for treating blood disorders, such as a corticosteroid, an anti-leukemic agent, or a growth factor; or an agent for treating immunodeficiency disorders, such as gamma globulin.

[0160] The above-mentioned second therapeutically active agents, one or more of which can be used in combination with a Compound of the Disclosure, are prepared and administered as described in the art.

[0161] Compounds of the Disclosure typically are administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice. Pharmaceutical compositions for use in accordance with the present disclosure are formulated in a conventional manner using one or more physiologically acceptable carriers comprising excipients and/or auxiliaries that facilitate processing of Compound of the Disclosure.

[0162] These pharmaceutical compositions can be manufactured, for example, by conventional mixing, dissolving, granulating, dragee-making, emulsifying, encapsulating, entrapping, or lyophilizing processes. Proper formulation is dependent upon the route of administration chosen. When a therapeutically effective amount of the Compound of the Disclosure is administered orally, the composition typically is in the form of a tablet, capsule, powder, solution, or elixir. When administered in tablet form, the composition additionally can contain a solid carrier, such as a gelatin or an adjuvant. The tablet, capsule, and powder contain about 0.01% to about 95%, and preferably from about 1% to about 50%, of a Compound of the Disclosure. When administered in liquid form, a liquid carrier, such as water, petroleum, or oils of animal or plant origin, can be added. The liquid form of the composition can further contain physiological saline solution, dextrose or other saccharide solutions, or glycols. When administered in liquid form, the composition contains about 0.1% to about 90%, and preferably about 1% to about 50%, by weight, of a Compound of the Disclosure.

[0163] When a therapeutically effective amount of a Compound of the Disclosure is administered by intravenous, cutaneous, or subcutaneous injection, the composition is in the form of a pyrogen-free, parenterally acceptable aqueous solution. The preparation of such parenterally acceptable solutions, having due regard to pH, isotonicity, stability, and the like, is within the skill in the art. A preferred composition for intravenous, cutaneous, or subcutaneous injection typically contains, an isotonic vehicle.

[0164] Compounds of the Disclosure can be readily combined with pharmaceutically acceptable carriers well-known in the art. Standard pharmaceutical carriers are described in Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, PA, 19th ed. 1995. Such carriers enable the active agents to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral

ingestion by a patient to be treated. Pharmaceutical preparations for oral use can be obtained by adding the Compound of the Disclosure to a solid excipient, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients include, for example, fillers and cellulose preparations. If desired, disintegrating agents can be added.

[0165] Compound of the Disclosure can be formulated for parenteral administration by injection, e.g., by bolus injection or continuous infusion. Formulations for injection can be presented in unit dosage form, e.g., in ampules or in multidose containers, with an added preservative. The compositions can take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and can contain formulatory agents such as suspending, stabilizing, and/or dispersing agents.

[0166] Pharmaceutical compositions for parenteral administration include aqueous solutions of the active agent in water-soluble form. Additionally, suspensions of a Compound of the Disclosure can be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils or synthetic fatty acid esters. Aqueous injection suspensions can contain substances which increase the viscosity of the suspension. Optionally, the suspension also can contain suitable stabilizers or agents that increase the solubility of the compounds and allow for the preparation of highly concentrated solutions. Alternatively, a present composition can be in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

[0167] Compounds of the Disclosure also can be formulated in rectal compositions, such as suppositories or retention enemas, e.g., containing conventional suppository bases. In addition to the formulations described previously, the Compound of the Disclosure also can be formulated as a depot preparation. Such long-acting formulations can be administered by implantation (for example, subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the Compound of the Disclosure can be formulated with suitable polymeric or hydrophobic materials (for example, as an emulsion in an acceptable oil) or ion exchange resins.

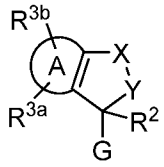
[0168] In particular, the Compounds of the Disclosure can be administered orally, buccally, or sublingually in the form of tablets containing excipients, such as starch or

lactose, or in capsules or ovules, either alone or in admixture with excipients, or in the form of elixirs or suspensions containing flavoring or coloring agents. Such liquid preparations can be prepared with pharmaceutically acceptable additives, such as suspending agents. Compound of the Disclosure also can be injected parenterally, for example, intravenously, intramuscularly, subcutaneously, or intracoronarily. For parenteral administration, the Compound of the Disclosure are typically used in the form of a sterile aqueous solution which can contain other substances, for example, salts or monosaccharides, such as mannitol or glucose, to make the solution isotonic with blood.

[0169] In another embodiment, the present disclosure provides kits which comprise a Compound of the Disclosure (or a composition comprising a Compound of the Disclosure) packaged in a manner that facilitates their use to practice methods of the present disclosure. In one embodiment, the kit includes a Compound of the Disclosure (or a composition comprising a Compound of the Disclosure) packaged in a container, such as a sealed bottle or vessel, with a label affixed to the container or included in the kit that describes use of the compound or composition to practice the method of the disclosure. In one embodiment, the compound or composition is packaged in a unit dosage form. The kit further can include a device suitable for administering the composition according to the intended route of administration.

[0170] In another aspect, the present disclosure is drawn to the following particular embodiments:

[0171] Embodiment I. A compound having Formula **I**:



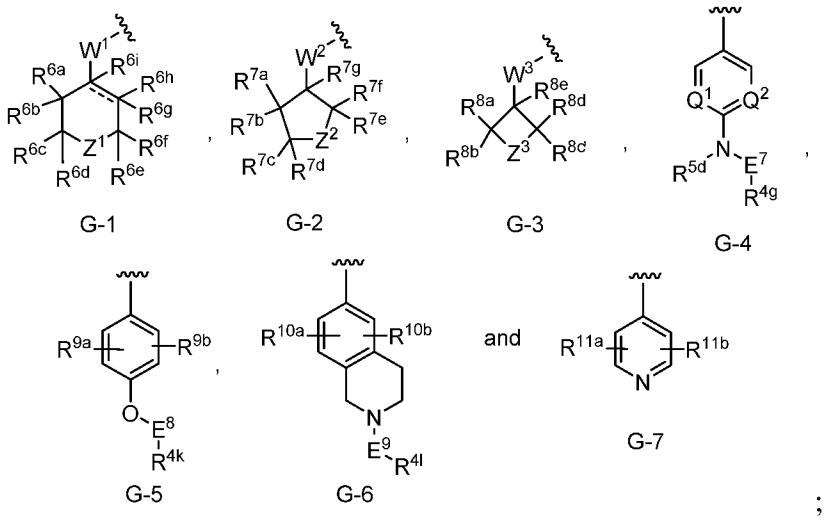
I,

[0172] or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein:

[0173] 

is a fused thienyl or fused phenyl group,

[0174] G is selected from the group consisting of:



;

[0175] W^1 is absent or $-CH_2-$;

[0176] Z^1 is selected from the group consisting of $-N(-E^1-R^{4a})-$ and $-C[-N(-E^2-R^{4b})(R^{4h})](R^{5a})-$;

[0177] W^2 is absent or $-CH_2-$;

[0178] Z^2 is selected from the group consisting of $-N(-E^3-R^{4c})-$ and $-C[-N(-E^4-R^{4d})(R^{4i})](R^{5b})-$;

[0179] W^3 is absent or $-CH_2-$;

[0180] Z^3 is selected from the group consisting of $-N(-E^5-R^{4e})-$ and $-C[-N(-E^6-R^{4f})(R^{4j})](R^{5c})-$;

[0181] ≡ is a single or double bond, with the proviso that when ≡ is a double bond, R^{6h} and R^{6i} are absent;

[0182] Q^1 and Q^2 are each independently CH or N;

[0183] X-Y is selected from the group consisting of

$-N(R^{1a})-C(=O)-$;

$-C(=O)-O-$;

$-C(=O)-N(R^{1b})-$;

$-CH_2N(R^{1c})-CH_2-$;

$-C(=O)N(R^{1d})-CH_2-$;

$-CH_2CH_2-N(R^{1e})-$;

$-CH_2N(R^{1f})-C(=O)-$; and

$-CH_2O-CH_2-$; or

[0184] X and Y do not form a chemical bond, and

[0185] X is selected from the group consisting of hydrogen, alkyl, halo, hydroxy, cyano, amino, alkylamino, dialkylamino, haloalkyl, alkoxy, and haloalkoxy; and

[0186] Y is selected from the group consisting of cyano, hydroxy, and $-CH_2-R^{12}$;

[0187] E^1, E^2, E^3, E^4, E^5, E^6, E^7, E^8, and E^9 are each independently selected from the group consisting of $-C(=O)-$, $-C(=O)N(R^{13})-$, $-[C(R^{14a})(R^{14b})]_mO-$, $-[C(R^{14a})(R^{14b})]_mN(R^{15})-$, $-[C(R^{14c})(R^{14d})]_n-$, $-CH_2(=O)-$, and $-S(=O)_2-$; or

[0188] E^1, E^2, E^3, E^4, E^5, E^6, E^7, E^8, and E^9 are each independently absent;

[0189] R^{1a} is selected from the group consisting of hydrogen and alkyl;

[0190] R^{1b} is selected from the group consisting of hydrogen, alkyl, and aralkyl;

[0191] R^{1c} is selected from the group consisting of hydrogen, alkyl, haloalkyl, optionally substituted cycloalkyl, optionally substituted heterocyclo, (cycloalkyl)alkyl, (heterocycloalkyl)alkyl, aralkyl, (heteroaryl)alkyl, alkylcarbonyl, arylcarbonyl, and alkoxycarbonyl;

[0192] R^{1d} is selected from the group consisting of hydrogen, alkyl, and aralkyl;

[0193] R^{1e} is selected from the group consisting of hydrogen, alkyl, and (aryloxy)alkyl;

[0194] R^{1f} is selected from the group consisting of hydrogen and alkyl;

[0195] R^2 is selected from the group consisting of hydrogen, alkyl, alkenyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclo, optionally substituted heteroaryl, and aralkyl;

[0196] R^{3a} and R^{3b} are each independently selected from the group consisting of hydrogen, alkyl, halo, hydroxy, cyano, amino, alkylamino, dialkylamino, haloalkyl, alkoxy, and haloalkoxy;

[0197] R^{4a}, R^{4b}, R^{4c}, R^{4d}, R^{4e}, R^{4f}, R^{4g}, R^{4k}, and R^{4l} are each independently selected from the group consisting of hydrogen, alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclo, optionally substituted heteroaryl, aralkyl, and (heteroaryl)alkyl;

[0198] R^{4h}, R^{4i}, and R^{4j} are each independently selected from the group consisting of hydrogen and alkyl;

[0199] R^{5a}, R^{5b}, R^{5c}, and R^{5d} are each independently selected from the group consisting of hydrogen and alkyl;

[0200] R^{6a}, R^{6b}, R^{6c}, R^{6d}, R^{6e}, R^{6f}, R^{6g}, and R^{6h} are each independently selected from the group consisting of hydrogen and alkyl;

[0201] R^{6i} is selected from the group consisting of hydrogen, alkyl, and halo;

[0202] R^{7a}, R^{7b}, R^{7c}, R^{7d}, R^{7e}, and R^{7f} are each independently selected from the group consisting of hydrogen and alkyl;

[0203] R^{7g} is selected from the group consisting of hydrogen, alkyl, and halo;

[0204] R^{8a}, R^{8b}, R^{8c}, and R^{8d} are each independently selected from the group consisting of hydrogen and alkyl;

[0205] R^{8e} is selected from the group consisting of hydrogen, alkyl, and halo;

[0206] R^{9a} and R^{9b} are each independently selected from the group consisting of hydrogen, alkyl, halo, hydroxy, cyano, amino, alkylamino, dialkylamino, haloalkyl, alkoxy, and haloalkoxy;

[0207] R^{10a} and R^{10b} are each independently selected from the group consisting of hydrogen, alkyl, halo, hydroxy, cyano, amino, alkylamino, dialkylamino, haloalkyl, alkoxy, and haloalkoxy;

[0208] R^{11a} and R^{11b} are each independently selected from the group consisting of hydrogen, alkyl, halo, hydroxy, cyano, amino, alkylamino, dialkylamino, haloalkyl, alkoxy, and haloalkoxy;

[0209] R^{12} is selected from the group consisting of hydroxy, amino, optionally substituted heteroaryl, optionally substituted heterocyclo, and -NHC(=O)-R^{16};

[0210] m is 2, 3, 4, or 5,

[0211] n is 1, 2, 3, 4, or 5

[0212] R^{13} is selected from the group consisting of hydrogen and alkyl;

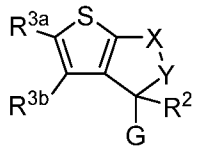
[0213] R^{14a} and R^{14b} are each independently selected from the group consisting of hydrogen and alkyl;

[0214] R^{14c} and R^{14d} are each independently selected from the group consisting of hydrogen and alkyl;

[0215] R^{15} is selected from the group consisting of hydrogen and alkyl; and

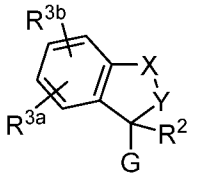
[0216] R^{16} is selected from the group consisting of alkyl, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted cycloalkyl.

[0217] Embodiment II. The compound of Embodiment I, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, having Formula **II**:



II.

[0218] Embodiment III. The compound of Embodiment I, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, having Formula **III**:



III.

[0219] Embodiment IV. The compound of any one of Embodiments I-III, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein G is G-1.

[0220] Embodiment V. The compound of any one of Embodiments I-III, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein G is G-2.

[0221] Embodiment VI. The compound of any one of Embodiments I-III, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein G is G-3.

[0222] Embodiment VII. The compound of any one of Embodiments I-III, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein G is G-4.

[0223] Embodiment VIII. The compound of any one of Embodiments I-III, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein G is G-5.

[0224] Embodiment IX. The compound of any one of Embodiments I-III, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein G is G-6.

[0225] Embodiment X. The compound of any one of Embodiments I-III, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein G is G-7.

[0226] Embodiment XI. The compound of Embodiment IV, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein W^1 is absent.

[0227] Embodiment XII. The compound of Embodiment V, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein W^2 is absent.

[0228] Embodiment XIII. The compound of Embodiment VI, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein W^3 is absent.

[0229] Embodiment XIV. The compound of Embodiments IX or XI, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein ═ is

a single bond and R^{6a}, R^{6b}, R^{6c}, R^{6d}, R^{6e}, R^{6f}, R^{6g}, R^{6h}, and R^{6i} are each independently selected from the group consisting of hydrogen and C_{1-3} alkyl.

[0230] Embodiment XV. The compound of Embodiment XIV, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein R^{6a}, R^{6b}, R^{6c}, R^{6d}, R^{6e}, R^{6f}, R^{6g}, R^{6h}, and R^{6i} are each hydrogen.

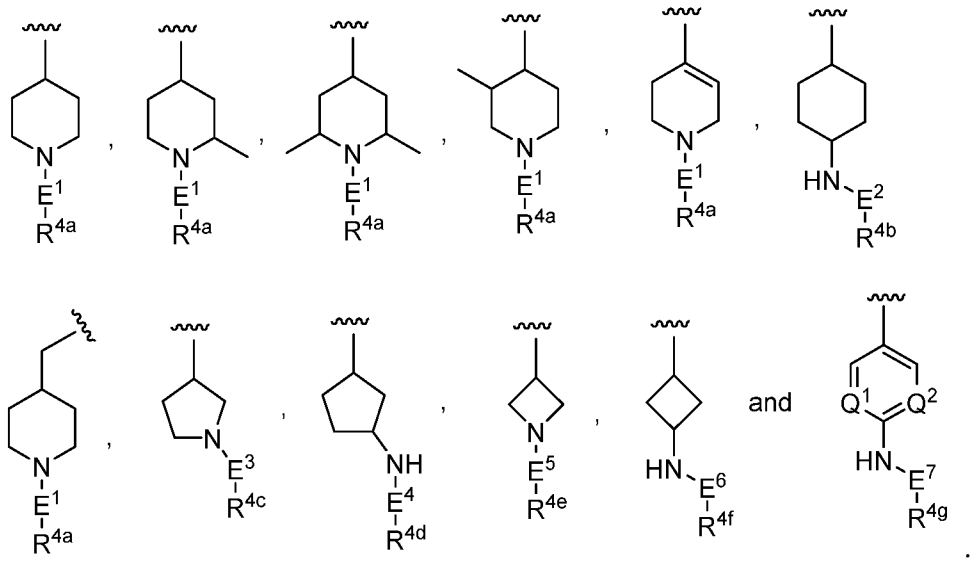
[0231] Embodiment XVI. The compound of Embodiments V or XII, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein R^{7a}, R^{7b}, R^{7c}, R^{7d}, R^{7e}, R^{7f}, and R^{7g} are each independently selected from the group consisting of hydrogen and C_{1-3} alkyl.

[0232] Embodiment XVII. The compound of Embodiment XVI, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein R^{7a}, R^{7b}, R^{7c}, R^{7d}, R^{7e}, R^{7f}, and R^{7g} are each hydrogen.

[0233] Embodiment XVIII. The compound of Embodiments VI or XIII, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein R^{8a}, R^{8b}, R^{8c}, R^{8d}, and R^{8e} are each independently selected from the group consisting of hydrogen and C_{1-3} alkyl.

[0234] Embodiment XIX. The compound of Embodiment XVIII, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein R^{8a}, R^{8b}, R^{8c}, R^{8d}, and R^{8e} are each hydrogen.

[0235] Embodiment XX. The compound of any one of Embodiments I-III, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein G is selected from the group consisting of:



[0236] with the proviso that Q^1 is N and Q^2 is selected from the group consisting of CH and N.

[0237] Embodiment XXI. The compound of any one of Embodiments I-III or XX, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein E^1, E^2, E^3, E^4, E^5, E^6, and E^7 are each independently selected from the group consisting of -C(=O)-, -C(=O)N(R^{13})-, -[C(R^{14a})(R^{14b})]$_m$O-, -[C(R^{14a})(R^{14b})]$_m$N(R^{15})-, -[C(R^{14c})(R^{14d})]$_n$-, -CH_2(=O)-, and -S(=O)$_2$-.

[0238] Embodiment XXII. The compound of Embodiment XXI, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein E^1, E^2, E^3, E^4, E^5, E^6, and E^7 are each -C(=O)-.

[0239] Embodiment XXIII. The compound of Embodiment XXI, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein E^1, E^2, E^3, E^4, E^5, E^6, and E^7 are each -C(=O)N(R^{13})-.

[0240] Embodiment XXIV. The compound of Embodiment XXI, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein E^1, E^2, E^3, E^4, E^5, E^6, and E^7 are each -[C(R^{14a})(R^{14b})]$_m$O-.

[0241] Embodiment XXV. The compound of Embodiment XXI, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein E^1, E^2, E^3, E^4, E^5, E^6, and E^7 are each -[C(R^{14a})(R^{14b})]$_m$N(R^{15})-.

[0242] Embodiment XXVI. The compound of Embodiment XXI, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein E^1, E^2, E^3, E^4, E^5, E^6, and E^7 are each -[C(R^{14c})(R^{14d})]$_n$-.

[0243] Embodiment XXVII. The compound of Embodiment XXVI, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein n is 1 and R^{14c} and R^{14d} are each hydrogen.

[0244] Embodiment XXVIII. The compound of Embodiment XXI, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein E^1, E^2, E^3, E^4, E^5, E^6, and E^7 are each -CH_2(=O)-.

[0245] Embodiment XXIX. The compound of Embodiment XXI, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein E^1, E^2, E^3, E^4, E^5, E^6, and E^7 are each -S(=O)$_2$-.

[0246] Embodiment XXX. The compound of any one of Embodiments I-III and XX, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein E^1, E^2, E^3, E^4, E^5, E^6, and E^7 are each absent.

[0247] Embodiment XXXI. The compound of any one of Embodiments I-III and XX-XXX, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein R^{4a}, R^{4b}, R^{4c}, R^{4d}, R^{4e}, R^{4f}, and R^{4g} are each independently selected from the group consisting of alkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclo, optionally substituted heteroaryl, aralkyl, (heterocyclo)alkyl, and (heteroaryl)alkyl.

[0248] Embodiment XXXII. The compound of Embodiment XXXI, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein R^{4a}, R^{4b}, R^{4c}, R^{4d}, R^{4e}, R^{4f}, and R^{4g} are each alkyl.

[0249] Embodiment XXXIII. The compound of Embodiment XXXI, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein R^{4a}, R^{4b}, R^{4c}, R^{4d}, R^{4e}, R^{4f}, and R^{4g} are each optionally substituted cycloalkyl.

[0250] Embodiment XXXIV. The compound of Embodiment XXXI, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein R^{4a}, R^{4b}, R^{4c}, R^{4d}, R^{4e}, R^{4f}, and R^{4g} are each optionally substituted aryl.

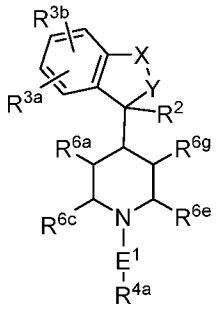
[0251] Embodiment XXXV. The compound of Embodiment XXXI, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein R^{4a}, R^{4b}, R^{4c}, R^{4d}, R^{4e}, R^{4f}, and R^{4g} are each optionally substituted heterocyclo.

[0252] Embodiment XXXVI. The compound of Embodiment XXXI, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein R^{4a}, R^{4b}, R^{4c}, R^{4d}, R^{4e}, R^{4f}, and R^{4g} are each optionally substituted heteroaryl.

[0253] Embodiment XXXVII. The compound of Embodiment XXXI, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein R^{4a}, R^{4b}, R^{4c}, R^{4d}, R^{4e}, R^{4f}, and R^{4g} are each aralkyl.

[0254] Embodiment XXXVIII. The compound of Embodiment XXXI, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein R^{4a}, R^{4b}, R^{4c}, R^{4d}, R^{4e}, R^{4f}, and R^{4g} are each (heteroaryl)alkyl.

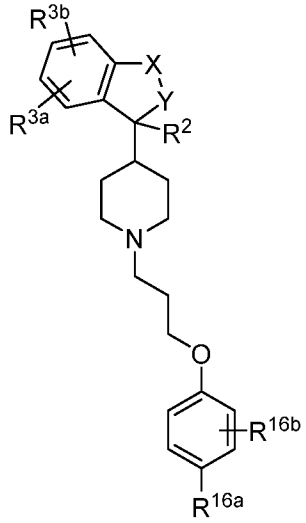
[0255] Embodiment XXXIX. The compound of Embodiment I, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, having Formula **IV**:



IV.

[0256] Embodiment XL. The compound of Embodiment XXXIX, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein E^1 is $-[C(R^{14a})(R^{14b})]_mO-$ and R^{4a} is selected from the group consisting of optionally substituted aryl and optionally substituted heteroaryl.

[0257] Embodiment XLI. The compound of Embodiment XL, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, having Formula **V**:



V,

[0258] wherein:

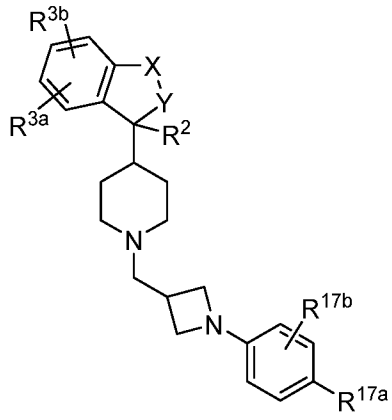
[0259] R^{16a} is selected from the group consisting of hydrogen, alkyl, halo, hydroxy, cyano, amino, alkylamino, dialkylamino, haloalkyl, alkoxy, haloalkoxy, alkylsulfonyl, haloalkylsulfonyl, cycloalkylsulfonyl, (cycloalkyl)alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, heterocyclosulfonyl, sulfonamido, optionally substituted heteroaryl, optionally substituted heterocyclo, carboxamido, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, carboxy, and carboxyalkyl; and

[0260] R^{16b} is selected from the group consisting of hydrogen, alkyl, halo, hydroxy, cyano, amino, alkylamino, dialkylamino, haloalkyl, alkoxy, and haloalkoxy.

[0261] Embodiment XLII. The compound of Embodiment XXXIX, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein E^1 is $-C(R^{14c})(R^{14d})_n-$ and R^{4a} is substituted C_{4-6} heterocyclo.

[0262] Embodiment XLIII. The compound of Embodiment XLII, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein n is 1 and R^{14c} and R^{14d} are hydrogen.

[0263] Embodiment XLIV. The compound of Embodiment XLIII, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, having Formula **VI**:



VI,

[0264] wherein:

[0265] R^{17a} is selected from the group consisting of hydrogen, alkyl, halo, hydroxy, cyano, amino, alkylamino, dialkylamino, haloalkyl, alkoxy, haloalkoxy, alkylsulfonyl, haloalkylsulfonyl, cycloalkylsulfonyl, (cycloalkyl)alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, heterocyclosulfonyl, sulfonamido, optionally substituted heteroaryl, optionally substituted heterocyclo, carboxamido, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, carboxy, and carboxyalkyl; and

[0266] R^{17b} is selected from the group consisting of hydrogen, alkyl, halo, hydroxy, cyano, amino, alkylamino, dialkylamino, haloalkyl, alkoxy, and haloalkoxy.

[0267] Embodiment XLV. The compound of Embodiment XLIV, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein:

[0268] R^{17a} is selected from the group consisting of alkylsulfonyl, cycloalkylsulfonyl, arylsulfonyl, and heteroarylsulfonyl; and

[0269] R^{17b} is hydrogen.

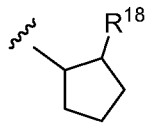
[0270] Embodiment XLVI. The compound of any one of Embodiments I-XLV, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein R^2 is selected

from the group consisting of alkyl, alkenyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclo, optionally substituted heteroaryl, and aralkyl.

[0271] Embodiment XLVII. The compound of Embodiment XLVI, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein R^2 is unsubstituted cycloalkyl.

[0272] Embodiment XLVIII. The compound of Embodiment XLVI, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein R^2 is substituted cycloalkyl.

[0273] Embodiment XLIX. The compound of Embodiment XLVIII, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein R^2 is substituted cycloalkyl having Formula **VII**:



VII,

[0274] wherein:

[0275] R^{18} is selected from the group consisting of halo, nitro, cyano, hydroxy, alkylcarbonyloxy, cycloalkylcarbonyloxy, amino, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, aryloxy, aralkyloxy, alkylthio, carboxamido, sulfonamido, alkylcarbonyl, arylcarbonyl, alkylsulfonyl, arylsulfonyl, carboxy, carboxyalkyl, optionally substituted alkyl, optionally substituted cycloalkyl, alkenyl, alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclo, alkoxyalkyl, (amino)alkyl, (carboxamido)alkyl, (heterocyclo)alkyl, -OC(=O)-amino, $-N(R^{19a})C(=O)-R^{19b}$, and $-N(R^{20a})SO_2-R^{20b}$;

[0276] R^{19a} is selected from the group consisting of hydrogen and alkyl;

[0277] R^{19b} is selected from the group consisting of amino, alkoxy, alkyl, and optionally substituted aryl;

[0278] R^{20a} is selected from the group consisting of hydrogen and alkyl; and

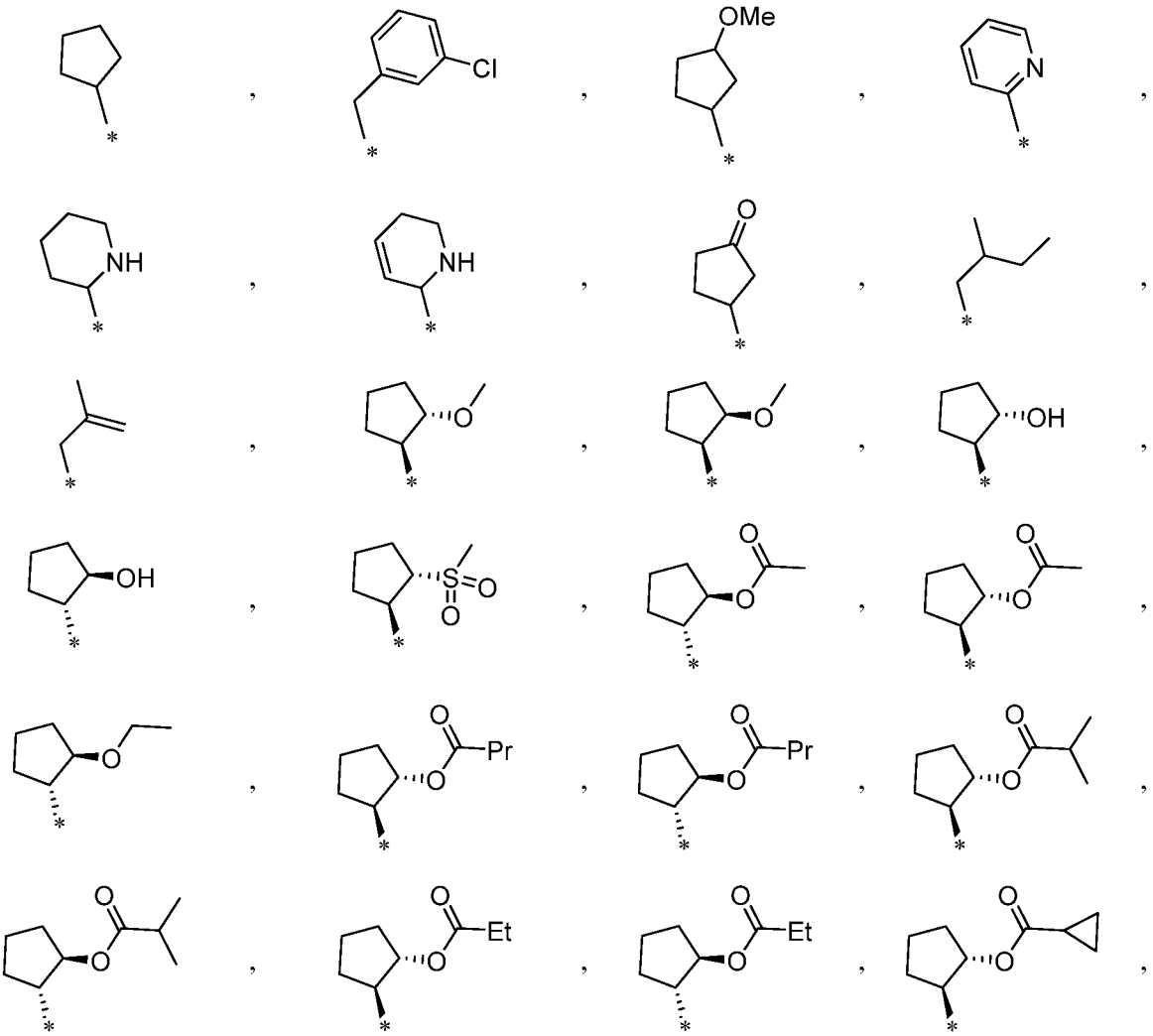
[0279] R^{20b} is selected from the group consisting of amino, alkyl, and optionally substituted aryl.

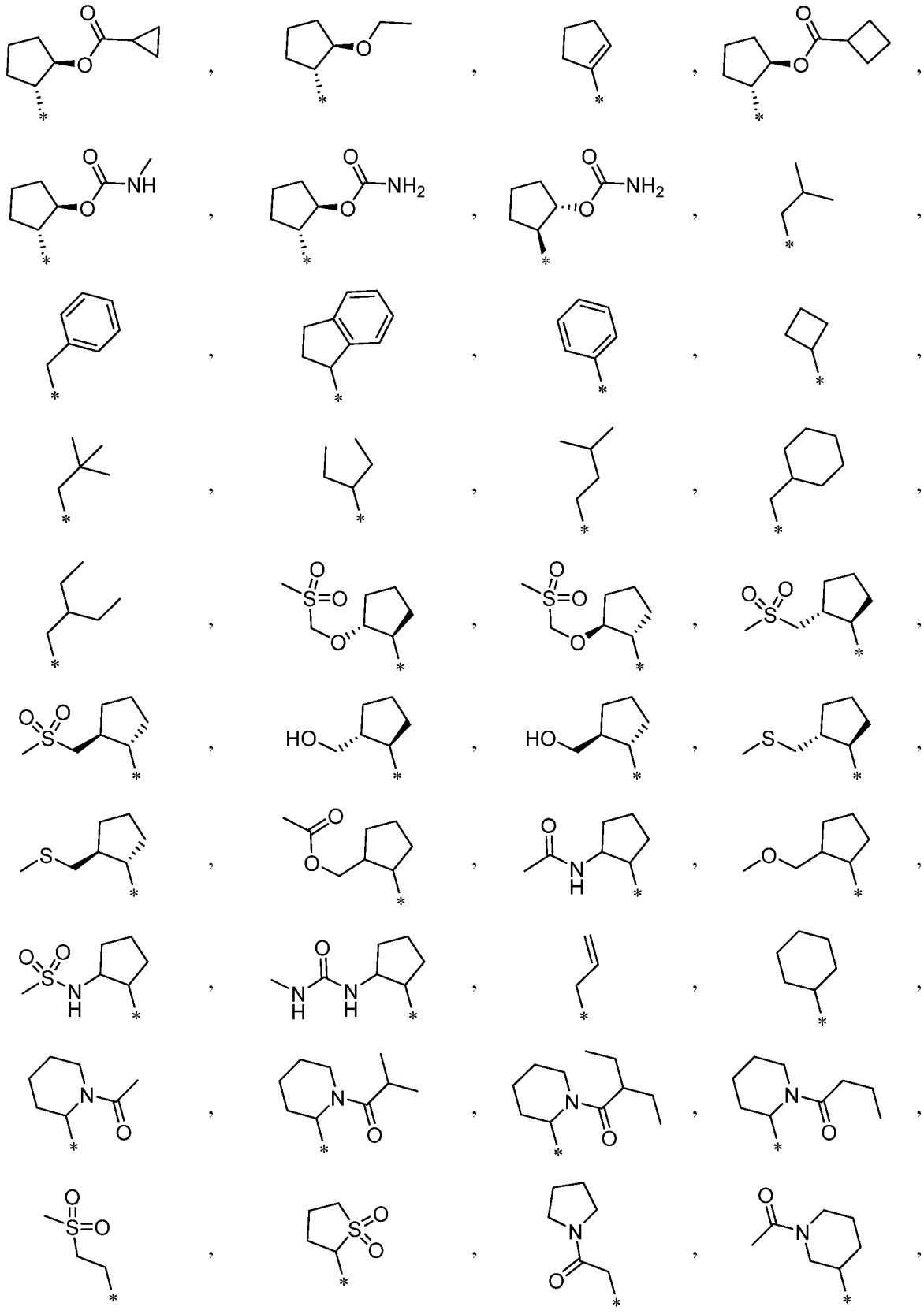
[0280] Embodiment L. The compound of Embodiment XLIX, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein R^{18} is selected

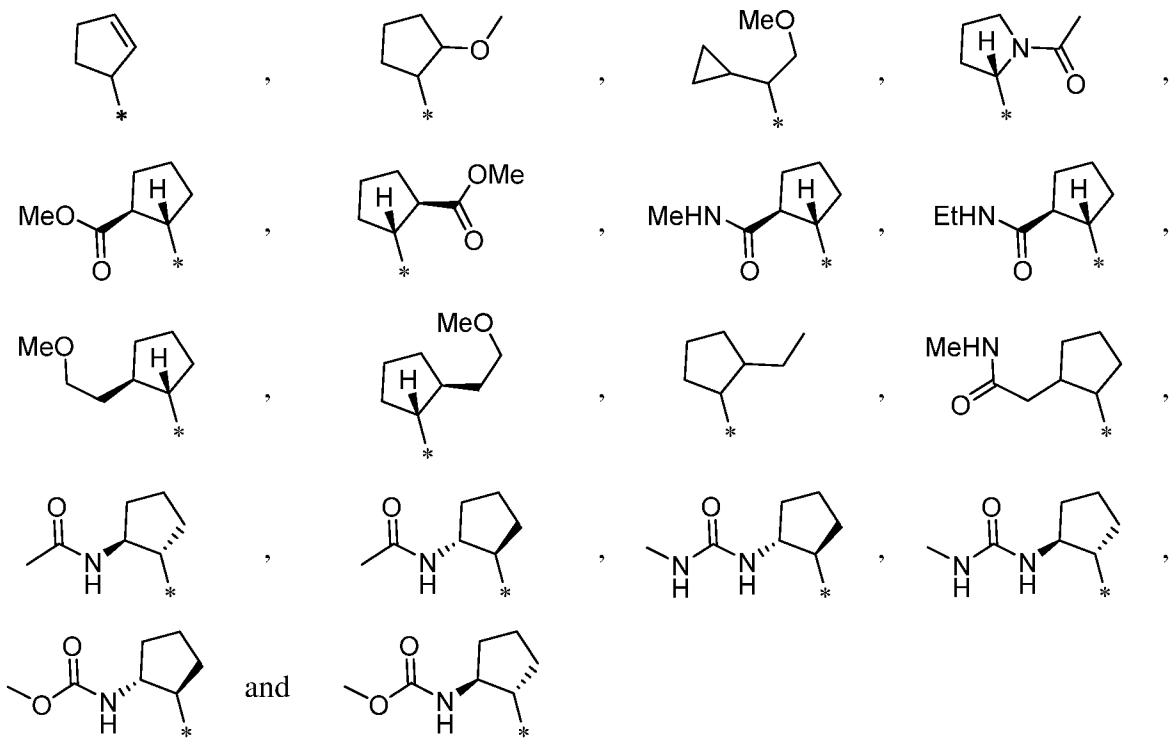
from the group consisting of alkylcarbonyloxy, cycloalkylcarbonyloxy, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, aryloxy, aralkyloxy, alkylthio, carboxamido, sulfonamido, alkylcarbonyl, arylcarbonyl, alkylsulfonyl, arylsulfonyl, carboxy, carboxyalkyl, optionally substituted alkyl, optionally substituted cycloalkyl, alkenyl, alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclo, alkoxyalkyl, (amino)alkyl, (carboxamido)alkyl, and (heterocyclo)alkyl.

[0281] Embodiment LI. The compound of Embodiment L, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein R^{18} is selected from the group consisting of -OC(=O)-amino and -NHC(=O)-R^{19b}.

[0282] Embodiment LII. The compound of Embodiment XLVI, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein R^2 is selected from the group consisting of:

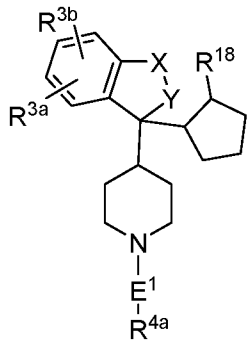






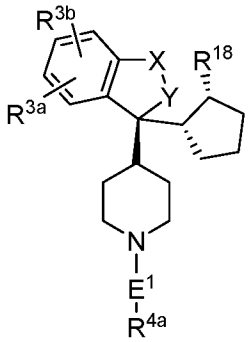
[0283] wherein " * " indicates the point of attachment to the remainder of the molecule.

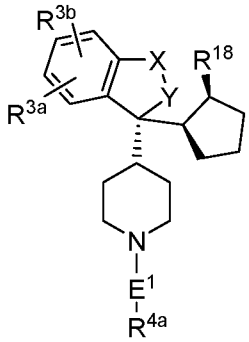
[0284] Embodiment LIII. The compound of Embodiment I, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, having Formula **VIII**:

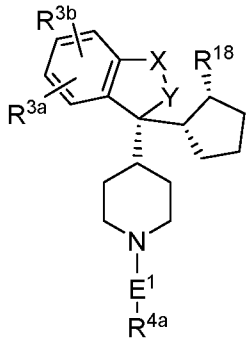


VIII,

[0285] Embodiment LIV. The compound of Embodiment LIII, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, having any one or more of the following formulae:

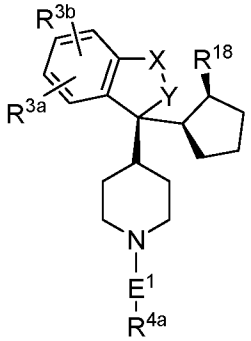


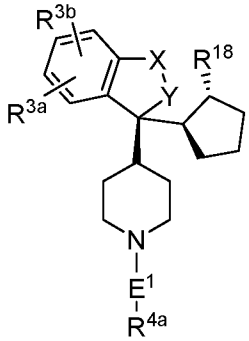
,


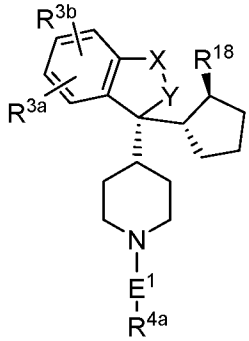
,


,

Formula **VIII-A** Formula **VIII-B** Formula **VIII-C**

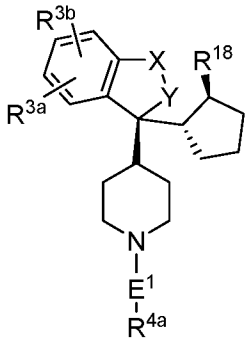


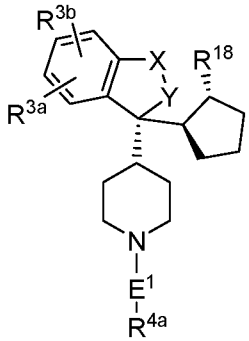
,


,


,

Formula **VIII-D** Formula **VIII-E** Formula **VIII-F**



and


.

[0286] Embodiment LV. The compound of any one of Embodiments I-LIV, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein X-Y is selected from the group consisting of -N(R^{1a})-C(=O)-; -C(=O)-O-; -C(=O)-N(R^{1b})-; -CH_2N(R^{1c})-CH_2-; -C(=O)N(R^{1d})-CH_2-; -CH_2CH_2-N(R^{1e})-; -CH_2N(R^{1f})-C(=O)-; and -CH_2O-CH_2-.

[0287] Embodiment LVI. The compound of Embodiment LV, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein X-Y is -N(R^{1a})-C(=O)-.

[0288] Embodiment LVII. The compound of Embodiment LV, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein X-Y is -C(=O)-O-.

[0289] Embodiment LVIII. The compound of Embodiment LV, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein X-Y is -C(=O)-N(R^{1b})-.

[0290] Embodiment LIX. The compound of Embodiment LV, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein X-Y is -CH_2N(R^{1c})-CH_2-.

[0291] Embodiment LX. The compound of Embodiment LV, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein X-Y is -C(=O)N(R^{1d})-CH_2-.

[0292] Embodiment LXI. The compound of Embodiment LV, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein X-Y is -CH_2CH_2-N(R^{1e})-.

[0293] Embodiment LXII. The compound of Embodiment LV, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein X-Y is -CH_2N(R^{1f})-C(=O)-.

[0294] Embodiment LXIII. The compound of Embodiment LV, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein X-Y is -CH_2O-CH_2-.

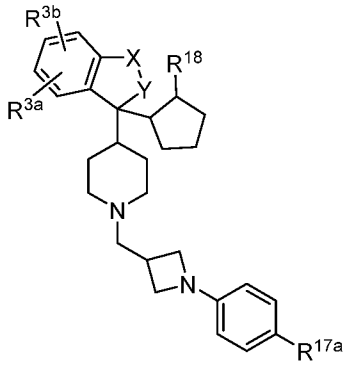
[0295] Embodiment LXIV. The compound of any one of Embodiments I-LIV, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein X and Y do not form a chemical bond and X is hydrogen.

[0296] Embodiment LXV. The compound of Embodiment LXIV, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein Y is selected from the group consisting of cyano and -CH_2-R^{12}.

[0297] Embodiment LXVI. The compound of Embodiment LXV, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein Y is cyano.

[0298] Embodiment LXVII. The compound of Embodiment LXV, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein Y is -CH_2-R^{12}.

[0299] Embodiment LXVIII. The compound of Embodiment I, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, having Formula **IX**:



IX,

[0300] wherein:

[0301] X-Y is $-CH_2N(R^{1c})-CH_2-$, or

[0302] X and Y do not form a chemical bond, and

[0303] X is hydrogen; and

[0304] Y is selected from the group consisting of -CN and $-CH_2-R^{12}$;

[0305] R^{1c} is C_{1-3} alkyl;

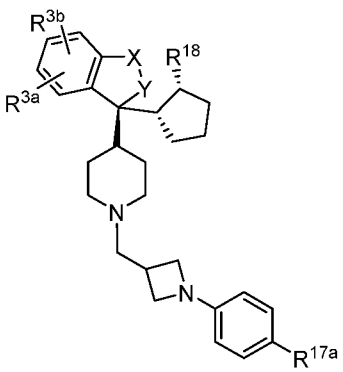
[0306] R^{12} is selected from the group consisting of amino and heteroaryl;

[0307] R^{17a} is selected from the group consisting of alkylsulfonyl, cycloalkylsulfonyl, arylsulfonyl, and heteroarylsulfonyl;

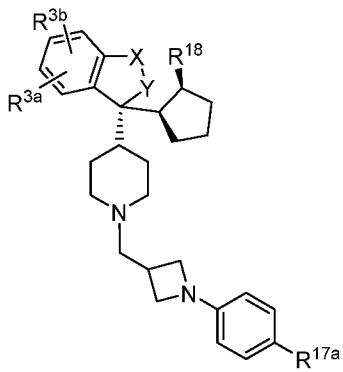
[0308] R^{18} is selected from the group consisting of -OC(=O)-amino and -NHC(=O)-R^{19b}; and

[0309] R^{19b} is selected from the group consisting of amino, alkoxy, alkyl, and optionally substituted aryl.

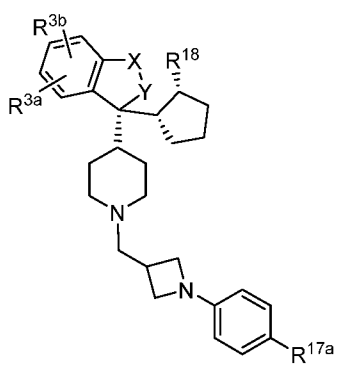
[0310] Embodiment LXIX: The compound of Embodiment LXVIII, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, having any one or more of the following formulae:



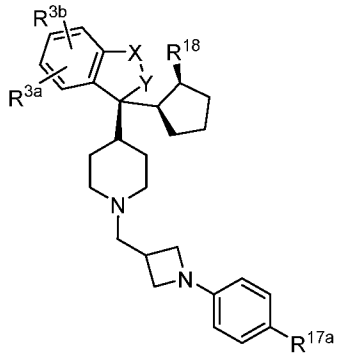
,



,

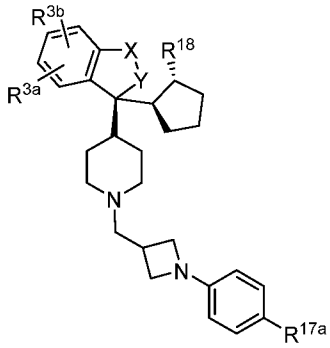


Formula **IX-A**



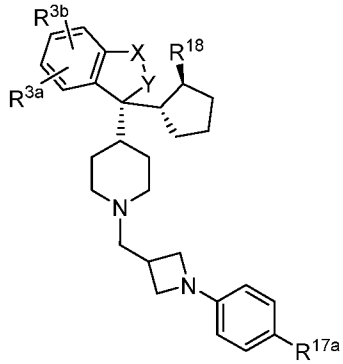
,

Formula **IX-B**

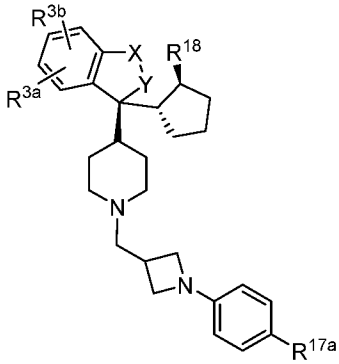


,

Formula **IX-C**

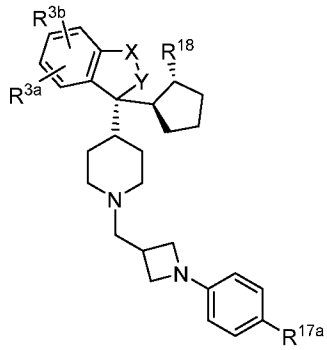


Formula **IX-D**



and

Formula **IX-E**



.

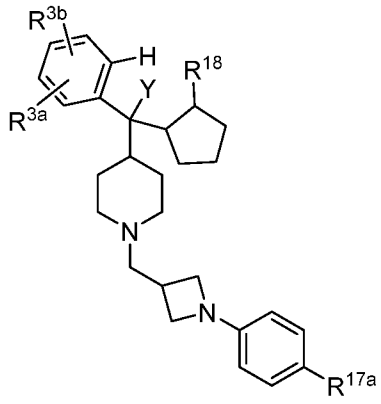
Formula **IX-G** Formula **IX-H**

[0311] Embodiment LXX. The compound of Embodiment LXVIII or LXIX, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein:

[0312] X-Y is $-CH_2N(R^{1c})-CH_2-$; and

[0313] R^{1c} is selected from the group consisting of hydrogen and C_{1-6} alkyl.

[0314] Embodiment LXXI. The compound of Embodiment I, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, having Formula **X**:



X,

wherein:

[0315] R^{17a} is selected from the group consisting of hydrogen, alkyl, halo, hydroxy, cyano, amino, alkylamino, dialkylamino, haloalkyl, alkoxy, haloalkoxy, alkylsulfonyl, haloalkylsulfonyl, cycloalkylsulfonyl, (cycloalkyl)alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, heterocyclosulfonyl, sulfonamido, optionally substituted heteroaryl, optionally substituted heterocyclo, carboxamido, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, carboxy, and carboxyalkyl;

[0316] R^{18} is selected from the group consisting of halo, nitro, cyano, hydroxy, alkylcarbonyloxy, cycloalkylcarbonyloxy, amino, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, aryloxy, aralkyloxy, alkylthio, carboxamido, sulfonamido, alkylcarbonyl, arylcarbonyl, alkylsulfonyl, arylsulfonyl, carboxy, carboxyalkyl, optionally substituted alkyl, optionally substituted cycloalkyl, alkenyl, alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclo, alkoxyalkyl, (amino)alkyl, (carboxamido)alkyl, (heterocyclo)alkyl, -OC(=O)-amino, -$N(R^{19a})C(=O)$-R^{19b}, and -$N(R^{20a})SO_2$-R^{20b};

[0317] R^{19a} is selected from the group consisting of hydrogen and alkyl;

[0318] R^{19b} is selected from the group consisting of amino, alkoxy, alkyl, and optionally substituted aryl;

[0319] R^{20a} is selected from the group consisting of hydrogen and alkyl; and

[0320] R^{20b} is selected from the group consisting of amino, alkyl, and optionally substituted aryl. In another embodiment, R18 is selected from the group consisting of alkylcarbonyloxy, cycloalkylcarbonyloxy, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, aryloxy, aralkyloxy, alkylthio, carboxamido, sulfonamido, alkylcarbonyl, arylcarbonyl, alkylsulfonyl, arylsulfonyl, carboxy, carboxyalkyl, optionally substituted alkyl, optionally substituted cycloalkyl, alkenyl, alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclo, alkoxyalkyl, (amino)alkyl, (carboxamido)alkyl, and (heterocyclo)alkyl.

[0321] Embodiment LXXII. The compound of Embodiment LXXI, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein:

[0322] Y is selected from the group consisting of cyano and -CH_2-R^{12};

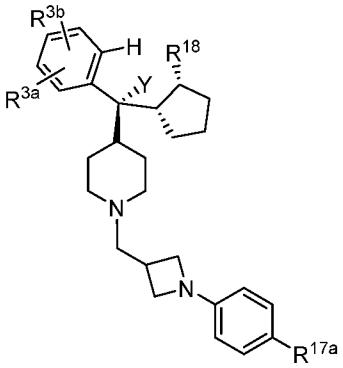
[0323] R^{12} is selected from the group consisting of amino and heteroaryl;

[0324] R^{18} is selected from the group consisting of -OC(=O)-amino and -NHC(=O)-R^{19b}; and

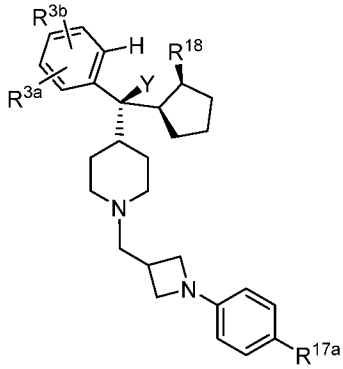
[0325] R^{19b} is selected from the group consisting of amino, alkoxy, alkyl, and optionally substituted aryl.

[0326] Embodiment LXXIII. The compound of Embodiments LXXI or LXXII, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein R^{17a} is selected from the group consisting of chloro, cyano, alkylsulfonyl, haloalkylsulfonyl, cycloalkylsulfonyl, arylsulfonyl, and heteroarylsulfonyl.

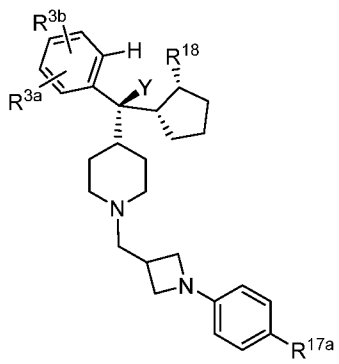
[0327] Embodiment LXXIV. The compound of any one of Embodiments LXXI-LXXIII, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, having any one or more of the following formulae:



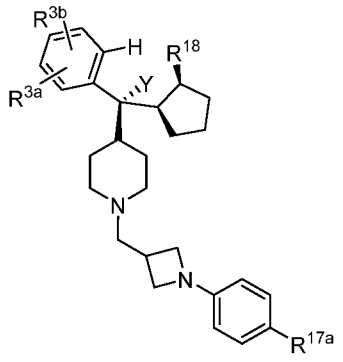
Formula **X-A**



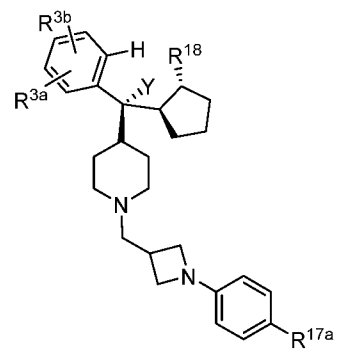
Formula **X-B**



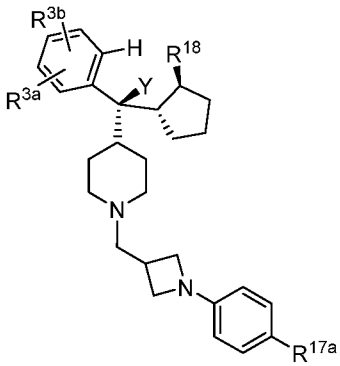
Formula **X-C**



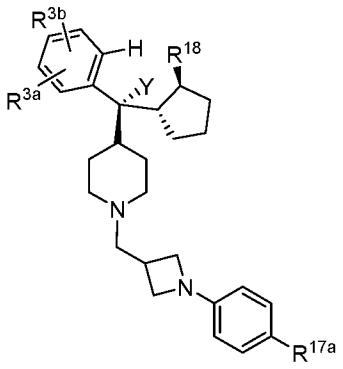
Formula **X-D**



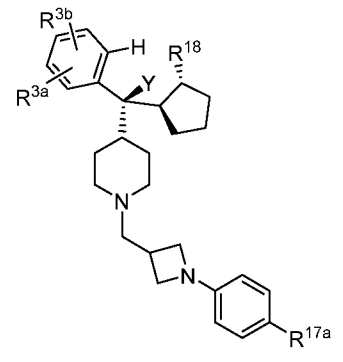
Formula **X-E**



Formula **X-F**



and



Formula **X-G** Formula **X-H**

[0328] Embodiment LXXV. The compound of any one of Embodiments LXXI-LXXIV, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein Y is $-CH_2-R^{12}$.

[0329] Embodiment LXXVI. The compound of any one of Embodiments LXXI-LXXV, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein R^{12} is 5-membered heteroaryl.

[0330] Embodiment LXXVII. The compound of any one of Embodiments LXXI-LXXVI or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein R^{12} is optionally substituted imidazol-1-yl.

[0331] To facilitate an understanding of the present disclosure, a number of terms and phrases are defined below.

[0332] In the present disclosure, the term "halo" as used by itself or as part of another group refers to -Cl, -F, -Br, or -I.

[0333] In the present disclosure, the term "nitro" as used by itself or as part of another group refers to $-NO_2$.

[0334] In the present disclosure, the term "cyano" as used by itself or as part of another group refers to -CN.

[0335] In the present disclosure, the term "hydroxy" as used by itself or as part of another group refers to -OH.

[0336] In the present disclosure, the term "alkyl" as used by itself or as part of another group refers to unsubstituted straight- or branched-chain aliphatic hydrocarbons containing from one to twelve carbon atoms, i.e., C_{1-12} alkyl, or the number of carbon atoms designated, e.g., a C_1 alkyl such as methyl, a C_2 alkyl such as ethyl, a C_3 alkyl such as propyl or isopropyl, a C_{1-3} alkyl such as methyl, ethyl, propyl, or isopropyl, and so on. In one embodiment, the alkyl is a C_{1-10} alkyl. In another embodiment, the alkyl is a C_{1-6} alkyl. In another embodiment, the alkyl is a C_{1-4} alkyl. In another embodiment, the alkyl is a straight chain C_{1-10} alkyl. In another embodiment, the alkyl is a branched chain C_{3-10} alkyl. In another embodiment, the alkyl is a straight chain C_{1-6} alkyl. In another embodiment, the alkyl is a branched chain C_{3-6} alkyl. In another embodiment, the alkyl is a straight chain C_{1-4} alkyl. In another embodiment, the alkyl is a branched chain C_{3-4} alkyl. In another embodiment, the alkyl is a straight or branched

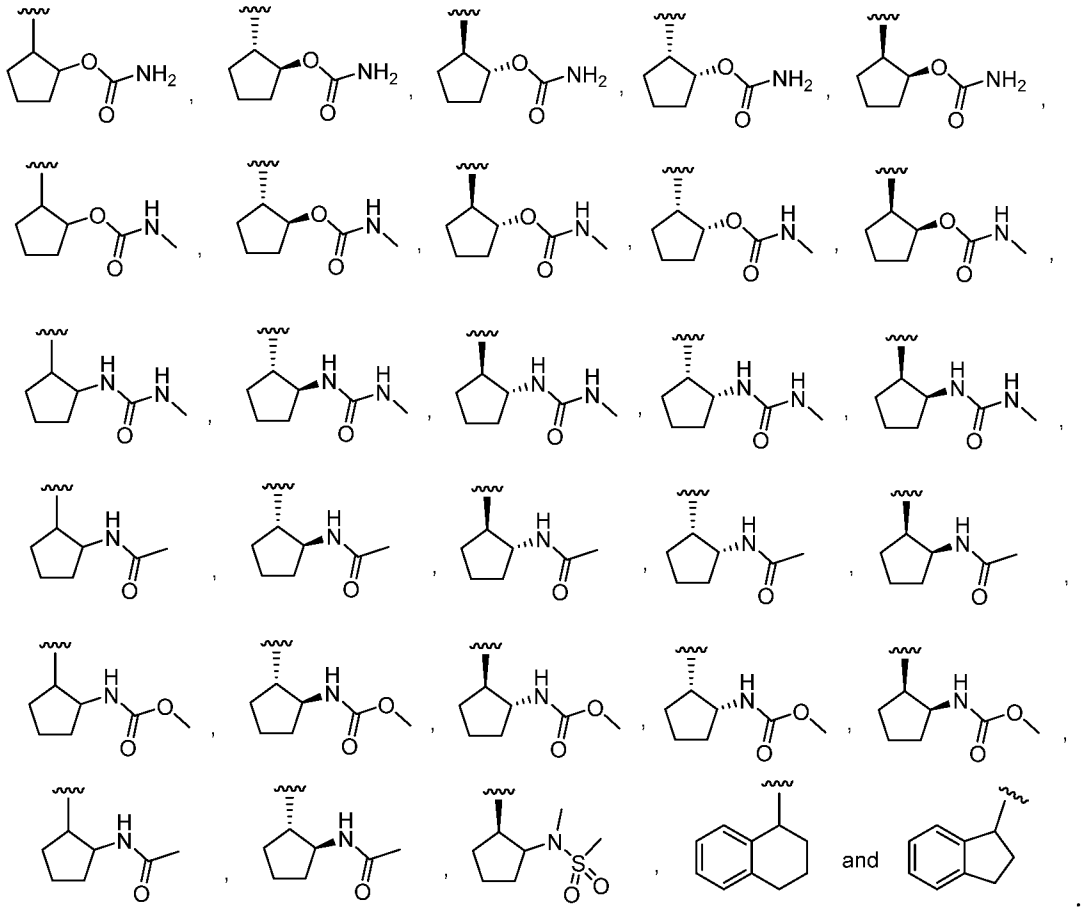
chain C_{3-4} alkyl. Non-limiting exemplary C_{1-10} alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, *tert*-butyl, *iso*-butyl, 3-pentyl, hexyl, heptyl, octyl, nonyl, and decyl. Non-limiting exemplary C_{1-4} alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, *tert*-butyl, and *iso*-butyl.

[0337] In the present disclosure, the term "optionally substituted alkyl" as used by itself or as part of another group refers to an alkyl that is either unsubstituted or substituted with one, two, or three substituents independently selected from the group consisting of nitro, haloalkoxy, aryloxy, aralkyloxy, alkylthio, sulfonamido, alkylcarbonyl, arylcarbonyl, alkylsulfonyl, arylsulfonyl, carboxy, carboxyalkyl, and alkylcarbonyloxy. In one embodiment, the optionally substituted alkyl is substituted with two substituents. In another embodiment, the optionally substituted alkyl is substituted with one substituent. In another embodiment, the optionally substituted alkyl is unsubstituted. Non-limiting exemplary substituted alkyl groups include $-CH_2CH_2NO_2$, $-CH_2SO_2CH_3$, $CH_2CH_2SO_2CH_3$,$-CH_2CH_2CO_2H$, $-CH_2SCH_3$, $-CH_2CH_2SO_2CH_3$, $-CH_2CH_2COPh$, and $-CH_2OC(=O)CH_3$.

[0338] In the present disclosure, the term "cycloalkyl" as used by itself or as part of another group refers to unsubstituted saturated or partially unsaturated, e.g., containing one or two double bonds, cyclic aliphatic hydrocarbons containing one to three rings having from three to twelve carbon atoms, i.e., C_{3-12} cycloalkyl, or the number of carbons designated. In one embodiment, the cycloalkyl has two rings. In another embodiment, the cycloalkyl has one ring. In another embodiment, the cycloalkyl is saturated. In another embodiment, the cycloalkyl is unsaturated. In another embodiment, the cycloalkyl is a C_{3-8} cycloalkyl. In another embodiment, the cycloalkyl is a C_{3-6} cycloalkyl. The term "cycloalkyl" is meant to include groups wherein a ring $-CH_2-$ is replaced with a $-C(=O)-$. Non-limiting exemplary cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, norbornyl, decalin, adamantyl, cyclohexenyl, cyclopentenyl, and cyclopentanone.

[0339] In the present disclosure, the term "optionally substituted cycloalkyl" as used by itself or as part of another group refers to a cycloalkyl that is either unsubstituted or substituted with one, two, or three substituents independently selected from the group consisting of halo, nitro, cyano, hydroxy, alkylcarbonyloxy, cycloalkylcarbonyloxy, amino, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, aryloxy, aralkyloxy, alkylthio,

carboxamido, sulfonamido, alkylcarbonyl, arylcarbonyl, alkylsulfonyl, arylsulfonyl, carboxy, carboxyalkyl, optionally substituted alkyl, optionally substituted cycloalkyl, alkenyl, alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclo, alkoxyalkyl, (amino)alkyl, (carboxamido)alkyl, (heterocyclo)alkyl, -OC(=O)-amino, $-N(R^{19a})C(=O)-R^{19b}$, and $-N(R^{20a})SO_2-R^{20b}$, wherein R^{19a} is selected from the group consisting of hydrogen and alkyl, R^{19b} is selected from the group consisting of amino, alkoxy, alkyl, and optionally substituted aryl, R^{20a} is selected from the group consisting of hydrogen and alkyl, and R^{20b} is selected from the group consisting of amino, alkyl, and optionally substituted aryl. The term optionally substituted cycloalkyl includes cycloalkyl groups having a fused optionally substituted aryl, e.g., phenyl, or fused optionally substituted heteroaryl, e.g., pyridyl. An optionally substituted cycloalkyl having a fused optionally substituted aryl or fused optionally substituted heteroaryl group may be attached to the remainder of the molecule at any available carbon atom on the cycloalkyl ring. In one embodiment, the optionally substituted cycloalkyl is substituted with two substituents. In another embodiment, the optionally substituted cycloalkyl is substituted with one substituent. In another embodiment, the optionally substituted cycloalkyl is unsubstituted. Non-limiting exemplary substituted cycloalkyl groups include:

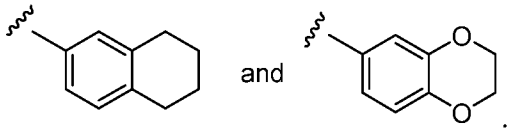


[0340] In the present disclosure, the term "aryl" as used by itself or as part of another group refers to unsubstituted monocyclic or bicyclic aromatic ring systems having from six to fourteen carbon atoms, i.e., a C_{6-14} aryl. Non-limiting exemplary aryl groups include phenyl (abbreviated as "Ph"), naphthyl, phenanthryl, anthracyl, indenyl, azulenyl, biphenyl, biphenylenyl, and fluorenyl groups. In one embodiment, the aryl group is phenyl or naphthyl.

[0341] In the present disclosure, the term "optionally substituted aryl" as used herein by itself or as part of another group refers to an aryl that is either unsubstituted or substituted with one to five substituents independently selected from the group consisting of halo, nitro, cyano, hydroxy, amino, $-CO_2CH_2Ph$, alkylamino, dialkylamino, optionally substituted alkyl, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, aryloxy, aralkyloxy, alkylthio, carboxamido, sulfonamido, alkylcarbonyl, arylcarbonyl, alkylsulfonyl, haloalkylsulfonyl cycloalkylsulfonyl, (cycloalkyl)alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, heterocyclosulfonyl, carboxy, carboxyalkyl, optionally substituted cycloalkyl, alkenyl, alkynyl, optionally substituted aryl, optionally

substituted heteroaryl, optionally substituted heterocyclo, alkoxycarbonyl, alkoxyalkyl, (amino)alkyl, (carboxamido)alkyl, and (heterocyclo)alkyl.

[0342] In one embodiment, the optionally substituted aryl is an optionally substituted phenyl. In another embodiment, the optionally substituted phenyl has four substituents. In another embodiment, the optionally substituted phenyl has three substituents. In another embodiment, the optionally substituted phenyl has two substituents. In another embodiment, the optionally substituted phenyl has one substituent. In another embodiment, the optionally substituted phenyl is unsubstituted. Non-limiting exemplary substituted aryl groups include 2-methylphenyl, 2-methoxyphenyl, 2-fluorophenyl, 2-chlorophenyl, 2-bromophenyl, 3-methylphenyl, 3-methoxyphenyl, 3-fluorophenyl, 3-chlorophenyl, 4-methylphenyl, 4-ethylphenyl, 4-methoxyphenyl, 4-fluorophenyl, 4-chlorophenyl, 2,6-di-fluorophenyl, 2,6-di-chlorophenyl, 2-methyl, 3-methoxyphenyl, 2-ethyl, 3-methoxyphenyl, 3,4-di-methoxyphenyl, 3,5-di-fluorophenyl 3,5-di-methylphenyl, 3,5-dimethoxy, 4-methylphenyl, 2-fluoro-3-chlorophenyl, 3-chloro-4-fluorophenyl, 4-(pyridin-4-ylsulfonyl)phenyl The term optionally substituted aryl includes phenyl groups having a fused optionally substituted cycloalkyl or fused optionally substituted heterocyclo group. An optionally substituted phenyl having a fused optionally substituted cycloalkyl or fused optionally substituted heterocyclo group may be attached to the remainder of the molecule at any available carbon atom on the phenyl ring. Non-limiting examples include:



[0343] In the present disclosure, the term "alkenyl" as used by itself or as part of another group refers to an alkyl containing one, two or three carbon-to-carbon double bonds. In one embodiment, the alkenyl has one carbon-to-carbon double bond. In another embodiment, the alkenyl is a C_{2-6} alkenyl. In another embodiment, the alkenyl is a C_{2-4} alkenyl. Non-limiting exemplary alkenyl groups include ethenyl, propenyl, isopropenyl, butenyl, *sec*-butenyl, pentenyl, and hexenyl.

[0344] In the present disclosure, the term "optionally substituted alkenyl" as used herein by itself or as part of another group refers to an alkenyl that is either unsubstituted or substituted with one, two or three substituents independently selected

from the group consisting of halo, nitro, cyano, hydroxy, amino, alkylamino, dialkylamino, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, aryloxy, aralkyloxy, alkylthio, carboxamido, sulfonamido, alkylcarbonyl, arylcarbonyl, alkylsulfonyl, arylsulfonyl, carboxy, carboxyalkyl, optionally substituted alkyl, optionally substituted cycloalkyl, alkenyl, alkynyl, optionally substituted aryl, heteroaryl, and optionally substituted heterocyclo.

[0345] In the present disclosure, the term "alkynyl" as used by itself or as part of another group refers to an alkyl containing one to three carbon-to-carbon triple bonds. In one embodiment, the alkynyl has one carbon-to-carbon triple bond. In another embodiment, the alkynyl is a C_{2-6} alkynyl. In another embodiment, the alkynyl is a C_{2-4} alkynyl. Non-limiting exemplary alkynyl groups include ethynyl, propynyl, butynyl, 2-butynyl, pentynyl, and hexynyl groups.

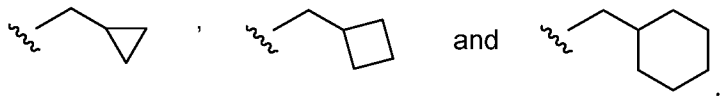
[0346] In the present disclosure, the term "optionally substituted alkynyl" as used herein by itself or as part refers to an alkynyl that is either unsubstituted or substituted with one, two or three substituents independently selected from the group consisting of halo, nitro, cyano, hydroxy, amino, alkylamino, dialkylamino, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, aryloxy, aralkyloxy, alkylthio, carboxamido, sulfonamido, alkylcarbonyl, arylcarbonyl, alkylsulfonyl, arylsulfonyl, carboxy, carboxyalkyl, optionally substituted alkyl, cycloalkyl, alkenyl, alkynyl, optionally substituted aryl, optionally substituted heteroaryl, and heterocyclo.

[0347] In the present disclosure, the term "haloalkyl" as used by itself or as part of another group refers to an alkyl substituted by one or more fluorine, chlorine, bromine and/or iodine atoms. In one embodiment, the alkyl group is substituted by one, two, or three fluorine and/or chlorine atoms. In another embodiment, the haloalkyl group is a C_{1-4} haloalkyl group. Non-limiting exemplary haloalkyl groups include fluoromethyl, 2-fluoroethyl, difluoromethyl, trifluoromethyl, pentafluoroethyl, 1,1-difluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 3,3,3-trifluoropropyl, 4,4,4-trifluorobutyl, and trichloromethyl groups.

[0348] In the present disclosure, the term "hydroxyalkyl" as used by itself or as part of another group refers to an alkyl substituted with one, two, or three hydroxy groups. In one embodiment, the hydroxyalkyl is a monohydroxyalkyl, i.e., a hydroxyalkyl substituted with one hydroxy group. In another embodiment, the hydroxyalkyl is a

dihydroxyalkyl, i.e., a hydroxyalkyl substituted with two hydroxy groups. Non-limiting exemplary hydroxyalkyl groups include hydroxymethyl, hydroxyethyl, hydroxypropyl and hydroxybutyl groups, such as 1-hydroxyethyl, 2-hydroxyethyl, 1,2-dihydroxyethyl, 2-hydroxypropyl, 3-hydroxypropyl, 3-hydroxybutyl, 4-hydroxybutyl, 2-hydroxy-1-methylpropyl, and 1,3-dihydroxyprop-2-yl.

[0349] In the present disclosure, the term "(cycloalkyl)alkyl," as used by itself or as part of another group refers to an alkyl substituted with an optionally substituted cycloalkyl. In one embodiment, the (cycloalkyl) alkyl, is a "(C_{3-6} cycloalkyl)C_{1-4} alkyl," i.e., a C_{1-4} alkyl substituted with an optionally substituted C_{3-6} cycloalkyl. Non-limiting exemplary (cycloalkyl) alkyl groups include:

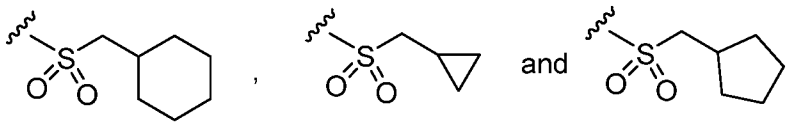


[0350] In the present disclosure, the term "alkylsulfonyl" as used by itself or as part of another group refers to a sulfonyl, i.e., -SO_2-, substituted with an optionally substituted alkyl. A non-limiting exemplary alkylsulfonyl group is -SO_2CH_3.

[0351] In the present disclosure, the term "haloalkylsulfonyl" as used by itself or as part of another group refers to a sulfonyl, i.e., -SO_2-, substituted with a haloalkyl. A non-limiting exemplary alkylsulfonyl group is -SO_2CF_3.

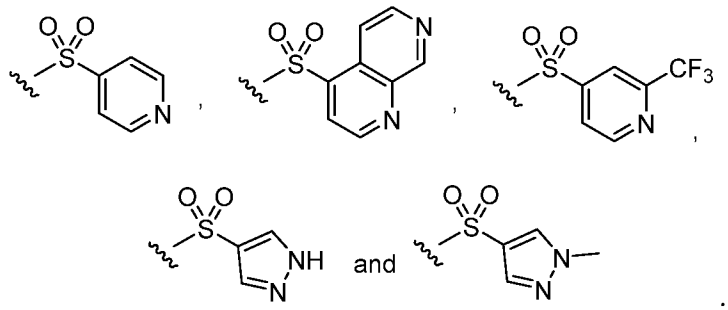
[0352] In the present disclosure, the term "cycloalkylsulfonyl" as used by itself or as part of another group refers to a sulfonyl, i.e., -SO_2-, substituted with an optionally substituted cycloalkyl. Non-limiting exemplary alkylsulfonyl group include -SO_2-cyclopropyl and -SO_2-cyclopenyl.

[0353] In the present disclosure, the term "(cycloalkyl)alkylsulfonyl" as used by itself or as part of another group refers to a sulfonyl, i.e., -SO_2-, substituted with a (cycloalkyl)alkyl. Non-limiting exemplary (cycloalkyl)alkylsulfonyl groups include:

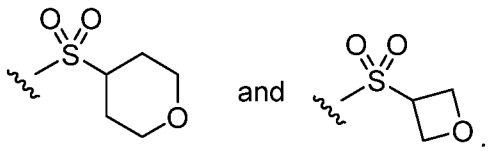


[0354] In the present disclosure, the term "arylsulfonyl" as used by itself or as part of another group refers to a sulfonyl, i.e., -SO_2-, substituted with an optionally substituted aryl. A non-limiting exemplary arylsulfonyl group is -SO_2Ph.

[0355] In the present disclosure, the term "heteroarylsulfonyl" as used by itself or as part of another group refers to a sulfonyl, i.e., -SO_2-, substituted with an optionally substituted heteroaryl group. Non-limiting exemplary heteroarylsulfonyl groups include:



[0356] In the present disclosure, the term "heterocyclosulfonyl" as used by itself or as part of another group refers to a sulfonyl, i.e., -SO_2-, substituted with an optionally substituted heterocyclo group. A non-limiting exemplary heterocyclosulfonyl group is:



[0357] In the present disclosure, the term "sulfonamido" as used by itself or as part of another group refers to a radical of the formula -$SO_2NR^{21a}R^{21b}$, wherein R^{21a} and R^{21b} are each independently selected from the group consisting of hydrogen, optionally substituted alkyl, and optionally substituted aryl, or R^{21a} and R^{21b} taken together with the nitrogen to which they are attached from a 3- to 8-membered heterocyclo group. Non-limiting exemplary sulfonamido groups include -SO_2NH_2, -$SO_2N(H)CH_3$, -$SO_2N(CH_3)_2$, and -$SO_2N(H)Ph$.

[0358] In the present disclosure, the term "alkoxy" as used by itself or as part of another group refers to an optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, or optionally substituted alkynyl attached to a terminal oxygen atom. In one embodiment, the alkoxy is an optionally substituted alkyl attached to a terminal oxygen atom. In one embodiment, the alkoxy group is a C_{1-6} alkyl attached to a terminal oxygen atom. In another embodiment, the alkoxy group is a C_{1-4} alkyl attached to a terminal oxygen atom. Non-limiting exemplary alkoxy groups include methoxy, ethoxy, *tert*-butoxy, and -$OCH_2SO_2CH_3$.

[0359] In the present disclosure, the term "alkylthio" as used by itself or as part of another group refers to an optionally substituted alkyl attached to a terminal sulfur atom. In one embodiment, the alkylthio group is a C_{1-4} alkylthio group. Non-limiting exemplary alkylthio groups include $-SCH_3$ and $-SCH_2CH_3$.

[0360] In the present disclosure, the term "alkoxyalkyl" as used by itself or as part of another group refers to an optionally alkyl substituted with an alkoxy group. Non-limiting exemplary alkoxyalkyl groups include methoxymethyl, methoxyethyl, methoxypropyl, methoxybutyl, ethoxymethyl, ethoxyethyl, ethoxypropyl, ethoxybutyl, propoxymethyl, iso-propoxymethyl, propoxyethyl, propoxypropyl, butoxymethyl, tert-butoxymethyl, isobutoxymethyl, sec-butoxymethyl, and pentyloxymethyl.

[0361] In the present disclosure, the term "haloalkoxy" as used by itself or as part of another group refers to a haloalkyl attached to a terminal oxygen atom. Non-limiting exemplary haloalkoxy groups include fluoromethoxy, difluoromethoxy, trifluoromethoxy, and 2,2,2-trifluoroethoxy.

[0362] In the present disclosure, the term "aryloxy" as used by itself or as part of another group refers to an optionally substituted aryl attached to a terminal oxygen atom. A non-limiting exemplary aryloxy group is PhO-.

[0363] In the present disclosure, the term "aralkyloxy" as used by itself or as part of another group refers to an aralkyl attached to a terminal oxygen atom. Non-limiting exemplary aralkyloxy groups include $PhCH_2O-$ and $PhCH_2CH_2O-$.

[0364] In the present disclosure, the term "heteroaryl" refers to unsubstituted monocyclic and bicyclic aromatic ring systems having 5 to 14 ring atoms, i.e., a 5- to 14-membered heteroaryl, wherein at least one carbon atom of one of the rings is replaced with a heteroatom independently selected from the group consisting of oxygen, nitrogen and sulfur. In one embodiment, the heteroaryl contains 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of oxygen, nitrogen and sulfur. In one embodiment, the heteroaryl has three heteroatoms. In another embodiment, the heteroaryl has two heteroatoms. In another embodiment, the heteroaryl has one heteroatom. In another embodiment, the heteroaryl is a 5- to 10-membered heteroaryl. In another embodiment, the heteroaryl is a 5- or 6-membered heteroaryl. In another embodiment, the heteroaryl has 5 ring atoms, e.g., thienyl, a 5-membered heteroaryl having four carbon atoms and one sulfur atom. In another

embodiment, the heteroaryl has 6 ring atoms, e.g., pyridyl, a 6-membered heteroaryl having five carbon atoms and one nitrogen atom. Non-limiting exemplary heteroaryl groups include thienyl, benzo[b]thienyl, naphtho[2,3-b]thienyl, thianthrenyl, furyl, benzofuryl, pyranyl, isobenzofuranyl, benzooxazonyl, chromenyl, xanthenyl, 2*H*-pyrrolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, isoindolyl, 3*H*-indolyl, indolyl, indazolyl, purinyl, isoquinolyl, quinolyl, phthalazinyl, naphthyridinyl, cinnolinyl, quinazolinyl, pteridinyl, 4a*H*-carbazolyl, carbazolyl, β-carbolinyl, phenanthridinyl, acridinyl, pyrimidinyl, phenanthrolinyl, phenazinyl, thiazolyl, isothiazolyl, phenothiazolyl, isoxazolyl, furazanyl, and phenoxazinyl. In one embodiment, the heteroaryl is selected from the group consisting of thienyl (e.g., thien-2-yl and thien-3-yl), furyl (e.g., 2-furyl and 3-furyl), pyrrolyl (e.g., 1H-pyrrol-2-yl and 1H-pyrrol-3-yl), imidazolyl (e.g., 2H-imidazol-2-yl and 2H-imidazol-4-yl), pyrazolyl (e.g., 1H-pyrazol-3-yl, 1H-pyrazol-4-yl, and 1H-pyrazol-5-yl), pyridyl (e.g., pyridin-2-yl, pyridin-3-yl, and pyridin-4-yl), pyrimidinyl (e.g., pyrimidin-2-yl, pyrimidin-4-yl, and pyrimidin-5-yl), thiazolyl (e.g., thiazol-2-yl, thiazol-4-yl, and thiazol-5-yl), isothiazolyl (*e.g.*, isothiazol-3-yl, isothiazol-4-yl, and isothiazol-5-yl), oxazolyl (*e.g.*, oxazol-2-yl, oxazol-4-yl, and oxazol-5-yl), isoxazolyl (e.g., isoxazol-3-yl, isoxazol-4-yl, and isoxazol-5-yl), and indazolyl (e.g., 1H-indazol-3-yl). The term "heteroaryl" is also meant to include possible N-oxides. A non-limiting exemplary N-oxide is pyridyl N-oxide.

[0365] In one embodiment, the heteroaryl is a 5- or 6-membered heteroaryl. In one embodiment, the heteroaryl is a 5-membered heteroaryl, i.e., the heteroaryl is a monocyclic aromatic ring system having 5 ring atoms wherein at least one carbon atom of the ring is replaced with a heteroatom independently selected from nitrogen, oxygen, and sulfur. Non-limiting exemplary 5-membered heteroaryl groups include thienyl, furyl, pyrrolyl, oxazolyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, and isoxazolyl. In another embodiment, the heteroaryl is a 6-membered heteroaryl, e.g., the heteroaryl is a monocyclic aromatic ring system having 6 ring atoms wherein at least one carbon atom of the ring is replaced with a nitrogen atom. Non-limiting exemplary 6-membered heteroaryl groups include pyridyl, pyrazinyl, pyrimidinyl, and pyridazinyl.

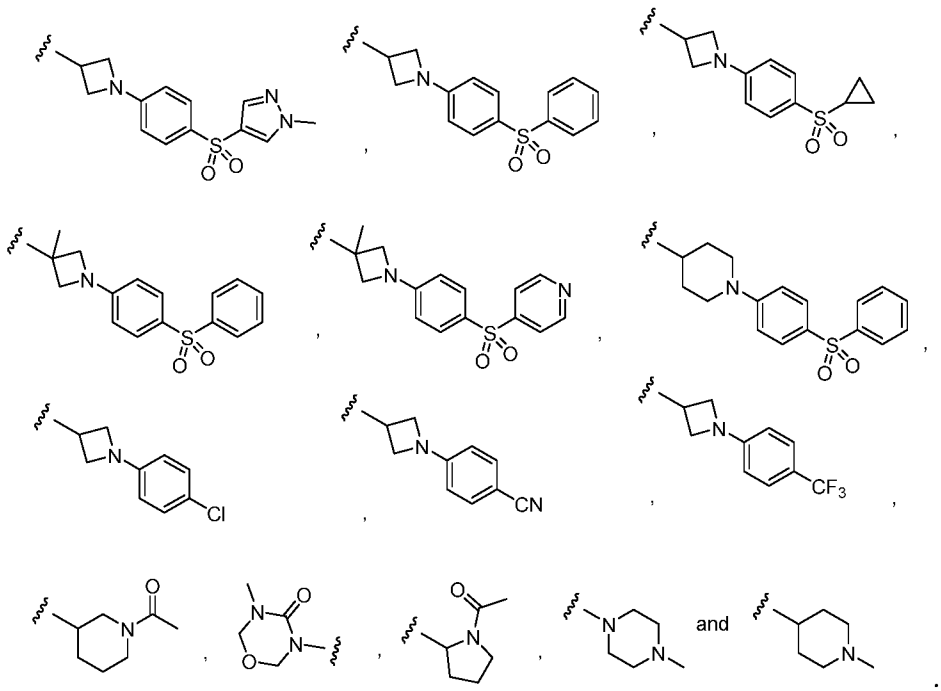
[0366] In the present disclosure, the term "optionally substituted heteroaryl" as used by itself or as part of another group refers to a heteroaryl that is either unsubstituted or

substituted with one two, three, or four substituents, independently selected from the group consisting of halo, nitro, cyano, hydroxy, amino, alkylamino, dialkylamino, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, aryloxy, aralkyloxy, alkylthio, carboxamido, sulfonamido, alkylcarbonyl, arylcarbonyl, alkylsulfonyl, haloalkylsulfonyl cycloalkylsulfonyl, (cycloalkyl)alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, carboxy, carboxyalkyl, optionally substituted alkyl, optionally substituted cycloalkyl, alkenyl, alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclo, alkoxyalkyl, (amino)alkyl, (carboxamido)alkyl, and (heterocyclo)alkyl. In one embodiment, the optionally substituted heteroaryl has one substituent. In another embodiment, the optionally substituted heteroaryl is unsubstituted. Any available carbon or nitrogen atom can be substituted. The term optionally substituted heteroaryl includes heteroaryl groups having a fused optionally substituted cycloalkyl or fused optionally substituted heterocyclo group. An optionally substituted heteroaryl having a fused optionally substituted cycloalkyl or fused optionally substituted heterocyclo group may be attached to the remainder of the molecule at any available carbon atom on the heteroaryl ring.

[0367] In the present disclosure, the term "heterocyclo" as used by itself or as part of another group refers to unsubstituted saturated and partially unsaturated, e.g., containing one or two double bonds, cyclic groups containing one, two, or three rings having from three to fourteen ring members, i.e., a 3- to 14-membered heterocyclo, wherein at least one carbon atom of one of the rings is replaced with a heteroatom. Each heteroatom is independently selected from the group consisting of oxygen, sulfur, including sulfoxide and sulfone, and/or nitrogen atoms, which can be oxidized or quaternized. The term "heterocyclo" includes groups wherein a ring $-CH_2-$ is replaced with a -C(=O)-, for example, cyclic ureido groups such as 2-imidazolidinone and cyclic amide groups such as β-lactam, γ-lactam, δ-lactam, ε-lactam, and piperazin-2-one. The term "heterocyclo" also includes groups having fused optionally substituted aryl groups, e.g., indolinyl or chroman-4-yl. In one embodiment, the heterocyclo group is a C_{4-6} heterocyclo, i.e., a 4-, 5- or 6-membered cyclic group, containing one ring and one or two oxygen and/or nitrogen atoms. In one embodiment, the heterocyclo group is a C_{4-6} heterocyclo containing one ring and one nitrogen atom. The heterocyclo can be

optionally linked to the rest of the molecule through any available carbon or nitrogen atom. Non-limiting exemplary heterocyclo groups include azetidinyl, dioxanyl, tetrahydropyranyl, 2-oxopyrrolidin-3-yl, piperazin-2-one, piperazine-2,6-dione, 2-imidazolidinone, piperidinyl, morpholinyl, piperazinyl, pyrrolidinyl, and indolinyl.

[0368] In the present disclosure, the term "optionally substituted heterocyclo" as used herein by itself or part of another group refers to a heterocyclo that is either unsubstituted or substituted with one, two, three, or four substituents independently selected from the group consisting of halo, nitro, cyano, hydroxy, amino, alkylamino, dialkylamino, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, aryloxy, aralkyloxy, alkylthio, carboxamido, sulfonamido, alkylcarbonyl, cycloalkylcarbonyl, alkoxycarbonyl, $CF_3C(=O)$-, arylcarbonyl, alkylsulfonyl, arylsulfonyl, carboxy, carboxyalkyl, alkyl, optionally substituted cycloalkyl, alkenyl, alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclo, alkoxyalkyl, (amino)alkyl, (carboxamido)alkyl, or (heterocyclo)alkyl. Substitution may occur on any available carbon or nitrogen atom, or both. Non-limiting exemplary substituted heterocyclo groups include:

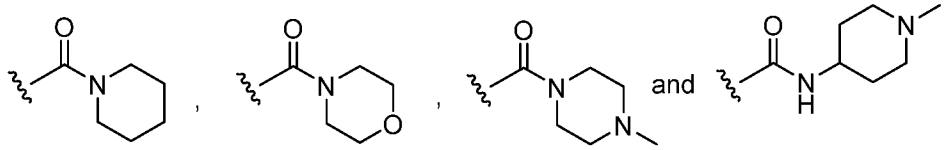


[0369] In the present disclosure, the term "amino" as used by itself or as part of another group refers to a radical of the formula $-NR^{22a}R^{22b}$, wherein R^{22a} and R^{22b} are each independently selected from the group consisting of hydrogen, alkyl, aralkyl,

hydroxyalkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclo, and optionally substituted heteroaryl, or R^{22a} and R^{22b} are taken together to form a 3- to 8-membered optionally substituted heterocyclo. Non-limiting exemplary amino groups include $-NH_2$ and $-N(H)(CH_3)$.

[0370] In the present disclosure, the term "(amino)alkyl" as used by itself or as part of another group refers to an alkyl substituted with an amino. Non-limiting exemplary (amino)alkyl groups include $-CH_2CH_2NH_2$, and $-CH_2CH_2N(H)CH_3$, $-CH_2CH_2N(CH_3)_2$, and $-CH_2N(H)$-cyclopropyl.

[0371] In the present disclosure, the term "carboxamido" as used by itself or as part of another group refers to a radical of formula $-C(=O)NR^{23a}R^{23b}$, wherein R^{23a} and R^{23b} are each independently selected from the group consisting of hydrogen, optionally substituted alkyl, hydroxyalkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclo, and optionally substituted heteroaryl, or R^{23a} and R^{23b} taken together with the nitrogen to which they are attached form a 3- to 8-membered optionally substituted heterocyclo group. In one embodiment, R^{23a} and R^{23b} are each independently hydrogen or optionally substituted alkyl. In one embodiment, R^{23a} and R^{23b} are taken together to taken together with the nitrogen to which they are attached form a 3- to 8-membered optionally substituted heterocyclo group. Non-limiting exemplary carboxamido groups include $-CONH_2$, $-CON(H)CH_3$, $-CON(CH_3)_2$, -CON(H)Ph,



[0372] In the present disclosure, the term "alkylcarbonyl" as used by itself or as part of another group refers to a carbonyl group, i.e., -C(=O)-, substituted with an alkyl. Non-limiting exemplary alkylcarbonyl groups include $-C(=O)CH_3$ and $-C(=O)CH_2CH_2CH_2CH_3$.

[0373] In the present disclosure, the term "cycloalkylcarbonyl" as used by itself or as part of another group refers to a carbonyl group, i.e., -C(=O)-, substituted with a cycloalkyl. A non-limiting exemplary cycloalkylcarbonyl group is -C(=O)-cyclopropyl.

[0374] In the present disclosure, the term "arylcarbonyl" as used by itself or as part of another group refers to a carbonyl group, i.e., -C(=O)-, substituted with an optionally substituted aryl. A non-limiting exemplary arylcarbonyl group is -COPh.

[0375] In the present disclosure, the term "alkoxycarbonyl" as used by itself or as part of another group refers to a carbonyl group, i.e., -C(=O)-, substituted with an alkoxy. In one embodiment, the alkoxy is a C_{1-4} alkoxy. Non-limiting exemplary alkoxycarbonyl groups include -C(=O)OMe, -C(=O)OEt, and -C(=O)OtBu.

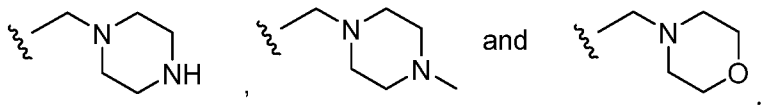
[0376] In the present disclosure, the term "(alkoxycarbonyl)alkyl" as used by itself or as part of another group refers to an alkyl substituted by an alkoxycarbonyl group. Non-limiting exemplary (alkoxycarbonyl)alkyl groups include -CH_2C(=O)OMe, -CH_2C(=O)OEt, and -CH_2C(=O)OtBu.

[0377] In the present disclosure, the term "carboxy" as used by itself or as part of another group refers to a radical of the formula -CO_2H.

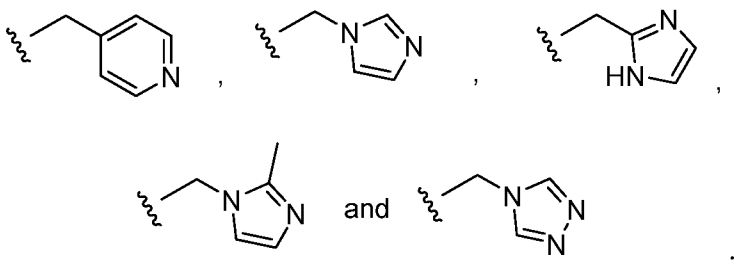
[0378] In the present disclosure, the term "carboxyalkyl" as used by itself or as part of another group refers to an alkyl substituted with a -CO_2H. A non-limiting exemplary carboxyalkyl group is -CH_2CO_2H.

[0379] In the present disclosure, the term "aralkyl" as used by itself or as part of another group refers to an alkyl substituted with one, two, or three optionally substituted aryl groups. In one embodiment, aralkyl is a C_{1-4} alkyl substituted with one optionally substituted C_5 or C_6 aryl group. In another embodiment, the aralkyl is a C_1 alkyl substituted with one optionally substituted aryl group. In another embodiment, the aralkyl is a C_2 alkyl substituted with one optionally substituted aryl group. In another embodiment, the aralkyl is a C_3 alkyl substituted with one optionally substituted aryl group. In one embodiment, the aralkyl is a C_1 or C_2 alkyl substituted with one optionally substituted phenyl group. Non-limiting exemplary aralkyl groups include benzyl, phenethyl, -$CHPh_2$, -$CH(CH_3)$Ph, -CH_2(4-F-Ph), -CH_2(4-Me-Ph), -CH_2(4-CF_3-Ph), and -CH(4-F-Ph)$_2$.

[0380] In the present disclosure, the term "(heterocyclo)alkyl" as used by itself or part of another group refers to an alkyl substituted with an optionally substituted heterocyclo group. In one embodiment, the (heterocyclo)alkyl is a C_{1-4} alkyl substituted with one optionally substituted heterocyclo group. Non-limiting exemplary (heterocyclo)alkyl groups include:



[0381] In the present disclosure, the term "(heteroaryl)alkyl" as used by itself or part of another group refers to an alkyl substituted with an optionally substituted heteroaryl group. In one embodiment, the (heteroaryl)alkyl is a C_{1-4} alkyl substituted with one optionally substituted heteroaryl group. In another embodiment, the (heteroaryl)alkyl is a C_1 alkyl substituted with one optionally substituted heteroaryl group Non-limiting exemplary (heteroaryl)alkyl groups include:



[0382] In the present disclosure, the term "(carboxamido)alkyl" as used by itself or as part of another group refers to an alkyl substituted with one or two carboxamido groups. In one embodiment, the (carboxamido)alkyl is a C_{1-4} alkyl substituted with one carboxamido group, i.e., a (carboxamido)C_{1-4} alkyl. In another embodiment, the (carboxamido)alkyl is a C_{1-4} alkyl substituted with two carboxamido groups. Non-limiting exemplary (carboxamido)alkyl groups include -CH_2CONH_2, -$C(H)CH_3$-$CONH_2$, and -$CH_2CON(H)CH_3$.

[0383] In the present disclosure, the term "(aryloxy)alkyl" as used by itself or as part of another group refers to an alkyl substituted with an aryloxy group. In one embodiment, the "(aryloxy)alkyl" is a C_{1-4} alkyl substituted with an aryloxy. In one embodiment, the "(aryloxy)alkyl" is a C_{2-4} alkyl substituted with an aryloxy. Non-limiting exemplary (aryloxy)alkyl groups include -CH_2CH_2OPh and -$CH_2CH_2CH_2OPh$.

[0384] In the present disclosure, the term "alkylcarbonyloxy" as used by itself or as part of another group refers to an oxy, e.g., -O-, substituted with an alkylcarbonyl group. Non-limiting exemplary "alkylcarbonyloxy" groups include -$OC(=O)CH_2CH_3$, -$OC(=O)CH_3$, i.e., acetoxy, -$OC(=O)CH_2CH_2CH_3$, and -$OC(=O)CH(CH_3)_2$.

[0385] In the present disclosure, the term "cycloalkylcarbonyloxy" as used by itself or as part of another group refers to an oxy, e.g., -O-, substituted with an

cycloalkylcarbonyl group. Non-limiting exemplary "cycloalkylcarbonyloxy" groups include -OC(=O)-cyclopropyl and -OC(=O)-cyclopenyl.

[0386] The term "menin inhibitor" or "inhibitor of menin" as used herein refers to a compound that disrupts, e.g., inhibits, the menin-MLL fusion protein interaction.

[0387] The term "a disease or condition wherein inhibition of menin provides a benefit" pertains to a disease or condition in which menin and/or the interaction of menin with a menin-interacting protein is important or necessary, e.g., for the onset, progress, or expression of that disease or condition, or a disease or a condition which is known to be treated by a menin inhibitor. Examples of such conditions include, but are not limited to, a cancer, a chronic autoimmune disease, an inflammatory disease, a proliferative disease, sepsis, and a viral infection. One of ordinary skill in the art is readily able to determine whether a compound treats a disease or condition mediated by menin for any particular cell type, for example, by assays which conveniently can be used to assess the activity of particular compounds.

[0388] The term "second therapeutic agent" refers to a therapeutic agent different from a Compound of the Disclosure and that is known to treat the disease or condition of interest. For example when a cancer is the disease or condition of interest, the second therapeutic agent can be a known chemotherapeutic drug, like taxol, or radiation, for example.

[0389] The term "disease" or “condition” denotes disturbances and/or anomalies that as a rule are regarded as being pathological conditions or functions, and that can manifest themselves in the form of particular signs, symptoms, and/or malfunctions. As demonstrated below, Compounds of the Disclosure are menin inhibitors and can be used in treating diseases and conditions wherein menin inhibition provides a benefit.

[0390] As used herein, the terms "treat," "treating," "treatment," and the like refer to eliminating, reducing, or ameliorating a disease or condition, and/or symptoms associated therewith. Although not precluded, treating a disease or condition does not require that the disease, condition, or symptoms associated therewith be completely eliminated. As used herein, the terms "treat," "treating," "treatment," and the like may include "prophylactic treatment," which refers to reducing the probability of redeveloping a disease or condition, or of a recurrence of a previously-controlled disease or condition, in a subject who does not have, but is at risk of or is susceptible

to, redeveloping a disease or condition or a recurrence of the disease or condition. The term "treat" and synonyms contemplate administering a therapeutically effective amount of a Compound of the Disclosure to an individual in need of such treatment.

[0391] Within the meaning of the disclosure, "treatment" also includes relapse prophylaxis or phase prophylaxis, as well as the treatment of acute or chronic signs, symptoms and/or malfunctions. The treatment can be orientated symptomatically, for example, to suppress symptoms. It can be effected over a short period, be oriented over a medium term, or can be a long-term treatment, for example within the context of a maintenance therapy.

[0392] The term "therapeutically effective amount" or "effective dose" as used herein refers to an amount of the active ingredient(s) that is(are) sufficient, when administered by a method of the disclosure, to efficaciously deliver the active ingredient(s) for the treatment of condition or disease of interest to an individual in need thereof. In the case of a cancer or other proliferation disorder, the therapeutically effective amount of the agent may reduce (i.e., retard to some extent and preferably stop) unwanted cellular proliferation; reduce the number of cancer cells; reduce the tumor size; inhibit (i.e., retard to some extent and preferably stop) cancer cell infiltration into peripheral organs; inhibit (i.e., retard to some extent and preferably stop) tumor metastasis; inhibit, to some extent, tumor growth; reduce menin interactions in the target cells; and/or relieve, to some extent, one or more of the symptoms associated with the cancer. To the extent the administered compound or composition prevents growth and/or kills existing cancer cells, it may be cytostatic and/or cytotoxic.

[0393] The term "container" means any receptacle and closure therefore suitable for storing, shipping, dispensing, and/or handling a pharmaceutical product.

[0394] The term "insert" means information accompanying a pharmaceutical product that provides a description of how to administer the product, along with the safety and efficacy data required to allow the physician, pharmacist, and patient to make an informed decision regarding use of the product. The package insert generally is regarded as the "label" for a pharmaceutical product.

[0395] "Concurrent administration," "administered in combination," "simultaneous administration," and similar phrases mean that two or more agents are administered concurrently to the subject being treated. By "concurrently," it is meant that each agent

is administered either simultaneously or sequentially in any order at different points in time. However, if not administered simultaneously, it is meant that they are administered to an individual in a sequence and sufficiently close in time so as to provide the desired therapeutic effect and can act in concert. For example, a Compound of the Disclosure can be administered at the same time or sequentially in any order at different points in time as a second therapeutic agent. A Compound of the Disclosure and the second therapeutic agent can be administered separately, in any appropriate form and by any suitable route. When a Compound of the Disclosure and the second therapeutic agent are not administered concurrently, it is understood that they can be administered in any order to a subject in need thereof. For example, a Compound of the Disclosure can be administered prior to (e.g., 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks before), concomitantly with, or subsequent to (e.g., 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks after) the administration of a second therapeutic agent treatment modality (e.g., radiotherapy), to an individual in need thereof. In various embodiments, a Compound of the Disclosure and the second therapeutic agent are administered 1 minute apart, 10 minutes apart, 30 minutes apart, less than 1 hour apart, 1 hour apart, 1 hour to 2 hours apart, 2 hours to 3 hours apart, 3 hours to 4 hours apart, 4 hours to 5 hours apart, 5 hours to 6 hours apart, 6 hours to 7 hours apart, 7 hours to 8 hours apart, 8 hours to 9 hours apart, 9 hours to 10 hours apart, 10 hours to 11 hours apart, 11 hours to 12 hours apart, no more than 24 hours apart or no more than 48 hours apart. In one embodiment, the components of the combination therapies are administered at about 1 minute to about 24 hours apart.

[0396] The use of the terms "a", "an", "the", and similar referents in the context of this disclosure (especially in the context of the claims) are to be construed to cover both the singular and the plural, unless otherwise indicated. Recitation of ranges of values herein are intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited

herein. The use of any and all examples, or exemplary language (e.g., "such as") provided herein, is intended to better illustrate the disclosure and is not a limitation on the scope of the disclosure unless otherwise claimed. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the disclosure.

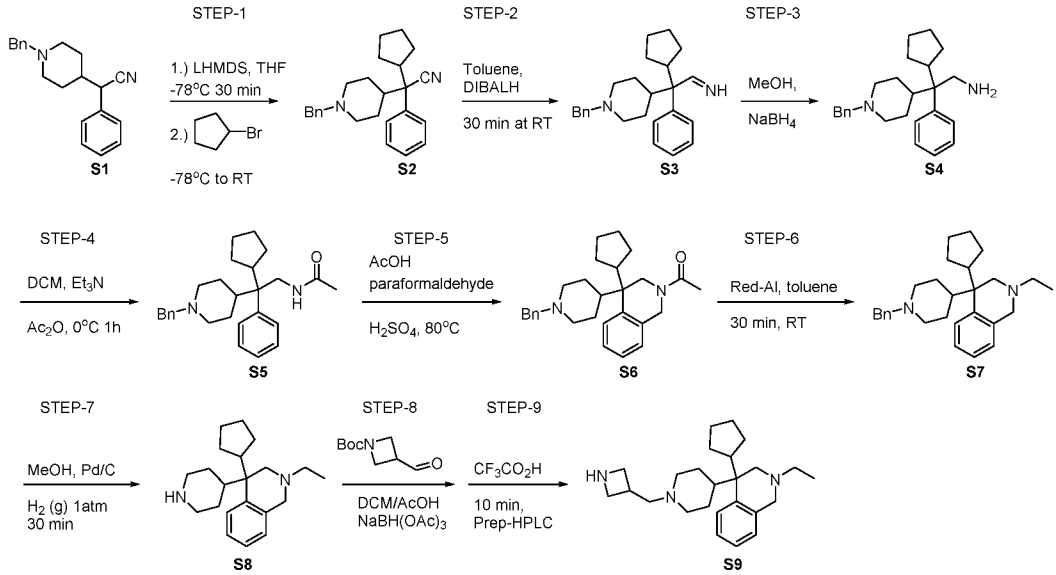
[0397] The term "about," as used herein, includes the recited number ± 10%. Thus, "about 10" means 9 to 11.

EXAMPLES

EXAMPLE 1

Synthesis of 4-(1-(azetidin-3-ylmethyl)piperidin-4-yl)-4-cyclopentyl-2-ethyl-1,2,3,4-tetrahydroisoquinoline (S9)

Scheme 1



[0398] STEP 1 – Synthesis of 2-(1-benzylpiperidin-4-yl)-2-cyclopentyl-2-phenylacetonitrile

[0399] LHMDS (1M in THF, 20.66 mL, 20.66 mmol) was added dropwise to a -78°C stirred solution of S1 (3g, 10.33 mmol) dissolved in dry THF (100 mL). After 30 minutes at -78°C, cyclopentylbromide (3.32 mL, 30.99 mmol) was added dropwise and the reaction was allowed to slowly warm to room temperature. After stirring overnight at RT, the reaction was quenched with saturated NH_4Cl, extracted with EtOAc,

concentrated and purified by column chromatography on silica gel to produce 3.64 g of compound S2 as an oil.

[0400] STEP 2 – Synthesis of 2-(1-benzylpiperidin-4-yl)-2-cyclopentyl-2-phenylethan-1-imine

[0401] DIBALH (0.5 M in toluene, 4.01 mL, 7.06 mmol) was added dropwise to a solution of S2 (506 mg, 1.41 mmol) from STEP 1 in toluene (20 mL) and stirred at RT. After one hour, the reaction was quenched by dropwise addition of 2M NaOH, and the aqueous layer was extracted with EtOAc and concentrated.

[0402] STEP 3 – Synthesis of 2-(1-benzylpiperidin-4-yl)-2-cyclopentyl-2-phenylethan-1-amine

[0403] The crude product from STEP 2 was dissolved in MeOH and $NaBH_4$ (107 mg, 2.82 mmol) was slowly added and the reaction was stirred. After stirring overnight, the reaction was quenched with water, extracted with EtOAc, dried over Na_2SO_4, filtered through celite, and concentrated to produce S4 that was used in the next step without further purification.

[0404] STEP 4 – Synthesis of N-(2-(1-benzylpiperidin-4-yl)-2-cyclopentyl-2-phenylethyl)acetamide

[0405] Acetic anhydride (108 mg, 1.06 mmol) was added to a solution, at 0°C, of crude S4 (0.705 mmol) and Et_3N (0.2 mL, 1.41 mmol) in DCM (3 mL) and stirred. After 30 minutes at 0°C, the reaction was put at RT and stirred. After 30 min at RT, the reaction was quenched with water and brine, extracted with EtOAc, dried over Na_2SO_4, filtered and concentrated to give 272 mg of crude S5 that was used without further purification.

[0406] STEP 5 – Synthesis of 1-(4-(1-benzylpiperidin-4-yl)-4-cyclopentyl-3,4-dihydroisoquinolin-2(1H)-yl)ethan-1-one

[0407] Crude S5 was dissolved in AcOH (6 mL), paraformaldehyde (100 mg) and concentrated H_2SO_4 (0.3 mL) were added and the reaction was heated to 80°C. After stirring overnight, the reaction was cooled to RT, slowly quenched with saturated $NaHCO_3$, extracted with EtOAc, dried over Na_2SO_4, filtered and concentrated to give crude S6 that was used without further purification.

[0408] STEP 6 – Synthesis of 4-(1-benzylpiperidin-4-yl)-4-cyclopentyl-2-ethyl-1,2,3,4-tetrahydroisoquinoline

[0409] Red-Al (3.2 M in toluene, 0.7 mL) was added dropwise to a solution, at RT, of crude S6 in toluene (5 mL) and stirred. After 30 minutes, the reaction was quenched by dropwise addition of 2M NaOH and the aqueous was extracted with EtOAc and concentrated. The crude S7 was purified by reverse phase prep HPLC and the pure compound was lyophilized to produce S7-TFA salt as a white powder.

[0410] STEP 7 – Synthesis of 4-cyclopentyl-2-ethyl-4-(piperidin-4-yl)-1,2,3,4-tetrahydroisoquinoline

[0411] S7 (280 mg) was dissolved in MeOH (5 mL) and the solution was vacuumed briefly then put under N_2 atmosphere – this was repeated 3 times. Pd/C (10% wt/wt, 200 mg) was quickly added to the solution that was vacuumed and put under N_2 atmosphere. The solution was briefly vacuumed to remove the N_2 atmosphere then put under H_2 atmosphere – this was repeated 3 times. After 30 minutes, the reaction was filtered through celite and concentrated to give crude S8 (200 mg) that was used without further purification.

[0412] STEP 8 – Synthesis of tert-butyl 3-((4-(4-cyclopentyl-2-ethyl-1,2,3,4-tetrahydroisoquinolin-4-yl)piperidin-1-yl)methyl)azetidine-1-carboxylate

[0413] 1-Boc-azetidine-3-carboxaldehyde (475 mg, 2.56 mmol) was added to a solution of crude S8 (200 mg, 0.641 mmol) in DCM/AcOH (1:1, 6 mL) and stirred. After 10 minutes, $NaBH(OAc)_3$ (1.08 g, 5.12 mmol) was slowly added to the reaction. After overnight, the reaction was slowly quenched with saturated $NaHCO_3$, extracted with EtOAc, dried over Na_2SO_4, filtered, and concentrated to produce crude Boc-protected-S9.

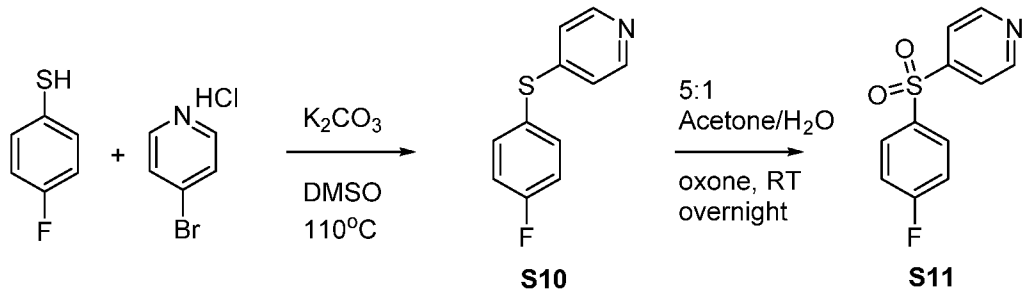
[0414] STEP 9 – Synthesis of 4-(1-(azetidin-3-ylmethyl)piperidin-4-yl)-4-cyclopentyl-2-ethyl-1,2,3,4-tetrahydroisoquinoline

[0415] The crude product from STEP 8 was dissolved in trifluoroacetic acid and stirred. After 10 minutes, the TFA was removed in vacuo, the crude purified by reverse phase prep HPLC, and the pure product was lyophilized to give S9-TFA salt (169 mg) as white solid.

EXAMPLE 2

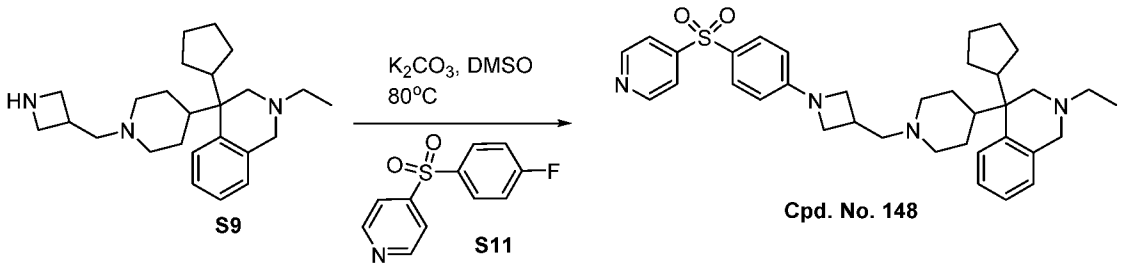
Synthesis of 4-cyclopentyl-2-ethyl-4-(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1,2,3,4-tetrahydroisoquinoline (Cpd. No. 148)

[0416] STEP 1 - Synthesis of S11



[0417] 4-Bromopyridine.HCl (4.02g, 20.68 mmol) was added to a solution of 4-fluorobenzenethiol (2.41 g, 18.80 mmol) and K_2CO_3 (7.78 g, 56.4 mmol) in DMSO (20 mL) and the reaction was heated to 110°C. After overnight, the reaction was cooled, quenched with saturated NH_4Cl and extracted with EtOAc. The combined organic layers were washed twice with saturated $NaHCO_3$, once with brine, dried over Na_2SO_4, filtered, and concentrated to produce crude S10 (4.01 g, quantitative yield) that was used without further purification. Oxone monopersulfate (15.03 g, 48.90 mmol) was added to a solution of crude S10 in Acetone/H_2O (5:1, 84 mL). After overnight, the reaction was quenched with saturated $NaHCO_3$, extracted with EtOAc, and purified by column chromatography to give S11 (quantitative yield) as a white solid.

[0418] STEP 2 – Synthesis of Cpd. No. 148



[0419] S11 (74 mg, 0.314 mmol) was added to a solution of Compound S9 (60 mg, 0.157 mmol) and K_2CO_3 (87 mg, 0.628 mmol) in DMSO (2 mL) then stirred and heated to 80°C. After overnight, the reaction was quenched with TFA (0.5 mL), diluted with 3:1 MeOH/H_2O and purified by prep HPLC. The pure fractions were combined, concentrated, diluted with water, frozen and lyophilized to give Cpd. No. 148 as a yellow powder. ^{1}H-NMR (400MHz, CD_3OD) δ ppm 8.75 (d, 2H, J = 5.8 Hz), 7.82 (dd, 2H, J = 1.5 Hz, J = 4.6 Hz), 7.76 (d, 2H, J = 8.8 Hz), 7.57 (d, 1H, J = 7.7 Hz), 7.47 (t, 1H, J = 7.9 Hz), 7.40-7.29 (m, 2H), 6.50 (d, 2H, J = 8.9 Hz), 4.53-4.08 (m, 4H), 3.85-3.68 (m, 3H), 3.58-3.38 (m, 7H), 3.10-2.89 (m, 2H), 2.87-2.67 (m, 1H), 2.57-2.26 (m,

1H), 2.16 (d, 1H, J = 12.7 Hz), 1.93-1.80 (m, 2H), 1.80-1.53 (m, 6H), 1.48 (t, 3H, J = 7.3 Hz), 1.36-1.19 (m, 2H), 1.17-0.99 (m, 1H), 0.96-0.71 (m, 1H); ESI-MS m/z 599.67 $(M+H)^+$.

EXAMPLE 3

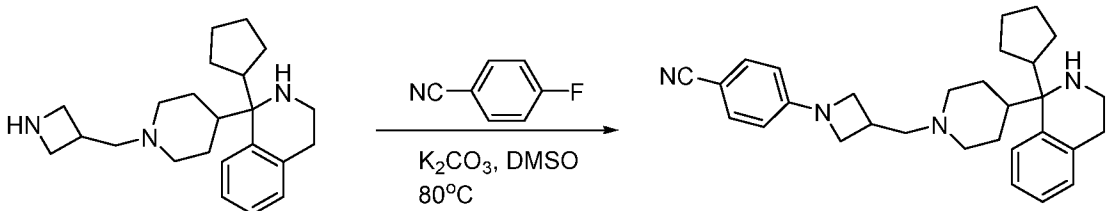
Synthesis of 4-(3-((4-(1-cyclopentyl-1,2,3,4-tetrahydroisoquinolin-1-yl)piperidin-1-yl)methyl)azetidin-1-yl)benzonitrile (Cpd. No. 129)

[0420] STEP 1 - Synthesis of S12

M-104 **S12**

[0421] S12 was obtained using STEP7 to STEP 9 described for the synthesis of S9 in Scheme 1.

[0422] STEP 2 - Synthesis of Cpd. No. 129



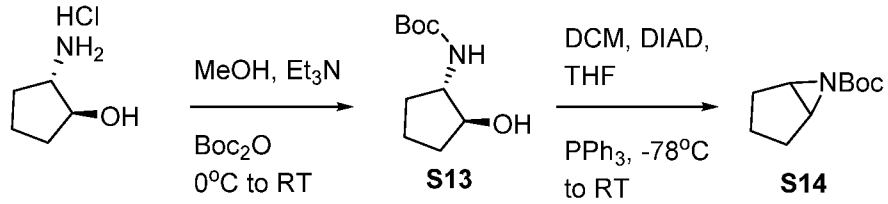
S12 **Cpd. No. 129**

[0423] Starting with compound S12 and 4-fluorobenzonitrile, Cpd. No. 129 was synthesized using a similar procedure described for the synthesis of Cpd. No. 148. ESI-MS m/z 455.83 $(M+H)^+$

EXAMPLE 4

Synthesis of methyl (rac-(1S,2R)-2-(cyano(phenyl)(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl) azetidin-3-yl)methyl)piperidin-4-yl)methyl)cyclopentyl)carbamate (Cpd. No. 345) and methyl (rac-(1R,2S)-2-(cyano(phenyl)(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)methyl)cyclopentyl)carbamate (Cpd. No. 346)

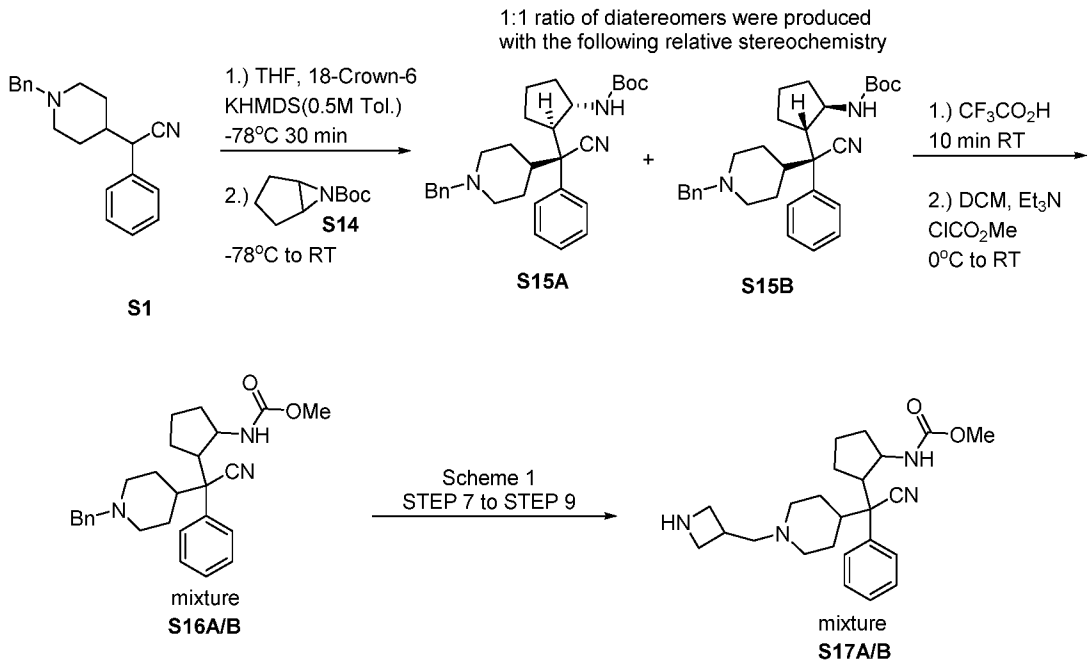
[0424] STEP 1 - Synthesis of S14



[0425] Boc_2O (3.49 g, 15.98 mmol) was added to a solution, at 0°C, of (1*S*,2*S*)-2-aminocyclopentan-1-ol-HCl (2.0 g, 14.53 mmol) and Et_3N (4.05 mL, 29.06 mmol) in methanol (20 mL) and stirred. The reaction was allowed to warm to room temperature and after overnight the reaction was concentrated and the crude was purified by column chromatography to give S13 (2.87 g) as a white solid.

[0426] At -78°C, DIAD (4.17 mL, 21.25 mmol) was added to a solution of PPh_3 (5.57 g, 21.25 mmol) in THF (40 mL). After 1 hour at -78°C, a solution of compound S13 (2.87 g, 14.16 mmol) in THF (40 mL) was added to the reaction. After overnight at RT, the reaction was concentrated and then diluted with Et_2O. The white precipitate was filtered off and the oil was purified by column chromatography to produce compound S14 (2.21 g) as an oil.

[0427] STEP 2 - Synthesis of S17



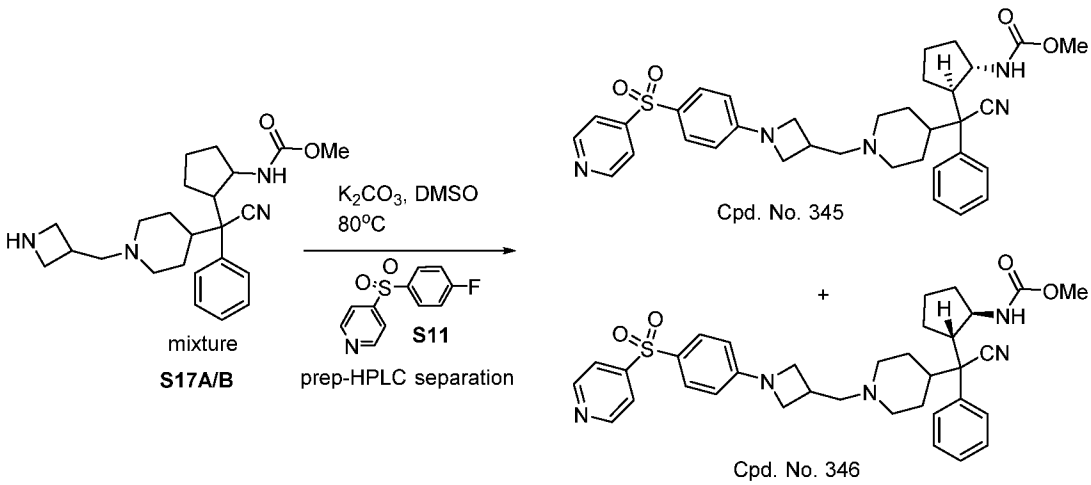
[0428] S1 (1.0g, 3.45 mmol), 18-Crown-6 (2.73 g, 10.34 mmol) were added to a dry 100 mL RB-flask and the system was vacuumed. After 30 minutes under vacuum, N_2 atmosphere was slowly introduced, dry THF (30 mL) was added, and the system was vacuumed briefly then put under N_2 atmosphere – this purging was repeated three

times. The reaction was cooled to -78°C, KHMDS (0.5M in toluene, 20.69 mL, 10.34 mmol) was added dropwise and the reaction stirred. After 30 minutes, at -78°C, compound S14 (2.52 g, 13.79 mmol) was added dropwise then the reaction system was vacuumed and put under N_2 atmosphere three times and allowed to slowly warm to RT. After overnight at RT, the reaction was quenched with saturated NH_4Cl, extracted with EtOAc, and purified by column chromatography to give a 1:1 diastereomer mixture of S15A and S15B (1.1 g) as a white solid.

[0429] The mixture of S15A and S15B (1.0 g, 2.11 mmol) was stirred in TFA (5 mL). After 30 minutes, the TFA was removed in vacuo. The crude product was dissolved in DCM (10 mL), Et_3N (1.15 mL, 8.46 mmol) was added and the reaction was stirred and cooled to 0°C. Methyl chloroformate (0.327 mL, 4.23 mmol) was added dropwise to the reaction and stirred at 0°C for 30 minutes then at RT for 30 minutes. The reaction was quenched with MeOH, concentrated, and purified by column chromatography to produce compound a mixture of S16A and S16B (0.910 g) that was dissolved in acetonitrile and lyophilized to give a solid.

[0430] A mixture S17A and S17B was obtained following STEP 7 to STEP 9 described in Scheme 1 for the synthesis of S9.

[0431] STEP 3 – Synthesis of Cpd. Nos. 345 and 346



[0432] Starting with a mixture of S17A and S17B and using a similar procedure described for the synthesis of Cpd. No. 148, a mixture of Cpd. No. 345 and Cpd. No. 346 was obtained and separated by prep HPLC.

[0433] Cpd. No. 345: ^{1}H-NMR (400MHz, CD_3OD) δ ppm 8.76 (s, 2H), 7.82 (d, 2H, J = 5.2 Hz), 7.75 (d, 2H, J = 8.8 Hz), 7.52 (d, 2H, J = 7.0 Hz), 7.46-7.33 (m, 3H), 6.50 (d,

2H, J = 8.8 Hz), 4.16 (dt, 2H, J = 1.8 Hz, J = 7.7 Hz), 3.96-3.85 (m, 1H), 3.73 (dd, 2H, J = 5.9 Hz, J = 7.8 Hz), 3.60-3.38 (m, 8H), 3.24-3.12 (m, 1H), 3.09-2.94 (m, 2H), 2.91-2.79 (m, 1H), 2.49 (t, 1H, J = 12.2 Hz), 2.27 (d, 1H, J = 14.4 Hz), 2.18-2.05 (m, 1H), 1.94 (d, 1H, J = 14.4 Hz), 1.82-1.39 (m, 7H); ESI-MS m/z 628.50 $(M+H)^+$.

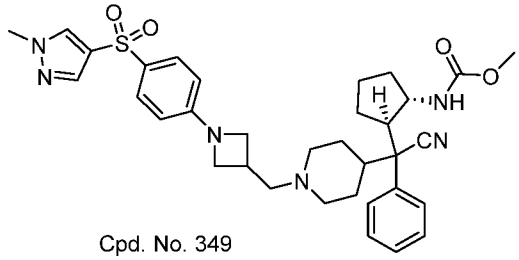
[0434] Cpd. No. 346: ^{1}H-NMR (400MHz, CD_3OD) δ ppm 8.75 (d, 2H, J=4.7Hz), 7.81 (d, 2H, J=4.7Hz), 7.75 (d, 2H, J=7.7Hz), 7.53-7.35 (m, 5H), 6.49 (d, 2H, J=7.8Hz), 4.21-4.05 (m, 3H), 3.79-3.65 (m, 5H), 3.55 (t, 2H, J=13.3Hz), 3.41 (d, 2H, J=6.9Hz), 3.23-3.02 (m, 2H), 2.99-2.76 (m, 2H), 2.59 (t, 1H, J=11.7Hz), 2.28 (d, 1H, J=14.1Hz), 2.07-1.88 (m, 2H), 1.87-1.74 (m, 1H), 1.71-1.53 (m, 3H), 1.53-1.35 (m, 2H), 1.34-1.18 (m, 1H); ESI-MS m/z 628.50 $(M+H)^+$.

EXAMPLE 5

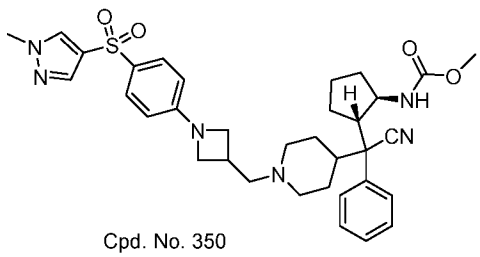
Synthesis of methyl (rac-(1S,2R)-2-(cyano(1-((1-(4-((1-methyl-1H-pyrazol-4-yl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)(phenyl)methyl)cyclopentyl)carbamate (Cpd. No. 349)

and

methyl (rac-(1R,2S)-2-(cyano(1-((1-(4-((1-methyl-1H-pyrazol-4-yl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)(phenyl)methyl)cyclopentyl)carbamate (Cpd. No. 350)



Cpd. No. 349



Cpd. No. 350

[0435] Cpd. Nos. 349 and 350 were obtained using the synthetic strategy described for Cpd Nos. 345 and 346.

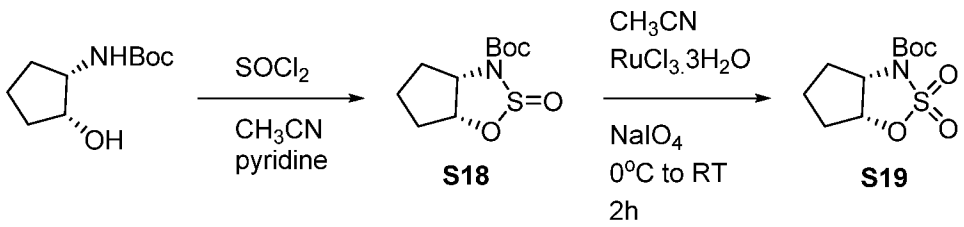
[0436] Cpd. No. 349: ^{1}H-NMR (400MHz, CD_3OD) δ ppm 8.09 (s, 1H), 7.74-7.68 (m, 3H), 7.52 (d, 2H, J = 7.1 Hz), 7.47-7.34 (m, 3H), 6.48 (d, 2H, J = 7.6 Hz), 4.14 (t, 2H, J = 7.7 Hz), 3.88 (s, 3H), 3.74-3.66 (m, 2H), 3.64-3.39 (m, 8H), 3.24-3.11 (m, 1H), 3.10-2.95 (m, 2H), 2.90-2.80 (m, 1H), 2.50 (t, 1H, J = 11.6 Hz), 2.28 (d, 1H, J = 14.2 Hz), 2.18-2.08 (m, 1H), 1.94 (d, 1H, J = 13.9 Hz), 1.83-1.39 (m, 8H); ESI-MS m/z 631.42 $(M+H)^+$.

[0437] Cpd. No. 350: Was obtained using the synthetic strategy described for Cpd. Nos. 345 and 346. ^{1}H NMR (400MHz, CD_3OD) δ ppm 8.09 (s, 1H), 7.74-7.68 (m, 3H), 7.50-7.34 (m, 5H), 6.47 (d, 2H, J = 8.8 Hz), 4.16-4.06 (m, 3H), 3.88 (s, 3H), 3.78-3.63 (m, 5H), 3.63-3.49 (m, 2H), 3.41 (d, 2H, J = 7.1 Hz), 3.24-3.03 (m, 2H), 2.97-2.75 (m, 2H), 2.64-2.51 (m, 1H), 2.33-2.17 (m, 1H), 2.08-1.87 (m, 2H), 1.87-1.73 (m, 1H), 1.73-1.52 (m, 3H), 1.52-1.36 (m, 2H), 1.36-1.16 (m, 1H); ESI-MS m/z 631.83 $(M+H)^+$.

EXAMPLE 6

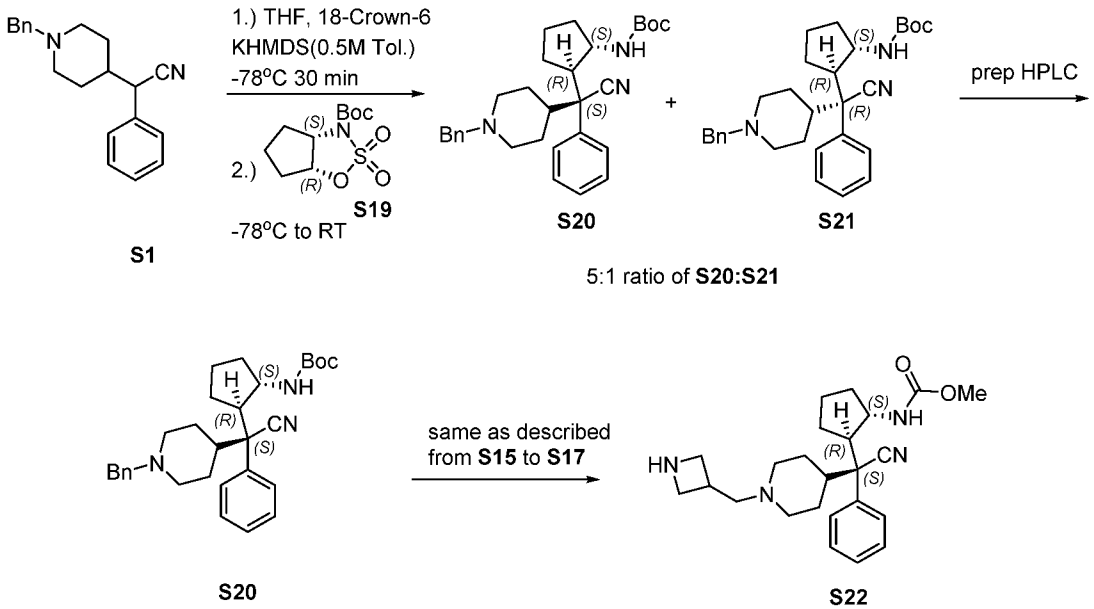
Synthesis of methyl ((1S,2R)-2-((S)-cyano(phenyl)(1-((1-(4-((trifluoromethyl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)methyl)cyclopentyl)carbamate (Cpd. No. 403)

[0438] STEP 1 - Synthesis of chiral S19



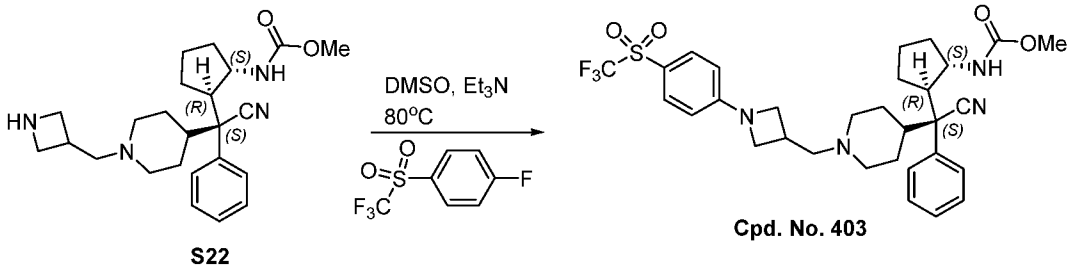
[0439] S19 was synthesized using the method described in *J. Org. Chem.* 2010, 75, 937–940.

[0440] STEP 2 - Chiral synthesis of S22



[0441] S1 (50 mg, 0.172 mmol) and 18-Crown-6 (137 mg, 0.517 mmol) were added to a dry 50 mL RB flask and the system was vacuumed. After 30 minutes under vacuum, N_2 atmosphere was slowly introduced, dry THF (1.5 mL) was added, and the system was vacuumed briefly then put under N_2 atmosphere – this purging was repeated three times. The reaction was cooled to -78°C, KHMDS (0.5M in toluene, 1.03 mL, 0.517 mmol) was added dropwise and the reaction stirred. After 30 minutes, at -78°C, compound S19 (227 g, 0.82 mmol) was added dropwise then the reaction system was vacuumed and put under N_2 atmosphere three times and allowed to slowly warm to RT. After overnight at RT, the reaction was quenched with saturated NH_4Cl, extracted with EtOAc, and concentrated to give a 5:1 mixture of S20:S21. The 5:1 mixture was separated by prep HPLC. Pure S22 (10 mg) was obtained from pure S20 using the same synthetic strategy described for the synthesis of S17 from S15.

[0442] STEP 3 – Synthesis of Cpd. No. 403

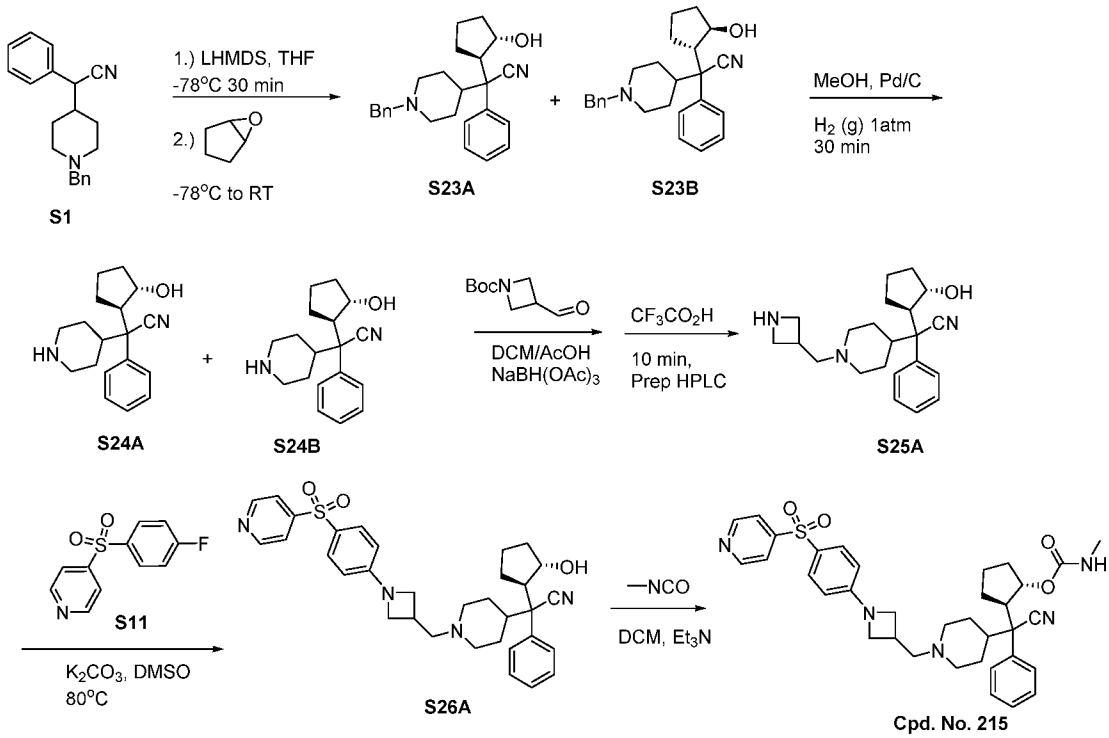


[0443] Starting with S22 and using Et_3N as the base, Cpd. No. 403 (as a single isomer) was obtained using a similar procedure described for the synthesis of Cpd. No. 148. ESI-MS m/z 619.50 $(M+H)^+$.

EXAMPLE 7

Synthesis of rac-(1S,2R)-2-(cyano(phenyl)(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)methyl)cyclopentyl methylcarbamate (Cpd. No. 215)

Scheme 2



[0444] STEP 1 - Synthesis of a mixture of rac-2-(1-benzylpiperidin-4-yl)-2-((1R,2S)-2-hydroxycyclopentyl)-2-phenylacetonitrile (S23A) and rac-2-(1-benzylpiperidin-4-yl)-2-((1S,2R)-2-hydroxycyclopentyl)-2-phenylacetonitrile (S23B)

[0445] LHMDS (1M in THF, 20 mmol) was added dropwise to a solution of S1 (10 mmol) dissolved in dry THF (100 mL) at -78°C and stirred. After 30 minutes, cyclopentene oxide (20 mmol) was added dropwise at -78°C and the reaction was allowed to slowly warm to room temperature. After overnight at RT, the reaction was quenched with saturated NH_4Cl, extracted with EtOAc, concentrated and purified by column chromatography to produce 3.58 g (96% yield) of a mixture of S23A and S23B.

[0446] STEP 2 - Synthesis of a mixture of rac-2-((1R,2S)-2-hydroxycyclopentyl)-2-phenyl-2-(piperidin-4-yl)acetonitrile (S24A) and rac-2-((1S,2R)-2-hydroxycyclopentyl)-2-phenyl-2-(piperidin-4-yl)acetonitrile (S24B)

[0447] The S23A/B mixture (2.7 mmol) from STEP 1 was dissolved in MeOH (5 mL) and the solution was vacuumed briefly then put under N_2 atmosphere – this was repeated 3 times. Pd/C (10% wt/wt, 500 mg) was quickly added to the solution that was vacuumed and put under N_2 atmosphere. The solution was briefly vacuumed to remove the N_2 atmosphere then put under H_2 atmosphere – this was repeated 3 times. After 4 h,

the reaction was filtered through celite and concentrated to give 750 mg a mixture of S24A and S24B (98% yield) that was used without further purification.

[0448] STEP 3 - Synthesis of rac-2-(1-(azetidin-3-ylmethyl)piperidin-4-yl)-2-((1R,2S)-2-hydroxycyclopentyl)-2-phenylacetonitrile (S25)

[0449] 1-Boc-azetidine-3-carboxaldehyde (3.5 mmol) was added to a solution of a mixture of S24A and S24B (2.65 mmol) from STEP 2 in DCM/AcOH (1:1, 15 mL) and stirred. After 10 minutes, $NaBH(OAc)_3$ (8.0 mmol) was slowly added to the reaction. After stirring overnight, the reaction was slowly quenched with saturated $NaHCO_3$, extracted with EtOAc, dried over Na_2SO_4, filtered, and concentrated to produce crude Boc-protected-product. The crude product was dissolved in trifluoroacetic acid and stirred. After 10 minutes, the TFA was removed in vacuo, the crude product purified by reverse phase prep HPLC, and the pure product was lyophilized to give 1.05g of S25A-TFA (85% yield) salt as white solid.

[0450] STEP 4 - Synthesis of rac-2-((1R,2S)-2-hydroxycyclopentyl)-2-phenyl-2-(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)acetonitrile (S26A)

[0451] S11 (1.0 mmol) was added to a solution of S25A from STEP 3 (0.5 mmol) and K_2CO_3 (1.6 mmol) in DMSO (3 mL) then stirred and heated to 80°C. After stirring overnight, the reaction was quenched with TFA (0.5 mL), diluted with 3:1 MeOH/H_2O and purified by prep HPLC. The pure fractions were combined, concentrated, diluted with water, frozen and lyophilized to give S26A as a white powder.

[0452] Step 5 - Synthesis of rac-(1S,2R)-2-(cyano(phenyl)(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)methyl)cyclopentyl methylcarbamate (Cpd. No. 215)

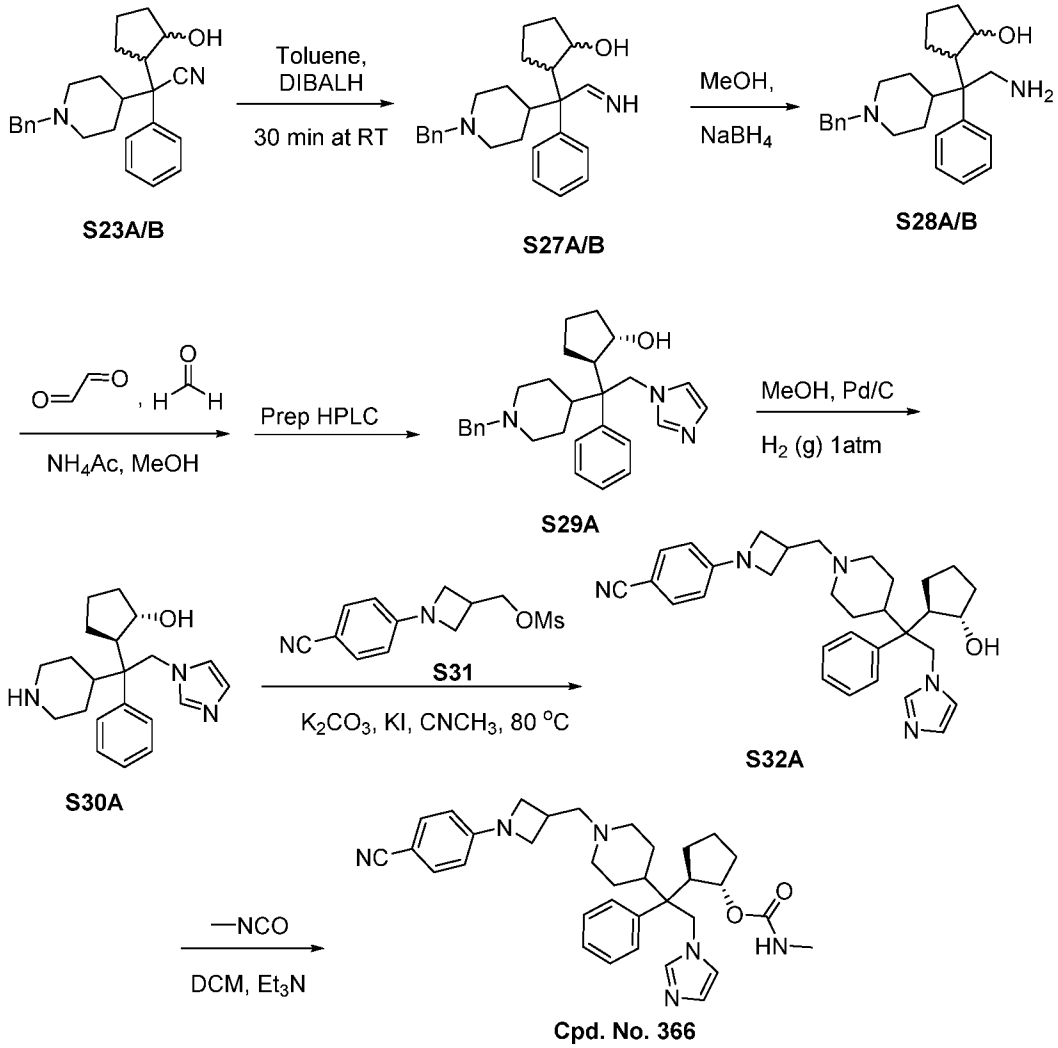
[0453] Methylisocyanate (0.6 mmol) was added to a solution of S26A from STEP 4 (0.2 mmol) and NEt_3 (0.8 mmol) in DCM (2 mL) then stirred at RT for 4h. The reaction was quenched with TFA (0.5 mL), diluted with 3:1 MeOH/H_2O and purified by prep-HPLC. The pure fractions were combined, concentrated, diluted with water, frozen and lyophilized to give Cpd. No. 215 as a white powder. ^1H NMR (400 MHz, MeOD) δ 8.76 (s, 2H), 7.83 (dd, J = 4.4, 1.7 Hz, 2H), 7.76 (dd, J = 8.9, 2.6 Hz, 2H), 7.44 (m, 5H), 6.50 (dd, J = 8.9, 2.6 Hz, 2H), 4.16 (t, J = 8.0 Hz, 2H), 3.74 (d, J = 5.8 Hz, 2H), 3.54 (t, J = 11.4 Hz, 2H), 3.41 (d, J = 6.9 Hz, 2H), 3.31 (dd, J = 3.1, 1.5 Hz, 2H), 3.18 (dd, J = 17.8, 9.8 Hz, 2H), 3.05 (d, J = 11.8 Hz, 2H), 2. 54 (s, 3H), 2.48 (t, J = 12.2 Hz,

1H), 2.37 (d, *J* = 15.0 Hz, 1H), 2.28 – 2.11 (m, 2H), 2.02 (d, *J* = 14.1 Hz, 1H), 1.82 – 1.62 (m, 4H), 1.53 (dd, *J* = 26.5, 13.4 Hz, 2H). MS (ESI) m/z: $[M + H]^+$ calcd, 627.3; found, 628.4.

EXAMPLE 8

Synthesis of rac-(1S,2R)-2-(1-(1-((1-(4-cyanophenyl)azetidin-3-yl)methyl)piperidin-4-yl)-2-(1H-imidazol-1-yl)-1-phenylethyl)cyclopentyl methylcarbamate (Cpd. No. 366)

Scheme 3



[0454] STEP 1 - Synthesis of a mixture of rac-(1S,2R)-2-(2-amino-1-(1-benzylpiperidin-4-yl)-1-phenylethyl)cyclopentan-1-ol (S28A) and rac-(1R,2S)-2-(2-amino-1-(1-benzylpiperidin-4-yl)-1-phenylethyl)cyclopentan-1-ol (S28B)

[0455] DIBALH (40 mmol) was added dropwise to a solution of a mixture of S23A/B (10 mmol), *see* EXAMPLE 7, in toluene (40 mL) and stirred at RT. After one hour, the

reaction was quenched by dropwise addition of 2M NaOH and the aqueous was extracted with EtOAc and concentrated. The crude S27A/B mixture thus obtained was dissolved in MeOH and $NaBH_4$ (15 mmol) was slowly added and the reaction was stirred. After stirring overnight, the reaction was quenched with water, extracted with EtOAc, dried over Na_2SO_4, filtered through celite, and concentrated to produce a mixture of S28A and S28B that was used in the next step without further purification.

[0456] STEP 2 - Synthesis of rac-(1S,2R)-2-(1-(1-benzylpiperidin-4-yl)-2-(1H-imidazol-1-yl)-1-phenylethyl)cyclopentan-1-ol (S29A)

[0457] NH_4Ac (40 mmol) was added to a solution of crude S28A/B mixture from STEP 1 (10 mmol), oxalaldehyde (40 mmol), paraformaldehyde (40 mmol) in MeOH (15 mL) and stirred at 50 ^oC for 2 h or microwave 50 ^oC for 30 min. The crude product was purified by reverse phase prep HPLC, and the pure product was lyophilized to give S29A-TFA (active isomer, 35% yield in three steps) salt as a white solid.

[0458] STEP 3 - Synthesis of rac-(1S,2R)-2-(2-(1H-imidazol-1-yl)-1-phenyl-1-(piperidin-4-yl)ethyl)cyclopentan-1-ol (S30A)

[0459] Compound S29A (active isomer, 2 mmol) from STEP 2 was dissolved in MeOH (10 mL) and the solution was vacuumed briefly then put under N_2 atmosphere – this was repeated 3 times. Pd/C (10% wt/wt, 500 mg) was quickly added to the solution that was vacuumed and put under N_2 atmosphere. The solution was briefly vacuumed to remove the N_2 atmosphere then put under H_2 atmosphere – this was repeated 3 times. After 4 h, the reaction was filtered through celite and concentrated to give 650 mg crude S30A (96% yield) that was used without further purification.

[0460] STEP 4 - Synthesis of rac-4-(3-((4-(1-((1R,2S)-2-hydroxycyclopentyl)-2-(1H-imidazol-1-yl)-1-phenylethyl)piperidin-1-yl)methyl)azetidin-1-yl)benzonitrile (S32A)

[0461] To a solution of S30A (0.05 mmol) from STEP 3 in acetonitrile (2 mL) was added S31 (0.06 mmol), K_2CO_3 (0.15 mmol) and KI (0.005 mmol). The mixture was stirred at 80 °C overnight. Then, the mixture was extracted with ethyl acetate, washed with brine, dried (Na_2SO_4), and the solvent was evaporated. The residue was purified with prep HPLC to give S32A-TFA (75% yield) salt as white solid.

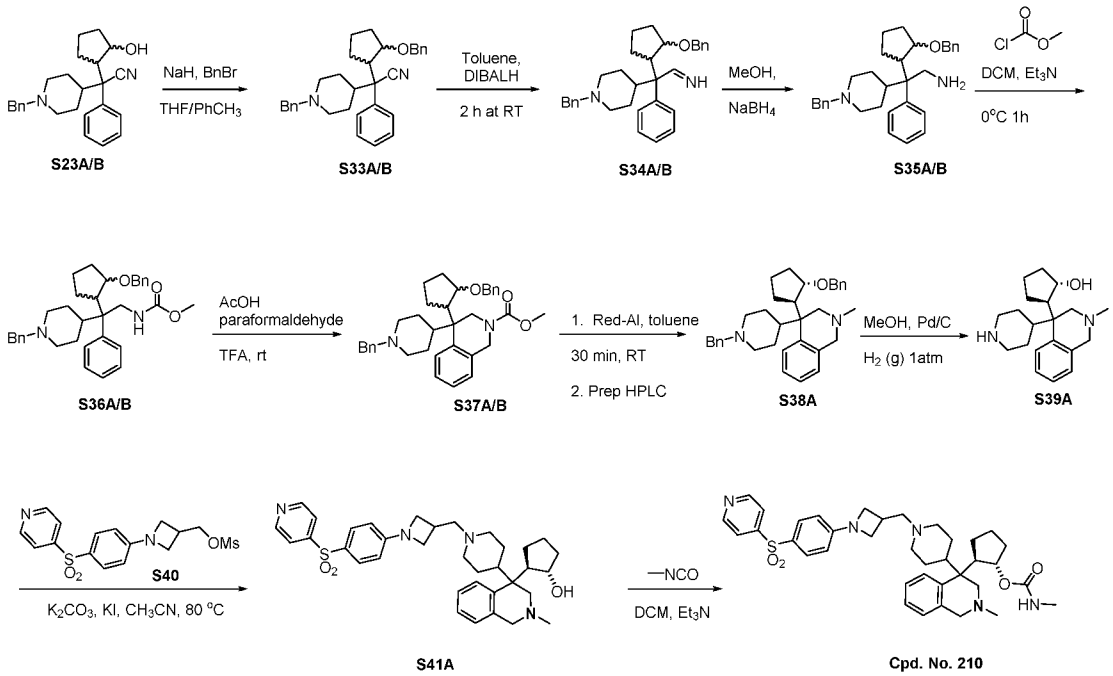
[0462] STEP 5 - Synthesis of rac-(1S,2R)-2-(1-(1-((1-(4-cyanophenyl)azetidin-3-yl)methyl)piperidin-4-yl)-2-(1H-imidazol-1-yl)-1-phenylethyl)cyclopentyl methylcarbamate (Cpd. No. 366)

[0463] Methylisocyanate (0.3 mmol) was added to a solution of S32A from STEP 4 (0.05 mmol) and NEt_3 (0.2 mmol) in DCM (1 mL) then stirred at RT for 4h. The reaction was diluted with 3:1 MeOH/H_2O (10% TFA) and purified by prep-HPLC. The pure fractions were combined, concentrated, diluted with water, frozen and lyophilized to give Cpd. No. 366 as a white powder. ^{1}H NMR (400 MHz, MeOD) δ 8.81 (s, 1H), 7.69 (d, *J* = 7.7 Hz, 2H), 7.54 (t, *J* = 7.5 Hz, 2H), 7.51 – 7.42 (m, 4H), 7.40 (s, 1H), 6.47 (d, *J* = 8.2 Hz, 2H), 4.22 – 4.11 (m, 2H), 3.74 (s, 2H), 3.64 (d, *J* = 11.7 Hz, 1H), 3.52 – 3.40 (m, 3H), 3.25 (dd, *J* = 13.5, 6.9 Hz, 1H), 3.05 (t, *J* = 12.0 Hz, 1H), 2.96 (t, *J* = 11.9 Hz, 1H), 2.85 (s, 1H), 2.70 (s, 3H), 2.55 (d, *J* = 11.2 Hz, 1H), 2.29 (d, *J* = 13.4 Hz, 1H), 2.17 (s, 1H), 2.08 – 1.90 (m, 3H), 1.75 – 1.58 (m, 2H), 1.50 (dd, *J* = 30.5, 12.1 Hz, 3H), 1.31 (d, *J* = 0.8 Hz, 3H), 1.14 (d, *J* = 11.0 Hz, 1H), 0.91 (d, *J* = 11.6 Hz, 1H). MS (ESI) m/z: $[M + H]^+$ calcd, 566.3; found, 567.5.

EXAMPLE 8

Synthesis of rac-(1S,2R)-2-(2-methyl-4-(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1,2,3,4-tetrahydroisoquinolin-4-yl)cyclopentyl methylcarbamate (Cpd. No. 210)

Scheme 4



[0464] STEP 1 - Synthesis of rac-2-((1R,2S)-2-(benzyloxy)cyclopentyl)-2-(1-benzylpiperidin-4-yl)-2-phenylacetonitrile (S33A) and rac-2-((1S,2R)-2-(benzyloxy)cyclopentyl)-2-(1-benzylpiperidin-4-yl)-2-phenylacetonitrile (S33B)

[0465] NaH (65%, 30 mmol) was added to a solution of S23A/B (15 mmol) dissolved in dry THF/$PhCH_3$ (1:1, 100 mL) at 0°C and stirred. After 30 minutes at 0°C, BnBr (16 mmol) was added dropwise and the reaction was allowed to warm to room temperature. After overnight at RT, the reaction was quenched with saturated NH_4Cl, extracted with EtOAc, concentrated and purified by column chromatography to produce a mixture of S33A and S33B (96% yield).

[0466] STEP 2 - Synthesis of rac-2-((1R,2S)-2-(benzyloxy)cyclopentyl)-2-(1-benzylpiperidin-4-yl)-2-phenylethan-1-amine (S35A) and rac-2-((1S,2R)-2-(benzyloxy)cyclopentyl)-2-(1-benzylpiperidin-4-yl)-2-phenylethan-1-amine (S35B)

[0467] DIBALH (40 mmol) was added dropwise to a solution S33A/B (10 mmol) from STEP 1 in toluene (40 mL) and stirred at RT. After one hour, the reaction was quenched by dropwise addition of 2M NaOH and the aqueous was extracted with EtOAc and concentrated. The crude S34A/B was dissolved in MeOH and $NaBH_4$ (15 mmol) was slowly added and the reaction was stirred. After overnight, the reaction was quenched with water, extracted with EtOAc, dried over Na_2SO_4, filtered through celite, and concentrated to produce a mixture of S35A and S35B that was used in the next step without further purification.

[0468] STEP 3- Synthesis of rac-4-((1R,2S)-2-(benzyloxy)cyclopentyl)-4-(1-benzylpiperidin-4-yl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (S38A)

[0469] Methyl chloroformate (6 mmol) was added to a solution, at 0°C, of crude S35A/B (5 mmol) from STEP 2 and Et_3N (15 mmol) in DCM (20 mL) and stirred. After 30 minutes at 0°C, the reaction was put at RT and stirred. After 30 min at RT, the reaction was quenched with water and brine, extracted with EtOAc, dried over Na_2SO_4, filtered and concentrated to give crude S36A/B that was used without further purification.

[0470] Crude S36A/B was dissolved in AcOH (5 mL), paraformaldehyde (3 eq. base on S35A/B) and concentrated TFA (2 mL) were added at RT. After overnight, the reaction was slowly quenched with saturated $NaHCO_3$, extracted with EtOAc, dried

over Na_2SO_4, filtered and concentrated to give crude S37A/B that was used without further purification.

[0471] Red-Al (3.2 M in toluene, 3 eq. base on S35A/B) was added dropwise to a solution, at RT, of crude S37A/B in toluene (15 mL) and stirred. After 30 minutes, the reaction was quenched by dropwise addition of 2M NaOH and the aqueous was extracted with EtOAc and concentrated. The crude S38A/B was purified by reverse phase prep HPLC and the pure compound was lyophilized to produce S38A-TFA (12% yield in 5 steps) salt as a white powder.

[0472] STEP 4 - Synthesis of rac-(1S,2R)-2-(2-methyl-4-(piperidin-4-yl)-1,2,3,4-tetrahydroisoquinolin-4-yl)cyclopentan-1-ol (S39A)

[0473] Compound S38A (0.5 mmol) from STEP 3 was dissolved in MeOH (5 mL) and the solution was vacuumed briefly then put under N_2 atmosphere – this was repeated 3 times. Pd/C (10% wt/wt, 100 mg) was quickly added to the solution that was vacuumed and put under N_2 atmosphere. The solution was briefly vacuumed to remove the N_2 atmosphere then put under H_2 atmosphere – this was repeated 3 times. After 4 h, the reaction was filtered through celite and concentrated to give crude S39A (96% yield) that was used without further purification.

[0474] STEP 5 - Synthesis of rac-(1S,2R)-2-(2-methyl-4-(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1,2,3,4-tetrahydroisoquinolin-4-yl)cyclopentan-1-ol (S41A)

[0475] To a solution of the intermediate S39A (0.05 mmol) from STEP 4 in acetonitrile (2 mL) was added S40 (0.06 mmol), K_2CO_3 (0.15 mmol) and KI (0.005 mmol). The mixture was stirred at 80 °C overnight. Then, the mixture was extracted with ethyl acetate, washed with brine, dried (Na_2SO_4), and the solvent was evaporated. The residue was purified by prep HPLC to give S41A-TFA (75% yield) salt as white solid.

[0476] STEP 6 - Synthesis of rac-(1S,2R)-2-(2-methyl-4-(1-((1-(4-(pyridin-4-ylsulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1,2,3,4-tetrahydroisoquinolin-4-yl)cyclopentyl methylcarbamate (Cpd. No. 210)

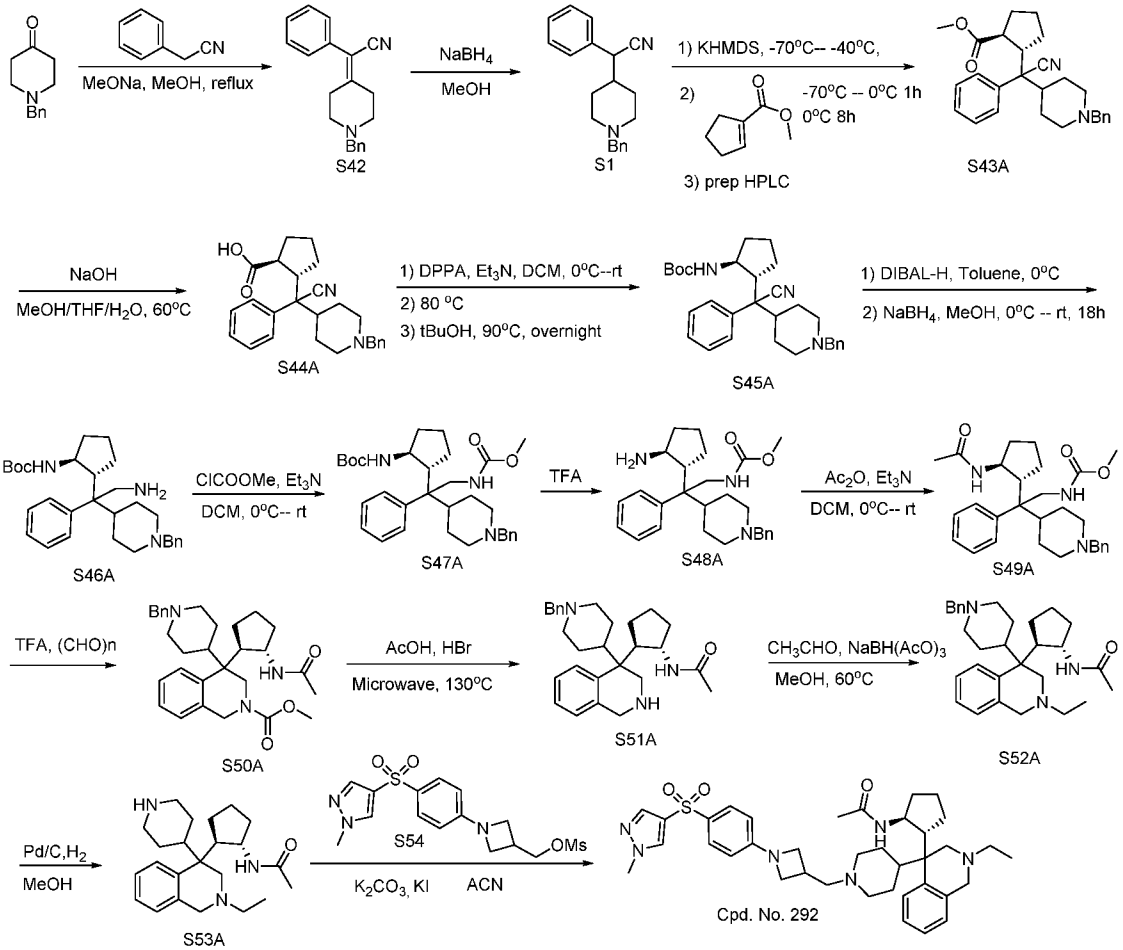
[0477] Methylisocyanate (0.3 mmol) was added to a solution of compound S41A (0.05 mmol) from STEP 5 and NEt_3 (0.2 mmol) in DCM (1 mL) then stirred at RT for 4h. The reaction was diluted with 3:1 MeOH/H_2O (10% TFA) and purified by prep HPLC. The pure fractions were combined, concentrated, diluted with water, frozen and

lyophilized to give Cpd. No. 210 as a white powder. ^{1}H NMR (400 MHz, MeOD) δ 8.66 (d, *J* = 5.6 Hz, 2H), 7.73 (d, *J* = 5.9 Hz, 2H), 7.63 (dd, *J* = 20.6, 8.6 Hz, 2H), 7.44 (d, *J* = 7.8 Hz, 1H), 7.31 (t, *J* = 7.7 Hz, 1H), 7.23 (d, *J* = 7.3 Hz, 1H), 7.14 (d, *J* = 7.4 Hz, 1H), 6.38 (d, *J* = 8.7 Hz, 2H), 4.99 (d, *J* = 7.4 Hz, 2H), 4.25 (d, *J* = 18.7 Hz, 2H), 4.05 (t, *J* = 8.0 Hz, 2H), 3.63 (s, 3H), 3.45 (d, *J* = 11.7 Hz, 1H), 3.28 (d, *J* = 6.6 Hz, 4H), 3.14 (d, *J* = 16.5 Hz, 4H), 2.97 – 2.71 (m, 2H), 2.18 (s, 3H), 1.94 (d, *J* = 19.7 Hz, 3H), 1.69 (d, *J* = 39.4 Hz, 6H). MS (ESI) m/z: $[M + H]^+$ calcd, 657.3; found, 658.4.

EXAMPLE 9

Synthesis of rac-N-((1S,2R)-2-(2-ethyl-4-(1-((1-(4-((1-methyl-1H-pyrazol-4-yl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1,2,3,4-tetrahydroisoquinolin-4-yl)cyclopentyl)acetamide (Cpd. No. 292)

Scheme 5



[0478] STEP 1 - Synthesis of 2-(1-benzylpiperidin-4-ylidene)-2-phenylacetonitrile (S42)

[0479] Sodium methoxide (25% wt. in MeOH) (46.8 mL, 205 mmol) was added to a solution of 1-benzylpiperidin-4-one (32.3 g, 171 mmol) and 2-phenylacetonitrile (20 g, 171 mmol) in anhydrous methanol (200 mL) under argon, and the mixture was stirred under reflux overnight. Then, the reaction mixture was cooled to room temperature and poured into ice (200 g). The resulting mixture was extracted with ethyl acetate. The separated organic layer was dried with Na_2SO_4, filtered and the solvent was evaporated in vacuum to yield the title product (48 g, 95%). MS (ESI) m/z 289.1 $[M+H]^+$.

[0480] STEP 2 - Synthesis of 2-(1-Benzylpiperidin-4-yl)-2-phenylacetonitrile (S1)

[0481] Sodium borohydride (12.6 g, 333 mmol) was added to a solution of S42 (48 g, 166 mmol) from STEP 1 in methanol (100 ml). The mixture was stirred under room temperature overnight. Then, a mixture of water and ice (200 ml) was added, the light yellow precipitate was formed and filtered. The residue was washed with water and dried in vacuum to yield the yellow product (38 g, 79%). MS (ESI) m/z 291.1 $[M+H]^+$.

[0482] STEP 3 - Synthesis of methyl rac-(1S,2S)-2-((1-benzylpiperidin-4-yl)(cyano)(phenyl)methyl)cyclopentane-1-carboxylate (S43A).

[0483] To a solution of S1 (1 g, 3.44 mmol) from STEP 2 in anhydrous toluene (15 mL) at -78 °C under argon was added potassium bis(trimethylsilyl)amide (0.5 M in toluene) (17.2 mL, 8.61 mmol). The mixture was stirred at -78 °C for 1 h, and then the corresponding methyl cyclopent-1-ene-1-carboxylate (3.48 g, 28 mmol) was added dropwise. The resulting mixture was stirred and warned to 0 °C for 1 h. The reaction was monitored by HPLC-Mass. Upon transformation of the starting material, the reaction was quenched with saturated aqueous NH_4Cl (5 mL). The mixture was extracted with dichloromethane (2 × 30 mL), dried (Na_2SO_4), and the solvent was evaporated. The diastereoisomeric mixture was purified by prep HPLC to give 350 mg (24%) of methyl rac-(1S,2S)-2-((1-benzylpiperidin-4-yl)(cyano)(phenyl)methyl)cyclopentane-1-carboxylate (S43A) and 450 mg (31%) of methyl rac-(1R,2R)-2-((1-benzylpiperidin-4-yl)(cyano)(phenyl)methyl)cyclopentane-1-carboxylate (S43B). MS (ESI) m/z 417.2 $[M+H]^+$.

[0484] STEP 4 - Synthesis of rac-(1S,2S)-2-((1-Benzylpiperidin-4-yl)(cyano)(phenyl)methyl)cyclopentane-1-carboxylic acid (S44A)

[0485] A solution of NaOH (33 mg, 0.84 mmol) in 10 mL of H_2O was added at room temperature to solution of S43A (0.21 g, 0.41 mmol) from STEP 3 in 10 mL of

methanol. The resulting mixture was stirred at 60 °C overnight before being evaporated. The residue was partitioned between 2M HCl and ethyl acetate. The aqueous layer was back extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and evaporated to give the title product (310mg, 89%). The product was used in the next step without purification. MS (ESI) m/z 403.2 $[M+H]^+$.

[0486] STEP 5 - Synthesis of tert-butyl rac-((1S,2R)-2-((1-benzylpiperidin-4-yl)(cyano)(phenyl)methyl)cyclopentyl)carbamate (S45A).

[0487] S44A (0.8 g, 2 mmol) from STEP 4, diphenylphosphoryl azide (0.51 mL, 2.4 mmol) and triethylamine (0.83 mL, 6 mmol) were dissolved in dichloromethane (25 mL). The mixture was stirred at room temperature for 5 h and then diluted with dichloromethane. The organic phase was washed with brine, and dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was warmed without solvent at 80 °C, until no further gas evolution occurred. The reaction mixture was then cooled, the resulting oil was dissolved in anhydrous t-BuOH (5 mL, 99.9% anhydrous packed under argon; Alfa Aesar), placed under and atmosphere of nitrogen, and refluxed in a 90 °C bath overnight. After this time, the reaction mixture was cooled and concentrated under reduced pressure to afford an oil crude product, which was then purified with flash column chromatography to afford the title compound (400 mg, 50.4%). MS (ESI) m/z 474.3 $[M+H]^+$.

[0488] STEP 6 - Synthesis of tert-butyl rac-((1S,2R)-2-(2-amino-1-(1-benzylpiperidin-4-yl)-1-phenylethyl)cyclopentyl)carbamate (S46A)

[0489] To an ice cold solution of S45A (256 mg, 0.54 mmol) from STEP 5 in toluene (3 mL) was added diisobutylaluminiumhydride (25% in toluene, 1.8 mL) under argon. The mixture was then allowed to warm to room temperature and stirred for 20 min. The mixture was cooled to 0 °C and quenched by careful addition of water (1 mL). The suspension was stirred for another 10 minutes, and filtered. The filtrate was extracted with ethyl acetate, dried over Na_2SO_4 and evaporated. The residue was dried in vacuum and then dissolved in methanol (10 mL). $NaBH_4$ (40 mg, 1 mmol) was added into the mixture, and the reaction mixture was stirred at room temperature overnight. The mixture was concentrated in vacuum and diluted with ethyl acetate and water. The mixture was extracted with ethyl acetate, dried (Na_2SO_4), and the solvent was

evaporated. Then the residue was purified with prep HPLC to yield the title compound (200 mg, 77%). MS (ESI) m/z 478.3 $[M+H]^+$.

[0490] STEP 7 - Synthesis of tert-butyl rac-((1S,2R)-2-(1-(1-benzylpiperidin-4-yl)-2-((methoxycarbonyl)amino)-1-phenylethyl)cyclopentyl)carbamate (S47A)

[0491] To a solution of S46A (213 mg, 0.45 mmol) from STEP 6 in dichloromethane (20 mL) was added methyl chloroformate (51 mg, 0.54 mmol) and triethylamine (90 mg, 0.89 mmol) in ice/water bath. Then, the ice/water bath was removed, the mixture was stirred at room temperature for 1 h. After this time, the reaction mixture was quenched with water, extracted with dichloromethane, dried (Na_2SO_4), and the solvent was evaporated to obtain the title compound (230 mg, 96%). The product was used in the next step without further purification. MS (ESI) m/z 536.3 $[M+H]^+$.

[0492] STEP 8 - Synthesis of methyl rac-(2-((1R,2S)-2-aminocyclopentyl)-2-(1-benzylpiperidin-4-yl)-2-phenylethyl)carbamate (S48A)

[0493] To a solution of S47 (230 mg, 0.43 mmol) from STEP 7 in dichloromethane (5 mL) was added trifluoroacetic acid (0.5 mL). The reaction was stirred at room temperature for 2 h. The mixture was basified with saturated $NaHCO_3$, extracted with dichloromethane, dried (Na_2SO_4), and the solvent was evaporated to obtain the title compound (180 mg, 96%). The product was used in the next step without further purification. MS (ESI) m/z 436.3 $[M+H]^+$.

[0494] STEP 9 - Synthesis of methyl rac-(2-((1R,2S)-2-acetamidocyclopentyl)-2-(1-benzylpiperidin-4-yl)-2-phenylethyl)carbamate (S49A)

[0495] To a solution of S48 A(192 mg, 0.44 mmol) from STEP 8 in dichloromethane (10 mL) was added acetic anhydride (67.5 mg, 0.66 mmol) and triethylamine (89 mg, 0.88 mmol). The reaction was stirred at room temperature for 2 h. The mixture was quenched with saturated $NaHCO_3$, extracted with dichloromethane, dried (Na_2SO_4), and the solvent was evaporated to obtain the title compound (195 mg, 93%). The product was used in the next step without further purification. MS (ESI) m/z 478.3 $[M+H]^+$.

[0496] STEP 10 - Synthesis of methyl rac-4-((1R,2S)-2-acetamidocyclopentyl)-4-(1-benzylpiperidin-4-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (S50A)

[0497] To a solution of the intermediate S49A (195 mg, 0.41 mmol) from STEP 9 in trifluoroacetic acid (2 mL) was added paraformaldehyde (123 mg, 4.1 mmol). The

reaction was stirred at room temperature overnight. The mixture was quenched and basified with saturated $NaHCO_3$, extracted with dichloromethane, dried (Na_2SO_4), and the solvent was evaporated. The residue was purified with pre-HPLC to give the title compound (143 mg, 72%). MS (ESI) m/z 490.3 $[M+H]^+$.

[0498] STEP 11 - Synthesis of rac-N-((1S,2R)-2-(4-(1-benzylpiperidin-4-yl)-1,2,3,4-tetrahydroisoquinolin-4-yl)cyclopentyl)acetamide (S51A)

[0499] To a solution of S50A (143 mg, 0.29 mmol) from STEP 10 in acetic acid (1 mL) was added HBr (40% wt. in H_2O) (0.5 mL). The reaction mixture was heated to 130 °C under microwave and stirred for 2 h. The mixture was basified carefully with saturated $NaHCO_3$ at 0 °C, extracted with DCM, dried (Na_2SO_4), and the solvent was evaporated to obtain the title compound (110 mg, 87%). The product was used in the next step without further purification. MS (ESI) m/z 432.3 $[M+H]^+$.

[0500] STEP 12 - Synthesis of rac-N-((1S,2R)-2-(4-(1-benzylpiperidin-4-yl)-2-ethyl-1,2,3,4-tetrahydroisoquinolin-4-yl)cyclopentyl)acetamide (S52A)

[0501] To a solution of the intermediate S51A (110 mg, 0.25 mmol) from STEP 11in methanol (5 mL) was added acetaldehyde (108 mg, 0.51 mL) and sodium triacetoxyborohydride (22 mg, 0.51 mmol). The mixture was stirred overnight and evaporated to half its volume and partitioned between saturated $NaHCO_3$ and dichloromethane. The organic phase was washed with brine, dried (Na_2SO_4) and evaporated. The crude product was purified by pre-HPLC to obtain the title compound (74 mg, 63%). MS (ESI) m/z 460.3 $[M+H]^+$.

[0502] STEP 13 - Synthesis of rac-N-((1S,2R)-2-(2-ethyl-4-(piperidin-4-yl)-1,2,3,4-tetrahydroisoquinolin-4-yl)cyclopentyl)acetamide (S53A)

[0503] To a solution of S52A (74 mg, 0.16 mmol) from STEP 12 in methanol (5 mL) was added 10% Pd/C (17 mg). The mixture was stirred for 4 h at room temperature under hydrogen atmosphere (normal pressure). After the Pd/C catalyst was filtered off, the solvent was removed by rotary evaporation to give the title compound (55mg, 92%). The product was used in the next step without further purification. MS (ESI) m/z 370.3 $[M+H]^+$.

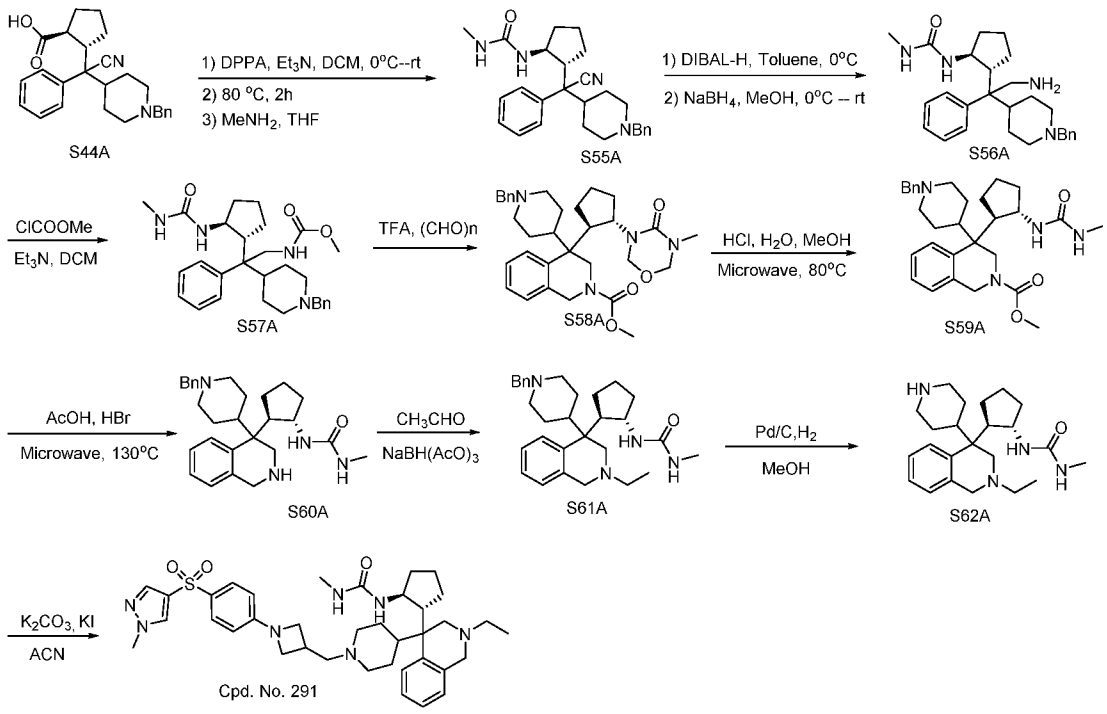
[0504] STEP 14 - Synthesis of rac-N-((1S,2R)-2-(2-ethyl-4-(1-((1-(4-((1-methyl-1H-pyrazol-4-yl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1,2,3,4-tetrahydroisoquinolin-4-yl)cyclopentyl)acetamide (Cpd. No. 292)

[0505] To a solution of S53A (20 mg, 0.054 mmol) from STEP 13 in acetonitrile (2 mL) was added (1-(4-((1-methyl-1H-pyrazol-4-yl)sulfonyl)phenyl)azetidin-3-yl)methyl methanesulfonate (S54) (22 mg, 0.057 mmol), K_2CO_3 (15 mg, 0.11 mmol) and KI (1 mg, 0.005 mmol). The mixture was stirred at 80 °C overnight. Then, the mixture was extracted with ethyl acetate, washed with brine, dried (Na_2SO_4), and the solvent was evaporated. The residue was purified with pre-HPLC to give the title compound (20 mg, 56%). ^{1}H NMR (400 MHz, MeOD, a mixture of rotamers) δ 8.09 (s, 1H), 8.02 (d, J = 9.6 Hz, 0.5H) and 7.71 (d, J = 8.4 Hz, 2.5 H), 7.51 (d, J = 8.0, 1H), 7.45 (t, J = 6.8 Hz, 1H), 7.34-7.29 (m, 2H), 6.46 (d, J = 8.8 Hz, 2H), 4.47 (d, J = 12. 8 Hz, 1H), 4.15-4.10 (m, 3H), 3.99-3.93 (m, 1H), 3.88 (s, 3H), 3.82-3.79 (m, 1H), 3.71-3.58 (m, 4H), 3.44-3.35 (m, 4H), 3.27-3.25 (m, 1H), 3.18-3.13 (m, 1H), 3.02-2.90 (m, 2H), 2.76-2.68 (m, 1H), 2.27-2.24 (m, 1H), 2.10-1.94 (m, 3H), 1.89-1.61 (m, 6H), 1.56 (t, J = 7.2 Hz, 3H), 1.17 (s, 3H), 0.66-0.58 (m, 1H). MS (ESI) m/z 659.3 $[M+H]^+$.

EXAMPLE 11

Synthesis of rac-1-((1S,2R)-2-(2-ethyl-4-(1-((1-(4-((1-methyl-1H-pyrazol-4-yl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1,2,3,4-tetrahydroisoquinolin-4-yl)cyclopentyl)-3-methylurea (Cpd. No. 291)

Scheme 6



[0506] STEP 1 - Synthesis of rac-1-((1S,2R)-2-((1-benzylpiperidin-4-yl)(cyano)(phenyl)methyl)cyclopentyl)-3-methylurea (S55A)

[0507] S44A (0.7 g, 1.74 mmol), diphenylphosphoryl azide (0.45 mL, 2.1 mmol) and triethylamine (0.73 mL, 5.2 mmol) were dissolved in dichloromethane (25 mL). The mixture was stirred at room temperature for 5 h and then diluted with dichloromethane. The organic phase was washed with brine, and dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was warmed without solvent at 80 °C, until no further gas evolution occurred. The reaction mixture was then cooled, and dissolved in anhydrous THF. Methylamine (2M, in THF) (1.74 mL, 3.5 mmol) was added into the mixture, the reaction mixture was stirring at room temperature for 2 h. After this time, the reaction mixture was cooled and concentrated under reduced pressure to afford an oil crude product, which was then purified with prep HPLC to afford the title compound (597 mg, 80%). MS (ESI) m/z 431.3 $[M+H]^+$.

[0508] S57A and S58A were prepared according to the methods for S47A and S50A.

[0509] STEP 2 - Synthesis of methyl rac-4-(1-benzylpiperidin-4-yl)-4-((1R,2S)-2-(3-methylureido)cyclopentyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (S59A)

[0510] To a solution of S58A (639 mg, 1.2 mmol) in methanol (3 mL) was added 0.2 mL of concentrated aqueous HCl (wt. 37%). The reaction mixture was heated to 80 °C under microwave and stirred for 2 h. The mixture was basified carefully with saturated $NaHCO_3$ at 0 °C, extracted with DCM, dried (Na_2SO_4), and the solvent was evaporated to obtain the title compound (550 mg, 93%). The product was used in the next step without further purification. MS (ESI) m/z 505.5 $[M+H]^+$.

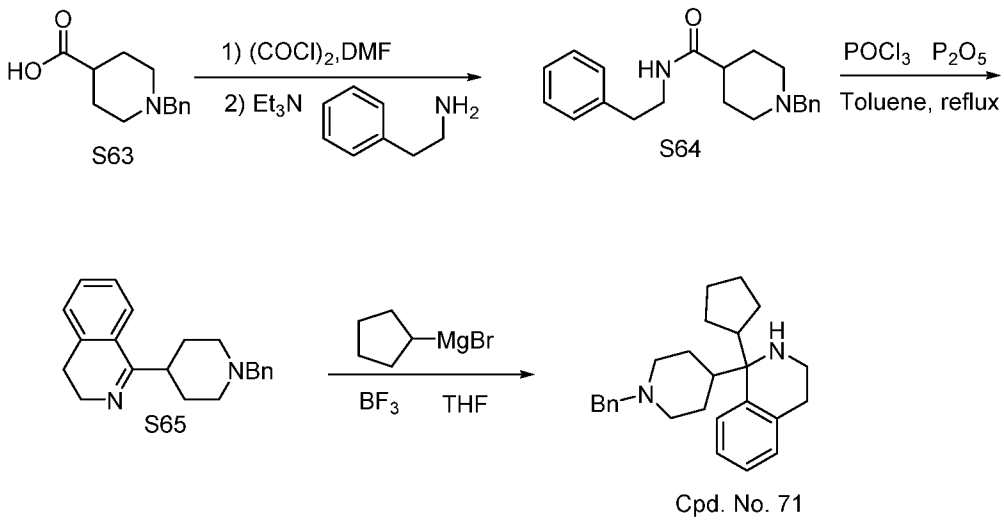
[0511] S60A, S61A, S62A and Cpd. No. 291 were prepared according to the methods for S51A, S52A, S53A, and Cpd. No. 292, respectively.

[0512] Cpd. No. 291; ^1H NMR (400 MHz, MeOD) δ 8.09 (s, 1H), 7.72-7.69 (m, 3H), 7.50 (d, J = 8.0 Hz, 1H), 7.39 (t, J = 6.8 Hz, 1H), 7.32-7.25 (m, 2H), 6.46 (d, J = 9.2, 2H), 4.40 (d, J = 12.8, 1H), 4.13-4.08 (m, 3H), 3.88 (s, 3H), 3.82-3.75 (m, 2H), 3.71-3.66 (m, 2H), 3.60-3.53 (m, 2H), 3.42-3.34 (m, 4H), 3.17 (d, J = 14.0 Hz, 2H), 3.01-2.90 (m, 2H), 2.74-2.67 (m, 1H), 2.27-2.24 (m, 1H), 2.20 (s, 3H), 2.04-1.67 (m, 8H), 1.55 (t, J = 7.6 Hz, 3H). MS (ESI) m/z 674.3 $[M+H]^+$.

EXAMPLE 12

Synthesis of 1-(1-benzylpiperidin-4-yl)-1-cyclopentyl-1,2,3,4-tetrahydroisoquinoline (Cpd. No. 71)

Scheme 7



[0513] STEP 1 - Synthesis of 1-benzyl-N-phenethylpiperidine-4-carboxamide (S64)

[0514] To a suspension of 1-benzylpiperidine-4-carboxylic acid (15 g, 68.4 mmol) in dichloromethane (100 mL) was added DMF (1 drop) followed by oxalyl chloride (7 mL, 82 mmol) dropwise. The mixture was stirred for 4 h then concentrated under vacuum, affording acid chloride, rediluted with dichloromethane (100 mL). Triethylamine (23.8 mL, 171 mmol) was added into the mixture, followed by 2-phenylethan-1-amine (8.29 g, 68.4 mmol) at 0 °C. The reaction mixture was stirred at room temperature overnight. The organic phase was washed with brine, dried (Na_2SO_4) and evaporated. The crude product was purified by recrystallization in dichloromethane to obtain the title compound (14.9 g, 68%). MS (ESI) m/z 323.2 $[M+H]^+$.

[0515] STEP 2 - Synthesis of 1-(1-benzylpiperidin-4-yl)-3,4-dihydroisoquinoline (S65)

[0516] To a solution of S64 from STEP 1 in toluene (15 mL) were added phosphoryl chloride (3.3 mL, 35.4 mmol) and phosphorus pentoxide (3.35g, 23.6 mmol). The reaction mixture was stirring under reflux overnight. The mixture was quenched and basified with saturated $NaHCO_3$, extracted with dichloromethane, dried (Na_2SO_4), and the solvent was evaporated to give the title compound (3.5g, 97%). The product was used in the next step without further purification. MS (ESI) m/z 305.3 $[M+H]^+$.

[0517] STEP 3 - Synthesis of 1-(1-benzylpiperidin-4-yl)-1-cyclopentyl-1,2,3,4-tetrahydroisoquinoline (Cpd. No. 71)

[0518] To a solution of S65 from STEP 2 was added boron trifluoride diethyl etherate (0.6 mL) at 0 °C under nitrogen atmosphere. After the mixture was stirring for 5 min, the cyclopentylmagnesium bromide solution (2M, in diethyl ether) (3.3 mL, 6.6 mmol) was added into the mixture dropwise at 0 °C. The reaction mixture was stirred overnight, warming slowly to room temperature. The, the reaction was quenched with saturated aqueous NH_4Cl, extracted with dicloromethane, dried (Na_2SO_4), and the solvent was evaporated. The crude product was purified by prep HPLC to give the title compound (740 mg, 60%). MS (ESI) m/z 375.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.48-7.35 (m, 5H), 7.32-7.28 (m, 2H), 7.21-7.13 (m, 2H), 4.11 (dd, J = 25.6, 12.9 Hz, 2H), 3.65-3.37 (m, 4H), 3.16-2.91 (m, 2H), 2.86-2.75 (m, 2H), 2.69 (t, J = 11.5 Hz, 1H), 2.40 (d, J = 11.7 Hz, 1H), 2.27-2.12 (m, 2H), 1.96-1.80 (m, 2H), 1.75-1.57 (m, 4H), 1.46 (dd, J = 33.9, 3.1 Hz, 2H), 1.37-1.25 (m, 1H), 1.22-1.09 (m, 1H).

EXAMPLE 13

[0519] The following Compounds of the Disclosure, *see* Tables 1 and 2, were prepared using the illustrative methods described in Examples 1-12, and/or methods known to those skilled in the art in view of this disclosure, and characterized by ESI-MS and/or ^{1}NMR as follows.

[0520] Cpd. No. 128; ESI-MS m/z 469.83 $(M+H)^+$.

[0521] Cpd. No. 130; ESI-MS m/z 456.83 $(M+H)^+$.

[0522] Cpd. No. 131; ^{1}H-NMR (400MHz, CD_3OD) δ ppm 7.66 (d, 2H, J = 8.8 Hz), 7.47-7.41 (m, 1H), 7.40-7.29 (m, 3H), 6.97 (d, 2H, J = 8.8 Hz), 5.00-4.93 (m, 1H), 3.97-3.84 (m, 1H), 3.63 (d, 1H, J= 12.1 Hz), 3.59-3.44 (m, 3H), 3.16-3.01 (m, 2H), 2.97-2.71 (m, 6H), 2.69-2.51 (m, 3H), 2.26 (d, 1H, J = 12.6 Hz), 2.02-1.88 (m, 2H), 1.88-1.73 (m, 3H), 1.73-1.40 (m, 6H), 1.26-1.10 (m, 1H); ESI-MS m/z 456.83 $(M+H)^+$.

[0523] Cpd. No. 132; ESI-MS m/z 508.83 $(M+H)^+$.

[0524] Cpd. No. 323; ESI-MS m/z 532.92 $(M+H)^+$.

[0525] Cpd. No. 324; ESI-MS m/z 532.83 $(M+H)^+$.

[0526] Cpd. No. 325; ESI-MS m/z 488.83 $(M+H)^+$.

[0527] Cpd. No. 326; ESI-MS m/z 488.83 $(M+H)^+$.

[0528] Cpd. No. 327; ESI-MS m/z 493.92 $(M+H)^+$.

[0529] Cpd. No. 328; ESI-MS m/z 493.83 $(M+H)^+$.

[0530] Cpd. No. 43; ESI-MS m/z 455.92 $(M+H)^+$.

[0531] Cpd. No. 44; ESI-MS m/z 511.50 $(M+H)^+$.

[0532] Cpd. No. 45; ^{1}H-NMR (400MHz, CD_3OD) δ ppm 7.58 (d, 1H, J = 7.9 Hz), 7.51-7.43 (m, 3H), 7.36 (t, 1H, J = 7.4 Hz), 7.29 (d, 1H, J = 7.3 Hz), 6.47 (d, 2H, J = 8.7 Hz), 4.46-4.23 (m, 3H), 4.17 (t, 2H, J = 7.6 Hz), 3.78-3.72 (m, 2H), 3.52 (d, 2H, J = 13.4 Hz), 3.43 (d, 3H, J = 6.4 Hz), 3.15 (s, 3H), 3.08-2.90 (m, 3H), 2.17 (d, 1H, J = 14.6 Hz), 1.93-1.80 (m, 3H), 1.73-1.44 (m, 8H), 1.36-1.21 (m, 2H); ESI-MS m/z 469.67 $(M+H)^+$.

[0533] Cpd. No. 46; ESI-MS m/z 482.17 $(M+H)^+$.

[0534] Cpd. No. 133; ESI-MS m/z 522.50 $(M+H)^+$.

[0535] Cpd. No. 134; ESI-MS m/z 536.67 $(M+H)^+$.

[0536] Cpd. No. 135; ^{1}H-NMR (400MHz, CD_3OD) δ ppm 7.66 (d, 2H, J=7.6Hz), 7.48-7.42 (m, 1H), 7.39-7.29 (m, 3H), 6.52 (d, 2H, J=7.8Hz), 4.19 (t, 1H, J=7.7Hz), 3.81-3.73 (m, 2H), 3.64 (d, 1H, J=11.3Hz), 3.61-3.42 (m, 7H), 3.16-2.98 (m, 5H), 2.85-2.72 (m, 1H), 2.67-2.52 (m, 2H), 2.25 (d, 1H, J=13.8Hz), 2.01-1.90 (m, 2H), 1.86-1.41 (m, 9H), 1.34-1.18 (m, 1H), 1.18-1.12 (m, 2H), 1.03-0.96 (m, 2H); ESI-MS m/z 534.50 $(M+H)^+$.

[0537] Cpd. No. 329; ESI-MS m/z 458.58 $(M+H)^+$.

[0538] Cpd. No. 136; ESI-MS m/z 550.67 $(M+H)^+$.

[0539] Cpd. No. 137; ESI-MS m/z 562.67 $(M+H)^+$

[0540] Cpd. No. 330 ; ESI-MS m/z 487.83 $(M+H)^+$.

[0541] Cpd. No. 331; ESI-MS m/z 487.67 $(M+H)^+$.

[0542] Cpd. No. 138; ESI-MS m/z 469.50 $(M+H)^+$.

[0543] Cpd. No. 139; ESI-MS m/z 489.50 $(M+H)^+$.

[0544] Cpd. No. 140; ^{1}H-NMR (400MHz, CD_3OD) δ ppm 7.71 (d, 2H, J=8.6Hz), 7.45 (m, 1H), 7.35 (m, 3H), 6.62 (d, 2H, J=8.7Hz), 4.25 (m, 4H), 3.73 (m, 1H), 3.53 (m, 7H), 3.12 (m, 4H), 2.80 (m, 1H), 2.57 (m, 2H), 2.22 (d, 1H, J=13.7Hz), 1.97 (m, 2H), 1.63 (m, 9H), 1.27 (m, 1H), 1.15 (m, 2H), 1.00 (m, 2H); ESI-MS m/z 552.67 $(M+H)^+$.

[0545] Cpd. No. 141; ESI-MS m/z 580.58 $(M+H)^+$.

[0546] Cpd. No. 47; ESI-MS m/z 580.58 $(M+H)^+$.

[0547] Cpd. No. 142; ESI-MS m/z 590.67 $(M+H)^+$.

[0548] Cpd. No. 143; ESI-MS m/z 576.58 $(M+H)^+$.

[0549] Cpd. No. 144; ESI-MS m/z 597.00 $(M+H)^+$.

[0550] Cpd. No. 145; ESI-MS m/z 590.67 $(M+H)^+$.

[0551] Cpd. No. 146; ESI-MS m/z 562.92 $(M+H)^+$.

[0552] Cpd. No. 147; ESI-MS m/z 598.58 $(M+H)^+$.

[0553] Cpd. No. 149; ESI-MS m/z 570.50 $(M+H)^+$.

[0554] Cpd. No. 151; ^{1}H-NMR (400MHz, CD_3OD) δ ppm 8.75 (d, 2H, J = 5.7 Hz), 7.82 (dd, 2H, J = 1.5 Hz, J = 4.6 Hz), 7.76 (d, 2H, J = 8.8 Hz), 7.47-7.41 (m, 1H), 7.41-7.28 (m, 3H), 6.51 (d, 2H, J = 8.9 Hz), 4.19 (t, 2H, J = 7.9 Hz), 3.81-3.73 (m, 2H), 3.67-3.39 (m, 8H), 3.19-2.96 (m, 4H) 2.89-2.73 (m, 1H), 2.67-2.52 (m, 1H), 2.24 (d, 1H, J = 12.8 Hz), 2.04-1.88 (m, 2H), 1.88-1.37 (m, 8H), 1.37-1.13 (m, 1H); ESI-MS m/z 571.67 $(M+H)^+$.

[0555] Cpd. No. 152; ESI-MS m/z 599.58 $(M+H)^+$.

[0556] Cpd. No. 153; ESI-MS m/z 613.67 $(M+H)^+$.

[0557] Cpd. No. 154; ESI-MS m/z 613.67 $(M+H)^+$.

[0558] Cpd. No. 332; ^{1}H-NMR (400MHz, CD_3OD) δ ppm 7.66 (d, 2H, J = 8.8 Hz), 7.50-7.30 (m, 5H), 6.53 (d, 2H, J = 8.8 Hz), 4.17 (t, 1H, J = 7.8 Hz), 3.77-3.69 (m, 2H), 3.54 (d, 3H, J = 11.5 Hz), 3.49-3.37 (m, 6H), 3.24-2.96 (m, 2H), 2.61-2.47 (m, 2H), 2.46-2.35 (m, 1H), 2.32-2.17 (m, 2H), 2.08 (d, 1H, J = 14.5 Hz), 2.00-1.88 (m, 1H), 1.88-1.71 (m, 4H), 1.63-1.46 (m, 1H), 1.41-1.27 (m, 1H), 1.19-1.11 (m, 2H), 1.03-0.95 (m, 2H); ESI-MS m/z 576.75 $(M+H)^+$.

[0559] Cpd. No. 333; ^{1}H-NMR (400MHz, CD_3OD) δ ppm 7.65 (d, 2H, J = 8.8 Hz), 7.55-7.38 (m, 5H), 6.52 (d, 2H, J = 8.8 Hz), 4.15 (t, 2H, J = 7.9 Hz), 3.78 (s, 3H), 3.76-3.69 (m, 2H), 3.63-3.48 (m, 2H), 3.42 (d, 2H, J = 7.1 Hz), 3.24-3.07 (m, 2H), 2.97-2.83 (m, 2H), 2.61-2.50 (m, 1H), 2.44-2.25 (m, 2H), 2.06 (d, 1H, J = 14.6 Hz), 1.99-1.81 (m, 3H), 1.70-1.59 (m, 2H), 1.58-1.45 (m, 1H), 1.45-1.27 (m, 2H), 1.18-1.11 (m, 2H), 1.04-0.96 (m, 2H); ESI-MS m/z 576.42 $(M+H)^+$.

[0560] Cpd. No. 334; ESI-MS m/z 575.50 $(M+H)^+$.

[0561] Cpd. No. 335; ESI-MS m/z 589.58 $(M+H)^+$.

[0562] Cpd. No. 336; ESI-MS m/z 627.75 $(M+H)^+$.

[0563] Cpd. No. 337; ESI-MS m/z 627.58 $(M+H)^+$.

[0564] Cpd. No. 155; ESI-MS m/z 627.67 $(M+H)^+$.

[0565] Cpd. No. 338; ESI-MS m/z 583.67 $(M+H)^+$.

[0566] Cpd. No. 48; ^{1}H-NMR (400MHz, CD_3OD) δ ppm 8.76 (m, 2H), 7.83 (d, 2H, J=5.7Hz), 7.76 (d, 2H, J=8.8Hz), 7.56 (d, 1H, J=7.9Hz), 7.46 (t, 1H, J=7.5Hz), 7.40-7.29 (m, 2H), 6.49 (d, 2H, J=8.8Hz), 4.46-4.25 (m, 2H), 4.24-4.11 (m, 2H), 3.87-3.70 (m, 4H), 3.56-3.37 (m, 5H), 3.09-2.89 (m, 2H), 2.24-2.04 (m, 2H), 1.93-1.78 (m, 2H), 1.78-1.59 (m, 6H), 1.51 (d, 6H, J=6.6Hz), 1.38-1.06 (m, 2H); ESI-MS m/z 613.58 $(M+H)^+$.

[0567] Cpd. No. 49; ESI-MS m/z 625.58 $(M+H)^+$.

[0568] Cpd. No. 50; ESI-MS m/z 625.75 $(M+H)^+$.

[0569] Cpd. No. 156; ESI-MS m/z 627.58 $(M+H)^+$.

[0570] Cpd. No. 157; ESI-MS m/z 667.67 $(M+H)^+$.

[0571] Cpd. No. 339; ESI-MS m/z 627.25 $(M+H)^+$.

[0572] Cpd. No. 340; ESI-MS m/z 626.58 $(M+H)^+$.

[0573] Cpd. No. 158; ESI-MS m/z 650.50 $(M+H)^+$.

[0574] Cpd. No. 51; ^{1}H-NMR (400MHz, CD_3OD) δ ppm 8.76 (s, 2H), 7.83 (d, 2H, J=5.0Hz), 7.76 (d, 2H, J=8.7Hz), 7.55 (d, 1H, J=8.1Hz), 7.43 (t, 1H, J=7.1Hz), 7.37-7.25 (m, 2H), 6.50 (d, 2H, J=8.8Hz), 4.33-4.22 (m, 2H), 4.18 (t, 2H, J=7.7Hz), 3.79-3.72 (m, 2H), 3.60-3.47 (m, 4H), 3.47-3.39 (m, 4H), 3.08-2.90 (m, 2H), 2.62-2.49 (m, 1H), 2.32-2.19 (m, 1H), 2.15 (d, 1H, J=13.4Hz), 1.90-1.72 (m, 4H), 1.69-1.44 (m, 8H), 1.35-1.22 (m, 1H), 1.19-1.02 (m, 1H); ESI-MS m/z 571.58 $(M+H)^+$.

[0575] Cpd. No. 52; ESI-MS m/z 641.93 $(M+H)^+$.

[0576] Cpd. No. 53; ESI-MS m/z 662.58 $(M+H)^+$.

[0577] Cpd. No. 54; ESI-MS m/z 684.50 $(M+H)^+$.

[0578] Cpd. No. 341; ESI-MS m/z 599.50 $(M+H)^+$.

[0579] Cpd. No. 342; ESI-MS m/z 599.50 $(M+H)^+$.

[0580] Cpd. No. 159; ESI-MS m/z 533.58 $(M+H)^+$.

[0581] Cpd. No. 160; ESI-MS m/z 649.75 $(M+H)^+$.

[0582] Cpd. No. 161; ^{1}H-NMR (400MHz, CD_3OD) δ ppm 8.76 (d, 2H, J = 4.8 Hz), 7.83 (d, 2H, J = 4.7 Hz), 7.76 (d, 2H, J = 7.6 Hz), 7.57 (d, 1H, J = 8.1 Hz), 7.46 (t, 1H, J = 7.3 Hz), 7.40-7.29 (m, 2H), 6.52 (d, 2H, J = 8.0 Hz), 4.57-4.11 (m, 2H), 3.86 (d, 2H, J = 7.9 Hz), 3.78 (d, 2H, J = 7.9 Hz), 3.57-3.38 (m, 6H), 3.18-2.96 (m, 2H), 2.83-2.66 (m, 1H), 2.57-2.27 (m, 1H), 2.14 (d, 1H, J = 13.6 Hz), 1.93-1.75 (m, 3H), 1.74-1.35 (m, 12H), 1.35-1.09 (m, 3H), 1.00-0.69 (m, 1H); ESI-MS m/z 613.58 $(M+H)^+$.

[0583] Cpd. No. 343; ESI-MS m/z 578.42 $(M+H)^+$.

[0584] Cpd. No. 344; ESI-MS m/z 451.75 $(M+H)^+$.

[0585] Cpd. No. 162; ESI-MS m/z 636.50 $(M+H)^+$.

[0586] Cpd. No. 163; ESI-MS m/z 520.50 $(M+H)^+$.

[0587] Cpd. No. 347; ESI-MS m/z 627.75 $(M+H)^+$.

[0588] Cpd. No. 348; ESI-MS m/z 627.50 $(M+H)^+$.

[0589] Cpd. No. 351; ESI-MS m/z 671.83 $(M+H)^+$.

[0590] Cpd. No. 352; ESI-MS m/z 671.42 $(M+H)^+$.

[0591] Cpd. No. 164; ESI-MS m/z 642.58 $(M+H)^+$.

[0592] Cpd. No. 392; ESI-MS m/z 686.67 $(M+H)^+$.

[0593] Cpd. No. 393; ESI-MS m/z 619.42 $(M+H)^+$.

[0594] Cpd. No. 394; ESI-MS m/z 645.50 $(M+H)^+$.

[0595] Cpd. No. 395; ESI-MS m/z 625.50 $(M+H)^+$.

[0596] Cpd. No. 396; ESI-MS m/z 645.75 $(M+H)^+$.

[0597] Cpd. No. 397; ESI-MS m/z 649.58 $(M+H)^+$.

[0598] Cpd. No. 398; ESI-MS m/z 645.50 $(M+H)^+$.

[0599] Cpd. No. 399; ESI-MS m/z 670.42 $(M+H)^+$.

[0600] Cpd. No. 400; ESI-MS m/z 512.58 $(M+H)^+$.

[0601] Cpd. No. 401; ESI-MS m/z 555.58 $(M+H)^+$.

[0602] Cpd. No. 402; ESI-MS m/z 487.58 $(M+H)^+$.

[0603] Cpd. No. 404; ESI-MS m/z 495.67 $(M+H)^+$.

[0604] Cpd. No. 405; ESI-MS m/z 602.58 $(M+H)^+$.

[0605] Cpd. No. 1; MS (ESI) m/z: $[M + H]^+$ calcd, 216.1; found, 217.4.

[0606] Cpd. No. 2; MS (ESI) m/z: $[M + H]^+$ calcd, 286.1; found, 287.3.

[0607] Cpd. No. 3; MS (ESI) m/z: $[M + H]^+$ calcd, 301.2; found, 302.4.

[0608] Cpd. No. 4; MS (ESI) m/z: $[M + H]^+$ calcd, 375.2; found, 376.3.

[0609] Cpd. No. 5; MS (ESI) m/z: $[M + H]^+$ calcd, 285.2; found, 286.3.

[0610] Cpd. No. 6; MS (ESI) m/z: $[M + H]^+$ calcd, 355.2; found, 356.5.

[0611] Cpd. No. 7; MS (ESI) m/z: $[M + H]^+$ calcd, 434.2; found, 435.5.

[0612] Cpd. No. 8; MS (ESI) m/z: $[M + H]^+$ calcd, 433.3; found, 434.4.

[0613] Cpd. No. 9; MS (ESI) m/z: $[M + H]^+$ calcd, 340.1; found, 341.4.

[0614] Cpd. No. 10; MS (ESI) m/z: $[M + H]^+$ calcd, 464.1; found, 465.4.

[0615] Cpd. No. 11; MS (ESI) m/z: $[M + H]^+$ calcd, 410.2; found, 411.4.

[0616] Cpd. No. 12; MS (ESI) m/z: $[M + H]^+$ calcd, 489.2; found, 490.4.

[0617] Cpd. No. 13; MS (ESI) m/z: $[M + H]^+$ calcd, 499.2; found, 500.3.

[0618] Cpd. No. 14; MS (ESI) m/z: $[M + H]^+$ calcd, 623.2; found, 624.5.

[0619] Cpd. No. 15; MS (ESI) m/z: $[M + H]^+$ calcd, 312.2; found, 313.3.

[0620] Cpd. No. 16; MS (ESI) m/z: $[M + H]^+$ calcd, 285.2; found, 286.3.

[0621] Cpd. No. 17; MS (ESI) m/z: $[M + H]^+$ calcd, 444.2; found, 445.3.

[0622] Cpd. No. 18; MS (ESI) m/z: $[M + H]^+$ calcd, 443.3; found, 444.5.

[0623] Cpd. No. 19; ^{1}H NMR (400 MHz, MeOD) δ 7.73 – 7.63 (m, 2H), 7.58 (dt, *J* = 11.2, 5.6 Hz, 1H), 7.48 – 7.40 (m, 1H), 7.40 – 7.26 (m, 2H), 7.13 – 7.02 (m, 2H), 4.43 – 4.22 (m, 2H), 4.17 (tt, *J* = 14.2, 7.1 Hz, 2H), 3.75 – 3.52 (m, 3H), 3.48 – 3.37 (m, 1H), 3.31 – 3.25 (m, 1H), 3.02 (tdd, *J* = 12.2, 11.4, 2.4 Hz, 2H), 2.65 – 2.52 (m, 1H), 2.36 – 2.22 (m, 3H), 2.22 – 2.13 (m, 1H), 1.93 – 1.75 (m, 4H), 1.71 – 1.47 (m, 6H), 1.40 – 1.26 (m, 1H), 1.21 – 1.05 (m, 1H). MS (ESI) m/z: $[M + H]^+$ calcd, 443.3; found, 444.5.

[0624] Cpd. No. 20; ^{1}H NMR (400 MHz, MeOD) δ 7.66 (dd, *J* = 9.2, 2.2 Hz, 2H), 7.54 – 7.43 (m, 4H), 7.40 (d, *J* = 7.1 Hz, 1H), 7.06 (d, *J* = 8.9 Hz, 2H), 4.16 (dd, *J* = 13.4, 7.7 Hz, 2H), 3.73 – 3.56 (m, 2H), 3.30 – 3.20 (m, 2H), 3.18 – 2.98 (m, 2H), 2.93 (dd, *J* = 16.1, 8.1 Hz, 1H), 2.43 (dd, *J* = 16.9, 7.6 Hz, 1H), 2.31 (d, *J* = 14.4 Hz, 1H), 2.20 (dt, *J* = 15.8, 5.7 Hz, 2H), 2.14 – 1.95 (m, 2H), 1.86 – 1.68 (m, 2H), 1.68 – 1.53 (m, 4H), 1.53 – 1.37 (m, 2H), 1.28 – 1.14 (m, 1H). MS (ESI) m/z: $[M + H]^+$ calcd, 427.3; found, 428.4.

[0625] Cpd. No. 21; ^{1}H NMR (400 MHz, MeOD) δ 8.05 (t, *J* = 8.7 Hz, 1H), 7.67 (d, *J* = 8.6 Hz, 2H), 7.63 – 7.55 (m, 1H), 7.53 – 7.45 (m, 1H), 7.41 (t, *J* = 8.0 Hz, 1H), 7.06 (d, *J* = 8.6 Hz, 2H), 4.15 (t, *J* = 5.5 Hz, 2H), 3.64 (dd, *J* = 25.6, 14.4 Hz, 4H), 3.31 – 3.20 (m, 2H), 3.02 (d, *J* = 5.5 Hz, 2H), 2.91 – 2.74 (m, 1H), 2.67 (s, 1H), 2.25 (dt, *J* = 14.7, 12.2 Hz, 3H), 2.08 (d, *J* = 14.8 Hz, 1H), 1.91 (s, 2H), 1.81 – 1.39 (m, 6H), 1.17 (m, 2H). MS (ESI) m/z: $[M + H]^+$ calcd, 457.3; found, 458.5.

[0626] Cpd. No. 22; MS (ESI) m/z: $[M + H]^+$ calcd, 461.3; found, 462.4.

[0627] Cpd. No. 55; MS (ESI) m/z: $[M + H]^+$ calcd, 468.3; found, 469.5.

[0628] Cpd. No. 56; MS (ESI) m/z: $[M + H]^+$ calcd, 402.3; found, 403.5.

[0629] Cpd. No. 57; MS (ESI) m/z: $[M + H]^+$ calcd, 346.2; found, 347.3.

[0630] Cpd. No. 58; MS (ESI) m/z: $[M + H]^+$ calcd, 442.3; found, 443.5.

[0631] Cpd. No. 59; MS (ESI) m/z: $[M + H]^+$ calcd, 443.3; found, 444.5.

[0632] Cpd. No. 60; ^{1}H NMR (400 MHz, MeOD) δ 7.68 (d, *J* = 9.0 Hz, 2H), 7.59 (d, *J* = 8.6 Hz, 1H), 7.55 – 7.44 (m, 2H), 7.40 (d, *J* = 6.6 Hz, 1H), 7.06 (d, *J* = 9.0 Hz, 2H), 4.36 (s, 2H), 4.09 (t, *J* = 5.7 Hz, 2H), 3.86 (s, 1H), 3.69 – 3.57 (m, 1H), 3.41 – 3.36 (m, 2H), 3.28 (dt, *J* = 3.3, 1.6 Hz, 1H), 3.20 (dd, *J* = 18.2, 10.7 Hz, 2H), 3.13 (dd, *J* = 13.6, 5.7 Hz, 3H), 2.87 (s, 1H), 2.02 (s, 2H), 1.91 – 1.79 (m, 2H), 1.77 – 1.51 (m, 4H), 1.20 (s, 1H). MS (ESI) m/z: $[M + H]^+$ calcd, 415.3; found, 416.4.

[0633] Cpd. No. 61; MS (ESI) m/z: $[M + H]^+$ calcd, 574.3; found, 575.4.

[0634] Cpd. No. 23; ^{1}H NMR (400 MHz, MeOD) δ 7.70 – 7.63 (m, 2H), 7.63 – 7.55 (m, 1H), 7.48 (t, *J* = 7.7 Hz, 1H), 7.38 (t, *J* = 7.5 Hz, 1H), 7.31 (d, *J* = 7.6 Hz, 1H), 7.08 (d, *J* = 8.8 Hz, 2H), 4.37 (s, 2H), 4.18 (t, *J* = 5.4 Hz, 2H), 3.79 – 3.57 (m, 3H), 3.37 (dd, *J* = 3.2, 1.6 Hz, 1H), 3.29 (dd, *J* = 4.7, 3.1 Hz, 2H), 3.17 (s, 3H), 3.02 (dd, *J* = 28.7, 15.3 Hz, 2H), 2.39 – 2.15 (m, 4H), 1.94 – 1.78 (m, 3H), 1.59 (d, *J* = 6.8 Hz, 6H), 1.31 (s, 2H). MS (ESI) m/z: $[M + H]^+$ calcd, 457.3; found, 458.5.

[0635] Cpd. No. 62; ^{1}H NMR (400 MHz, MeOD) δ 7.72 – 7.64 (m, 2H), 7.57 (d, *J* = 7.0 Hz, 1H), 7.44 (dd, *J* = 10.4, 6.0 Hz, 2H), 7.38 (t, *J* = 7.1 Hz, 1H), 7.05 (d, *J* = 8.9 Hz, 2H), 4.31 (s, 2H), 4.06 (t, *J* = 5.8 Hz, 2H), 3.83 (s, 2H), 3.67 – 3.54 (m, 1H), 3.42 – 3.37 (m, 2H), 3.27 (dt, *J* = 17.6, 8.0 Hz, 1H), 3.24 – 3.08 (m, 3H), 3.08 – 2.95 (m, 1H), 2.84 (s, 1H), 1.82 (s, 4H), 1.77 – 1.50 (m, 6H), 1.32 (s, 1H), 1.20 (s, 1H). MS (ESI) m/z: $[M + H]^+$ calcd, 429.3; found, 430.4.

[0636] Cpd. No. 63; ^{1}H NMR (400 MHz, MeOD) δ 7.67 (dd, *J* = 9.3, 2.3 Hz, 2H), 7.48 – 7.28 (m, 4H), 7.07 (dd, *J* = 8.9, 7.1 Hz, 2H), 4.70 – 4.48 (m, 2H), 4.22 – 3.99 (m, 3H), 3.94 – 3.79 (m, 2H), 3.64 (s, 1H), 3.47 (dd, *J* = 20.1, 8.5 Hz, 3H), 3.21 – 3.00 (m, 3H), 2.91 (d, *J* = 12.0 Hz, 2H), 2.81 (s, 2H), 2.17 (s, 1H), 1.93 (d, *J* = 5.9 Hz, 2H), 1.90 – 1.76 (m, 4H), 1.76 – 1.60 (m, 2H), 1.57 (d, *J* = 19.4 Hz, 2H), 1.43 – 1.18 (m, 2H). MS (ESI) m/z: $[M + H]^+$ calcd, 457.3; found, 458.4.

[0637] Cpd. No. 64; MS (ESI) m/z: $[M + H]^+$ calcd, 521.3; found, 522.5.

[0638] Cpd. No. 165; MS (ESI) m/z: $[M + H]^+$ calcd, 383.2; found, 384.5.

[0639] Cpd. No. 166; MS (ESI) m/z: $[M + H]^+$ calcd, 327.3; found, 328.5.

[0640] Cpd. No. 167; MS (ESI) m/z: $[M + H]^+$ calcd, 325.3; found, 326.5.

[0641] Cpd. No. 168; MS (ESI) m/z: $[M + H]^+$ calcd, 466.3; found, 467.5.

[0642] Cpd. No. 169; MS (ESI) m/z: $[M + H]^+$ calcd, 505.2; found, 506.3.

[0643] Cpd. No. 170; MS (ESI) m/z: $[M + H]^+$ calcd, 530.3; found, 531.5.

[0644] Cpd. No. 171; MS (ESI) m/z: $[M + H]^+$ calcd, 477.3; found, 478.5.

[0645] Cpd. No. 65; MS (ESI) m/z: $[M + H]^+$ calcd, 525.4; found, 526.5.

[0646] Cpd. No. 66; MS (ESI) m/z: $[M + H]^+$ calcd, 452.3; found, 453.5.

[0647] Cpd. No. 67; MS (ESI) m/z: $[M + H]^+$ calcd, 452.3; found, 453.5.

[0648] Cpd. No. 24; ^{1}H NMR (400 MHz, MeOD) δ 8.27 (d, *J* = 7.7 Hz, 1H), 7.77 (dt, *J* = 11.4, 7.2 Hz, 2H), 7.68 (d, *J* = 8.9 Hz, 2H), 7.58 (t, *J* = 7.3 Hz, 1H), 7.08 (d, *J* = 8.9 Hz, 2H), 4.17 (t, *J* = 5.7 Hz, 2H), 3.68 (d, *J* = 11.7 Hz, 1H), 3.59 (d, *J* = 10.5 Hz, 1H), 3.45 – 3.35 (m, 2H), 3.30 – 3.25 (m, 2H), 3.04 (dt, *J* = 24.2, 12.4 Hz, 2H), 2.77 (dd, *J* = 17.6, 7.6 Hz, 2H), 2.31 – 2.07 (m, 4H), 1.73 (dd, *J* = 30.6, 13.0 Hz, 4H), 1.52 (d, *J* = 7.9 Hz, 4H), 1.41 – 1.22 (m, 2H). MS (ESI) m/z: $[M + H]^+$ calcd, 457.3; found, 458.5.

[0649] Cpd. No. 68; MS (ESI) m/z: $[M + H]^+$ calcd, 510.3; found, 511.5.

[0650] Cpd. No. 172; MS (ESI) m/z: $[M + H]^+$ calcd, 445.3; found, 446.5.

[0651] Cpd. No. 25; MS (ESI) m/z: $[M + H]^+$ calcd, 611.3; found, 612.4.

[0652] Cpd. No. 26;MS (ESI) m/z: $[M + H]^+$ calcd, 487.3; found, 488.5.

[0653] Cpd. No. 173; MS (ESI) m/z: $[M + H]^+$ calcd, 429.3; found, 430.4.

[0654] Cpd. No. 69; MS (ESI) m/z: $[M + H]^+$ calcd, 535.3; found, 536.5.

[0655] Cpd. No. 70; ^{1}H NMR (400 MHz, MeOD) δ 8.10 – 7.82 (m, 1H), 7.67 (d, *J* = 8.7 Hz, 1H), 7.62 – 7.53 (m, 2H), 7.47 (d, *J* = 6.5 Hz, 1H), 7.42 – 7.34 (m, 1H), 7.31 (d, *J* = 6.2 Hz, 1H), 6.53 (d, *J* = 8.7 Hz, 1H), 4.36 (s, 2H), 4.20 (s, 1H), 3.78 (s, 1H), 3.56 (s, 4H), 3.16 (s, 3H), 3.08 – 2.89 (m, 1H), 2.63 – 2.49 (m, 2H), 2.16 (s, 2H), 1.86 (s, 3H), 1.58 (s, 8H), 1.25 (dd, *J* = 20.1, 17.7 Hz, 3H), 1.21 – 0.92 (m, 7H). MS (ESI) m/z: $[M + H]^+$ calcd, 547.3; found, 548.4.

[0656] Cpd. No. 174; MS (ESI) m/z: $[M + H]^+$ calcd, 457.3; found, 458.5.

[0657] Cpd. No. 175; MS (ESI) m/z: $[M + H]^+$ calcd, 457.3; found, 458.5.

[0658] Cpd. No. 176; ^{1}H NMR (400 MHz, MeOD) δ 7.75 – 7.66 (m, 2H), 7.64 – 7.46 (m, 5H), 7.11 (dd, *J* = 7.8, 6.0 Hz, 2H), 5.00 (s, 2H), 4.19 (d, *J* = 5.5 Hz, 2H), 3.78 – 3.61 (m, 2H), 3.61 – 3.42 (m, 3H), 3.39 – 3.35 (m, 2H), 3.29 (dt, *J* = 3.3, 1.7 Hz, 1H), 3.02 – 2.91 (m, 2H), 2.56 (s, 1H), 2.32 (d, *J* = 5.5 Hz, 2H), 2.14 (s, 3H), 1.99 (ddd, *J* = 43.6, 17.6, 11.4 Hz, 4H), 1.84 – 1.71 (m, 1H), 1.56 – 1.37 (m, 1H). MS (ESI) m/z: $[M + H]^+$ calcd, 457.3; found, 458.6.

[0659] Cpd. No. 177; MS (ESI) m/z: $[M + H]^+$ calcd, 457.3; found, 458.6.

[0660] Cpd. No. 178; MS (ESI) m/z: $[M + H]^+$ calcd, 507.3; found, 508.5.

[0661] Cpd. No. 179; MS (ESI) m/z: $[M + H]^+$ calcd, 507.3; found, 508.5.

[0662] Cpd. No. 180; MS (ESI) m/z: $[M + H]^+$ calcd, 521.3; found, 522.4.

[0663] Cpd. No. 181; MS (ESI) m/z: $[M + H]^+$ calcd, 521.3; found, 522.4.

[0664] Cpd. No. 182; MS (ESI) m/z: $[M + H]^+$ calcd, 569.2; found, 570.3.

[0665] Cpd. No. 183; MS (ESI) m/z: $[M + H]^+$ calcd, 549.3; found, 550.5.

[0666] Cpd. No. 184; MS (ESI) m/z: $[M + H]^+$ calcd, 549.3; found, 550.5.

[0667] Cpd. No. 185; ^{1}H NMR (400 MHz, MeOD) δ 8.77 (s, 2H), 7.84 (dd, *J* = 4.4, 1.7 Hz, 2H), 7.77 (dd, *J* = 8.9, 2.6 Hz, 2H), 7.55-7.35 (m, 5H), 6.51 (dd, *J* = 8.9, 2.6 Hz, 2H), 4.17 (t, *J* = 8.0 Hz, 2H), 3.75 (d, *J* = 5.8 Hz, 2H), 3.55 (t, *J* = 11.4 Hz, 2H), 3.42 (d, *J* = 6.9 Hz, 2H), 3.19 (m, 3H), 3.11 – 2.99 (m, 2H), 2.40 (d, *J* = 11.9 Hz, 1H), 2.27 (d, *J* = 10.6 Hz, 2H), 2.13 – 2.00 (m, 1H), 1.77 (m, 5H), 1.73 – 1.59 (m, 3H), 1.55 (d, *J* = 12.4 Hz, 1H), 1.41 (d, *J* = 12.4 Hz, 1H). MS (ESI) m/z: $[M + H]^+$ calcd, 612.3; found, 613.4.

[0668] Cpd. No. 186; MS (ESI) m/z: $[M + H]^+$ calcd, 612.3; found, 613.4.

[0669] Cpd. No. 187; ^{1}H NMR (400 MHz, MeOD) δ 7.72 – 7.64 (m, 2H), 7.49 (q, *J* = 7.2 Hz, 5H), 6.52 (d, *J* = 8.5 Hz, 2H), 5.21 (s, 1H), 4.16 (t, *J* = 7.8 Hz, 2H), 3.80 – 3.68 (m, 2H), 3.63 – 3.52 (m, 2H), 3.49 – 3.39 (m, 2H), 3.27 – 3.06 (m, 3H), 2.99 (t, *J* = 11.9 Hz, 1H), 2.63 – 2.49 (m, 2H), 2.31 (d, *J* = 14.6 Hz, 1H), 2.15 – 2.08 (m, 3H), 1.93 (dd, *J* = 17.8, 12.2 Hz, 2H), 1.71 (m, 4H), 1.50 (m, 2H), 1.30 (dd, *J* = 15.0, 5.4 Hz, 1H), 1.19 – 1.12 (m, 2H), 1.05 – 0.95 (m, 2H). MS (ESI) m/z: $[M + H]^+$ calcd, 575.3; found, 576.6.

[0670] Cpd. No. 188; MS (ESI) m/z: $[M + H]^+$ calcd, 575.3; found, 576.6.

[0671] Cpd. No. 189; MS (ESI) m/z: $[M + H]^+$ calcd, 535.3; found, 536.5.

[0672] Cpd. No. 190; MS (ESI) m/z: $[M + H]^+$ calcd, 554.3; found, 555.4

[0673] Cpd. No. 191; MS (ESI) m/z: $[M + H]^+$ calcd, 640.3; found, 641.5.

[0674] Cpd. No. 192; MS (ESI) m/z: $[M + H]^+$ calcd, 640.3; found, 641.5.

[0675] Cpd. No. 193; MS (ESI) m/z: $[M + H]^+$ calcd, 640.3; found, 641.4.

[0676] Cpd. No. 194; MS (ESI) m/z: $[M + H]^+$ calcd, 640.3; found, 641.5.

[0677] Cpd. No. 195; ^{1}H NMR (400 MHz, MeOD) δ 8.65 (s, 2H), 7.72 (t, *J* = 7.6 Hz, 2H), 7.64 (t, *J* = 7.7 Hz, 2H), 7.43 – 7.31 (m, 5H), 6.39 (t, *J* = 7.7 Hz, 2H), 5.08 (s, 1H), 4.05 (td, *J* = 8.1, 1.9 Hz, 2H), 3.67 – 3.57 (m, 2H), 3.51 – 3.39 (m, 2H), 3.35 – 3.23 (m,

2H), 3.09 (dd, *J* = 14.1, 7.2 Hz, 1H), 3.03 – 2.94 (m, 2H), 2.93 – 2.78 (m, 1H), 2.45 (t, *J* = 12.2 Hz, 1H), 2.34 – 2.22 (m, 2H), 2.18 (d, *J* = 14.4 Hz, 1H), 1.95 – 1.68 (m, 3H), 1.66 – 1.53 (m, 3H), 1.38 (dd, *J* = 29.8, 15.6 Hz, 2H), 1.19 (ddd, *J* = 12.9, 8.9, 5.2 Hz, 1H), 1.09 – 1.00 (m, 3H). MS (ESI) m/z: $[M + H]^+$ calcd, 626.3; found, 627.5.

[0678] Cpd. No. 196; MS (ESI) m/z: $[M + H]^+$ calcd, 626.3; found, 627.5.

[0679] Cpd. No. 197; ^{1}H NMR (400 MHz, MeOD) δ 8.79 (s, 2H), 7.92 – 7.84 (m, 2H), 7.82 – 7.65 (m, 2H), 7.55 – 7.30 (m, 5H), 6.51 (d, *J* = 8.9 Hz, 2H), 4.18 (t, *J* = 8.1 Hz, 2H), 3.80 – 3.71 (m, 2H), 3.57 (dd, *J* = 24.9, 11.1 Hz, 2H), 3.42 (d, *J* = 7.1 Hz, 2H), 3.19 (ddd, *J* = 11.8, 9.3, 5.0 Hz, 2H), 3.06 (dd, *J* = 22.1, 10.8 Hz, 2H), 2.39 (d, *J* = 11.3 Hz, 1H), 2.27 (d, *J* = 11.0 Hz, 2H), 2.03 (d, *J* = 18.9 Hz, 1H), 1.76 (d, *J* = 30.7 Hz, 3H), 1.68 (dd, *J* = 22.4, 12.6 Hz, 3H), 1.55 (d, *J* = 12.9 Hz, 1H), 1.50 – 1.34 (m, 3H), 0.88 – 0.72 (m, 3H), 0.71 – 0.56 (m, 1H). MS (ESI) m/z: $[M + H]^+$ calcd, 638.3; found, 639.4.

[0680] Cpd. No. 198; MS (ESI) m/z: $[M + H]^+$ calcd, 638.3; found, 639.4.

[0681] Cpd. No. 199; MS (ESI) m/z: $[M + H]^+$ calcd, 598.3; found, 599.5.

[0682] Cpd. No. 200; MS (ESI) m/z: $[M + H]^+$ calcd, 626.3; found, 627.4.

[0683] Cpd. No. 201; ^{1}H NMR (400 MHz, MeOD) δ 8.66 (d, *J* = 5.4 Hz, 1H), 7.85 (s, 1H), 7.77 (t, *J* = 5.8 Hz, 2H), 7.75 (d, *J* = 5.4 Hz, 1H), 7.63 (d, *J* = 7.7 Hz, 1H), 7.48 (t, *J* = 7.3 Hz, 1H), 7.41 (t, *J* = 7.5 Hz, 1H), 7.34 (d, *J* = 7.6 Hz, 1H), 6.51 (d, *J* = 8.9 Hz, 2H), 4.45 (s, 2H), 4.20 (t, *J* = 8.0 Hz, 2H), 3.79 (s, 2H), 3.61 (s, 2H), 3.52 (d, *J* = 13.7 Hz, 2H), 3.45 (d, *J* = 6.6 Hz, 2H), 3.18 (s, 3H), 3.14 (d, *J* = 8.1 Hz, 1H), 3.06 (d, *J* = 12.2 Hz, 1H), 2.98 (d, *J* = 10.8 Hz, 1H), 2.66 (s, 3H), 2.19 – 2.16 (m, 2H), 2.09 – 2.06 (m, 5H), 1.96 (s, 2H), 1.69 (s, 7H). MS (ESI) m/z: $[M + H]^+$ calcd, 656.3; found, 657.4.

[0684] Cpd. No. 202; MS (ESI) m/z: $[M + H]^+$ calcd, 656.3; found, 657.5.

[0685] Cpd. No. 203; MS (ESI) m/z: $[M + H]^+$ calcd, 605.3; found, 606.5.

[0686] Cpd. No. 204; MS (ESI) m/z: $[M + H]^+$ calcd, 605.3; found, 606.5.

[0687] Cpd. No. 205; MS (ESI) m/z: $[M + H]^+$ calcd, 596.3; found, 597.6.

[0688] Cpd. No. 206; ^{1}H NMR (400 MHz, MeOD) δ 8.77 (d, *J* = 5.6 Hz, 2H), 7.84 (dd, *J* = 4.6, 1.6 Hz, 2H), 7.78 (d, *J* = 8.8 Hz, 2H), 7.58 (d, *J* = 7.7 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 1H), 7.38 (t, *J* = 7.5 Hz, 1H), 7.29 (d, *J* = 7.5 Hz, 1H), 6.53 (t, *J* = 12.2 Hz, 2H), 4.40 (s, 2H), 4.19 (t, *J* = 8.1 Hz, 2H), 3.81 – 3.73 (m, 2H), 3.55 (d, *J* = 11.8 Hz, 3H), 3.43 (d, *J* = 7.0 Hz, 2H), 3.37 (dd, *J* = 3.3, 1.7 Hz, 2H), 3.31 – 3.27 (m, 1H), 3.19 (d, *J* = 15.5 Hz, 3H), 3.03 – 2.92 (m, 2H), 2.89 (s, 1H), 2.14 (s, 3H), 1.80 (s, 2H), 1.77 (m,

5H), 1.73 – 1.62 (m, 3H), 1.31 (s, 1H). MS (ESI) m/z: $[M + H]^+$ calcd, 642.3; found, 643.4.

[0689] Cpd. No. 207; MS (ESI) m/z: $[M + H]^+$ calcd, 612.3; found, 613.5.

[0690] Cpd. No. 208; ^{1}H NMR (400 MHz, MeOD) δ 8.78 (s, 2H), 7.85 (d, *J* = 4.5 Hz, 2H), 7.77 (d, *J* = 8.5 Hz, 2H), 7.52 – 7.38 (m, 5H), 6.50 (d, *J* = 8.5 Hz, 2H), 4.16 (t, *J* = 7.7 Hz, 2H), 3.80 – 3.69 (m, 2H), 3.55 (s, 2H), 3.41 (d, *J* = 6.8 Hz, 2H), 3.18 (d, *J* = 10.2 Hz, 3H), 3.06 (d, *J* = 11.5 Hz, 2H), 2.98 – 2.85 (m, 1H), 2.39 (s, 1H), 2.27 (s, 2H), 2.05 (dd, *J* = 27.6, 8.6 Hz, 4H), 1.72 (dd, *J* = 30.5, 20.9 Hz, 6H), 1.64 (s, 1H), 1.53 (d, *J* = 11.5 Hz, 1H), 1.38 (d, *J* = 12.3 Hz, 2H). MS (ESI) m/z: $[M + H]^+$ calcd, 652.3; found, 653.4.

[0691] Cpd. No. 209; MS (ESI) m/z: $[M + H]^+$ calcd, 652.3; found, 653.4.

[0692] Cpd. No. 211; ^{1}H NMR (400 MHz, MeOD) δ 8.77 (d, *J* = 5.6 Hz, 2H), 7.83 (dd, *J* = 4.6, 1.5 Hz, 2H), 7.77 (d, *J* = 8.8 Hz, 2H), 7.52 – 7.40 (m, 5H), 6.51 (d, *J* = 8.9 Hz, 2H), 5.23 (d, *J* = 6.9 Hz, 1H), 4.17 (td, *J* = 8.1, 2.8 Hz, 2H), 3.79 – 3.70 (m, 2H), 3.55 (s, 2H), 3.41 (d, *J* = 7.1 Hz, 2H), 3.16 (ddd, *J* = 30.7, 19.7, 9.5 Hz, 4H), 2.93 (t, *J* = 11.6 Hz, 1H), 2.50 (t, *J* = 12.0 Hz, 1H), 2.29 (d, *J* = 14.0 Hz, 1H), 2.17 (d, *J* = 14.5 Hz, 1H), 2.08 – 1.93 (m, 1H), 1.80 (d, *J* = 16.2 Hz, 3H), 1.75 – 1.61 (m, 2H), 1.43 (dd, *J* = 23.1, 12.0 Hz, 2H), 1.34 – 1.19 (m, 1H). MS (ESI) m/z: $[M + H]^+$ calcd, 613.3; found, 614.6.

[0693] Cpd. No. 212; MS (ESI) m/z: $[M + H]^+$ calcd, 613.3; found, 614.6.

[0694] Cpd. No. 213; ^{1}H NMR (400 MHz, MeOD) δ 8.79 (s, 2H), 7.86 (d, *J* = 5.8 Hz, 2H), 7.82 – 7.74 (m, 2H), 7.44 (ddd, *J* = 22.4, 18.2, 7.1 Hz, 5H), 6.51 (d, *J* = 8.9 Hz, 2H), 4.17 (dd, *J* = 8.0, 6.1 Hz, 2H), 3.79 – 3.69 (m, 2H), 3.56 (dd, *J* = 23.5, 12.4 Hz, 2H), 3.42 (d, *J* = 7.0 Hz, 2H), 3.20 (dd, *J* = 20.0, 12.8 Hz, 2H), 3.12 – 2.93 (m, 5H), 2.43 (d, *J* = 11.8 Hz, 1H), 2.32 (d, *J* = 14.0 Hz, 1H), 2.21 (s, 1H), 1.99 (d, *J* = 13.6 Hz, 1H), 1.72 (d, *J* = 5.5 Hz, 5H), 1.54 (m, 3H), 1.03 (t, *J* = 7.1 Hz, 3H). MS (ESI) m/z: $[M + H]^+$ calcd, 641.3; found, 642.4.

[0695] Cpd. No. 214; MS (ESI) m/z: $[M + H]^+$ calcd, 641.3; found, 642.4.

[0696] Cpd. No. 216; MS (ESI) m/z: $[M + H]^+$ calcd, 627.3; found, 628.4.

[0697] Cpd. No. 217; MS (ESI) m/z: $[M + H]^+$ calcd, 717.3; found, 718.5.

[0698] Cpd. No. 218; MS (ESI) m/z: $[M + H]^+$ calcd, 717.3; found, 718.5.

[0699] Cpd. No. 219; MS (ESI) m/z: $[M + H]^+$ calcd, 643.3; found, 644.5.

[0700] Cpd. No. 220; MS (ESI) m/z: $[M + H]^+$ calcd, 641.3; found, 642.5.

[0701] Cpd. No. 221; ^{1}H NMR (400 MHz, MeOD) δ 8.77 (d, *J* = 6.0 Hz, 2H), 7.83 (dd, *J* = 4.6, 1.5 Hz, 2H), 7.78 (d, *J* = 8.8 Hz, 2H), 7.58 – 7.42 (m, 5H), 6.53 (d, *J* = 8.9 Hz, 2H), 4.18 (dd, *J* = 7.8, 5.5 Hz, 2H), 3.87 (s, 2H), 3.78 – 3.71 (m, 2H), 3.60 – 3.49 (m, 3H), 3.43 (d, *J* = 7.1 Hz, 2H), 3.20 (s, 1H), 3.12 – 3.00 (m, 3H), 2.44 (s, 2H), 2.33 – 2.17 (m, 3H), 1.98 – 1.9 (m, 2H), 1.60-1.80 (m, 5H), 1.30-1.49 (m, 3H). MS (ESI) m/z: $[M + H]^+$ calcd, 653.3; found, 654.4.

[0702] Cpd. No. 222; MS (ESI) m/z: $[M + H]^+$ calcd, 653.3; found, 654.4.

[0703] Cpd. No. 224; MS (ESI) m/z: $[M + H]^+$ calcd, 612.3; found, 613.5.

[0704] Cpd. No. 225; ^{1}H NMR (400 MHz, MeOD) δ 7.90 – 7.81 (m, 2H), 7.73 (d, *J* = 8.7 Hz, 2H), 7.59 – 7.38 (m, 8H), 6.57 – 6.39 (m, 2H), 4.14 (s, 2H), 3.70 (s, 2H), 3.54 (s, 2H), 3.39 (m, 3H), 3.23 – 2.98 (m, 3H), 2.89 (s, 1H), 2.74 (d, *J* = 15.0 Hz, 2H), 2.58 (s, 3H), 2.46 (m, 2H), 1.96 (s, 1H), 1.69 (m, 4H), 1.49 (d, *J* = 45.9 Hz, 1H), 1.31 (s, 1H). MS (ESI) m/z: $[M + H]^+$ calcd, 626.3; found, 627.4.

[0705] Cpd. No. 223; MS (ESI) m/z: $[M + H]^+$ calcd, 612.3; found, 613.5.

[0706] Cpd. No. 226; ^{1}H NMR (400 MHz, MeOD) δ 7.72 – 7.63 (m, 2H), 7.54 – 7.37 (m, 5H), 6.52 (t, *J* = 10.0 Hz, 2H), 4.18 (td, *J* = 7.9, 2.6 Hz, 2H), 3.79 – 3.68 (m, 2H), 3.57 (dd, *J* = 27.8, 11.5 Hz, 3H), 3.44 (t, *J* = 7.1 Hz, 2H), 3.25 – 3.15 (m, 1H), 3.11 (d, *J* = 36.0 Hz, 3H), 2.64 – 2.52 (m, 3H), 2.53 – 2.42 (m, 1H), 2.35 (d, *J* = 13.2 Hz, 1H), 2.22 (s, 1H), 1.99 (d, *J* = 14.3 Hz, 1H), 1.84 – 1.64 (m, 4H), 1.53 (dd, *J* = 35.4, 22.4 Hz, 3H), 1.29 – 1.21 (m, 1H), 1.21 – 1.12 (m, 2H), 1.12 – 1.04 (m, 1H),1.04 – 0.95 (m, 2H). MS (ESI) m/z: $[M + H]^+$ calcd, 590.3; found, 591.4.

[0707] Cpd. No. 227; MS (ESI) m/z: $[M + H]^+$ calcd, 590.3; found, 591.4.

[0708] Cpd. No. 228; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.7 Hz, 2H), 7.42 (t, *J* = 17.0 Hz, 6H), 6.34 (d, *J* = 8.6 Hz, 2H), 5.05 (s, 1H), 4.62 (s, 2H), 4.22 – 4.09 (m, 5H), 3.69 (s, 4H), 3.28 (s, 3H), 2.72 (d, *J* = 37.7 Hz, 6H), 2.37 (s, 1H), 2.17 (d, *J* = 13.0 Hz, 1H), 2.02 (s, 1H), 1.77 (s, 2H), 1.63 (s, 5H), 1.46 (s, 1H). MS (ESI) m/z: $[M + H]^+$ calcd, 708.2; found, 709.5.

[0709] Cpd. No. 229; MS (ESI) m/z: $[M + H]^+$ calcd, 708.2; found, 709.5.

[0710] Cpd. No. 230; ^{1}H NMR (400 MHz, MeOD) δ 7.82 – 7.69 (m, 2H), 7.55 – 7.38 (m, 6H), 6.79 (d, *J* = 2.0 Hz, 1H), 6.54 (dd, *J* = 19.9, 8.8 Hz, 2H), 4.26 – 4.08 (m, 2H), 3.95 (s, 3H), 3.80 – 3.70 (m, 2H), 3.56 (dd, *J* = 24.1, 12.0 Hz, 2H), 3.44 (d, *J* = 7.0 Hz,

2H), 3.33 (dt, *J* = 3.1, 1.5 Hz, 3H), 3.28 – 3.18 (m, 1H), 3.06 (d, *J* = 5.3 Hz, 3H), 2.55 (d, *J* = 19.7 Hz, 2H), 2.46 (t, *J* = 11.8 Hz, 1H), 2.33 (d, *J* = 14.2 Hz, 1H), 2.20 (s, 1H), 1.98 (d, *J* = 14.7 Hz, 1H), 1.83 – 1.65 (m, 4H), 1.65 – 1.40 (m, 3H). MS (ESI) m/z: $[M + H]^+$ calcd, 630.3; found, 631.4.

[0711] Cpd. No. 231; MS (ESI) m/z: $[M + H]^+$ calcd, 629.3; found, 630.5.

[0712] Cpd. No. 232; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.72 (s, 1H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.50-7.30 (m, 5H), 6.89 (d, *J* = 8.5 Hz, 2H), 5.07 (s, 1H), 4.72 (s, 1H), 4.06 (s, 2H), 3.74 (dd, *J* = 35.4, 10.5 Hz, 2H), 3.19 (s, 2H), 2.92 – 2.59 (m, 6H), 2.42 (s, 1H), 2.26 (s, 3H), 2.04 (s, 2H), 1.78 (s, 2H), 1.59 (d, *J* = 38.0 Hz, 4H), 1.49 – 1.20 (m, 1H). MS (ESI) m/z: $[M + H]^+$ calcd, 500.3; found, 501.4.

[0713] Cpd. No. 233; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.8 Hz, 2H), 7.54 – 7.26 (m, 5H), 6.99 (d, *J* = 8.7 Hz, 2H), 5.17 (s, 1H), 4.08 (t, *J* = 5.2 Hz, 2H), 3.59 (t, *J* = 12.2 Hz, 2H), 3.27 (d, *J* = 1.2 Hz, 1H), 3.20 (dd, *J* = 17.9, 10.3 Hz, 2H), 3.08 (d, *J* = 11.7 Hz, 2H), 2.92 – 2.78 (m, 1H), 2.68 (d, *J* = 15.1 Hz, 2H), 2.47 (dd, *J* = 23.7, 11.6 Hz, 1H), 2.24 (d, *J* = 14.5 Hz, 1H), 2.19 – 2.03 (m, 3H), 2.01 – 1.84 (m, 1H), 1.83 – 1.54 (m, 4H), 1.39 (d, *J* = 6.4 Hz, 2H), 1.24 (dd, *J* = 18.0, 8.9 Hz, 1H). MS (ESI) m/z: $[M + H]^+$ calcd, 500.3; found, 501.4.

[0714] Cpd. No. 234; MS (ESI) m/z: $[M + H]^+$ calcd, 640.3; found, 641.5.

[0715] Cpd. No. 235; MS (ESI) m/z: $[M + H]^+$ calcd, 640.3; found, 641.5.

[0716] Cpd. No. 236; MS (ESI) m/z: $[M + H]^+$ calcd, 681.3; found, 682.5.

[0717] Cpd. No. 237; MS (ESI) m/z: $[M + H]^+$ calcd, 681.3; found, 682.5.

[0718] Cpd. No. 238; ^{1}H NMR (400 MHz, MeOD) δ 8.82 (s, 1H), 8.11 (s, 1H), 7.77 – 7.71 (m, 3H), 7.68 (d, *J* = 7.4 Hz, 2H), 7.53 (dd, *J* = 14.7, 6.9 Hz, 3H), 7.43 (dd, *J* = 16.3, 8.8 Hz, 2H), 6.48 (d, *J* = 8.5 Hz, 2H), 4.15 (t, *J* = 6.8 Hz, 2H), 3.95 – 3.87 (m, 3H), 3.72 (s, 2H), 3.63 (d, *J* = 12.2 Hz, 1H), 3.41 (d, *J* = 21.1 Hz, 4H), 3.25 (d, *J* = 18.8 Hz, 2H), 3.13 – 3.01 (m, 1H), 2.94 (d, *J* = 11.6 Hz, 1H), 2.85 (s, 1H), 2.71 (d, *J* = 12.6 Hz, 3H), 2.55 (d, *J* = 15.8 Hz, 1H), 2.29 (d, *J* = 13.1 Hz, 1H), 1.99 (dd, *J* = 35.5, 16.1 Hz, 2H), 1.75 – 1.57 (m, 2H), 1.57 – 1.36 (m, 4H), 1.12 (s, 1H), 0.90 (d, *J* = 12.6 Hz, 1H). MS (ESI) m/z: $[M + H]^+$ calcd, 685.3; found, 686.4.

[0719] Cpd. No. 239; MS (ESI) m/z: $[M + H]^+$ calcd, 685.3; found, 686.4.

[0720] Cpd. No. 240; ^{1}H NMR (400 MHz, MeOD) δ 8.11 (s, 1H), 7.72 (d, *J* = 7.0 Hz, 2H), 7.66 (d, *J* = 8.2 Hz, 1H), 7.56 – 7.32 (m, 5H), 6.70 (d, *J* = 8.4 Hz, 1H), 6.47 (d, *J* =

8.2 Hz, 1H), 5.22 (s, 1H), 4.13 (t, J = 7.7 Hz, 1H), 3.98 – 3.84 (m, 3H), 3.70 (dd, J = 12.7, 5.5 Hz, 2H), 3.63 – 3.51 (m, 2H), 3.42 (d, J = 6.9 Hz, 1H), 3.24 – 3.06 (m, 4H), 2.98 – 2.84 (m, 1H), 2.79 – 2.68 (m, 3H), 2.50 (s, 1H), 2.28 (d, J = 14.7 Hz, 2H), 2.12 (d, J = 14.7 Hz, 1H), 1.97 (d, J = 7.4 Hz, 1H), 1.77 (d, J = 14.4 Hz, 2H), 1.66 (s, 2H), 1.46 (d, J = 12.0 Hz, 2H), 1.33 – 1.19 (m, 1H). MS (ESI) m/z: $[M + H]^+$ calcd, 630.3; found, 631.5.

[0721] Cpd. No. 241; MS (ESI) m/z: $[M + H]^+$ calcd, 630.3; found, 631.5.

[0722] Cpd. No. 355; MS (ESI) m/z: $[M + H]^+$ calcd, 609.3; found, 610.5.

[0723] Cpd. No. 356; MS (ESI) m/z: $[M + H]^+$ calcd, 609.3; found, 610.5.

[0724] Cpd. No. 357; MS (ESI) m/z: $[M + H]^+$ calcd, 613.3; found, 614.5.

[0725] Cpd. No. 358; MS (ESI) m/z: $[M + H]^+$ calcd, 680.3; found, 681.4.

[0726] Cpd. No. 359; MS (ESI) m/z: $[M + H]^+$ calcd, 680.3; found, 681.4.

[0727] Cpd. No. 360; MS (ESI) m/z: $[M + H]^+$ calcd, 684.4; found, 685.5.

[0728] Cpd. No. 361; MS (ESI) m/z: $[M + H]^+$ calcd, 684.4; found, 685.5.

[0729] Cpd. No. 362; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (s, 1H), 8.07 (d, J = 8.3 Hz, 2H), 7.89 (d, J = 8.3 Hz, 2H), 7.68 (d, J = 8.7 Hz, 2H), 7.61 (s, 2H), 7.50 – 7.40 (m, 3H), 7.35 (dd, J = 15.3, 8.6 Hz, 2H), 6.41 (d, J = 8.2 Hz, 2H), 4.09 (s, 2H), 3.66 (s, 2H), 3.56 (s, 1H), 3.35 (s, 4H), 3.16 (s, 1H), 3.04 – 2.72 (m, 3H), 2.63 (d, J = 9.3 Hz, 3H), 2.45 (s, 1H), 2.22 (s, 1H), 1.93 (s, 2H), 1.55 (s, 2H), 1.43 (s, 3H), 1.34 – 1.22 (m, 1H), 1.04 (s, 1H), 0.85 (s, 1H). MS (ESI) m/z: $[M + H]^+$ calcd, 725.3; found, 726.5.

[0730] Cpd. No. 363; MS (ESI) m/z: $[M + H]^+$ calcd, 725.3; found, 726.5.

[0731] Cpd. No. 364; MS (ESI) m/z: $[M + H]^+$ calcd, 511.3; found, 512.5.

[0732] Cpd. No. 365; MS (ESI) m/z: $[M + H]^+$ calcd, 566.3; found, 567.5.

[0733] Cpd. No. 367; MS (ESI) m/z: $[M + H]^+$ calcd, 554.3; found, 555.5.

[0734] Cpd. No. 368; MS (ESI) m/z: $[M + H]^+$ calcd, 554.3; found, 555.5.

[0735] Cpd. No. 369; MS (ESI) m/z: $[M + H]^+$ calcd, 648.3; found, 649.5.

[0736] Cpd. No. 370; MS (ESI) m/z: $[M + H]^+$ calcd, 648.3; found, 649.5.

[0737] Cpd. No. 371; MS (ESI) m/z: $[M + H]^+$ calcd, 644.3; found, 645.5.

[0738] Cpd. No. 372; MS (ESI) m/z: $[M + H]^+$ calcd, 644.3; found, 645.5.

[0739] Cpd. No. 373; MS (ESI) m/z: $[M + H]^+$ calcd, 544.3; found, 545.5.

[0740] Cpd. No. 374; MS (ESI) m/z: $[M + H]^+$ calcd, 544.3; found, 545.5.

[0741] Cpd. No. 27; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.4 Hz, 2H), 7.36-7.29 (m, 2H), 7.23-7.15 (m, 2H), 6.90 (d, *J* = 8.5 Hz, 2H), 4.10 (s, 2H), 3.84-3.71 (m, 1H), 3.67-3.52 (m, 2H), 3.49-3.36 (m, 1H), 3.27-2.93 (m, 4H), 2.90-2.72 (m, 3H), 2.58-2.43 (m, 1H), 2.36-2.17 (m, 4H), 2.06-1.84 (m, 2H), 1.77-1.45 (m, 4H), 1.37-1.12 (m, 2H). MS (ESI) m/z 444.3 $[M+H]^+$.

[0742] Cpd. No. 72; ^{1}H NMR (400 MHz, DMSO) δ 7.43-7.38 (m, 1H), 7.34-7.26 (m, 3H), 3.49-3.41 (m, 1H), 3.30 (t, *J* = 11.6 Hz, 3H), 3.00 (t, *J* = 5.9 Hz, 2H), 2.96-2.89 (m, 1H), 2.86-2.74 (m, 2H), 2.41-2.30 (m, 1H), 1.98 (d, *J* = 13.1 Hz, 1H), 1.89-1.79 (m, 1H), 1.70-1.39 (m, 7H), 1.35-1.18 (m, 3H). MS (ESI) m/z 285.2 $[M+H]^+$.

[0743] Cpd. No. 242; MS (ESI) m/z 432.3 $[M+H]^+$.

[0744] Cpd. No. 73; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.29 (m, 2H), 7.24-7.17 (m, 2H), 3.72 (d, *J* = 10.7 Hz, 1H), 3.62-3.53 (m, 2H), 3.47-3.39 (m, 3H), 3.15-2.93 (m, 4H), 2.90 -2.63 (m, 3H), 2.51-2.39 (m, 1H), 2.35-2.17 (m, 2H), 2.06-1.87 (m, 4H), 1.78-1.45 (m, 6H), 1.37-1.24 (m, 1H), 1.23-1.08 (m, 1H). MS (ESI) m/z 357.3 $[M+H]^+$.

[0745] Cpd. No. 74; ^{1}H NMR (400 MHz, DMSO) δ 7.44-7.39 (m, 1H), 7.37-7.25 (m, 3H), 4.06 (s, 2H), 3.54-3.44 (m, 3H), 3.33 (t, *J* = 6.8 Hz, 4H), 3.29-3.18 (m, 1H), 3.07-2.97 (m, 2H), 2.96-2.86 (m, 2H), 2.27-2.15 (m, 1H), 2.05-1.95 (m, 1H), 1.93-1.84 (m, 5H), 1.83-1.75 (m, 2H), 1.69-1.52 (m, 3H), 1.49-1.33 (m, 4H), 1.30-1.15 (m, 2H). MS (ESI) m/z 396.2 $[M+H]^+$.

[0746] Cpd. No. 75; MS (ESI) m/z 299.2 $[M+H]^+$.

[0747] Cpd. No. 76; MS (ESI) m/z 419.3 $[M+H]^+$.

[0748] Cpd. No. 243; MS (ESI) m/z 466.2 $[M+H]^+$.

[0749] Cpd. No. 244; MS (ESI) m/z 492.3 $[M+H]^+$.

[0750] Cpd. No. 245; MS (ESI) m/z 446.3 $[M+H]^+$.

[0751] Cpd. No. 246; ^{1}H NMR (400 MHz, DMSO) δ 7.78 (d, *J* = 8.5 Hz, 2H), 7.52-7.38 (m, 6H), 7.36 (d, *J* = 8.2 Hz, 1H), 7.29 (d, *J* = 7.5 Hz, 2H), 7.09 (d, *J* = 8.6 Hz, 2H), 4.14 (t, *J* = 5.9 Hz, 2H), 3.58 (t, *J* = 8.6 Hz, 2H), 3.49-3.36 (m, 1H), 3.25-3.03 (m, 5H), 3.00-2.86 (m, 2H), 2.79- 2.68 (m, 1H), 2.18- 2.06 (m, 2H), 1.99- 1.83 (m, 2H), 1.73 (d, *J* = 14.5 Hz, 1H), 1.62- 1.49 (m, 1H). MS (ESI) m/z 452.2 $[M+H]^+$.

[0752] Cpd. No. 77; ^{1}H NMR (400 MHz, MeOD) δ 7.79-7.71 (m, 4H), 7.61 (d, *J* = 8.8 Hz, 2H), 7.47 (d, *J* = 7.0 Hz, 1H), 7.38-7.33 (m, 2H), 7.33-7.27 (m, 1H), 7.13 (d, *J* =

8.9 Hz, 2H), 3.95 (d, *J* = 12.1 Hz, 1H), 3.83 (d, *J* = 12.7 Hz, 1H), 3.56-3.46 (m, 2H), 3.11-3.06 (m, 2H), 2.99-2.91 (m, 1H), 2.90-2.82 (m, 1H), 2.80-2.70 (m, 1H), 2.51 (t, *J* = 11.8 Hz, 1H), 2.14 (d, *J* = 12.5 Hz, 1H), 1.99-1.90 (m, 1H), 1.89-1.82 (m, 1H), 1.70-1.55 (m, 7H), 1.36-1.28 (m, 1H), 1.21-1.10 (m, 1H). MS (ESI) m/z 462.3 $[M+H]^+$.

[0753] Cpd. No. 247; ^{1}H NMR (400 MHz, DMSO) δ 7.79 (d, *J* = 8.2 Hz, 2H), 7.41-7.28 (m, 4H), 7.10 (d, *J* = 8.4 Hz, 2H), 4.15 (t, *J* = 5.8 Hz, 2H), 3.62 (d, *J* = 11.8 Hz, 1H), 3.55-3.43 (m, 2H), 3.30-3.08 (m, 5H), 3.06-2.86 (m, 3H), 2.66-2.54 (m, 1H), 2.19-2.08 (m, 2H), 2.00-1.65 (m, 7H), 1.59-1.40 (m, 3H). MS (ESI) m/z 430.3 $[M+H]^+$.

[0754] Cpd. No. 78; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (d, *J* = 5.2 Hz, 2H), 7.91 (d, *J* = 5.4 Hz, 2H), 7.50-7.41 (m, 2H), 7.41-7.36 (m, 1H), 7.35-7.30 (m, 1H), 3.72-3.62 (m, 1H), 3.38-3.25 (m, 1H), 3.20-3.04 (m, 2H), 2.87 (d, *J* = 16.7 Hz, 1H), 1.88-1.71 (m, 3H), 1.70-1.57 (m, 4H), 1.56-1.45 (m, 1H). MS (ESI) m/z 279.2 $[M+H]^+$.

[0755] Cpd. No. 79; MS (ESI) m/z 442.3 $[M+H]^+$.

[0756] Cpd. No. 80; MS (ESI) m/z 467.3 $[M+H]^+$.

[0757] Cpd. No. 81; MS (ESI) m/z 467.3 $[M+H]^+$.

[0758] Cpd. No. 248; MS (ESI) m/z 524.3 $[M+H]^+$.

[0759] Cpd. No. 28; MS (ESI) m/z 458.3 $[M+H]^+$.

[0760] Cpd. No. 249; ^{1}H NMR (400 MHz, MeOD) δ 7.65 (d, *J* = 8.9 Hz, 2H), 7.48-7.27 (m, 4H), 7.05 (d, *J* = 8.9 Hz, 2H), 4.14 (t, *J* = 5.8 Hz, 2H), 3.70 (d, *J* = 11.3 Hz, 1H), 3.65-3.55 (m, 2H), 3.38-3.32 (m, 1H), 3.29-3.22 (m, 2H), 3.14-3.05 (m, 3H), 3.04-2.96 (m, 1H), 2.59 (t, *J* = 11.6 Hz, 1H), 2.25-2.16 (m, 3H), 2.09 (d, *J* = 14.1 Hz, 2H), 2.02-1.91 (m, 1H), 1.90-1.79 (m, 1H), 1.54-1.42 (m, 1H), 1.39-1.32 (m, 2H), 1.24-1.17 (m, 1H), 1.13 (t, *J* = 7.4 Hz, 3H), 0.92 (t, *J* = 7.4 Hz, 3H). MS (ESI) m/z 446.3 $[M+H]^+$.

[0761] Cpd. No. 250; ^{1}H NMR (400 MHz, MeOD) δ 7.68 (d, *J* = 8.2 Hz, 2H), 7.44-7.31 (m, 4H), 7.09 (d, *J* = 8.2 Hz, 2H), 4.20 (t, *J* = 5.7 Hz, 2H), 3.79 (d, *J* = 12.5 Hz, 1H), 3.72-3.63 (m, 2H), 3.50-3.40 (m, 1H), 3.16-3.11 (m, 2H), 3.10-2.93 (m, 2H), 2.51 (t, *J* = 11.6 Hz, 1H), 2.34-2.16 (m, 6H), 2.06-1.88 (m, 3H), 1.63-1.52 (m, 2H), 1.36-1.23 (m, 1H), 1.12-0.99 (m, 1H), 0.96-0.88 (m, 6H). MS (ESI) m/z 446.3 $[M+H]^+$.

[0762] Cpd. No. 251; ^{1}H NMR (400 MHz, MeOD) δ 7.65 (d, *J* = 8.8 Hz, 2H), 7.40-7.27 (m, 4H), 7.06 (d, *J* = 8.8 Hz, 2H), 4.18 (t, *J* = 5.7 Hz, 2H), 3.81-3.59 (m, 3H), 3.44-3.33 (m, 1H), 3.28-3.24 (m, 1H), 3.18-3.12 (m, 2H), 3.05-2.91 (m, 2H), 2.42 (d, *J*

= 12.9 Hz, 1H), 2.30-2.23 (m, 2H), 2.21-2.14 (m, 2H), 2.10-2.02 (m, 1H), 1.99-1.82 (m, 2H), 1.66 (t, *J* = 13.3 Hz, 2H), 1.60-1.48 (m, 3H), 1.45-1.34 (m, 1H), 1.31-1.20 (m, 3H), 1.16-0.99 (m, 3H), 0.87-0.74 (m, 1H). MS (ESI) m/z 472.3 $[M+H]^+$.

[0763] Cpd. No. 252; ^{1}H NMR (400 MHz, MeOD) δ 7.66 (d, *J* = 8.4 Hz, 2H), 7.43-7.26 (m, 4H), 7.07 (d, *J* = 8.5 Hz, 2H), 4.18 (t, *J* = 5.7 Hz, 2H), 3.80 (d, *J* = 11.8 Hz, 1H), 3.72-3.60 (m, 2H), 3.48-3.38 (m, 2H), 3.18-3.12 (m, 2H), 3.09-2.92 (m, 2H), 2.55 (t, *J* = 11.9 Hz, 1H), 2.31-2.15 (m, 4H), 2.09-2.02 (m, 1H), 1.99-1.86 (m, 2H), 1.56-1.43 (m, 2H), 1.37-1.24 (m, 3H), 1.23-1.13 (m, 1H), 1.12-1.01 (m, 1H), 0.81 (t, *J* = 7.3 Hz, 3H), 0.71 (t, *J* = 7.3 Hz, 3H). MS (ESI) m/z 460.3 $[M+H]^+$.

[0764] Cpd. No. 82; MS (ESI) m/z 444.3 $[M+H]^+$.

[0765] Cpd. No. 83; ^{1}H NMR (400 MHz, MeOD, a mixture of rotamers) δ 7.61-7.55 (m, 2H), 7.46 (d, *J* = 7.0 Hz, 1H), 7.42-7.30 (m, 4H), 4.79 (s, 1.2H) and 4.66 (s, 0.8H), 4.28 (s, 2H), 3.83 (t, *J* = 5.9 Hz, 1H), 3.74-3.56 (m, 4H), 3.51-3.37 (m, 2H), 3.17-3.08 (m, 3H), 3.01 (t, *J* = 5.7 Hz, 1H), 2.94-2.90 (m, 1H), 2.90-2.83 (m, 1H), 2.60-2.46 (m, 1H), 2.22 (d, *J* = 14.0 Hz, 1H), 2.05-1.90 (m, 3H), 1.79-1.61 (m, 5H), 1.60-1.52 (m, 1H), 1.44-1.27 (m, 2H). MS (ESI) m/z 483.3 $[M+H]^+$.

[0766] Cpd. No. 84; ^{1}H NMR (400 MHz, MeOD) δ 8.09 (d, *J* = 7.7 Hz, 1H), 7.63-7.57 (m, 1H), 7.49-7.43 (m, 2H), 7.40-7.30 (m, 4H), 4.74 (s, 1H), 4.17-4.12 (m, 1H), 4.02 (s, 1H), 3.77-3.67 (m, 2H), 3.64-3.55 (m, 1H), 3.53-3.43 (m, 2H), 3.22-3.14 (m, 2H), 3.14-3.05 (m, 3H), 3.01-2.94 (m, 1H), 2.90-2.82 (m, 1H), 2.64-2.53 (m, 1H), 2.28-2.17 (m, 1H), 2.06-1.87 (m, 4H), 1.79-1.61 (m, 6H), 1.59-1.52 (m, 1H), 1.47-1.38 (m, 1H), 1.35-1.24 (m, 1H). MS (ESI) m/z 458.3 $[M+H]^+$.

[0767] Cpd. No. 85; MS (ESI) m/z 548.3 $[M+H]^+$.

[0768] Cpd. No. 86; ^{1}H NMR (400 MHz, MeOD) δ 7.63 (d, *J* = 8.8 Hz, 2H), 7.46-7.41 (m, 1H), 7.40-7.34 (m, 2H), 7.34-7.29 (m, 1H), 6.51 (d, *J* = 8.8 Hz, 2H), 4.18 (t, *J* = 8.0 Hz, 2H), 3.81-3.74 (m, 2H), 3.65 (d, *J* = 12.6 Hz, 1H), 3.59-3.42 (m, 6H), 3.21 (d, *J* = 7.2 Hz, 2H), 3.13-3.00 (m, 3H), 2.85-2.70 (m, 1H), 2.69-2.54 (m, 2H), 2.25 (d, *J* = 14.5 Hz, 1H), 2.02-1.92 (m, 4H), 1.92-1.83 (m, 2H), 1.82-1.71 (m, 6H), 1.69-1.56 (m, 4H), 1.55-1.45 (m, 1H), 1.30-1.14 (m, 1H). MS (ESI) m/z 562.3 $[M+H]^+$.

[0769] Cpd. No. 87; MS (ESI) m/z 550.3 $[M+H]^+$.

[0770] Cpd. No. 88; ^{1}H NMR (400 MHz, MeOD) δ 7.57 (d, *J* = 8.8 Hz, 2H), 7.47-7.42 (m, 1H), 7.40-7.35 (m, 2H), 7.34-7.29 (m, 1H), 6.52 (d, *J* = 8.9 Hz, 2H), 4.17 (t, *J* = 8.0

Hz, 2H), 3.79-3.73 (m, 2H), 3.65 (d, *J* = 11.3 Hz, 1H), 3.60-3.43 (m, 5H), 3.28-3.21 (m, 1H), 3.15-3.00 (m, 4H), 2.81-2.75 (m, 1H), 2.69-2.64 (m, 1H), 2.61 (s, 6H), 2.25 (d, *J* = 14.1 Hz, 1H), 2.04-1.91 (m, 2H), 1.85-1.73 (m, 3H), 1.72-1.56 (m, 4H), 1.54-1.44 (m, 1H), 1.27-1.14 (m, 1H). MS (ESI) m/z 537.3 $[M+H]^+$.

[0771] Cpd. No. 89; ^{1}H NMR (400 MHz, MeOD) δ 7.82 (d, *J* = 8.9 Hz, 2H), 7.47-7.41 (m, 1H), 7.39-7.35 (m, 2H), 7.34-7.29 (m, 1H), 7.05 (d, *J* = 8.9 Hz, 2H), 4.74-4.64 (m, 1H), 3.65-3.52 (m, 3H), 3.50-3.40 (m, 2H), 3.14-3.07 (m, 2H), 3.06-2.99 (m, 2H), 2.96-2.86 (m, 2H), 2.85-2.76 (m, 1H), 2.65-2.56 (m, 2H), 2.47-2.35 (m, 2H), 2.25 (d, *J* = 13.9 Hz, 1H), 2.00-1.84 (m, 3H), 1.78-1.54 (m, 6H), 1.50-1.39 (m, 1H), 1.32-1.23 (m, 1H), 1.22-1.16 (m, 2H), 1.06-0.99 (m, 2H). MS (ESI) m/z 535.3 $[M+H]^+$.

[0772] Cpd. No. 90; MS (ESI) m/z 535.3 $[M+H]^+$.

[0773] Cpd. No. 91; ^{1}H NMR (400 MHz, MeOD) δ 7.66 (d, *J* = 7.6 Hz, 2H), 7.44 (d, *J* = 6.6 Hz, 1H), 7.41-7.35 (m, 2H), 7.32 (t, *J* = 5.2 Hz, 1H), 6.51 (d, *J* = 7.8 Hz, 2H), 4.22-4.11 (m, 2H), 3.77 (t, *J* = 6.6 Hz, 2H), 3.64 (d, *J* = 11.4 Hz, 1H), 3.60-3.43 (m, 5H), 3.29-3.21 (m, 1H), 3.16 (d, *J* = 6.7 Hz, 2H), 3.12-3.01 (m, 4H), 2.82-2.73 (m, 1H), 2.65 (t, *J* = 12.1 Hz, 1H), 2.25 (d, *J* = 14.0 Hz, 1H), 2.16-2.07 (m, 1H), 2.04-1.90 (m, 3H), 1.86-1.75 (m, 6H), 1.71-1.56 (m, 6H), 1.56-1.44 (m, 4H), 1.30-1.15 (m, 3H). MS (ESI) m/z 576.3 $[M+H]^+$.

[0774] Cpd. No. 92; ^{1}H NMR (400 MHz, MeOD) δ 7.61 (d, *J* = 7.4 Hz, 2H), 7.45 (d, *J* = 6.5 Hz, 1H), 7.41-7.29 (m, 3H), 6.52 (d, *J* = 7.6 Hz, 2H), 4.19 (t, *J* = 8.0 Hz, 2H), 3.78 (t, *J* = 6.7 Hz, 2H), 3.65 (d, *J* = 11.9 Hz, 1H), 3.60-3.44 (m, 5H), 3.29-3.22 (m, 1H), 3.16-3.01 (m, 4H), 2.98-2.87 (m, 1H), 2.84-2.73 (m, 1H), 2.70-2.58 (m, 1H), 2.25 (d, *J* = 14.8 Hz, 1H), 2.06-1.91 (m, 4H), 1.89-1.73 (m, 5H), 1.72-1.60 (m, 4H), 1.58-1.43 (m, 2H), 1.38-1.19 (m, 5H), 1.19-1.05 (m, 1H). MS (ESI) m/z 576.4 $[M+H]^+$.

[0775] Cpd. No. 93; ^{1}H NMR (400 MHz, MeOD) δ 7.66 (d, *J* = 7.3 Hz, 2H), 7.45 (d, *J* = 7.1 Hz, 1H), 7.40-7.29 (m, 3H), 6.52 (d, *J* = 7.4 Hz, 4H), 4.18 (t, *J* = 7.9 Hz, 2H), 3.84-3.74 (m, 2H), 3.64 (d, *J* = 12.1 Hz, 1H), 3.59-3.42 (m, 5H), 3.29-3.19 (m, 1H), 3.15-3.04 (m, 3H), 3.00 (d, *J* = 4.8 Hz, 2H), 2.84-2.73 (m, 1H), 2.65 (t, *J* = 11.9 Hz, 1H), 2.26 (d, *J* = 13.8 Hz, 1H), 2.07-1.92 (m, 2H), 1.87-1.73 (m, 6H), 1.72-1.56 (m, 7H), 1.55-1.40 (m, 2H), 1.31-1.14 (m, 4H), 1.11-0.98 (m, 2H). MS (ESI) m/z 590.3 $[M+H]^+$.

[0776] Cpd. No. 94; MS (ESI) m/z 576.3 $[M+H]^+$.

[0777] Cpd. No. 95; MS (ESI) m/z 576.3 $[M+H]^+$.

[0778] Cpd. No. 96; MS (ESI) m/z 576.3 $[M+H]^+$.

[0779] Cpd. No. 97; ^{1}H NMR (400 MHz, MeOD) δ 7.64 (d, *J* = 5.4 Hz, 2H), 7.48-7.41 (m, 1H), 7.41--7.30 (m, 3H), 6.54 (d, *J* = 8.8 Hz, 2H), 4.21 (t, *J* = 8.0 Hz, 2H), 4.03-3.93 (m, 2H), 3.82-3.75 (m, 2H), 3.68-3.49 (m, 4H), 3.46 (d, *J* = 6.8 Hz, 2H), 3.39-3.34 (m, 2H), 3.28-3.19 (m, 2H), 3.14-2.99 (m, 4H), 2.85-2.74 (m, 1H), 2.66-2.55 (m, 1H), 2.24 (d, *J* = 14.3 Hz, 1H), 2.00-1.92 (m, 2H), 1.85-1.72 (m, 5H), 1.70-1.54 (m, 7H), 1.51-1.40 (m, 1H), 1.33-1.16 (m, 1H). MS (ESI) m/z 578.3 $[M+H]^+$.

[0780] Cpd. No. 98; ^{1}H NMR (400 MHz, MeOD) δ 7.65 (d, *J* = 8.8 Hz, 2H), 7.47-7.42 (m, 1H), 7.40-7.34 (m, 2H), 7.34-7.29 (m, 1H), 6.88 (s, 1H), 6.84 (dd, *J* = 4.0, 1.8 Hz, 1H), 6.48 (d, *J* = 8.7 Hz, 2H), 6.13 (dd, *J* = 3.9, 2.7 Hz, 1H), 4.17 (t, *J* = 7.8 Hz, 2H), 3.75 (t, *J* = 6.0 Hz, 2H), 3.65 (s, 3H), 3.63-3.47 (m, 4H), 3.44 (d, *J* = 6.6 Hz, 2H), 3.28-3.19 (m, 1H), 3.15-2.96 (m, 4H), 2.85-2.71 (m, 1H), 2.68-2.54 (m, 1H), 2.24 (d, *J* = 13.5 Hz, 1H), 2.02-1.90 (m, 2H), 1.87-1.40 (m, 8H), 1.31-1.12 (m, 1H). MS (ESI) m/z 573.3 $[M+H]^+$.

[0781] Cpd. No. 99; MS (ESI) m/z 541.3 $[M+H]^+$.

[0782] Cpd. No. 100; ^{1}H NMR (400 MHz, MeOD) δ 7.88-7.74 (m, 2H), 7.57-7.21 (m, 7H), 7.16-6.97 (m, 2H), 4.73 (s, 2H), 4.00 (s, 2H), 3.86-3.71 (m, 2H), 3.49-3.41 (m, 1H), 3.28-3.11 (m, 3H), 2.90-2.74 (m, 3H), 2.69-2.58 (m, 1H), 2.00-1.87 (m, 1H), 1.81-1.60 (m, 5H), 1.57-1.45 (m, 2H), 1.25-1.16 (m, 2H), 1.08-1.00 (m, 2H). MS (ESI) m/z 555.2 $[M+H]^+$.

[0783] Cpd. No. 253; ^{1}H NMR (400 MHz, MeOD) δ 9.09 (d, *J* = 5.2 Hz, 2H), 8.59-8.45 (m, 2H), 7.93-7.77 (m, 2H), 7.64-7.36 (m, 5H), 7.06-6.82 (m, 2H), 4.61-4.16 (m, 2H), 3.93-3.59 (m, 4H), 3.56-3.36 (m, 2H), 3.27-2.97 (m, 4H), 2.81-2.72 (m, 3H), 2.70-2.56 (m, 1H), 2.52-2.32 (m, 1H), 2.28-2.01 (m, 2H), 2.00-1.52 (m, 9H), 1.51-1.36 (m, 1H). MS (ESI) m/z 663.2 $[M+H]^+$.

[0784] Cpd. No. 254; ^{1}H NMR (400 MHz, MeOD) δ 9.10 (d, *J* = 5.3 Hz, 2H), 8.52 (d, *J* = 5.5 Hz, 2H), 7.81 (d, *J* = 8.8 Hz, 2H), 7.57-7.36 (m, 5H), 6.89 (d, *J* = 8.9 Hz, 2H), 4.75 (dd, *J* = 34.7, 11.9 Hz, 2H), 4.59-4.25 (m, 2H), 3.75-3.59 (m, 4H), 3.46-3.35 (m, 2H), 3.25-3.09 (m, 3H), 3.10-2.98 (m, 3H), 2.88-2.55 (m, 3H), 2.31-2.20 (m, 1H), 2.00-1.80 (m, 3H), 1.77-1.62 (m, 3H), 1.59-1.40 (m, 3H), 1.32-1.12 (m, 1H). MS (ESI) m/z 663.2 $[M+H]^+$.

[0785] Cpd. No. 255; ^{1}H NMR (400 MHz, MeOD) δ 8.79 (s, 2H), 7.85 (d, *J* = 4.4 Hz, 2H), 7.80-7.76 (m, 2H), 7.60 (d, *J* = 7.3 Hz, 2H), 7.54 (t, *J* = 7.3 Hz, 2H), 7.50-7.42 (m, 1H), 6.55-6.49 (m, 2H), 4.17 (t, *J* = 8.1 Hz, 2H), 3.79-3.70 (m, 2H), 3.55 (t, *J* = 11.6 Hz, 2H), 3.42 (d, *J* = 6.9 Hz, 2H), 3.26-3.16 (m, 1H), 3.07 (dd, *J* = 25.3, 12.3 Hz, 2H), 2.94-2.80 (m, 2H), 2.63 (d, *J* = 14.3 Hz, 1H), 2.50-2.43 (m, 1H), 2.42 (s, 3H), 2.31-2.06 (m, 4H), 1.94-1.58 (m, 6H), 1.39-1.22 (m, 1H). MS (ESI) m/z 647.3 $[M+H]^+$.

[0786] Cpd. No. 256; ^{1}H NMR (400 MHz, MeOD) δ 8.78 (d, *J* = 4.4 Hz, 2H), 7.84 (d, *J* = 4.7 Hz, 2H), 7.78 (d, *J* = 8.6 Hz, 2H), 7.57-7.38 (m, 5H), 6.53 (d, *J* = 8.7 Hz, 2H), 4.19 (t, *J* = 7.0 Hz, 2H), 3.81-3.73 (m, 2H), 3.63 (d, *J* = 10.7 Hz, 1H), 3.53-3.43 (m, 4H), 3.39-3.35 (m, 1H), 3.26-3.18 (m, 1H), 3.17-3.09 (m, 1H), 3.05 (s, 3H), 3.01 (d, *J* = 10.6 Hz, 1H), 2.92-2.85 (m, 1H), 2.69-2.54 (m, 2H), 2.38 (d, *J* = 14.5 Hz, 1H), 2.01 (d, *J* = 14.8 Hz, 1H), 1.94-1.79 (m, 2H), 1.77-1.53 (m, 4H), 1.49-1.29 (m, 2H). MS (ESI) m/z 647.3 $[M+H]^+$.

[0787] Cpd. No. 257; ^{1}H NMR (400 MHz, MeOD) δ 8.77 (d, *J* = 6.0 Hz, 2H), 7.83 (d, *J* = 6.1 Hz, 2H), 7.78 (d, *J* = 8.9 Hz, 2H), 7.55 (d, *J* = 7.3 Hz, 2H), 7.49 (t, *J* = 7.6 Hz, 2H), 7.45-7.39 (m, 1H), 6.52 (d, *J* = 8.9 Hz, 2H), 4.18 (t, *J* = 7.8 Hz, 2H), 3.77-3.70 (m, 2H), 3.54 (d, *J* = 11.6 Hz, 2H), 3.41 (d, *J* = 7.1 Hz, 2H), 3.23-3.13 (m, 2H), 3.12-3.00 (m, 3H), 2.69 (dd, *J* = 13.2, 8.2 Hz, 1H), 2.43 (t, *J* = 12.3 Hz, 1H), 2.29 (d, *J* = 14.3 Hz, 1H), 2.19-2.06 (m, 2H), 1.95-1.87 (m, 1H), 1.84-1.75 (m, 1H), 1.74-1.53 (m, 5H), 1.40-1.20 (m, 2H). MS (ESI) m/z 585.3 $[M+H]^+$.

[0788] Cpd. No. 258; ^{1}H NMR (400 MHz, MeOD) δ 8.75 (d, *J* = 4.9 Hz, 2H), 7.81 (d, *J* = 4.6 Hz, 2H), 7.76 (d, *J* = 7.4 Hz, 2H), 7.52-7.34 (m, 5H), 6.51 (d, *J* = 7.4 Hz, 2H), 4.16 (t, *J* = 8.4 Hz, 2H), 3.80-3.69 (m, 2H), 3.59 (d, *J* = 6.0 Hz, 2H), 3.57-3.45 (m, 3H), 3.40 (d, *J* = 6.7 Hz, 2H), 3.23-3.15 (m, 1H), 3.15-3.04 (m, 1H), 3.01-2.91 (m, 1H), 2.86-2.77 (m, 1H), 2.56-2.47 (m, 1H), 2.35 (d, *J* = 13.5 Hz, 1H), 2.30-2.21 (m, 1H), 2.16 (d, *J* = 13.0 Hz, 1H), 1.86-1.75 (m, 1H), 1.71-1.43 (m, 6H), 1.40-1.24 (m, 3H). MS (ESI) m/z 585.3 $[M+H]^+$.

[0789] Cpd. No. 259; MS (ESI) m/z 615.3 $[M+H]^+$.

[0790] Cpd. No. 260; MS (ESI) m/z 615.2 $[M+H]^+$.

[0791] Cpd. No. 261; ^{1}H NMR (400 MHz, MeOD) δ 7.68 (d, *J* = 7.4 Hz, 2H), 7.55 (d, *J* = 7.2 Hz, 2H), 7.50 (t, *J* = 7.4 Hz, 2H), 7.45 (d, *J* = 7.0 Hz, 1H), 6.54 (d, *J* = 7.5 Hz, 2H), 4.18 (t, *J* = 8.0 Hz, 2H), 3.77-3.71 (m, 2H), 3.63-3.53 (m, 4H), 3.44 (d, *J* = 7.0 Hz,

2H), 3.25-3.17 (m, 1H), 3.16-3.03 (m, 2H), 2.77 (dd, *J* = 13.8, 8.1 Hz, 1H), 2.62-2.53 (m, 1H), 2.44 (t, *J* = 11.8 Hz, 1H), 2.29-2.03 (m, 4H), 1.97 (s, 3H), 1.87-1.55 (m, 6H), 1.37-1.23 (m, 1H), 1.21-1.12 (m, 2H), 1.07-0.94 (m, 2H). MS (ESI) m/z 590.3 $[M+H]^+$.

[0792] Cpd. No. 262; ^{1}H NMR (400 MHz, MeOD) δ 7.66 (d, *J* = 7.5 Hz, 2H), 7.55-7.36 (m, 5H), 6.52 (d, *J* = 7.5 Hz, 2H), 4.26 (dd, *J* = 11.0, 4.3 Hz, 1H), 4.17 (t, *J* = 7.2 Hz, 2H), 4.01-3.94 (m, 1H), 3.77-3.70 (m, 2H), 3.64-3.58 (m, 1H), 3.54 (d, *J* = 12.8 Hz, 1H), 3.45 (d, *J* = 7.1 Hz, 2H), 3.25-3.02 (m, 3H), 2.76 (dd, *J* = 13.7, 8.0 Hz, 1H), 2.61-2.51 (m, 2H), 2.42-2.31 (m, 1H), 2.10 (s, 3H), 2.04-1.94 (m, 1H), 1.88-1.78 (m, 1H), 1.68-1.50 (m, 5H), 1.48-1.29 (m, 2H), 1.20-1.10 (m, 2H), 1.04-0.94 (m, 2H). MS (ESI) m/z 590.2 $[M+H]^+$.

[0793] Cpd. No. 263; ^{1}H NMR (400 MHz, MeOD) δ 8.75 (d, *J* = 6.1 Hz, 2H), 7.82 (d, *J* = 6.2 Hz, 2H), 7.76 (d, *J* = 8.8 Hz, 2H), 7.53 (d, *J* = 7.5 Hz, 2H), 7.45 (t, *J* = 7.4 Hz, 2H), 7.39 (d, *J* = 7.1 Hz, 1H), 6.51 (d, *J* = 8.9 Hz, 2H), 4.24-4.13 (m, 3H), 3.74 (t, *J* = 6.2 Hz, 2H), 3.61-3.48 (m, 2H), 3.42 (d, *J* = 7.2 Hz, 2H), 3.24-3.15 (m, 1H), 3.08-2.98 (m, 2H), 2.88-2.79 (m, 1H), 2.54 (t, *J* = 12.3 Hz, 1H), 2.25 (d, *J* = 14.7 Hz, 1H), 2.21-2.11 (m, 1H), 1.94 (d, *J* = 14.9 Hz, 1H), 1.79-1.67 (m, 2H), 1.65 (s, 3H), 1.62-1.42 (m, 4H), 1.38-1.26 (m, 1H). MS (ESI) m/z 612.3 $[M+H]^+$.

[0794] Cpd. No. 264; ^{1}H NMR (400 MHz, MeOD) δ 8.76 (d, *J* = 4.2 Hz, 2H), 7.82 (d, *J* = 4.6 Hz, 2H), 7.76 (d, *J* = 7.3 Hz, 2H), 7.53-7.36 (m, 4H), 7.31-7.01 (m, 1H), 6.55-6.44 (m, 2H), 4.38-4.33 (m, 1H), 4.15 (t, *J* = 8.1 Hz, 2H), 3.76-3.69 (m, 2H), 3.53 (dd, *J* = 21.5, 12.3 Hz, 2H), 3.40 (d, *J* = 6.9 Hz, 2H), 3.24-3.13 (m, 1H), 3.08 (t, *J* = 12.6 Hz, 1H), 2.93-2.81 (m, 2H), 2.65 (t, *J* = 11.6 Hz, 1H), 2.28 (d, *J* = 14.4 Hz, 1H), 2.00 (s, 3H), 1.94 (d, *J* = 10.1 Hz, 2H), 1.89-1.80 (m, 1H), 1.75-1.57 (m, 3H), 1.52-1.36 (m, 2H), 1.35-1.23 (m, 1H). MS (ESI) m/z 612.3 $[M+H]^+$.

[0795] Cpd. No. 265; ^{1}H NMR (400 MHz, MeOD) δ 7.66 (d, *J* = 7.5 Hz, 2H), 7.57-7.38 (m, 5H), 6.53 (d, *J* = 7.6 Hz, 2H), 4.17 (t, *J* = 7.9 Hz, 2H), 3.77-3.71 (m, 2H), 3.60-3.51 (m, 2H), 3.43 (d, *J* = 7.2 Hz, 2H), 3.24-3.11 (m, 2H), 3.09 (d, *J* = 1.2 Hz, 3H), 3.06-3.00 (m, 1H), 2.95-2.86 (m, 2H), 2.77-2.68 (m, 1H), 2.60-2.52 (m, 1H), 2.49-2.39 (m, 1H), 2.30 (d, *J* = 14.2 Hz, 1H), 2.18-1.94 (m, 3H), 1.83-1.70 (m, 1H), 1.68-1.53 (m, 5H), 1.40-1.26 (m, 2H), 1.19-1.11 (m, 2H), 1.04-0.96 (m, 2H). MS (ESI) m/z 562.3 $[M+H]^+$.

[0796] Cpd. No. 266; MS (ESI) m/z 562.3 $[M+H]^+$.

[0797] Cpd. No. 101; ^1H NMR (400 MHz, MeOD) δ 7.66 (d, *J* = 8.8 Hz, 2H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.47 (t, *J* = 7.2 Hz, 1H), 7.39-7.31 (m, 2H), 7.25-7.24 (m, 1H), 6.71 (t, *J* = 2.8 Hz, 1H), 6.45 (d, *J* = 8.8 Hz, 2H), 6.31-6.29 (m, 1H), 4.52-4.36 (m, 1H), 4.35-4.22 (m, 1H), 4.13 (t, *J* = 7.2 Hz, 2H), 3.73-3.69 (m, 2H), 3.67 (s, 3H), 3.57-3.47 (m, 6H), 3.27-3.21 (m, 1H), 3.08-2.95 (m, 2H), 2.87-2.68 (m, 1H), 2.48-2.38 (m, 1H), 2.18-2.15 (m, 1H), 2.11-1.94 (m, 2H), 1.89-1.83 (m, 1H), 1.81-1.52 (m, 8H), 1.48 (t, *J* = 7.2 Hz, 3H), 1.36-1.22 (m, 1H), 1.12-0.83 (m, 1H). MS (ESI) m/z 601.3 $[M+H]^+$.

[0798] Cpd. No. 102; MS (ESI) m/z 602.3 $[M+H]^+$.

[0799] Cpd. No. 103; ^1H NMR (400 MHz, MeOD) δ 8.15 (s, 1H), 7.77-7.71 (m, 3H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 1H), 7.38-7.30 (m, 2H), 6.47 (d, *J* = 7.6 Hz, 2H), 4.50-4.37 (m, 1H), 4.34-4.25 (m, 1H), 4.21-4.13 (m, 4H), 3.79-3.69 (m, 3H), 3.53-3.42 (m, 6H), 3.24-3.13 (m, 1H), 3.02-2.96 (m, 2H), 2.84-2.67 (m, 1H), 2.51-2.32 (m, 1H), 2.16 (d, *J* = 13.2 Hz, 1H), 1.93-1.81 (m, 2H), 1.78-1.52 (m, 8H), 1.50-1.41 (m, 6H), 1.34-1.23 (m, 1H), 1.15-0.79 (m, 1H). MS (ESI) m/z 616.3 $[M+H]^+$.

[0800] Cpd. No. 267; ^1H NMR (400 MHz, MeOD) δ 8.77 (s, 2H), 7.84 (d, *J* = 4.6 Hz, 2H), 7.79-7.73 (m, 2H), 7.62 (d, *J* = 7.9 Hz, 2H), 7.49 (t, *J* = 7.4 Hz, 2H), 7.45-7.38 (m, 1H), 6.53-6.49 (m, 2H), 4.24-4.14 (m, 2H), 3.81-3.71 (m, 2H), 3.66 (d, *J* = 11.7 Hz, 1H), 3.52-3.43 (m, 4H), 3.27-3.19 (m, 1H), 3.15-2.88 (m, 4H), 2.83-2.78 (m, 1H), 2.76 (s, 3H), 2.59 (d, *J* = 14.0 Hz, 1H), 2.09-1.98 (m, 1H), 1.88-1.71 (m, 3H), 1.67-1.55 (m, 2H), 1.45-1.20 (m, 2H). MS (ESI) m/z 648.3 $[M+H]^+$.

[0801] Cpd. No. 268; ^1H NMR (400 MHz, MeOD) δ 8.75 (d, *J* = 5.1 Hz, 2H), 7.81 (d, *J* = 6.1 Hz, 2H), 7.75 (d, *J* = 8.8 Hz, 2H), 7.51-7.37 (m, 5H), 6.49 (d, *J* = 8.9 Hz, 2H), 4.19-4.09 (m, 2H), 4.04 (dd, *J* = 13.2, 6.6 Hz, 1H), 3.75-3.65 (m, 2H), 3.52 (d, *J* = 11.9 Hz, 2H), 3.39 (d, *J* = 7.1 Hz, 2H), 3.23-3.12 (m, 1H), 3.06 (s, 3H), 3.04-2.96 (m, 3H), 2.88 (t, *J* = 12.4 Hz, 1H), 2.36 (d, *J* = 14.2 Hz, 1H), 2.29-2.16 (m, 2H), 1.83-1.65 (m, 4H), 1.42-1.19 (m, 3H). MS (ESI) m/z 648.2 $[M+H]^+$.

[0802] Cpd. No. 269; ^1H NMR (400 MHz, MeOD) δ 8.75 (d, *J* = 6.1 Hz, 2H), 7.82 (d, *J* = 6.3 Hz, 2H), 7.77 (d, *J* = 8.7 Hz, 2H), 7.59 (d, *J* = 7.5 Hz, 2H), 7.46 (t, *J* = 7.5 Hz, 2H), 7.41 (d, *J* = 7.1 Hz, 1H), 6.52 (d, *J* = 8.8 Hz, 2H), 4.23- 4.09 (m, 3H), 3.75 (dd, *J* = 8.2, 5.7 Hz, 2H), 3.65-3.58 (m, 1H), 3.50-3.43 (m, 3H), 3.23- 3.17 (m, 1H), 3.10-2.95 (m, 2H), 2.80- 2.65 (m, 2H), 2.60 (s, 3H), 2.36 (d, *J* = 13.9 Hz, 1H), 2.11-2.06 (m,

1H), 1.90-1.79 (m, 1H), 1.73-1.42 (m, 5H), 1.33-1.23 (m, 2H). MS (ESI) m/z 627.2 $[M+H]^+$.

[0803] Cpd. No. 270; ^{1}H NMR (400 MHz, MeOD) δ 8.75 (dd, *J* = 4.6, 1.6 Hz, 2H), 7.81 (dd, *J* = 4.6, 1.7 Hz, 2H), 7.76 (d, *J* = 8.8 Hz, 2H), 7.47-7.43 (m, 4H), 7.42-7.38 (m,1H), 6.50 (d, *J* = 8.9 Hz, 2H), 4.30 (d, *J* = 19.5 Hz, 1H), 4.15 (d, *J* = 19.2 Hz, 1H), 3.72 (d, *J* = 21.3 Hz, 1H), 3.51 (d, *J* = 32.3 Hz, 2H), 3.39 (d, *J* = 11.4 Hz, 2H), 3.15 (d, *J* = 36.3 Hz, 1H), 2.92 (s, 1H), 2.73 (s, 1H), 2.64 (s, 1H), 2.30 (d, *J* = 25.8 Hz, 1H), 2.03 (d, *J* = 45.8 Hz, 1H), 1.81 (d, *J* = 38.3 Hz, 1H), 1.62 (d, *J* = 42.0 Hz, 2H), 1.30 (d, *J* = 82.4 Hz, 3H). MS (ESI) m/z 627.2 $[M+H]^+$.

[0804] Cpd. No. 271; ^{1}H NMR (400 MHz, MeOD) δ 8.75 (d, *J* = 5.2 Hz, 2H), 7.81 (d, *J* = 5.2 Hz, 2H), 7.75 (d, *J* = 8.0 Hz, 2H), 7.51 (d, *J* = 8.0, 1H), 7.45 (t, *J* = 7.2 Hz, 1H), 7.35 (t, *J* = 7.6 Hz, 1H), 7.25 (d, *J* = 8.0 Hz, 1H), 6.49 (d, *J* = 8.4 Hz, 2H), 4.37-4.22 (m, 2H), 4.14 (t, *J* = 8.4, 2H), 4.03-4.01 (m, 1H), 3.84 (d, *J* = 14.0 Hz, 1H), 3.73-3.69 (m, 2H), 3.60-3.57 (m, 1H), 3.42-3.34 (m, 3H), 3.25-3.23 (m, 1H), 3.21 (s, 3H), 3.10-2.90 (m, 2H), 2.74-2.67 (m, 1H), 2.26 (d, *J* = 13.2 Hz, 1H), 2.07-1.94 (m, 3H), 1.88-1.81 (m, 3H), 1.73-1.60 (m, 3H), 1.33-1.29 (m, 1H), 1.18 (s, 3H). MS (ESI) m/z 642.3 $[M+H]^+$.

[0805] Cpd. No. 272; ^{1}H NMR (400 MHz, MeOD) δ 8.78-8.77 (m, 2H), 7.85-7.83 (m, 2H), 7.78 (d, *J* = 8.8 Hz, 2H), 7.63-7.56 (m, 1H), 7.48-7.40 (m, 2H), 7.34-7.32 (m, 1H), 6.53 (d, *J* = 9.2 Hz, 2H), 4.71 (d, *J* = 15.6 Hz, 1H), 4.33-4.30 (m, 1H), 4.24-4.20 (m, 2H), 3.82-3.77 (m, 2H), 3.67-3.59 (m, 3H), 3.53-3.51 (m, 1H), 3.49-3.46 (m, 2H), 3.44-3.39 (m, 1H), 3.13 (s, 3H), 3.08-2.91 (m, 2H), 2.59-2.47 (m, 2H), 2.20-2.02 (m, 3H), 1.99 (s, 3H), 1.85-1.52 (m, 5H), 1.39 -1.36 (m, 2H), 1.00-0.87 (m, 1H). MS (ESI) m/z 642.3 $[M+H]^+$.

[0806] Cpd. No. 273; ^{1}H NMR (400 MHz, MeOD) δ 7.68-7.59 (m, 4H), 7.51-7.40 (m, 3H), 6.81-6.71 (m, 1H), 6.55-6.50 (m, 1H), 4.64-4.55 (m, 1H), 4.22-4.12 (m, 1H), 3.83-3.66 (m, 3H), 3.55-3.41 (m, 3H), 3.23-3.13 (m, 2H), 3.11-3.02 (m, 2H), 3.00-2.95 (m, 3H), 2.94-2.86 (m, 1H), 2.84 (s, 3H), 2.59-2.53 (m, 1H), 2.40-2.33 (m, 1H), 2.26-2.11 (m, 1H), 2.08-1.51 (m, 7H), 1.45-1.23 (m, 2H), 1.17-1.09 (m, 2H), 1.05-0.98 (m, 2H). MS (ESI) m/z 625.3 $[M+H]^+$.

[0807] Cpd. No. 274; ^{1}H NMR (400 MHz, MeOD) δ 7.68-7.39 (m, 7H), 6.77-6.50 (m, 2H), 4.64-4.59 (m, 1H), 4.15 (t, *J* = 8.0 Hz, 1H), 3.77-3.69 (m, 2H), 3.60-3.49 (m, 2H),

3.42 (d, *J* = 7.2 Hz, 2H), 3.24-3.14 (m, 3H), 3.05-3.01 (m, 1H), 2.98-2.95 (m, 6H), 2.88-2.80 (m, 1H), 2.58-2.52 (m, 1H), 2.24 (d, *J* = 14.0 Hz, 1H), 2.12 (d, *J* = 14.8 Hz, 1H), 2.01-1.94 (m, 2H), 1.84-1.70 (m, 3H), 1.43-1.24 (m, 4H), 1.19-1.14 (m, 2H), 0.99-0.96 (m, 2H). MS (ESI) m/z 625.3 $[M+H]^+$.

[0808] Cpd. No. 275; ^{1}H NMR (400 MHz, MeOD) δ 8.77 (s, 2H), 7.83 (d, *J* = 6.0 Hz, 2H), 7.76 (d, *J* = 8.8 Hz, 2H), 7.56 (d, *J* = 7.2 Hz, 2H), 7.44-7.38 (m, 3H), 6.51 (d, *J* = 8.8 Hz, 2H), 4.19-4.14 (m, 3H), 3.75-3.72 (m, 2H), 3.59 (d, *J* = 12.0 Hz, 1H), 3.51 (d, *J* = 12.8 Hz, 1H), 3.42 (d, *J* = 7.6 Hz, 2H), 3.23-3.18 (m, 1H), 3.07-2.92 (m, 3H), 2.71 (s, 6H), 2.56 (t, *J* = 11.6 Hz, 1H), 2.28 (d, *J* = 14.4 Hz, 1H), 2.14-2.10 (m, 1H), 1.92 (d, *J* = 15.2 Hz, 1H), 1.82-1.46 (m, 6H), 1.38-1.29 (m, 1H). MS (ESI) m/z 641.3 $[M+H]^+$.

[0809] Cpd. No. 276; ^{1}H NMR (400 MHz, MeOD) δ 8.76 (d, *J* = 5.2 Hz, 2H), 7.83-7.81 (m, 2H), 7.75 (d, *J* = 8.8 Hz, 2H), 7.45-7.37 (m, 5H), 6.49 (d, *J* = 8.8 Hz, 2H), 4.28 (q, *J* = 7.2 Hz, 1H), 4.17-4.12 (m, 2H), 3.74-3.69 (m, 2H), 3.54 (t, *J* = 12.0, 2H), 3.40 (d, *J* = 6.8 Hz, 2H), 3.21-3.08 (m, 2H), 3.04-2.99 (m, 1H), 2.94 (s, 6H), 2.77 (t, *J* = 11.2 Hz, 1H), 2.58 (t, *J* = 11.6 Hz, 1H), 2.27 (d, *J* = 14.4 Hz, 1H), 2.03-1.97 (m, 2H), 1.86-1.78 (m, 1H), 1.71-1.39 (m, 5H), 1.33-1.24 (m, 1H). MS (ESI) m/z 641.3 $[M+H]^+$.

[0810] Cpd. No. 277; ^{1}H NMR (400 MHz, MeOD) δ 8.78 (s, 2H), 7.86 (d, *J* = 6.0 Hz, 2H), 7.75 (d, *J* = 8.8 Hz, 2H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.37 (t, *J* = 7.2 Hz, 1H), 7.28 (t, *J* = 7.6 Hz, 1H), 7.21 (d, *J* = 7.2 Hz, 1H), 6.48 (d, *J* = 8.8 Hz, 2H), 4.30-4.18 (m, 2H), 4.13 (t, *J* = 8.0 Hz, 2H), 3.91-3.84 (m, 1H), 3.79 (d, *J* = 14.4 Hz, 1H), 3.73-3.68 (m, 2H), 3.58 (d, *J* = 12.0 Hz, 1H), 3.41-3.35 (m, 3H), 3.26-3.19 (m, 2H), 3.17 (s, 3H), 3.00-2.90 (m, 2H), 2.72-2.65 (m, 1H), 2.25 (s, 1H), 2.20 (s, 3H), 2.01-1.53 (m, 9H), 0.69-0.60 (m, 1H). MS (ESI) m/z 657.3 $[M+H]^+$.

[0811] Cpd. No. 278; ^{1}H NMR (400 MHz, MeOD) δ 8.77 (s, 2H), 7.84 (d, *J* = 8.8 Hz, 2H), 7.76 (d, *J* = 8.4 Hz, 2H), 7.56 (s, 1H), 7.42-7.36 (m, 2H), 7.30 (d, *J* = 7.2 Hz, 1H), 6.50 (d, *J* = 8.0 Hz, 2H), 4.65 (d, *J* = 15.2 Hz, 1H), 4.28 (d, *J* = 14.4 Hz, 1H), 4.19 (t, *J* = 8.0 Hz, 2H), 3.80-3.75 (m, 2H), 3.62 (d, *J* = 12.8 Hz, 2H), 3.49-3.43 (m, 5H), 3.08-2.94 (m, 5H), 2.71 (s, 3H), 2.60-2.54 (m, 1H), 2.48-2.37 (m, 1H), 2.22-2.06 (m, 2H), 2.04-1.91 (m, 1H), 2.93-1.31 (m, 7H), 1.12-0.95 (m, 1H). MS (ESI) m/z 657.3 $[M+H]^+$.

[0812] Cpd. No. 279; ^{1}H NMR (400 MHz, MeOD) δ 8.76 (s, 2H), 7.82 (d, *J* = 4.8 Hz, 2H), 7.79-7.74 (m, 2H), 7.55 (d, *J* = 7.2 Hz, 2H), 7.46-7.40 (m, 3H), 6.50 (d, *J* = 7.6 Hz, 2H), 4.64 (d, *J* = 8.4 Hz, 1H), 4.52 (d, *J* = 7.2 Hz, 1H), 4.43 (d, *J* = 6.8 Hz, 1H), 4.26-4.14 (m, 4H), 3.75-3.72 (m, 2H), 3.58-3.51 (m, 2H), 3.42 (d, *J* = 7.2 Hz, 2H), 3.28 (d, *J* = 8.4 Hz, 1H), 3.24-3.18 (m, 1H), 3.07-2.93 (m, 2H), 2.70 (s, 3H), 2.52 (t, *J* = 12.0, 1H), 2.23 (d, *J* = 14.4 Hz, 1H), 2.16-2.10 (m, 1H), 1.98 (d, *J* = 14.0 Hz, 1H), 1.84-1.56 (m, 5H), 1.47-1.29 (m, 2H). MS (ESI) m/z 668.3 $[M+H]^+$.

[0813] Cpd. No. 280; ^{1}H NMR (400 MHz, MeOD) δ 8.77 (s, 2H), 7.84 (d, *J* = 5.6 Hz, 2H), 7.75 (d, *J* = 8.8 Hz, 2H), 7.51 (d, *J* = 7.6 Hz, 2H), 7.45 (t, *J* = 7.2 Hz, 2H), 7.41-7.37 (m, 1H), 6.49 (d, *J* = 8.8 Hz, 2H), 5.07 (d, *J* = 8.8 Hz, 1H), 4.97 (d, *J* = 9.2 Hz, 1H), 4.83-4.78 (m, 2H), 4.74-4.68 (m, 1H), 4.14 (t, *J* = 8.0 Hz, 2H), 3.74-3.69 (m, 2H), 3.57-3.52 (m, 2H), 3.40 (d, *J* = 7.2 Hz, 2H), 3.23-3.18 (m, 2H), 3.11-3.05 (m, 1H), 2.88 (s, 3H), 2.74-2.68 (m, 1H), 2.60-2.54 (m, 1H), 2.26 (d, *J* = 14.4 Hz, 1H), 2.02 (d, *J* = 14.0 Hz, 1H), 1.97-1.80 (m, 2H), 1.78-1.55 (m, 3H), 1.46-1.29 (m, 3H). MS (ESI) m/z 668.3 $[M+H]^+$.

[0814] Cpd. No. 281; ^{1}H NMR (400 MHz, MeOD) δ 7.66 (d, *J* = 8.8 Hz, 2H), 7.53 (d, *J* = 7.6 Hz, 2H), 7.45 (t, *J* = 7.2 Hz, 2H), 7.40-7.37 (m, 1H), 6.52 (d, *J* = 9.2 Hz, 2H), 4.21-4.14 (m, 3H), 3.73 (t, *J* = 6.0 Hz, 2H), 3.60-3.52 (m, 2H), 3.43 (d, *J* = 7.2 Hz, 2H), 3.24-3.17 (m, 1H), 3.04 (t, *J* = 12.8, 2H), 2.88-2.82 (m, 1H), 2.59-2.49 (m, 2H), 2.24 (d, *J* = 14.4 Hz, 1H), 2.19-2.13 (m, 1H), 1.96 (d, *J* = 14.4 Hz, 1H), 1.78-1.68 (m, 3H), 1.64 (s, 3H), 1.62-1.46 (m, 4H), 1.17-1.12 (m, 2H), 1.02-0.96 (m, 2H). MS (ESI) m/z 574.2 $[M+H]^+$.

[0815] Cpd. No. 282; ^{1}H NMR (400 MHz, MeOD) δ 7.66 (d, *J* = 8.8 Hz, 2H), 7.49-7.45 (m, 4H), 7.43-7.39 (m, 1H), 7.29-7.05 (m, 1H), 6.52 (d, *J* = 8.8 Hz, 2H), 4.39 (m, 1H), 4.18-4.13 (m, 2H), 3.75-3.71 (m, 2H), 3.59-3.51 (m, 2H), 3.43 (d, *J* = 6.8 Hz, 2H), 3.22-3.16 (m, 1H), 3.13-3.07 (m, 1H), 2.92-2.85 (m, 2H), 2.69-2.63 (m, 1H), 2.59-2.52 (m, 1H), 2.29 (d, *J* = 14.4 Hz, 1H), 2.01 (s, 3H), 1.97-1.82 (m, 3H), 1.74-1.58 (m, 3H), 1.53-1.39 (m, 2H), 1.34-1.25 (m, 1H), 1.17-1.13 (m, 2H), 1.02-0.97 (m, 2H). MS (ESI) m/z 574.2 $[M+H]^+$.

[0816] Cpd. No. 283; ^{1}H NMR (400 MHz, MeOD) δ 7.65 (d, *J* = 8.8 Hz, 2H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.39 (t, *J* = 7.2 Hz, 1H), 7.30 (t, *J* = 7.6 Hz, 1H), 7.22 (d, *J* = 7.2 Hz, 1H), 6.51 (d, *J* = 8.8 Hz, 2H), 4.29 (d, *J* = 16.0, 1H), 4.20 (d, *J* = 14.8 Hz, 1H), 4.16-

4.12 (m, 2H), 3.92-3.86 (m, 1H), 3.81 (d, *J* = 15.0 Hz, 1H), 3.73-3.69 (m, 2H), 3.60 (d, *J* = 12.4Hz, 1H), 3.43-3.38 (m, 3H), 3.22 (d, *J* = 15.0 Hz, 1H), 3.18 (s, 3H), 3.02-2.91 (m, 2H), 2.74-2.66 (m, 2H), 2.59-2.52 (m, 1H), 2.27-2.24 (m, 1H), 2.21 (s, 3H), 2.03-1.54 (m, 9H), 1.16-1.12 (m, 2H), 1.01-0.96 (m, 2H), 0.70-0.61 (m, 1H). MS (ESI) m/z 620.3 $[M+H]^+$.

[0817] Cpd. No. 284; ^{1}H NMR (400 MHz, MeOD) δ 8.08 (s, 1H), 7.71-7.69 (m, 3H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.36 (t, *J* = 7.2 Hz, 1H), 7.30-7.22 (m, 2H), 6.45 (d, *J* = 8.8 Hz, 2H), 4.23-4.09 (m, 4H), 4.00-3.93 (m, 1H), 3.87 (s, 3H), 3.77 (d, *J* = 14.4 Hz, 1H), 3.70-3.65 (m, 2H), 3.58 (d, *J* =13.2, 1H), 3.40-3.34 (m, 3H), 3.20-3.12 (m, 2H), 3.00-2.88 (m, 2H), 2.71-2.63 (m, 1H), 2.25-2.22 (m, 1H), 2.19 (s, 3H), 2.07-1.97 (m, 2H), 1.96-1.51 (m, 9H), 0.69-0.60 (m, 1H). MS (ESI) m/z 646.3 $[M+H]^+$.

[0818] Cpd. No. 285; ^{1}H NMR (400 MHz, MeOD) δ 7.64 (d, *J* = 7.6 Hz, 2H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.37 (t, *J* = 7.2 Hz, 1H), 7.30-7.22 (m, 2H), 6.51 (d, *J* = 8.0 Hz, 2H), 4.23-4.18 (m, 2H), 4.14 (t, *J* = 8.0 Hz, 2H), 4.01-3.93 (m, 1H), 3.77 (d, *J* = 14.4 Hz, 1H), 3.72-3.68 (m, 2H), 3.59 (d, *J* = 11.2 Hz, 1H), 3.41-3.37 (m, 3H), 3.21-3.14 (m, 2H), 3.01-2.89 (m, 2H), 2.71-2.64 (m, 1H), 2.57-2.51 (m, 1H), 2.24 (d, *J* = 12.4 Hz, 1H), 2.19 (s, 3H), 2.06-2.02 (m, 2H), 1.96-1.51 (m, 8H), 1.15-1.11 (m, 2H), 1.00-0.95 (m, 2H), 0.70-0.61 (m, 1H). MS (ESI) m/z 606.3 $[M+H]^+$.

[0819] Cpd. No. 286; ^{1}H NMR (400 MHz, MeOD) δ 8.09 (s, 1H), 7.89 (d, *J* = 9.6 Hz, 1H), 7.72-7.70 (m, 2H), 7.52 (d, *J* = 8.4 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.33 (t, *J* = 7.6 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 1H), 6.47 (d, *J* = 7.2 Hz, 2H), 4.27-4.17 (m, 2H), 4.12 (t, *J* = 8.0 Hz, 2H), 3.88 (s, 3H), 3.80 (d, *J* = 14.4 Hz, 1H), 3.71-3.66 (m, 2H), 3.59 (d, *J* = 11.2 Hz, 1H), 3.41-3.36 (m, 3H), 3.23 (d, *J* = 14.4, 1H), 3.17-3.14 (m, 1H), 3.01-2.89 (m, 2H), 2.73-2.66 (m, 1H), 2.25 (d, *J* = 14.4 Hz, 1H), 2.09-2.06 (m, 1H), 1.94-1.58 (m, 8H), 1.33-1.29 (m, 1H), 1.17 (s, 3H), 0.68-0.59 (m, 1H). MS (ESI) m/z 631.3 $[M+H]^+$.

[0820] Cpd. No. 287; ^{1}H NMR (400 MHz, MeOD) δ 8.10 (s, 1H), 7.73-7.70 (m, 3H), 7.57 (d, *J* = 7.6 Hz, 1H), 7.44-7.31 (m, 3H), 6.47 (d, *J* = 8.8 Hz, 2H), 4.49 (d, *J* = 15.6 Hz, 1H), 4.30 (d, *J* = 15.6 Hz, 1H), 4.18-4.13 (m, 2H), 3.88 (s, 3H), 3.76-3.72 (m, 3H), 3.63-3.43 (m, 6H), 3.25-3.24 (m, 1H), 3.07 (t, *J* = 10.4 Hz, 1H), 2.95 (t, *J* = 12.4 Hz, 1H), 2.53 (t, *J* = 12.0 Hz, 1H), 2.44-2.41 (m, 1H), 2.13 (d, *J* = 14.0 Hz, 1H), 2.05-2.00 (m, 1H), 1.96 (s, 3H), 1.90-1.80 (m, 1H), 1.75-1.56 (m, 5h), 1.39 (d, *J* = 12.8 Hz, 1H), 1.10-1.00 (m, 1H). MS (ESI) m/z 631.3 $[M+H]^+$.

[0821] Cpd. No. 288; ^{1}H NMR (400 MHz, MeOD) δ 7.65 (d, *J* = 8.8 Hz, 2H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.38 (t, *J* = 7.6, 1H), 7.32-7.26 (m, 2H), 6.51 (d, *J* = 8.8 Hz, 2H), 4.30-4.12 (m, 4H), 3.91-3.86 (m, 1H), 3.82-3.75 (m, 1H), 3.74-3.67 (m, 2H), 3.64-3.59 (m, 2H), 3.42-3.38 (m, 3H), 3.23-3.19 (m, 2H), 3.02-2.91 (m, 2H), 2.76-2.69 (m, 1H), 2.58-2.52 (m, 1H), 2.27-2.24 (m, 1H), 2.19 (s, 3H), 2.08-1.68 (m, 9H), 1.57 (t, *J* = 6.8 Hz, 6H), 1.34-1.29 (m, 1H), 1.16-1.13 (m, 2H), 1.00-0.97 (m, 2H), 0.69-0.63 (m, 1H). MS (ESI) m/z 648.3 $[M+H]^+$.

[0822] Cpd. No. 289; ^{1}H NMR (400 MHz, MeOD) δ 7.65 (d, *J* = 8.8 Hz, 2H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.40 (t, *J* = 7.2 Hz, 1H), 7.33-7.26 (m, 2H), 6.51 (d, *J* = 8.8 Hz, 2H), 4.40 (d, *J* = 13.2 Hz, 1H), 4.17-4.09 (m, 3H), 3.85-3.69 (m, 4H), 3.62-3.55 (m, 2H), 3.43-3.38 (m, 4H), 3.18 (d, *J* = 13.2 Hz, 2H), 3.03-2.91 (m, 2H), 2.75-2.67 (m, 1H), 2.57-2.53 (m, 1H), 2.28-2.24 (m, 1H), 2.20 (s, 3H), 2.07-1.68 (m, 8H), 1.64-1.59 (m, 1H), 1.55 (t, *J* = 7.2 Hz, 3H), 1.15-1.13 (m, 2H), 1.00-0.98 (m, 2H), 0.70-0.60 (m, 1H). MS (ESI) m/z 634.3 $[M+H]^+$.

[0823] Cpd. No. 290; ^{1}H NMR (400 MHz, MeOD) δ 7.85 (d, *J* = 7.2 Hz, 2H), 7.71 (d, *J* = 8.8 Hz, 2H), 7.59-7.49 (m, 4H), 7.38 (t, *J* = 6.8 Hz, 1H), 7.32-7.25 (m, 2H), 6.46 (d, *J* = 8.8 Hz, 2H), 4.39 (d, *J* = 12.8 Hz, 1H), 4.13-4.08 (m, 3H), 3.87-3.75 (m, 2H), 3.70-3.65 (m, 2H), 3.59-3.52 (m, 2H), 3.42-3.35 (m, 4H), 3.17 (d, *J* = 13.2 Hz, 2H), 3.00-2.89 (m, 2H), 2.73-2.66 (m, 1H), 2.26-2.23 (m, 1H), 2.20 (s, 3H), 2.03-1.67 (m, 8H), 1.62-1.59 (m, 1H), 1.54 (t, *J* = 7.2 Hz, 3H). MS (ESI) m/z 670.3 $[M+H]^+$.

[0824] Cpd. No. 375; ^{1}H NMR (400 MHz, MeOD) δ 7.66 (d, *J* = 8.8 Hz, 2H), 7.50 (d, J = 8.0 Hz, 1H), 7.39 (t, *J* = 7.2 Hz, 1H), 7.32-7.23 (m, 3H), 6.71 (t, *J* = 2.6 Hz, 1H), 6.44 (d, *J* = 8.8 Hz, 2H), 6.30-6.29 (m, 1H), 4.40 (d, *J* = 12.8, 1H), 4.12-4.08 (m, 3H), 3.87-3.75 (m, 2H), 3.67 (s, 3H), 3.65-3.63 (m, 1H), 3.60-3.53 (m, 2H), 3.42-3.35 (m, 4H), 3.21-3.13 (m, 2H), 3.01-2.90 (m, 2H), 2.74-2.67 (m, 1H), 2.25 (d, *J* = 13.2 Hz, 1H), 2.20 (s, 3H), 2.04-1.67 (m, 8H), 1.55 (t, *J* = 7.2 Hz, 3H), 0.69-0.59 (m, 1H). MS (ESI) m/z 673.4 $[M+H]^+$.

[0825] Cpd. No. 376; ^{1}H NMR (400 MHz, MeOD) δ 8.76 (s, 1H), 8.10 (s, 1H), 7.73-7.71 (m, 3H), 7.65 (d, *J* = 7.6 Hz, 2H), 7.53 (t, *J* = 7.8 Hz, 2H), 7.48 (s, 1H), 7.43 (t, *J* = 7.4 Hz, 1H), 7.36 (s, 1H), 6.47 (d, *J* = 8.8 Hz, 2H), 5.15 (d, *J* = 15.2, 1H), 4.95 (d, *J* = 15.6 Hz, 1H), 4.33-4.28 (m, 1H), 4.14 (t, *J* = 8.0, 2H), 3.88 (s, 3H), 3.73-3.68 (m, 2H), 3.62 (d, *J* = 12.4 Hz, 1H), 3.46 (d, *J* = 13.6 Hz, 1H), 3.41 (d, *J* = 7.2 Hz, 2H), 3.24-3.19

(m, 1H), 3.11-3.05 (m, 1H), 2.93 (s, 6H), 2.89-2.85 (m, 1H), 2.78-2.71 (m, 1H), 2.46 (t, *J* = 11.8 Hz, 1H), 2.22 (d, *J* = 13.6 Hz, 1H), 2.05-2.00 (m, 1H), 1.91-1.84 (m, 1H), 1.72-1.41 (m, 4H), 1.16-1.03 (m, 2H), 0.90-0.82 (m, 1H). MS (ESI) m/z 699.4 $[M+H]^+$.

[0826] Cpd. No. 377; ^{1}H NMR (400 MHz, MeOD) δ 8.90 (s, 1H), 8.10 (s, 1H), 7.73-7.71 (m, 3H), 7.66 (d, *J* = 8.0 Hz, 2H), 7.56 (s, 1H), 7.53-7.48 (m, 3H), 7.42-7.38 (m, 1H), 6.47 (d, *J* = 8.8 Hz, 2H), 5.14 (d, *J* = 15.6, 1H), 4.95 (d, *J* = 14.4 Hz, 1H), 4.32-4.27 (m, 1H), 4.17-4.12 (m, 2H), 3.88 (s, 3H), 3.73-3.68 (m, 2H), 3.60 (d, *J* = 12.0 Hz, 1H), 3.45-3.38 (m, 3H), 3.23-3.18 (m, 1H), 3.03 (t, *J* = 12.0 Hz, 1H), 2.89-2.83 (m, 2H), 2.77 (s, 6H), 2.63-2.57 (s, 1H), 2.27 (d, *J* = 12.8 Hz, 1H), 1.97-1.85 (m, 2H), 1.59-1.34 (m, 4H), 1.22-1.15 (m, 1H), 1.08-0.98 (m, 2H). MS (ESI) m/z 699.3 $[M+H]^+$.

[0827] Cpd. No. 378; ^{1}H NMR (400 MHz, MeOD) δ 8.46 (s, 1H), 8.16 (s, 1H), 7.57 (d, *J* = 8.0 Hz, 2H), 7.49-7.45 (m, 4H), 7.34 (t, *J* = 7.2 Hz, 1H), 6.47 (d, *J* = 8.8 Hz, 2H), 4.37 (m, 1H), 4.19- 4.14 (m, 2H), 4.11-4.06 (m, 1H), 3.95 (d, *J* = 15.0 Hz, 2H), 3.72 (q, *J* = 6.0 Hz, 2H), 3.61 (d, *J* = 11.6 Hz, 1H), 3.46-3.42 (m, 3H), 3.23-3.18 (m, 1H), 3.0 (t, *J* = 11.2 Hz, 1H), 2.88 (t, *J* = 11.6, 1H), 2.73-2.70 (m, 1H), 2.68 (s, 3H), 2.37 -2.31 (m, 2H), 1.91-1.88 (m, 2H), 1.84-1.74 (m, 1H), 1.68-1.59 (m, 1H), 1.48-1.29 (m, 5H), 1.09-1.01 (m, 1H). MS (ESI) m/z 610.3 $[M+H]^+$.

[0828] Cpd. No. 379; ^{1}H NMR (400 MHz, MeOD) δ 8.46 (s, 1H), 8.16 (s, 1H), 7.54 (d, *J* = 8.0 Hz, 2H), 7.49-7.44 (m, 4H), 7.34 (t, *J* = 6.8 Hz, 1H), 6.47 (d, *J* = 8.0 Hz, 2H), 4.19-4.12 (m, 4H), 3.75-3.70 (m, 2H), 3.59 (d, *J* = 11.2 Hz, 1H), 3.45-3.41 (m, 3H), 3.36-3.35 (m, 1H), 3.23-3.18 (m, 1H), 3.08 (t, *J* = 12.0 Hz, 1H), 2.95 (t, *J* = 12.0 Hz, 1H), 2.71 (s, 3H), 2.50-2.42 (m, 2H), 2.26 (d, *J* = 6.8 Hz, 1H), 2.03 (s, 1H), 1.98-1.85 (m, 2H), 1.75-1.46 (m, 4H), 1.41-1.34 (m, 3H). MS (ESI) m/z 610.2 $[M+H]^+$.

[0829] Cpd. No. 380; ^{1}H NMR (400 MHz, MeOD) δ 8.74 (d, *J* = 26.3 Hz, 1H), 7.70-7.60 (m, 4H), 7.54-7.45 (m, 3H), 7.44-7.33 (m, 4H), 5.03-4.93 (m, 2H), 4.64-4.37 (m, 1H), 4.02-3.73 (m, 1H), 2.99 (t, *J* = 11.8 Hz, 1H), 2.85-2.77 (m, 1H), 2.74-2.69 (m, 1H), 2.68 (s, 3H), 2.58-2.42 (m, 2H), 2.39-2.33 (m, 1H), 2.32-2.22 (m, 1H), 2.13-2.05 (m, 1H), 2.02-1.93 (m, 1H), 1.91-1.77 (m, 2H), 1.71 (d, *J* = 12.5 Hz, 1H), 1.64-1.28 (m, 5H), 1.25-1.05 (m, 2H), 0.30-0.17 (m, 1H). MS (ESI) m/z 567.3 $[M+H]^+$.

[0830] Cpd. No. 29; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.76 (brs, 1H), 8.73 (brs, 3H), 7.51 (d, *J* = 8.8 Hz, 2H), 7.25 (dd, *J* = 14.0, 8.1 Hz, 1H), 7.02 (t, *J* = 8.4 Hz, 1H), 6.96

(d, J = 8.0 Hz, 1H), 6.83 (d, J = 8.8 Hz, 2H), 4.04 (s, 2H), 3.71 (d, J = 9.8 Hz, 1H), 3.35 (dd, J = 15.5, 7.0 Hz, 2H), 3.22 – 3.01 (m, 3H), 2.96 – 2.61 (m, 4H), 2.43 (m, 1H), 2.36 – 2.12 (m, 4H), 2.01 – 1.78 (m, 2H), 1.74 – 1.39 (m, 6H), 1.28 – 1.09 (m, 2H). MS (ESI) m/z 462.2 $[M+H]^+$.

[0831] Cpd. No. 30; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 – 7.51 (m, 2H), 7.20 (dd, J = 8.8, 5.7 Hz, 1H), 6.96 – 6.88 (m, 2H), 6.85 (td, J = 8.6, 2.9 Hz, 1H), 6.76 (dd, J = 9.3, 2.8 Hz, 1H), 4.02 (t, J = 6.4 Hz, 2H), 3.12 – 2.94 (m, 3H), 2.90 (d, J = 10.9 Hz, 1H), 2.66 (dd, J = 11.3, 6.0 Hz, 2H), 2.43 (t, J = 7.3 Hz, 2H), 2.39 – 2.29 (m, 1H), 2.01 – 1.88 (m, 3H), 1.88 – 1.74 (m, 2H), 1.73 – 1.59 (m, 2H), 1.50 – 1.37 (m, 6H), 1.36 – 1.27 (m, 2H), 1.22 – 1.08 (m, 2H), 0.93 – 0.79 (m, 1H). MS (ESI) m/z 462.2 $[M+H]^+$.

[0832] Cpd. No. 31; MS (ESI) m/z 476.3 $[M+H]^+$.

[0833] Cpd. No. 32; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.18 (brs, 2H), 8.50 (brs, 1H), 7.51 (d, J = 8.8 Hz, 2H), 7.23 (d, J = 5.3 Hz, 1H), 6.84 (d, J = 8.8 Hz, 2H), 6.76 (d, J = 5.3 Hz, 1H), 4.04 (s, 2H), 3.76 (d, J = 10.5 Hz, 1H), 3.65 – 3.53 (m, 2H), 3.48 (s, 1H), 3.16 (s, 2H), 3.01 (s, 2H), 2.84 – 2.58 (m, 3H), 2.46 – 2.30 (m, 1H), 2.27 – 2.18 (m, 3H), 2.04 (s, 1H), 1.82 (s, 1H), 1.67 (s, 1H), 1.60 – 1.37 (m, 6H), 1.25 – 1.08 (m, 1H). MS (ESI) m/z 450.2 $[M+H]^+$

[0834] Cpd. No. 33; ^{1}H NMR (400 MHz, MeOD) δ 7.48 (d, J = 8.7 Hz, 2H), 7.44 – 7.38 (m, 2H), 7.25 – 7.05 (m, 3H), 6.47 (d, J = 8.7 Hz, 2H), 4.54 – 4.27 (m, 2H), 4.18 (td, J = 8.0, 2.4 Hz, 2H), 3.77 (dd, J = 9.9, 3.8 Hz, 2H), 3.69 – 3.58 (m, 2H), 3.53 (d, J = 12.2 Hz, 1H), 3.51 – 3.41 (m, 2H), 3.14 (s, 3H), 3.09 – 2.91 (m, 2H), 2.91 – 2.77 (m, 1H), 2.71 – 2.53 (m, 1H), 2.30 – 2.11 (m, 1H), 2.05 – 1.82 (m, 3H), 1.77 – 1.58 (m, 4H), 1.53 – 1.40 (m, 2H), 1.41 – 1.27 (m, 1H), 1.24 – 1.07 (m, 1H). MS (ESI) m/z 487.2 $[M+H]^+$.

[0835] Cpd. No. 34; MS (ESI) m/z 492.2 $[M+H]^+$.

[0836] Cpd. No. 35; MS (ESI) m/z 445.2 $[M+H]^+$.

[0837] Cpd. No. 37; MS (ESI) m/z 433.3 $[M+H]^+$.

[0838] Cpd. No. 38; MS (ESI) m/z 535.3 $[M+H]^+$.

[0839] Cpd. No. 39; ^{1}H NMR (400 MHz, MeOD) δ 7.66 (d, J = 8.9 Hz, 2H), 7.55 – 7.45 (m, 2H), 7.43 – 7.33 (m, 3H), 7.06 (d, J = 8.9 Hz, 2H), 4.16 (t, J = 5.8 Hz, 2H), 3.71 (d, J = 12.6 Hz, 1H), 3.61 (d, J = 11.4 Hz, 1H), 3.57 (s, 2H), 3.28 (s, 2H), 3.13 – 2.95 (m, 1H), 2.57 – 2.44 (m, 1H), 2.33 (t, J = 12.3 Hz, 1H), 2.24 (dt, J = 16.0, 5.7 Hz,

2H), 2.14 (d, *J* = 14.1 Hz, 1H), 1.98 (d, *J* = 14.5 Hz, 1H), 1.84 – 1.66 (m, 3H), 1.66 – 1.46 (m, 5H), 1.37 – 1.14 (m, 1H). MS (ESI) m/z 432.3 $[M+H]^+$

[0840] Cpd. No. 40; MS (ESI) m/z 474.3 $[M+H]^+$.

[0841] Cpd. No. 41; MS (ESI) m/z 497.3 $[M+H]^+$.

[0842] Cpd. No. 42; ^{1}H NMR (400 MHz, MeOD) δ 7.65 (d, *J* = 8.7 Hz, 1H), 7.53 – 7.35 (m, 3H), 7.30 (d, *J* = 2.0 Hz, 1H), 6.93 (d, *J* = 1.9 Hz, 1H), 6.49 (d, *J* = 8.7 Hz, 1H), 4.64 (q, *J* = 15.4 Hz, 1H), 4.14 (t, *J* = 8.0 Hz, 1H), 3.73 (dd, *J* = 7.8, 5.8 Hz, 1H), 3.58 (d, *J* = 12.1 Hz, 1H), 3.51 (d, *J* = 12.0 Hz, 1H), 3.43 (d, *J* = 7.0 Hz, 1H), 3.24 (dt, *J* = 13.2, 6.5 Hz, 1H), 3.17 – 2.98 (m, 1H), 2.74 – 2.52 (m, 1H), 2.49 (t, *J* = 12.3 Hz, 1H), 2.42 (s, 1H), 2.09 (t, *J* = 14.5 Hz, 1H), 1.96 – 1.63 (m, 2H), 1.59 (s, 2H), 1.52 – 1.36 (m, 1H), 1.34 – 1.20 (m, 1H), 1.19 – 1.07 (m, 2H), 1.05 – 0.94 (m, 2H). MS (ESI) m/z 587.3 $[M+H]^+$.

[0843] Cpd. No. 104; MS (ESI) m/z 458.3 $[M+H]^+$.

[0844] Cpd. No. 105; MS (ESI) m/z 444.2 $[M+H]^+$.

[0845] Cpd. No. 106; MS (ESI) m/z 389.2 $[M+H]^+$.

[0846] Cpd. No. 107; MS (ESI) m/z 299.2 $[M+H]^+$.

[0847] Cpd. No. 108; MS (ESI) m/z 430.3 $[M+H]^+$.

[0848] Cpd. No. 109; MS (ESI) m/z 456.2 $[M+H]^+$.

[0849] Cpd. No. 110; MS (ESI) m/z 456.2 $[M+H]^+$.

[0850] Cpd. No. 111; MS (ESI) m/z 432.2 $[M+H]^+$.

[0851] Cpd. No. 112; MS (ESI) m/z 453.2 $[M+H]^+$.

[0852] Cpd. No. 113; MS (ESI) m/z 469.3 $[M+H]^+$.

[0853] Cpd. No. 114; MS (ESI) m/z 439.2 $[M+H]^+$.

[0854] Cpd. No. 115; MS (ESI) m/z 483.3 $[M+H]^+$.

[0855] Cpd. No. 116; MS (ESI) m/z 554.2 $[M+H]^+$.

[0856] Cpd. No. 117; MS (ESI) m/z 582.3 $[M+H]^+$.

[0857] Cpd. No. 118; MS (ESI) m/z 467.2 $[M+H]^+$.

[0858] Cpd. No. 119; ^{1}H NMR (400 MHz, MeOD) δ 7.94 – 7.82 (m, 1H), 7.62 (d, *J* = 7.6 Hz, 2H), 7.41 (dd, *J* = 14.3, 7.4 Hz, 1H), 7.30 (d, *J* = 8.5 Hz, 1H), 7.16 (t, *J* = 8.6 Hz, 1H), 6.47 (d, *J* = 7.7 Hz, 2H), 4.14 (t, *J* = 7.8 Hz, 2H), 3.73 (t, *J* = 6.5 Hz, 2H), 3.69 – 3.49 (m, 4H), 3.45 (d, *J* = 6.0 Hz, 2H), 3.26 (dd, *J* = 12.9, 7.4 Hz, 1H), 3.16 – 2.99 (m, 4H), 2.86 – 2.72 (m, 1H), 2.71 – 2.60 (m, 1H), 2.45 (d, *J* = 1.2 Hz, 3H), 2.24 (d, *J* =

13.7 Hz, 1H), 2.10 – 1.90 (m, 2H), 1.87 – 1.74 (m, 2H), 1.72 – 1.41 (m, 4H), 1.31 – 1.12 (m, 1H). MS (ESI) m/z 541.3 $[M+H]^+$.

[0859] Cpd. No. 120; MS (ESI) m/z 442.3 $[M+H]^+$.

[0860] Cpd. No. 121; MS (ESI) m/z 456.3 $[M+H]^+$.

[0861] Cpd. No. 122; MS (ESI) m/z 576.2 $[M+H]^+$.

[0862] Cpd. No. 123; MS (ESI) m/z 562.2 $[M+H]^+$.

[0863] Cpd. No. 124; MS (ESI) m/z 415.2 $[M+H]^+$.

[0864] Cpd. No. 125; MS (ESI) m/z 414.2 $[M+H]^+$.

[0865] Cpd. No. 126; MS (ESI) m/z 543.2 $[M+H]^+$.

[0866] Cpd. No. 127; MS (ESI) m/z 442.2 $[M+H]^+$.

[0867] Cpd. No. 293; MS (ESI) m/z 416.2 $[M+H]^+$.

[0868] Cpd. No. 294; MS (ESI) m/z 442.2 $[M+H]^+$.

[0869] Cpd. No. 295; MS (ESI) m/z 511.2 $[M+H]^+$.

[0870] Cpd. No. 296; MS (ESI) m/z 497.2 $[M+H]^+$.

[0871] Cpd. No. 297; ^{1}H NMR (400 MHz, MeOD) δ 7.79 (d, J = 7.8 Hz, 1H), 7.66 (d, J = 8.8 Hz, 2H), 7.58 – 7.52 (m, 1H), 7.45 (t, J = 7.2 Hz, 1H), 7.38 – 7.30 (m, 1H), 7.08 (d, J = 8.6 Hz, 2H), 4.33 – 4.25 (m, 1H), 4.19 (t, J = 5.6 Hz, 2H), 4.06 – 3.96 (m, 1H), 3.85 – 3.73 (m, 1H), 3.64 – 3.53 (m, 2H), 3.18 – 3.07 (m, 3H), 3.04 (s, 3H), 2.74 (t, J = 12.4 Hz, 1H), 2.28 (s, 2H), 2.15 (s, 3H), 1.86 – 1.65 (m, 4H), 1.43 – 1.28 (m, 2H), 1.10 (s, 1H). MS (ESI) m/z 515.3 $[M+H]^+$.

[0872] Cpd. No. 298; ^{1}H NMR (400 MHz, MeOD) δ 7.65 (d, J = 8.6 Hz, 2H), 7.46 – 7.27 (m, 4H), 7.05 (d, J = 6.9 Hz, 2H), 4.15 (t, J = 5.7 Hz, 2H), 3.66 (t, J = 13.6 Hz, 2H), 3.56 – 3.45 (m, 1H), 3.35 (d, J = 5.9 Hz, 1H), 3.26 (d, J = 7.9 Hz, 1H), 3.12 – 2.97 (m, 4H), 2.61 (t, J = 11.5 Hz, 1H), 2.30 (t, J = 11.7 Hz, 1H), 2.22 (dt, J = 15.9, 5.9 Hz, 2H), 2.12 (d, J = 14.3 Hz, 1H), 2.06 – 1.83 (m, 4H), 1.76 (dd, J = 27.9, 13.3 Hz, 2H), 1.56 (d, J = 12.4 Hz, 1H), 1.51 – 1.27 (m, 4H), 1.26 – 1.06 (m, 3H). MS (ESI) m/z 458.3 $[M+H]^+$.

[0873] Cpd. No. 299; MS (ESI) m/z 543.3 $[M+H]^+$.

[0874] Cpd. No. 300; MS (ESI) m/z 543.3 $[M+H]^+$.

[0875] Cpd. No. 301; MS (ESI) m/z 571.3 $[M+H]^+$.

[0876] Cpd. No. 302; MS (ESI) m/z 543.3 $[M+H]^+$.

[0877] Cpd. No. 303; MS (ESI) m/z 466.2 $[M+H]^+$.

[0878] Cpd. No. 304; MS (ESI) m/z 494.2 $[M+H]^+$.

[0879] Cpd. No. 305; MS (ESI) m/z 376.2 $[M+H]^+$.

[0880] Cpd. No. 306; MS (ESI) m/z 471.2 $[M+H]^+$.

[0881] Cpd. No. 307; MS (ESI) m/z 485.3 $[M+H]^+$.

[0882] Cpd. No. 308; MS (ESI) m/z 504.2 $[M+H]^+$.

[0883] Cpd. No. 309; MS (ESI) m/z 504.2 $[M+H]^+$.

[0884] Cpd. No. 310; MS (ESI) m/z 594.3 $[M+H]^+$.

[0885] Cpd. No. 311; MS (ESI) m/z 594.3 $[M+H]^+$.

[0886] Cpd. No. 312; ^{1}H NMR (400 MHz, MeOD) δ 7.86 (d, *J* = 7.2 Hz, 2H), 7.71 (d, *J* = 8.7 Hz, 2H), 7.58 (t, *J* = 7.2 Hz, 1H), 7.52 (t, *J* = 7.3 Hz, 2H), 7.49 – 7.44 (m, 1H), 7.34 (d, *J* = 7.8 Hz, 1H), 7.26 (d, *J* = 10.4 Hz, 1H), 7.16 (t, *J* = 8.4 Hz, 0H), 6.47 (d, *J* = 8.6 Hz, 2H), 4.13 (t, *J* = 7.9 Hz, 2H), 3.70 (t, J = 8.0 Hz, 2H), 3.54 (t, *J* = 11.2 Hz, 2H), 3.40 (d, *J* = 7.1 Hz, 2H), 3.23 – 3.09 (m, 2H), 3.09 – 2.99 (m, 2H), 2.40 (t, *J* = 11.8 Hz, 1H), 2.31 – 2.18 (m, 2H), 2.05 (d, *J* = 14.4 Hz, 1H), 1.90 – 1.74 (m, 5H), 1.73 – 1.59 (m, 2H), 1.52 (dd, *J* = 24.7, 11.2 Hz, 1H), 1.44 – 1.27 (m, 1H). MS (ESI) m/z 630.2 $[M+H]^+$.

[0887] Cpd. No. 313; MS (ESI) m/z 630.2 $[M+H]^+$.

[0888] Cpd. No. 314; MS (ESI) m/z 534.3 $[M+H]^+$

[0889] Cpd. No. 315; MS (ESI) m/z 534.3 $[M+H]^+$.

[0890] Cpd. No. 316; ^{1}H NMR (400 MHz, MeOD) δ 7.66 (d, *J* = 8.8 Hz, 2H), 7.41 – 7.29 (m, 2H), 7.23 – 7.10 (m, 1H), 6.52 (d, *J* = 8.8 Hz, 2H), 5.08 (s, 1H), 4.46 – 4.30 (m, 1H), 4.18 (t, *J* = 8.0 Hz, 2H), 3.76 (dd, *J* = 7.8, 5.5 Hz, 2H), 3.64 – 3.52 (m, 2H), 3.44 (d, *J* = 7.0 Hz, 2H), 3.05 – 2.80 (m, 2H), 2.64 – 2.50 (m, 1H), 2.23 – 2.09 (m, 2H), 2.01 – 1.59 (m, 5H), 1.51 (d, *J* = 14.7 Hz, 1H), 1.44 – 1.27 (m, 1H), 1.20 – 1.11 (m, 2H), 1.04 – 0.95 (m, 2H). MS (ESI) m/z 624.3 $[M+H]^+$.

[0891] Cpd. No. 317; MS (ESI) m/z 624.3 $[M+H]^+$.

[0892] Cpd. No. 318; MS (ESI) m/z 500.3 $[M+H]^+$.

[0893] Cpd. No. 320; ^{1}H NMR (400 MHz, MeOD) δ 7.66 (d, *J* = 8.6 Hz, 2H), 7.52 – 7.34 (m, 5H), 6.52 (d, *J* = 8.8 Hz, 2H), 4.25 – 4.04 (m, 3H), 3.80 – 3.68 (m, 5H), 3.63 – 3.52 (m, 2H), 3.43 (d, *J* = 7.0 Hz, 2H), 3.23 – 3.06 (m, 2H), 2.96 – 2.83 (m, 2H), 2.72 – 2.51 (m, 1H), 2.30 (d, *J* = 14.1 Hz, 1H), 2.09 – 1.89 (m, 2H), 1.86 – 1.77 (m, 1H), 1.70

– 1.56 (m, 2H), 1.50 – 1.39 (m, 1H), 1.32 – 1.24 (m, 1H), 1.19 – 1.10 (m, 2H), 1.05 – 0.94 (m, 2H). MS (ESI) m/z 591.3 $[M+H]^+$.

[0894] Cpd. No. 319; MS (ESI) m/z 591.3 $[M+H]^+$.

[0895] Cpd. No. 321; ^{1}H NMR (400 MHz, MeOD) δ 7.96 – 7.79 (m, 2H), 7.70 (d, *J* = 8.7 Hz, 2H), 7.61 – 7.43 (m, 3H), 7.42 – 7.22 (m, 5H), 6.55 – 6.33 (m, 2H), 4.29 – 4.00 (m, 2H), 3.85 – 3.56 (m, 4H), 3.51 (d, *J* = 12.5 Hz, 1H), 3.45 – 3.39 (m, 2H), 3.21 – 3.04 (m, 1H), 3.01 – 2.96 (m, 1H), 2.93 (d, *J* = 9.8 Hz, 1H), 2.87 (d, *J* = 11.6 Hz, 1H), 2.83 – 2.75 (m, 1H), 2.22 (s, 1H), 2.14 (d, *J* = 14.9 Hz, 1H), 1.95 (d, *J* = 14.0 Hz, 1H), 1.88 (s, 1H), 1.73 (s, 1H), 1.67 – 1.44 (m, 2H), 1.32 (d, *J* = 25.5 Hz, 1H), 0.94 (s, 1H). MS (ESI) m/z 630.3 $[M+H]^+$.

[0896] Cpd. No. 322; ^{1}H NMR (400 MHz, MeOD) δ 7.86 (d, *J* = 7.6 Hz, 2H), 7.72 (d, *J* =8.4Hz, 2H), 7.60-7.44 (m, 7H), 7.37 (t, *J* = 7.2Hz, 1H), 6.47 (d, *J* =8.8Hz, 2H), 4.16 (t, *J* = 8.0, 2H), 3.97-3.91 (m, 2H), 3.77-3.72 (m, 2H), 3.64 (d, *J* =12Hz, 1H), 3.54 (d, *J* =12Hz, 1H), 3.48-3.42 (m, 3H), 3.06(t, *J* = 11.2Hz, 1H), 2.96 (t, *J* = 12Hz, 1H), 2.73 (s, 3H), 2.50-2.38 (m, 2H), 2.08 (t, *J* = 16.4Hz, 2H), 1.88-1.77 (m, 2H), 1.69-1.63 (m, 1H), 1.53-1.51 (m, 1H), 1.36 (m, 4H). MS (ESI) m/z 630.3 $[M+H]^+$.

[0897] Cpd. No. 381; MS (ESI) m/z 666.3 $[M+H]^+$.

[0898] Cpd. No. 382; MS (ESI) m/z 496.3 $[M+H]^+$.

[0899] Cpd. No. 383; MS (ESI) m/z 496.3 $[M+H]^+$.

[0900] Cpd. No. 384; MS (ESI) m/z 532.2 $[M+H]^+$.

[0901] Cpd. No. 385; MS (ESI) m/z 532.2 $[M+H]^+$.

[0902] Cpd. No. 386; MS (ESI) m/z 466.2 $[M+H]^+$.

[0903] Cpd. No. 387; MS (ESI) m/z 466.2 $[M+H]^+$.

[0904] Cpd. No. 388; MS (ESI) m/z 516.2 $[M+H]^+$.

[0905] Cpd. No. 389; MS (ESI) m/z 516.2 $[M+H]^+$.

[0906] Cpd. No. 390; ^{1}H NMR (400 MHz, MeOD) δ 8.85 (s, 1H), 7.72 – 7.35 (m, 7H), 7.21 (t, *J* = 7.4 Hz, 1H), 6.48 (d, *J* = 8.8 Hz, 2H), 5.01 (q, *J* = 15.6 Hz, 2H), 4.17 (td, *J* = 8.0, 2.0 Hz, 2H), 3.74 (ddd, *J* = 8.3, 5.7, 3.0 Hz, 2H), 3.62 (d, *J* = 11.6 Hz, 1H), 3.51 – 3.41 (m, 3H), 3.26 – 3.21 (m, 1H), 3.07 (t, *J* = 12.3 Hz, 1H), 3.02 – 2.86 (m, 2H), 2.69 (s, 2H), 2.45 (t, *J* = 11.1 Hz, 1H), 2.30 – 2.17 (m, 1H), 2.13 – 1.93 (m, 2H), 1.75 – 1.37 (m, 6H), 1.20 – 1.09 (m, 1H), 1.07 – 0.97 (m, 1H). MS (ESI) m/z 585.3 $[M+H]^+$.

Cpd. No. 391; ^{1}H NMR (400 MHz, MeOD) δ 8.98 (s, 1H), 8.04 (d, *J* = 9.2 Hz, 1H), 7.98 (dd, *J* = 6.8, 0.8 Hz, 1H), 7.72 (d, *J* = 6.9 Hz, 1H), 7.41 (d, *J* = 7.5 Hz, 2H), 7.36 (t, *J* = 7.5 Hz, 2H), 7.33 – 7.26 (m, 1H), 7.03 (dd, *J* = 9.1, 2.2 Hz, 1H), 6.63 (d, *J* = 2.1 Hz, 1H), 4.87 – 4.80 (m, 1H), 4.31 (t, *J* = 7.9 Hz, 3H), 4.01 – 3.79 (m, 3H), 3.48 (t, *J* = 11.9 Hz, 2H), 3.39 (d, *J* = 7.3 Hz, 2H), 3.10 – 2.89 (m, 4H), 2.33 (t, *J* = 12.0 Hz, 2H), 2.24 – 2.07 (m, 3H), 1.97 (d, *J* = 14.5 Hz, 1H), 1.78 – 1.63 (m, 7H), 1.62 – 1.50 (m, 3H), 1.46 (dd, *J* = 13.4, 2.5 Hz, 1H), 1.39 – 1.26 (m, 2H). MS (ESI) m/z 523.2 $[M+H]^+$.

[0907] Cpd. No. 406; ^{1}H NMR (400 MHz, MeOD) δ 7.59 (d, *J* = 7.5 Hz, 2H), 7.54 – 7.46 (m, 4H), 7.44 (t, *J* = 7.3 Hz, 1H), 7.30 (s, 1H), 6.94 (s, 1H), 6.46 (d, *J* = 8.8 Hz, 2H), 5.00 (s, 1H), 4.76 (d, *J* = 15.5 Hz, 1H), 4.61 (d, *J* = 15.5 Hz, 1H), 4.15 (td, *J* = 8.0, 2.4 Hz, 2H), 3.77 – 3.70 (m, 2H), 3.66 (d, *J* = 11.5 Hz, 1H), 3.51 – 3.41 (m, 3H), 3.25 – 3.16 (m, 1H), 3.06 (t, *J* = 11.7 Hz, 1H), 2.95 (t, *J* = 11.7 Hz, 1H), 2.90 – 2.82 (m, 1H), 2.72 (s, 3H), 2.70 – 2.61 (m, 1H), 2.59 (s, 3H), 2.33 (d, *J* = 13.8 Hz, 1H), 2.09 – 1.94 (m, 2H), 1.73 – 1.35 (m, 5H), 1.16 – 0.98 (m, 2H). MS (ESI) m/z 581.4 $[M+H]^+$.

[0908] Cpd. No. 407; ^{1}H NMR (400 MHz, MeOD) δ 8.80 (s, 1H), 7.67 (d, *J* = 7.9 Hz, 2H), 7.56 – 7.48 (m, 3H), 7.46 – 7.35 (m, 2H), 7.14 (d, *J* = 8.8 Hz, 2H), 6.42 (d, *J* = 8.8 Hz, 2H), 5.07 – 4.96 (m, 2H), 4.08 – 3.99 (m, 2H), 3.65 – 3.53 (m, 3H), 3.46 – 3.37 (m, 3H), 3.21 – 3.10 (m, 1H), 3.03 (t, *J* = 11.5 Hz, 1H), 2.93 (t, *J* = 11.6 Hz, 1H), 2.88 – 2.81 (m, 1H), 2.68 (s, 3H), 2.57 – 2.46 (m, 1H), 2.27 (d, *J* = 13.4 Hz, 1H), 2.06 – 1.88 (m, 3H), 1.68 – 1.56 (m, 2H), 1.55 – 1.40 (m, 3H), 1.15 – 1.05 (m, 1H), 0.95 – 0.83 (m, 1H). MS (ESI) m/z 576.3 $[M+H]^+$.

[0909] Cpd. No. 408; ^{1}H NMR (400 MHz, MeOD) δ 7.60 (d, *J* = 7.7 Hz, 2H), 7.56 – 7.41 (m, 5H), 7.32 (s, 1H), 6.95 (s, 1H), 6.46 (d, *J* = 8.8 Hz, 2H), 4.99 (s, 1H), 4.78 (d, *J* = 11.7 Hz, 1H), 4.64 (d, *J* = 15.4 Hz, 1H), 4.15 (td, *J* = 8.0, 2.2 Hz, 2H), 3.78 – 3.68 (m, 2H), 3.65 (d, *J* = 11.5 Hz, 1H), 3.53 – 3.41 (m, 3H), 3.26 – 3.17 (m, 1H), 3.06 (t, *J* = 11.6 Hz, 1H), 3.01 – 2.86 (m, 4H), 2.72 (s, 3H), 2.61 (d, *J* = 11.0 Hz, 1H), 2.33 (d, *J* = 13.7 Hz, 1H), 2.00 (dd, *J* = 25.4, 21.6 Hz, 1H), 1.72 – 1.45 (m, 3H), 1.39 (t, *J* = 7.5 Hz, 2H), 1.12 – 0.96 (m, 1H). MS (ESI) m/z 595.3 $[M+H]^+$.

[0910] Cpd. No. 409; ^{1}H NMR (400 MHz, MeOD) δ 7.52 – 7.46 (m, 4H), 7.44 – 7.32 (m, 4H), 7.07 (s, 1H), 6.47 (d, *J* = 8.8 Hz, 2H), 5.26 (s, 1H), 4.71 (d, *J* = 16.4 Hz, 1H), 4.59 (d, *J* = 15.2 Hz, 1H), 4.16 (t, *J* = 8.0 Hz, 2H), 3.74 (dd, *J* = 7.9, 5.7 Hz, 2H), 3.57

(s, 2H), 3.45 (d, *J* = 7.1 Hz, 2H), 3.27 – 3.18 (m, 1H), 3.12 – 3.01 (m, 2H), 2.84 – 2.74 (m, 1H), 2.70 (s, 3H), 2.68 – 2.60 (m, 1H), 2.46 (d, *J* = 11.5 Hz, 2H), 2.19 (d, *J* = 14.3 Hz, 1H), 2.06 – 1.97 (m, 2H), 1.76 – 1.55 (m, 5H), 1.43 – 1.33 (m, 2H), 1.28 (t, *J* = 7.3 Hz, 3H). MS (ESI) m/z 595.3 $[M+H]^+$.

[0911] Cpd. No. 410; ^{1}H NMR (400 MHz, MeOD) δ 8.10 (s, 1H), 7.78 – 7.67 (m, 3H), 7.57 – 7.45 (m, 1H), 7.38 (d, *J* = 2.0 Hz, 1H), 7.28 – 7.10 (m, 3H), 7.07 (s, 1H), 6.48 (d, *J* = 8.9 Hz, 2H), 5.13 (s, 1H), 4.73 (d, *J* = 16.1 Hz, 1H), 4.61 (d, *J* = 15.5 Hz, 1H), 4.15 (t, *J* = 8.0 Hz, 2H), 3.88 (s, 3H), 3.72 (dd, *J* = 7.9, 5.7 Hz, 2H), 3.62 – 3.51 (m, 2H), 3.43 (d, *J* = 7.1 Hz, 2H), 3.27 – 3.19 (m, 1H), 3.06 (t, *J* = 11.6 Hz, 2H), 2.78 – 2.72 (m, 1H), 2.70 (s, 3H), 2.52 – 2.47 (m, 1H), 2.45 (s, 3H), 2.15 (d, *J* = 14.5 Hz, 1H), 2.09 – 1.93 (m, 2H), 1.74 – 1.51 (m, 5H), 1.40 – 1.23 (m, 2H). MS (ESI) m/z 718.4 $[M+H]^+$.

[0912] Cpd. No. 411; ^{1}H NMR (400 MHz, MeOD) δ 8.10 (s, 1H), 7.76 – 7.68 (m, 3H), 7.57 – 7.51 (m, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.38 (d, *J* = 11.8 Hz, 1H), 7.34 (s, 1H), 7.21 (t, *J* = 8.1 Hz, 1H), 6.96 (s, 1H), 6.47 (d, *J* = 8.9 Hz, 2H), 4.94 (s, 1H), 4.71 (dd, *J* = 28.9, 15.8 Hz, 2H), 4.15 (td, *J* = 8.0, 1.9 Hz, 2H), 3.88 (s, 3H), 3.75 – 3.68 (m, 2H), 3.64 (d, *J* = 11.4 Hz, 1H), 3.51 – 3.46 (m, 1H), 3.43 (d, *J* = 6.4 Hz, 2H), 3.25 – 3.17 (m, 1H), 3.06 (t, *J* = 12.0 Hz, 1H), 2.99 – 2.88 (m, 2H), 2.71 (s, 3H), 2.63 (s, 3H), 2.59 – 2.50 (m, 1H), 2.30 (d, *J* = 14.3 Hz, 1H), 2.11 – 1.96 (m, 2H), 1.70 – 1.50 (m, 4H), 1.47 – 1.27 (m, 1H), 1.17 – 0.97 (m, 2H). MS (ESI) m/z 718.4 $[M+H]^+$.

[0913] Cpd. No. 412; ^{1}H NMR (400 MHz, MeOD) δ 8.79 (s, 1H), 7.72 – 7.64 (m, 4H), 7.57 – 7.50 (m, 3H), 7.44 (d, *J* = 7.4 Hz, 1H), 7.41 (d, *J* = 8.0 Hz, 1H), 6.53 (d, *J* = 8.9 Hz, 2H), 4.99 (s, 2H), 4.79 – 4.74 (m, 3H), 4.62 – 4.52 (m, 1H), 4.18 (td, *J* = 8.0, 2.4 Hz, 2H), 3.80 – 3.72 (m, 2H), 3.62 (d, *J* = 10.5 Hz, 1H), 3.51 – 3.40 (m, 3H), 3.24 – 3.18 (m, 1H), 3.04 (t, *J* = 12.6 Hz, 1H), 2.96 (t, *J* = 11.9 Hz, 1H), 2.92 – 2.84 (m, 1H), 2.68 (s, 3H), 2.57 – 2.42 (m, 1H), 2.27 (d, *J* = 14.7 Hz, 1H), 2.07 – 1.93 (m, 2H), 1.69 – 1.43 (m, 6H), 1.38 – 1.27 (m, 1H), 1.16 – 1.04 (m, 1H), 0.97 – 0.85 (m, 1H). MS (ESI) m/z 662.3 $[M+H]^+$.

[0914] Cpd. No. 413; ^{1}H NMR (400 MHz, MeOD) δ 7.55 (dd, *J* = 14.5, 7.8 Hz, 1H), 7.44 (d, *J* = 7.8 Hz, 1H), 7.39 (d, *J* = 11.2 Hz, 1H), 7.33 (d, *J* = 1.8 Hz, 1H), 7.24 – 7.18 (m, 1H), 7.17 – 7.11 (m, 2H), 6.96 (s, 1H), 6.46 – 6.38 (m, 2H), 4.95 (s, 1H), 4.71 (dd, *J* = 35.2, 15.6 Hz, 2H), 4.03 (td, *J* = 7.5, 2.2 Hz, 2H), 3.64 (d, *J* = 11.7 Hz, 1H), 3.62 –

3.53 (m, 2H), 3.50 – 3.44 (m, 1H), 3.41 (d, *J* = 6.3 Hz, 2H), 3.20 – 3.11 (m, 1H), 3.06 (t, *J* = 12.1 Hz, 1H), 2.99 – 2.86 (m, 2H), 2.71 (s, 3H), 2.64 (s, 3H), 2.62 – 2.50 (m, 1H), 2.31 (d, *J* = 14.0 Hz, 1H), 2.09 – 1.98 (m, 2H), 1.70 – 1.51 (m, 3H), 1.45 – 1.29 (m, 1H), 1.17 – 0.98 (m, 2H). MS (ESI) m/z 608.3 $[M+H]^+$.

[0915] Cpd. No. 414; ^{1}H NMR (400 MHz, MeOD) δ 7.58 – 7.49 (m, 1H), 7.38 (d, *J* = 2.0 Hz, 1H), 7.26 (d, *J* = 7.3 Hz, 1H), 7.20 (td, *J* = 8.2, 2.2 Hz, 1H), 7.16 – 7.12 (m, 3H), 7.11 – 7.02 (m, 1H), 6.46 – 6.39 (m, 2H), 5.12 (s, 1H), 4.73 (d, *J* = 15.7 Hz, 1H), 4.61 (d, *J* = 15.6 Hz, 1H), 4.04 (t, *J* = 7.6 Hz, 2H), 3.64 – 3.51 (m, 4H), 3.42 (d, *J* = 7.1 Hz, 2H), 3.21 – 3.13 (m, 1H), 3.05 (t, *J* = 11.5 Hz, 2H), 2.78 – 2.73 (m, 1H), 2.71 (s, 3H), 2.45 (s, 3H), 2.43 – 2.32 (m, 1H), 2.15 (d, *J* = 14.0 Hz, 1H), 2.09 – 1.97 (m, 2H), 1.73 – 1.47 (m, 5H), 1.40 – 1.22 (m, 2H). MS (ESI) m/z 608.3 $[M+H]^+$.

[0916] Cpd. No. 415; MS (ESI) m/z 515.2 $[M+H]^+$.

[0917] Cpd. No. 416; MS (ESI) m/z 515.2 $[M+H]^+$.

[0918] Cpd. No. 417; ^{1}H NMR (400 MHz, MeOD) δ 7.85 (d, *J* = 7.7 Hz, 1H), 7.77 (d, *J* = 6.6 Hz, 1H), 7.71 (t, *J* = 7.8 Hz, 1H), 7.56 – 7.46 (m, 1H), 6.54 – 6.45 (m, 1H), 4.16 (td, *J* = 8.0, 2.3 Hz, 1H), 3.73 (ddd, *J* = 7.5, 5.8, 1.3 Hz, 1H), 3.58 (d, *J* = 12.3 Hz, 1H), 3.44 (d, *J* = 7.2 Hz, 1H), 3.26 – 3.23 (m, 0H), 3.22 – 3.17 (m, 1H), 3.16 – 3.03 (m, 1H), 2.52 – 2.40 (m, 1H), 2.37 – 2.27 (m, 1H), 2.20 – 2.10 (m, 1H), 1.93 – 1.77 (m, 2H), 1.75 (s, 2H), 1.72 – 1.64 (m, 1H), 1.52 – 1.40 (m, 1H), 1.38 – 1.24 (m, 1H). MS (ESI) m/z 565.3 $[M+H]^+$.

[0919] Cpd. No. 418; MS (ESI) m/z 565.3 $[M+H]^+$.

[0920] Cpd. No. 419; MS (ESI) m/z 572.3 $[M+H]^+$.

[0921] Cpd. No. 420; MS (ESI) m/z 572.3 $[M+H]^+$.

[0922] Cpd. No. 421; MS (ESI) m/z 610.3 [M+H]+.

[0923] Cpd. No. 422; MS (ESI) m/z 543.3 [M+H]+.

[0924] Cpd. No. 423; MS (ESI) m/z 543.3 [M+H]+.

[0925] Cpd. No. 424; MS (ESI) m/z 624.3 [M+H]+.

[0926] Cpd. No. 425; MS (ESI) m/z 624.3 [M+H]+.

[0927] The following Compounds of the Disclosure, *see* Table 5, were prepared using the illustrative methods described in Examples 1-12, and/or methods known to those skilled in the art in view of this disclosure, and characterized by ESI-MS as provided in Table 6.

Table 6

Cpd. No.	MS (ESI) m/z $[M+H]^+$
426	517.75
427	624.75
428	624.67
429	649.83
430	599.92
431	599.92
432	613.92
433	656.92
434	692.45
435	720.39
436	706.51
437	728.46
438	568.3
439	568.2
440	594.2
441	609.3
442	599.2
443	600.3
444	643.1
445	600.3
446	642.2
447	668.1
448	668.3
449	690.2
450	617.1
451	600.3
452	617.3
453	613.3
454	588.2
455	613.1
456	613.2
457	613.3
458	613.2
459	617.1
460	580.2
461	580.3
462	627.2
463	627.1
464	613.3
465	631.2
466	631.3
467	649.1
468	529.2

469	649.3
470	692.1
471	720.3
472	747.2
473	661.1
474	710.3
475	562.3
476	562.2
477	534.1
478	534.3
479	612.2
480	713.2
481	670.3
482	706.3
483	649.3
484	645.2
485	645.1
486	645.2
487	623.3
488	651.1
489	630.2
490	497.3
491	497.2
492	439.3
493	511.1
494	525.2
495	469.3
496	469.3
497	483.2
498	515.3
499	515.3
500	565.3
501	565.3
502	572.3
503	572.3
504	574.3
505	574.3
506	628.3
507	603.3
508	568.3
509	615.3
510	615.3
511	617.3
512	633.3
513	586.3
514	661.3

515	613.4
516	613.4
517	631.5
518	631.5
519	629.3
520	629.3
521	635.3
522	665.3

EXAMPLE 14

Menin Binding Affinity

[0928] A fluorescence polarization (FP) competitive binding assay was used to determine the binding affinities of representative menin inhibitors. A FAM labeled fluorescent probe was designed and synthesized based on a MLL1 peptide (FAM-MM2). Equilibrium dissociation constant (K_d) value of FAM-MM2 to menin protein was determined from protein saturation experiments by monitoring the total fluorescence polarization of mixtures composed with the fluorescent probe at a fixed concentration and the protein with increasing concentrations up to full saturation. Serial dilutions of the protein were mixed with FAM-MM2 to a final volume of 200 μl in the assay buffer (PBS with 0.02% Bovine γ-Globulin and 4% DMSO. 0.01% Triton X-100 was added right before assays). Final FAM-MM2 concentration was 2 nM. Plates were incubated at room temperature for 30 minutes with gentle shaking to assure equilibrium. FP values in millipolarization units (mP) were measured using the Infinite M-1000 plate reader (Tecan U.S., Research Triangle Park, NC) in Microfluor 1 96-well, black, v-bottom plates (Thermo Scientific, Waltham, MA) at an excitation wavelength of 485 nm and an emission wavelength of 530 nm. K_d value of FAM-MM2, which was calculated by fitting the sigmoidal dose-dependent FP increases as a function of protein concentrations using Graphpad Prism 6.0 software (Graphpad Software, San Diego, CA), is determined as 1.4 nM.

[0929] The IC_{50}, *see* Table 3, and K_i values of representative Compounds of the Disclosure were determined in a competitive binding experiment. Mixtures of 5 μl of the tested compounds in DMSO and 195 μl of preincubated protein/probe complex solution in the assay buffer were added into assay plates which were incubated at room temperature for 30 minutes with gentle shaking. Final concentration of the menin protein was 4 nM, and final probe concentration is 2 nM. Negative controls containing protein/probe complex only (equivalent to 0% inhibition), and positive controls containing only free probes (equivalent to 100% inhibition), were included in each assay plate. FP values were measured as described above. IC_{50} values were determined by nonlinear regression fitting of the competition curves.

Table 3

Cpd. No.	Menin Binding Affinity IC_{50} (μM)	Cpd. No.	Menin Binding Affinity IC_{50} (μM)
19	0.061	**222**	2.0
20	1.3	**223**	0.014
21	1.1	**224**	0.331
22	0.473	**225**	0.009
23	0.054	**226**	0.014
24	0.416	**227**	0.498
25	2.7	**228**	0.004
26	No inhibition	**229**	0.160
27	0.071	**230**	0.007
28	0.379	**231**	0.068
29	0.091	**232**	0.020
30	0.439	**233**	0.178
31	0.037	**234**	0.050
32	0.059	**235**	6.2
33	0.019	**236**	0.012
34	1.8	**237**	0.042
35	3.2	**238**	0.008
37	0.449	**239**	0.046
38	0.304	**240**	0.009
39	0.124	**241**	0.849
40	0.817	**242**	2.1
41	0.166	**243**	4.2
42	0.029	**244**	2.3

Cpd. No.	Menin Binding Affinity IC_{50} (μM)	Cpd. No.	Menin Binding Affinity IC_{50} (μM)
43	0.026	**245**	3.3
44	0.910	**246**	35.6
45	0.027	**247**	1.1
46	0.023	**248**	0.8
47	0.137	**249**	1.9
48	0.007	**250**	4.7
49	0.009	**251**	7.1
50	0.007	**252**	1.2
51	0.008	**253**	14.4
52	0.025	**254**	23.2
53	1.1	**255**	4.7
54	0.011	**256**	3.3
55	0.669	**257**	4.6
56	18.2	**258**	0.563
57	No inhibition	**259**	10.3
58	0.241	**260**	17.0
59	2.3	**261**	9.3
60	No inhibition	**262**	6.9
61	No inhibition	**263**	0.010
62	36.2	**264**	0.555
63	6.0	**265**	4.9
64	0.061	**266**	4.5
65	2.8	**267**	0.437
66	1.1	**268**	4.7
67	1.2	**269**	0.009
68	0.181	**270**	0.881
69	0.030	**271**	0.005
70	0.012	**272**	0.180
71	190	**273**	37.6
72	609.8	**274**	19.2
73	9.9	**275**	0.012
74	3.1	**276**	1.2
75	142.4	**277**	0.008
76	1.3	**278**	0.296
77	2581	**279**	0.065
78	No inhibition	**280**	1.4
79	0.7	**281**	0.029
80	11.6	**282**	3.3

Cpd. No.	Menin Binding Affinity IC_{50} (μM)	Cpd. No.	Menin Binding Affinity IC_{50} (μM)
81	1.9	**283**	0.010
82	6.2	**284**	0.011
83	0.847	**285**	0.009
84	8.2	**286**	0.004
85	0.036	**287**	0.247
86	0.055	**288**	0.012
87	0.122	**289**	0.004
88	0.075	**290**	0.009
89	13.1	**291**	0.007
90	2.4	**292**	0.011
91	0.042	**293**	2.8
92	0.019	**294**	11.1
93	0.052	**295**	1.9
94	0.029	**296**	0.4
95	0.024	**297**	2.1
96	0.587	**298**	0.3
97	0.049	**299**	16.8
98	0.021	**300**	56.5
99	0.802	**301**	34.8
100	4.7	**302**	6.5
101	0.010	**303**	75.3
102	0.011	**304**	10.7
103	0.012	**305**	42.1
104	32.7	**306**	40.0
105	20.2	**307**	30.6
106	84.1	**308**	0.066
107	298.7	**309**	11.4
108	56.5	**310**	0.045
109	0.825	**311**	5.7
110	575.4	**312**	0.013
111	46.2	**313**	13.8
112	41.6	**314**	0.031
113	0.067	**315**	0.131
114	32.6	**316**	0.003
115	4.0	**317**	0.161
116	6.0	**318**	20.9
117	7.2	**319**	0.031

Cpd. No.	Menin Binding Affinity IC_{50} (μM)	Cpd. No.	Menin Binding Affinity IC_{50} (μM)
118	21.8	**320**	5.1
119	0.015	**321**	0.004
120	5.7	**322**	0.108
121	13.1	**323**	10.4
122	57.5	**324**	9.6
123	No inhibition	**325**	1.8
124	No inhibition	**326**	2.7
125	No inhibition	**327**	485.2
126	58.4	**328**	119.4
127	293.9	**329**	19
128	4.1	**330**	111.4
129	0.036	**331**	23.3
130	10.6	**332**	0.261
131	1.1	**333**	5.1
132	0.077	**334**	3.2
133	0.030	**335**	5.6
134	0.067	**336**	29.4
135	0.025	**337**	25.8
136	0.009	**338**	10.2
137	0.008	**339**	5.2
138	0.099	**340**	2.9
139	0.073	**340**	1.5
140	0.104	**342**	0.897
141	0.028	**343**	8.8
142	0.008	**344**	180.5
143	0.028	**345**	0.011
144	0.023	**346**	0.569
145	0.015	**347**	0.014
146	0.013	**348**	0.819
147	0.009	**349**	0.015
148	0.006	**350**	1.2
149	0.012	**351**	0.015
151	0.015	**352**	2.7
152	0.009	**353**	0.006
153	0.007	**354**	0.062
154	0.006	**355**	0.045
155	0.016	**356**	0.022

Cpd. No.	Menin Binding Affinity IC_{50} (μM)	Cpd. No.	Menin Binding Affinity IC_{50} (μM)
156	0.008	**357**	0.032
157	0.016	**358**	0.221
158	0.008	**359**	0.012
159	No inhibition	**360**	1.4
160	No inhibition	**361**	0.063
161	0.021	**362**	0.008
162	No inhibition	**363**	0.027
163	No inhibition	**364**	3.1
164	0.008	**365**	0.281
165	2993	**366**	0.009
166	1412	**367**	0.030
167	172	**368**	0.506
168	5.6	**369**	0.068
169	49.9	**370**	3.6
170	47.6	**371**	2.1
171	No test	**372**	0.048
172	11.2	**373**	0.112
173	3.0	**374**	4.7
174	24.6	**375**	0.011
175	8.8	**376**	0.006
176	140.1	**377**	1.129
177	3.6	**378**	0.032
178	6.5	**379**	3.8
179	3.8	**380**	0.798
180	9.7	**381**	0.013
181	18.1	**382**	0.102
182	23.7	**383**	2.5
183	0.073	**384**	4.6
184	2.6	**385**	0.013
185	0.007	**386**	No inhibition
186	1.0	**387**	No inhibition
187	0.018	**388**	15.1
188	1.7	**389**	6.5
189	20.5	**390**	0.005
190	2.0	**392**	0.007
191	0.623	**393**	0.008

Cpd. No.	Menin Binding Affinity IC_{50} (μM)	Cpd. No.	Menin Binding Affinity IC_{50} (μM)
192	28.0	**394**	0.015
193	0.237	**395**	0.016
194	164.6	**396**	0.012
195	0.010	**397**	0.186
196	1.0	**398**	0.167
197	0.018	**399**	0.007
198	0.853	**400**	0.029
199	9.0	**401**	0.089
200	0.017	**402**	2.4
201	0.005	**403**	0.007
202	0.113	**404**	0.212
203	0.009	**405**	0.174
204	0.122	**406**	0.003
205	0.088	**407**	0.005
206	0.003	**408**	0.003
207	2.8	**409**	0.116
208	0.435	**410**	0.049
209	0.111	**411**	0.003
210	0.004	**412**	0.004
211	0.009	**413**	0.006
212	0.454	**414**	0.539
213	0.170	**415**	0.016
214	3.4	**416**	3.28
215	0.006	**417**	1.61
216	0.396	**418**	923.13
217	11.6	**419**	0.293
218	No inhibition	**420**	11.6
219	0.003	**421**	0.004
220	0.261	**422**	0.028
221	0.075	**423**	0.776

EXAMPLE 15

Cell Growth Inhibition

[0930] Cell growth inhibitory activity of representative menin inhibitors was determined using CellTiter-Glo® Luminescent Cell Viability Assay. Cells were seeded

in 384-well white opaque cell culture plates at a density of 2,000 cells/well with serially diluted compounds and incubated at 37°C in an atmosphere of 95% air and 5% CO_2 for 4 days. Cell viability was determined using the CellTiter-Glo® Luminescent Cell Viability Assay Kit (Promega, Madison, WI) according to the manufacture's instruction. Briefly, a volume of CellTiter-Glo® Reagent equal to the volume of cell culture medium was added to each well, and then the plates were incubated at room temperature for 10-20 minutes. The luminescent signal was measured using a Tecan Infinite M1000 multimode microplate reader (Tecan, Morrisville, NC). The half maximal inhibitory concentration (IC_{50}) was calculated using the GraphPad Prism 5 software (GraphPad Software, La Jolla, CA).

Table 4

Cpd. No.	Cell Growth Inhibition IC_{50} (μM)	
	MV4;11	MOLM13
19	1.6±0.1	7.3
23	1.0±0.4	5.0
27	0.9	3.6
43	0.896±0.056	2.1
45	0.845±0.436	5.0
46	0.972±0.558	5.1±0.2
48	0.908	2.8
49	0.898	4
51	0.67	1.46
70	2.2	3.5
85	1.6	4.2
86	0.864±0.017	1.2±0.5
91	1.3±0.3	1.7±0.004
92	0.961±0.384	1.6±0.1
93	0.779±0.068	1.1±0.7
94	2.0	2.3
95	1.8	1.9
101	0.3	0.73
102	0.2668	0.7075
103	0.49	2.26
111	14.4	96.2
113	1.6	2.4

Cpd. No.	Cell Growth Inhibition IC_{50} (μM)	
119	1.8	1.3
133	1.7±1.0	2.9±0.8
134	1.1	3.8
135	1.3±0.4	2.1±1.0
136	1.2	3.8
137	1.0±0.2	1.9±0.7
141	4.7	54.7
142	0.979±0.335	3.2±0.3
143	1.2±1.0	3.4±0.5
144	1.6±1.1	4.0±0.7
145	1.6±0.8	3.3±0.5
146	0.785±0.247	1.9±1.2
147	0.956±0.727	1.6±0.8
148	0.810±0.364	1.5±0.9
149	0.493	0.331
151	1.3	0.627
152	0.46	0.49
153	0.79	0.77
156	0.654	1.8
157	1.8	4.4
158	0.8	1.56
164	0.27	0.72
185	0.624±0.165	0.783±0.474
187	1.2±0.3	1.9±0.7
195	0.991	1.5
201	0.090±0.051	0.399±0.153
203	0.234	0.687
206	0.119±0.048	0.411±0.300
210	0.023±0.016	0.135±0.093
211	0.3017	0.5457
215	0.173±0.048	0.415±0.208
219	0.074±0.011	0.236
223	0.29	0.49
225	0.24	0.82
228	0.18	0.25
230	0.092	0.25
232	0.3	0.94
234	1.11	6.41
238	0.027	0.16

Cpd. No.	Cell Growth Inhibition IC_{50} (μM)	
240	0.2	0.54
263	0.254	1.4
269	0.2728	1.729
271	0.123±0.043	0.717±0.002
272	4.294±1.446	2.971
275	0.45	0.41
277	0.12	0.43
278	2.27	2.12
281	0.55	2.35
283	0.21	0.53
284	2.59	> 10
285	2.48	12.39
286	0.48	5.69
288	0.35	48.75
289	0.17	0.32
290	0.11	0.32
291	0.2	0.71
292	0.13	1.34
314	2.97	> 10
316	0.3	1.8
319	0.33	2.77
321	0.73	1.25
345	0.54	0.71
347	0.36	0.44
349	0.44	0.87
351	3.02	16.05
353	0.075	0.25
354	1.3	4.7
356	0.71	0.69
359	0.43	1.46
362	4.79	>10
363	0.56	2.64
366	0.035	0.14
367	1.66	2.96
369	3.5	7.71
372	2.03	5.01
375	0.39	1.73
376	10.46±2.08	>10
381	0.14	0.67
390	0.021	0.082

Cpd. No.	Cell Growth Inhibition IC_{50} (μM)	
392	0.084±0.032	0.76±0.32
393	0.25	0.88
394	0.43	1.94
395	0.65	2.29
396	0.46	1.46
397	4.54	> 10
398	4.57	> 10
399	0.11	1.63
400	0.83	6.11
403	0.19	1.3
404	>10	>10
406	0.004±0.002	0.009±0.0004
407	0.41±0.28	0.69±0.089
408	0.005±0.002	0.017±0.007
409	1.7	1.6
410	2.7	3.1
411	0.003	0.016

EXAMPLE 16

Mechanism of Action Studies

[0931] MOLM-13 or MV4-11 cells were seeded in a 6-well plate at a density of 500,000 cells/well in 2 ml of culture medium and treated with either Cpd. No. 210 or Cpd. No. 366 at the concentrations as indicated. About 4 days after the treatments, cells were harvested and the expression of each gene was measured with qPCR.

[0932] In MOLM-13 cells, Cpd. No. 210 and Cpd. No. 366 reduced MEIS1 after 4 days of treatment. These compounds also reduced HOX7 and HOX10 in a dose dependent manner. Cpd. No. 366 may reduce MYB gene at high concentration. MYB encodes the protein that plays an essential role in the regulation of hematopoiesis. *See* Fig. 1.

[0933] In MV4-11 cells, Cpd. No. 210 and Cpd. No. 366 reduced MEIS1 after 4 days of treatment. These compounds also reduced HOX10 at a dose dependent manner. Since the level of HOX7 in MV4-11 cells is low, the effect of these compounds on

HOX7 is not as robust as those of HOX10. There is no effect of Cpd. No. 210 and Cpd. No. 366 on MYB after 4 days of treatment at the concentration tested. *See* Fig. 2.

EXAMPLE 17

Mechanism of Action Studies

[0934] MOLM-13 cells were seeded in a 6-well plate at a density of 500,000 cells/well in 2 ml of culture medium and treated with either Cpd. No. 366 or Cpd. No. 238 at the concentrations as indicated. About 66 hours after the treatment, cells were harvested and the expression of each gene was measured with qPCR.

[0935] In MOLM-13 cells, Cpd. No. 366 or Cpd. No. 238 reduced MEIS1 after 66 hours of treatment. The compounds also reduced HOX7 and HOX10 aint a dose dependent manner. The compounds had not effect on ITGAM, a gene coding for CD11b. *See* Fig. 3.

EXAMPLE 18

Mechanism of Action Studies

[0936] MOLM-13 or MV4-11 cells were seeded in a 6-well plate at a density of 500,000 – 800,000 cells/well in 2 ml of culture medium and treated with either Cpd. No. 366 or Cpd. No. 215 at the concentrations as indicated. About 40 hours after the treatment, cells were harvested and the expression of each gene was measured with qPCR.

[0937] In MOLM-13 cells, Cpd. No. 366 reduced MEIS1 after 40 hours of treatment. Cpd. No. 366 also reduces all the tested HOX genes at a dose dependent manner. Cpd. No. 215 has a similar effect, except on HOX9 gene. *See* Fig. 4.

[0938] In MV4-11 cells, Cpd. No. 366 reduced MEIS1 after 40 hours of treatment. Cpd. No. 366 also significantly reduced HOX10 and HOX11 genes. Neither Cpd. No. 366 nor Cpd. No. 215 showed an effect on HOX7 gene at the concentrations tested and after 40 hours of treatment. *See* Fig. 5.

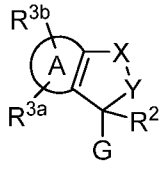
[0939] Having now fully described the methods, compounds, and compositions of matter provided herein, it will be understood by those of skill in the art that the same can be performed within a wide and equivalent range of conditions, formulations, and

other parameters without affecting the scope of the methods, compounds, and compositions provided herein or any embodiment thereof.

[0940] All patents, patent applications and publications cited herein are fully incorporated by reference herein in their entirety.

What is Claimed Is:

1. A compound having Formula **I**:

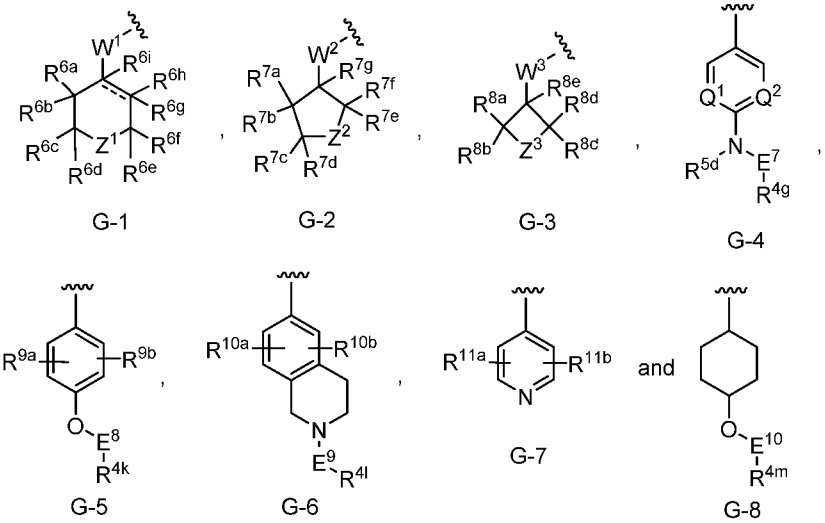


I,

or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein:

is a fused thienyl or fused phenyl group,

G is selected from the group consisting of:



G-1, G-2, G-3, G-4, G-5, G-6, G-7, and G-8;

W^1 is absent or $-CH_2-$;

Z^1 is selected from the group consisting of $-C(R)(-E^1-R^{4a})-$, $-N(-E^1-R^{4a})-$ and $-C[-N(-E^2-R^{4b})(R^{4h})](R^{5a})-$;

W^2 is absent or $-CH_2-$;

Z^2 is selected from the group consisting of $-N(-E^3-R^{4c})-$ and $-C[-N(-E^4-R^{4d})(R^{4i})](R^{5b})-$;

W^3 is absent or $-CH_2-$;

Z^3 is selected from the group consisting of $-N(-E^5-R^{4e})-$ and $-C[-N(-E^6-R^{4f})(R^{4j})](R^{5c})-$;

=== is a single or double bond, with the proviso that when === is a double bond, R^{6h} and R^{6i} are absent;

Q^1 and Q^2 are each independently CH or N;

X-Y is selected from the group consisting of

$-N(R^{1a})-C(=O)-$;

$-C(=O)-O-$;

$-C(=O)-N(R^{1b})-$;

$-CH_2N(R^{1c})-CH_2-$;

$-C(=O)N(R^{1d})-CH_2-$;

$-CH_2CH_2-N(R^{1e})-$;

$-CH_2N(R^{1f})-C(=O)-$; and

$-CH_2O-CH_2-$; or

X and Y do not form a chemical bond, and

X is selected from the group consisting of hydrogen, alkyl, halo, hydroxy, cyano, amino, alkylamino, dialkylamino, haloalkyl, alkoxy, and haloalkoxy; and

Y is selected from the group consisting of cyano, hydroxy, and $-CH_2-R^{12}$;

E^1, E^2, E^3, E^4, E^5, E^6, E^7, E^8, E^9, and E^{10} are each independently selected from the group consisting of $-C(=O)-$, $-C(=O)N(R^{13})-$, $-[C(R^{14a})(R^{14b})]_mO-$, $-C[(R^{14a})(R^{14b})]_mN(R^{15})-$, $-[C(R^{14c})(R^{14d})]_n-$, $-CH_2(=O)-$, and $-S(=O)_2-$; or

E^1, E^2, E^3, E^4, E^5, E^6, E^7, E^8, E^9, and E^{10} are each independently absent;

R is selected from the group consisting of hydrogen and alkyl;

R^{1a} is selected from the group consisting of hydrogen and alkyl;

R^{1b} is selected from the group consisting of hydrogen, alkyl, and aralkyl;

R^{1c} is selected from the group consisting of hydrogen, alkyl, haloalkyl, optionally substituted cycloalkyl, optionally substituted heterocyclo, (cycloalkyl)alkyl, (heterocycloalkyl)alkyl, aralkyl, (heteroaryl)alkyl, alkylcarbonyl, arylcarbonyl, and alkoxycarbonyl;

R^{1d} is selected from the group consisting of hydrogen, alkyl, and aralkyl;

R^{1e} is selected from the group consisting of hydrogen, alkyl, and (aryloxy)alkyl;

R^{1f} is selected from the group consisting of hydrogen and alkyl;

R^2 is selected from the group consisting of hydrogen, alkyl, alkenyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclo, optionally substituted heteroaryl, and aralkyl;

R^{3a} and R^{3b} are each independently selected from the group consisting of hydrogen, alkyl, halo, hydroxy, cyano, amino, alkylamino, dialkylamino, haloalkyl, alkoxy, and haloalkoxy;

R^{4a}, R^{4b}, R^{4c}, R^{4d}, R^{4e}, R^{4f}, R^{4g}, R^{4k}, R^{4l}, and R^{4m} are each independently selected from the group consisting of hydrogen, alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclo, optionally substituted heteroaryl, aralkyl, (heterocyclo)alkyl, and (heteroaryl)alkyl;

R^{4h}, R^{4i}, and R^{4j} are each independently selected from the group consisting of hydrogen and alkyl;

R^{5a}, R^{5b}, R^{5c}, and R^{5d} are each independently selected from the group consisting of hydrogen and alkyl;

R^{6a}, R^{6b}, R^{6c}, R^{6d}, R^{6e}, R^{6f}, R^{6g}, and R^{6h} are each independently selected from the group consisting of hydrogen and alkyl;

R^{6i} is selected from the group consisting of hydrogen, alkyl, and halo;

R^{7a}, R^{7b}, R^{7c}, R^{7d}, R^{7e}, and R^{7f} are each independently selected from the group consisting of hydrogen and alkyl;

R^{7g} is selected from the group consisting of hydrogen, alkyl, and halo;

R^{8a}, R^{8b}, R^{8c}, and R^{8d} are each independently selected from the group consisting of hydrogen and alkyl;

R^{8e} is selected from the group consisting of hydrogen, alkyl, and halo;

R^{9a} and R^{9b} are each independently selected from the group consisting of hydrogen, alkyl, halo, hydroxy, cyano, amino, alkylamino, dialkylamino, haloalkyl, alkoxy, and haloalkoxy;

R^{10a} and R^{10b} are each independently selected from the group consisting of hydrogen, alkyl, halo, hydroxy, cyano, amino, alkylamino, dialkylamino, haloalkyl, alkoxy, and haloalkoxy;

R^{11a} and R^{11b} are each independently selected from the group consisting of hydrogen, alkyl, halo, hydroxy, cyano, amino, alkylamino, dialkylamino, haloalkyl, alkoxy, and haloalkoxy;

R^{12} is selected from the group consisting of hydroxy, amino, optionally substituted heteroaryl, optionally substituted heterocyclo, and -NHC(=O)-R^{16};

m is 2, 3, 4, or 5,

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

R^{13} is selected from the group consisting of hydrogen and alkyl;

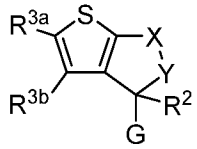
R^{14a} and R^{14b} are each independently selected from the group consisting of hydrogen and alkyl;

R^{14c} and R^{14d} are each independently selected from the group consisting of hydrogen and alkyl;

R^{15} is selected from the group consisting of hydrogen and alkyl; and

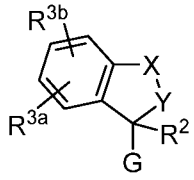
R^{16} is selected from the group consisting of alkyl, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted cycloalkyl.

2. The compound of claim 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, having Formula **II**:



II.

3. The compound of claim 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, having Formula **III**:



III.

4. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein G is G-1.

5. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein G is G-2.

6. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein G is G-3.

7. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein G is G-4.

8. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein G is G-5.

9. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein G is G-6.

10. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein G is G-7.

11. The compound of claim 4, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein W^1 is absent.

12. The compound of claim 5, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein W^2 is absent.

13. The compound of claim 6, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein W^3 is absent.

14. The compound of claims 4 or 11, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein ≡ is a single bond and R^{6a}, R^{6b}, R^{6c}, R^{6d}, R^{6e}, R^{6f}, R^{6g}, R^{6h}, and R^{6i} are each independently selected from the group consisting of hydrogen and C_{1-3} alkyl.

15. The compound of claim 14, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein R^{6a}, R^{6b}, R^{6c}, R^{6d}, R^{6e}, R^{6f}, R^{6g}, R^{6h}, and R^{6i} are each hydrogen.

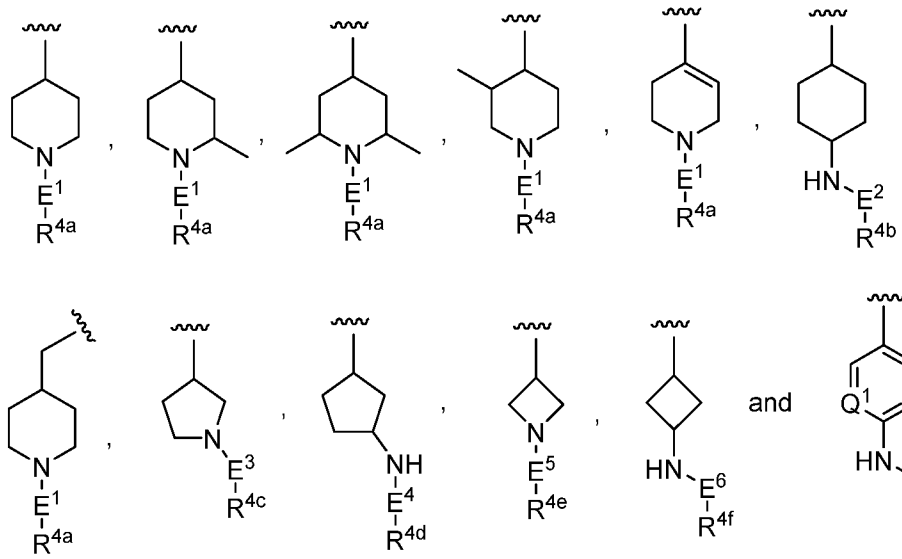
16. The compound of claims 5 or 12, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein R^{7a}, R^{7b}, R^{7c}, R^{7d}, R^{7e}, R^{7f}, and R^{7g} are each independently selected from the group consisting of hydrogen and C_{1-3} alkyl.

17. The compound of claim 16, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein R^{7a}, R^{7b}, R^{7c}, R^{7d}, R^{7e}, R^{7f}, and R^{7g} are each hydrogen.

18. The compound of claims 6 or 13, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein R^{8a}, R^{8b}, R^{8c}, R^{8d}, and R^{8e} are each independently selected from the group consisting of hydrogen and C_{1-3} alkyl.

19. The compound of claim 18, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein R^{8a}, R^{8b}, R^{8c}, R^{8d}, and R^{8e} are each hydrogen.

20. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein G is selected from the group consisting of:



with the proviso that Q^1 is N and Q^2 is selected from the group consisting of CH and N.

21. The compound of any one of claims 1-3 or 20, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein E^1, E^2, E^3, E^4, E^5, E^6, and E^7 are each independently selected from the group consisting of -C(=O)-, -C(=O)N(R^{13})-, -[C(R^{14a})(R^{14b})]$_m$O-, -[C(R^{14a})(R^{14b})]$_m$N(R^{15})-, -[C(R^{14c})(R^{14d})]$_n$-, -CH_2(=O)-, and -$S(=O)_2$-.

22. The compound of claim 21, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein E^1, E^2, E^3, E^4, E^5, E^6, and E^7 are each -C(=O)-.

23. The compound of claim 21, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein E^1, E^2, E^3, E^4, E^5, E^6, and E^7 are each -C(=O)N(R^{13})-.

24. The compound of claim 21, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein E^1, E^2, E^3, E^4, E^5, E^6, and E^7 are each -[C(R^{14a})(R^{14b})]$_m$O-.

25. The compound of claim 21, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein E^1, E^2, E^3, E^4, E^5, E^6, and E^7 are each -[C(R^{14a})(R^{14b})]$_m$N(R^{15})-.

26. The compound of claim 21, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein E^1, E^2, E^3, E^4, E^5, E^6, and E^7 are each -[C(R^{14c})(R^{14d})]$_n$-.

27. The compound of claim 26, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein n is 1 and R^{14c} and R^{14d} are each hydrogen.

28. The compound of claim 21, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein E^1, E^2, E^3, E^4, E^5, E^6, and E^7 are each -CH_2(=O)-.

29. The compound of claim 21, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein E^1, E^2, E^3, E^4, E^5, E^6, and E^7 are each $-S(=O)_2-$.

30. The compound of any one of claims 1-3 and 20, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein E^1, E^2, E^3, E^4, E^5, E^6, and E^7 are each absent.

31. The compound of any one of claims 1-3 and 20-30, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein R^{4a}, R^{4b}, R^{4c}, R^{4d}, R^{4e}, R^{4f}, and R^{4g} are each independently selected from the group consisting of alkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclo, optionally substituted heteroaryl, aralkyl, and (heteroaryl)alkyl.

32. The compound of claim 31, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein R^{4a}, R^{4b}, R^{4c}, R^{4d}, R^{4e}, R^{4f}, and R^{4g} are each alkyl.

33. The compound of claim 31, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein R^{4a}, R^{4b}, R^{4c}, R^{4d}, R^{4e}, R^{4f}, and R^{4g} are each optionally substituted cycloalkyl.

34. The compound of claim 31, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein R^{4a}, R^{4b}, R^{4c}, R^{4d}, R^{4e}, R^{4f}, and R^{4g} are each optionally substituted aryl.

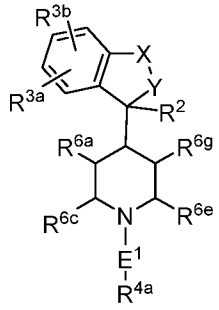
35. The compound of claim 31, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein R^{4a}, R^{4b}, R^{4c}, R^{4d}, R^{4e}, R^{4f}, and R^{4g} are each optionally substituted heterocyclo.

36. The compound of claim 31, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein R^{4a}, R^{4b}, R^{4c}, R^{4d}, R^{4e}, R^{4f}, and R^{4g} are each optionally substituted heteroaryl.

37. The compound of claim 31, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein R^{4a}, R^{4b}, R^{4c}, R^{4d}, R^{4e}, R^{4f}, and R^{4g} are each aralkyl.

38. The compound of claim 31, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein R^{4a}, R^{4b}, R^{4c}, R^{4d}, R^{4e}, R^{4f}, and R^{4g} are each (heteroaryl)alkyl.

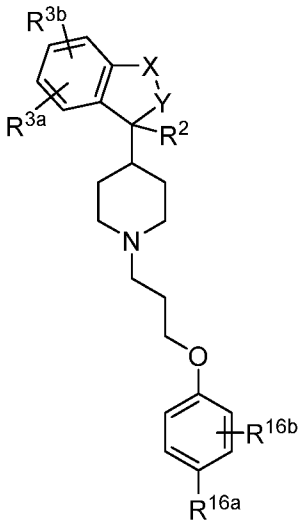
39. The compound of claim 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, having Formula **IV**:



IV.

40. The compound of claim 39, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein E^1 is -$[C(R^{14a})(R^{14b})]_mO$- and R^{4a} is selected from the group consisting of optionally substituted aryl and optionally substituted heteroaryl.

41. The compound of claim 40, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, having Formula **V**:



V,

wherein:

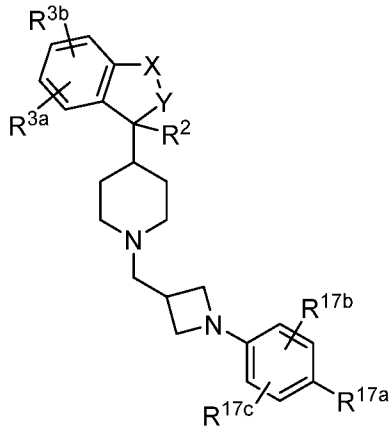
R^{16a} is selected from the group consisting of hydrogen, alkyl, halo, hydroxy, cyano, amino, alkylamino, dialkylamino, haloalkyl, alkoxy, haloalkoxy, alkylsulfonyl, haloalkylsulfonyl, cycloalkylsulfonyl, (cycloalkyl)alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, heterocyclosulfonyl, sulfonamido, optionally substituted heteroaryl, optionally substituted heterocyclo, carboxamido, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, carboxy, and carboxyalkyl; and

R^{16b} is selected from the group consisting of hydrogen, alkyl, halo, hydroxy, cyano, amino, alkylamino, dialkylamino, haloalkyl, alkoxy, and haloalkoxy.

42. The compound of claim 39, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein E^1 is $-C(R^{14c})(R^{14d})_n-$ and R^{4a} is substituted C_{4-6} heterocyclo.

43. The compound of claim 42, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein n is 1 and R^{14c} and R^{14d} are hydrogen.

44. The compound of claim 43, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, having Formula **VIi**:



VIi,

wherein:

R^{17a} is selected from the group consisting of hydrogen, alkyl, halo, hydroxy, cyano, amino, alkylamino, dialkylamino, haloalkyl, alkoxy, haloalkoxy, alkylsulfonyl, haloalkylsulfonyl, cycloalkylsulfonyl, (cycloalkyl)alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, heterocyclosulfonyl, sulfonamido, optionally substituted heteroaryl,

optionally substituted heterocyclo, carboxamido, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, carboxy, and carboxyalkyl; and

R^{17b} and R^{17c} are independently selected from the group consisting of hydrogen, alkyl, halo, hydroxy, cyano, amino, alkylamino, dialkylamino, haloalkyl, alkoxy, and haloalkoxy.

45. The compound of claim 44, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein:

R^{17a} is selected from the group consisting of alkylsulfonyl, cycloalkylsulfonyl, arylsulfonyl, and heteroarylsulfonyl; and

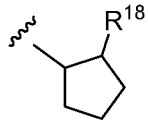
R^{17b} and R^{17c} are hydrogen.

46. The compound of any one of claims 1-45, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein R^2 is selected from the group consisting of alkyl, alkenyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclo, optionally substituted heteroaryl, and aralkyl.

47. The compound of claim 46, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein R^2 is unsubstituted cycloalkyl.

48. The compound of claim 46, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein R^2 is substituted cycloalkyl.

49. The compound of claim 48, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein R^2 is substituted cycloalkyl having Formula **VII**:



VII,

wherein:

R^{18} is selected from the group consisting of halo, nitro, cyano, hydroxy, alkylcarbonyloxy, cycloalkylcarbonyloxy, amino, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, aryloxy, aralkyloxy, alkylthio, carboxamido, sulfonamido, alkylcarbonyl,

arylcarbonyl, alkylsulfonyl, arylsulfonyl, carboxy, carboxyalkyl, optionally substituted alkyl, optionally substituted cycloalkyl, alkenyl, alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclo, alkoxyalkyl, (amino)alkyl, (carboxamido)alkyl, (heterocyclo)alkyl, -OC(=O)-amino, -N(R^{19a})C(=O)-R^{19b}, and -N(R^{20a})SO_2-R^{20b};

R^{19a} is selected from the group consisting of hydrogen and alkyl;

R^{19b} is selected from the group consisting of amino, alkoxy, alkyl, and optionally substituted aryl;

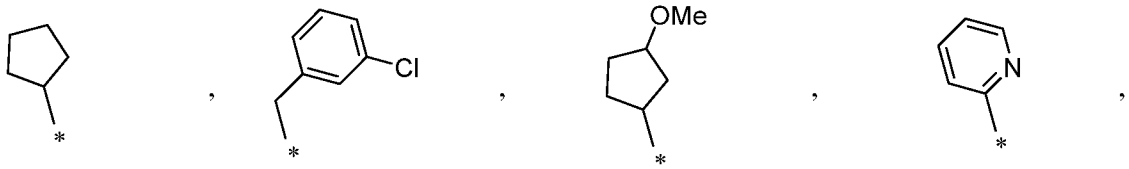
R^{20a} is selected from the group consisting of hydrogen and alkyl; and

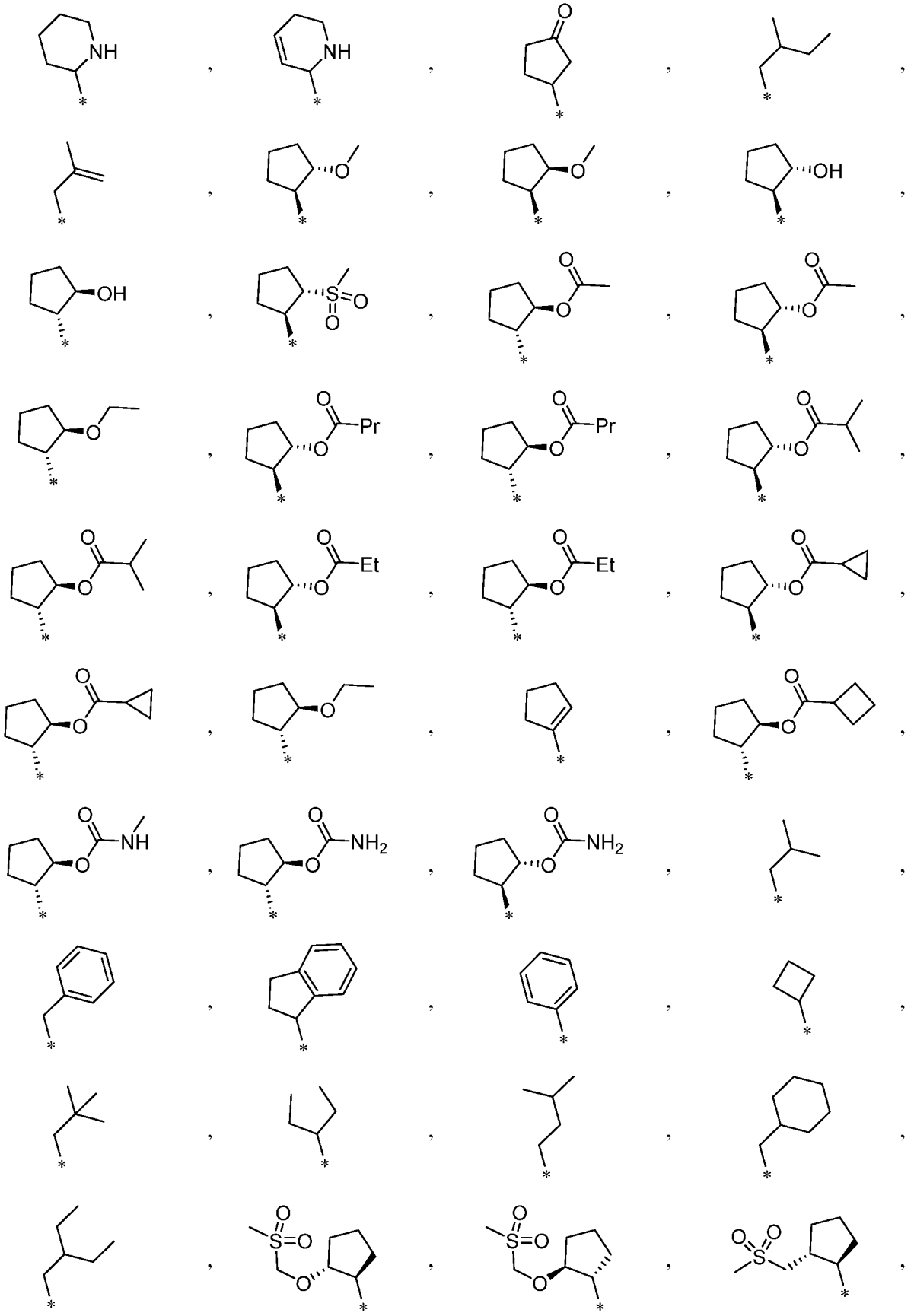
R^{20b} is selected from the group consisting of amino, alkyl, and optionally substituted aryl.

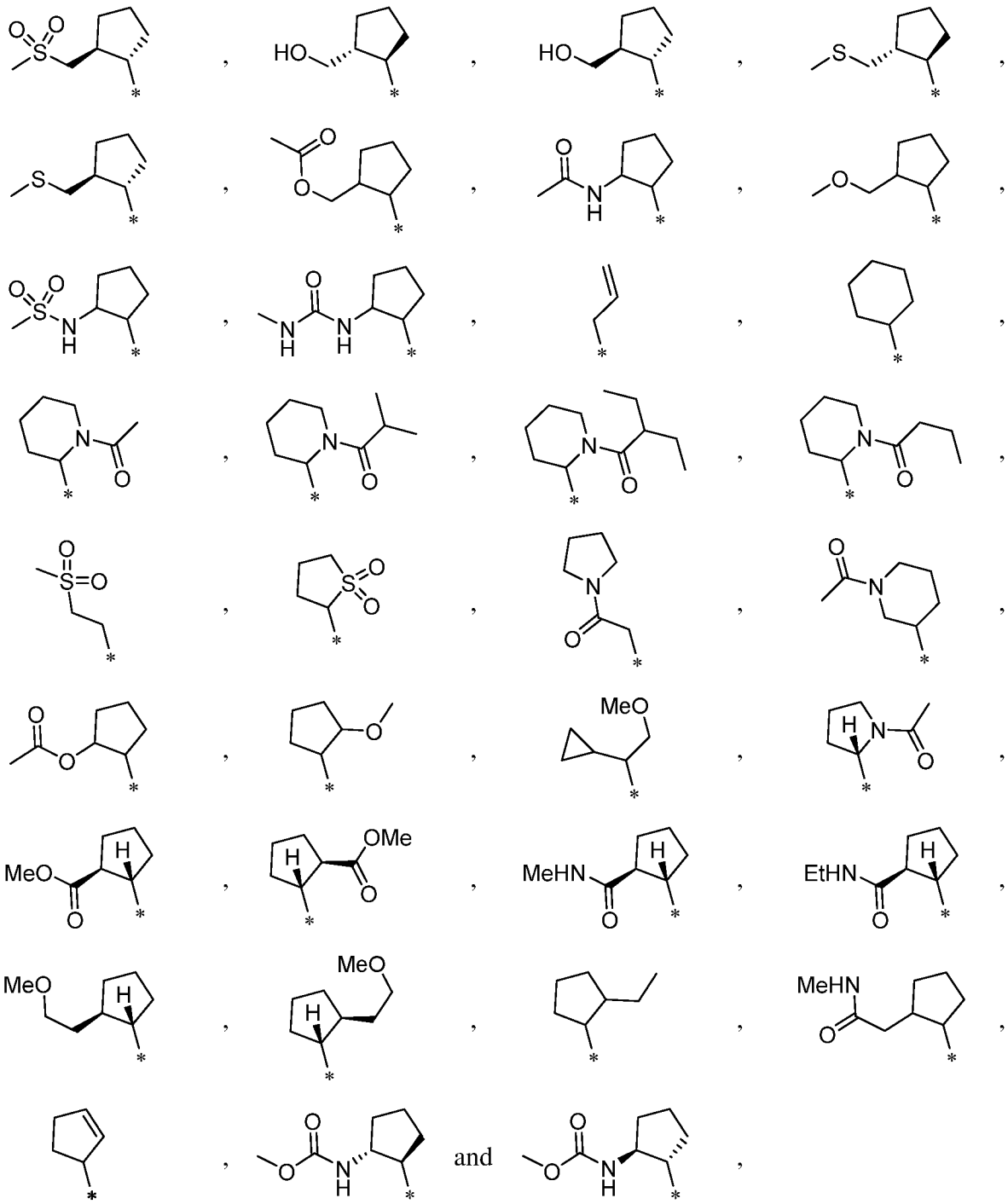
50. The compound of claim 49, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein R^{18} is selected from the group consisting of alkylcarbonyloxy, cycloalkylcarbonyloxy, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, aryloxy, aralkyloxy, alkylthio, carboxamido, sulfonamido, alkylcarbonyl, arylcarbonyl, alkylsulfonyl, arylsulfonyl, carboxy, carboxyalkyl, optionally substituted alkyl, optionally substituted cycloalkyl, alkenyl, alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclo, alkoxyalkyl, (amino)alkyl, (carboxamido)alkyl, and (heterocyclo)alkyl.

51. The compound of claim 50, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein R^{18} is selected from the group consisting of -OC(=O)-amino and -NHC(=O)-R^{19b}.

52. The compound of claim 46, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein R^2 is selected from the group consisting of:

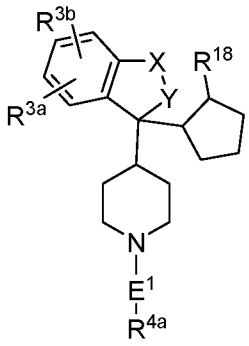






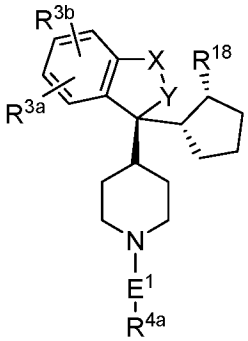
wherein " * " indicates the point of attachment to the remainder of the molecule.

53. The compound of claim 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, having Formula **VIII**:

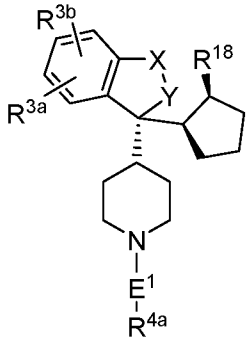


VIII.

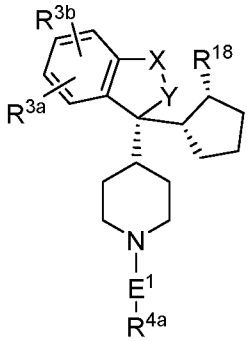
54. The compound of claim 53, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, having any one or more of the following formulae:



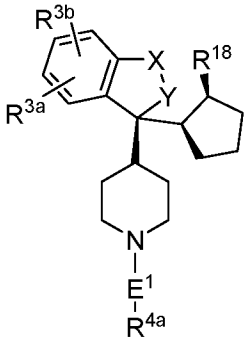
Formula **VIII-A**,



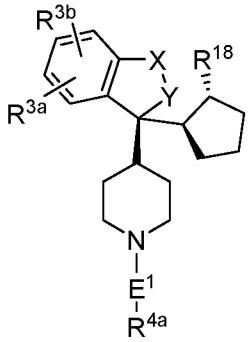
Formula **VIII-B**,



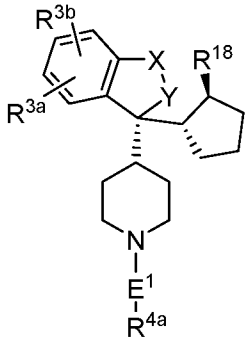
Formula **VIII-C**,



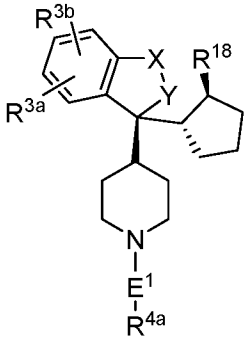
Formula **VIII-D**,



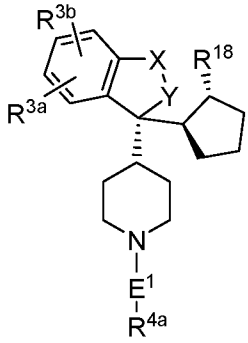
Formula **VIII-E**,



Formula **VIII-F**,



and



.

Formula **VIII-G** Formula **VIII-H**

55. The compound of any one of claims 1-54, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein X-Y is selected from the group consisting of $-N(R^{1a})-C(=O)-$; $-C(=O)-O-$; $-C(=O)-N(R^{1b})-$; $-CH_2N(R^{1c})-CH_2-$; $-C(=O)N(R^{1d})-CH_2-$; $-CH_2CH_2-N(R^{1e})-$; $-CH_2N(R^{1f})-C(=O)-$; and $-CH_2O-CH_2-$.

56. The compound of claim 55, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein X-Y is $-N(R^{1a})-C(=O)-$.

57. The compound of claim 55, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein X-Y is $-C(=O)-O-$.

58. The compound of claim 55, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein X-Y is $-C(=O)-N(R^{1b})-$.

59. The compound of claim 55, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein X-Y is $-CH_2N(R^{1c})-CH_2-$.

60. The compound of claim 55, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein X-Y is $-C(=O)N(R^{1d})-CH_2-$.

61. The compound of claim 55, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein X-Y is $-CH_2CH_2-N(R^{1e})-$.

62. The compound of claim 55, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein X-Y is $-CH_2N(R^{1f})-C(=O)-$.

63. The compound of claim 55, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein X-Y is $-CH_2O-CH_2-$.

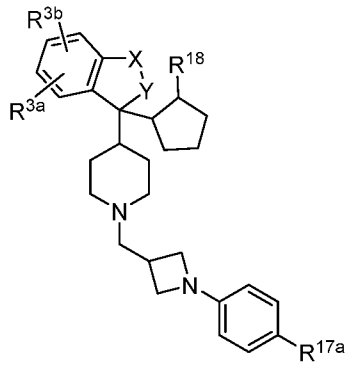
64. The compound of any one of claims 1-54, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein X and Y do not form a chemical bond and X is hydrogen.

65. The compound of claim 64, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein Y is selected from the group consisting of cyano and $-CH_2-R^{12}$.

66. The compound of claim 65, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein Y is cyano.

67. The compound of claim 65, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein Y is $-CH_2-R^{12}$.

68. The compound of claim 53, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, having Formula **IX**:



IX,

wherein:

X-Y is $-CH_2N(R^{1c})-CH_2-$, or

X and Y do not form a chemical bond, and

X is hydrogen; and

Y is selected from the group consisting of -CN and $-CH_2-R^{12}$;

R^{1c} is C_{1-3} alkyl;

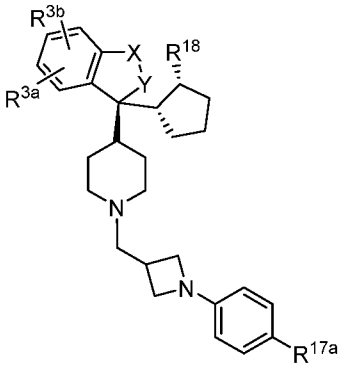
R^{12} is selected from the group consisting of amino and heteroaryl;

R^{17a} is selected from the group consisting of chloro, cyano, alkylsulfonyl, haloalkylsulfonyl, cycloalkylsulfonyl, arylsulfonyl, and heteroarylsulfonyl;

R^{18} is selected from the group consisting of -OC(=O)-amino and -NHC(=O)-R^{19b}; and

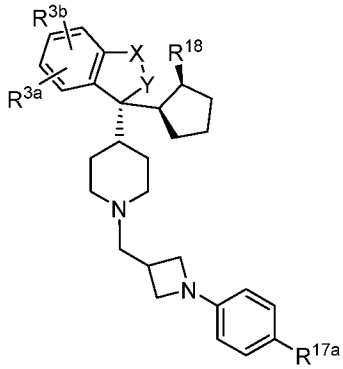
R^{19b} is selected from the group consisting of amino, alkoxy, alkyl, and optionally substituted aryl.

69. The compound of claim 68, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, having any one or more of the following formulae:



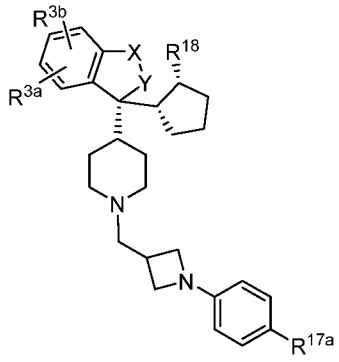
Formula **IX-A**

,

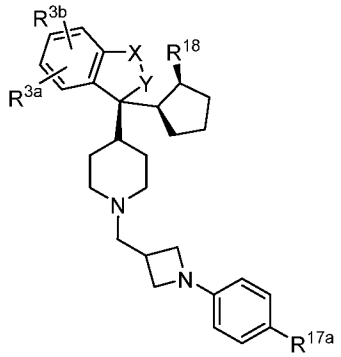


Formula **IX-B**

,

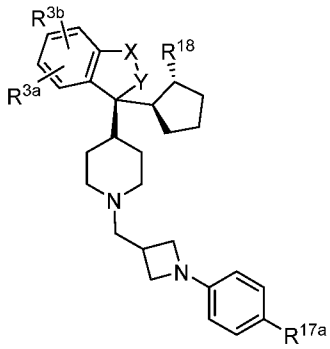


Formula **IX-C**



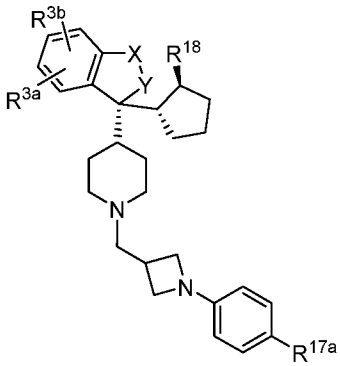
Formula **IX-D**

,

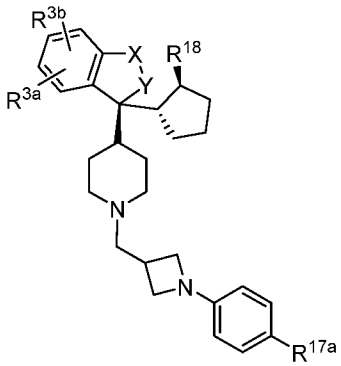


Formula **IX-E**

,

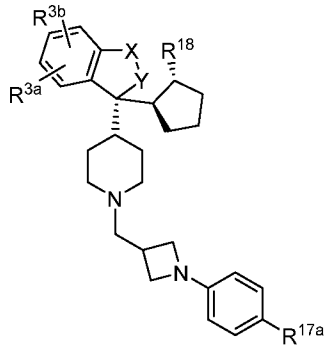


Formula **IX-F**



Formula **IX-G**

and



Formula **IX-H**

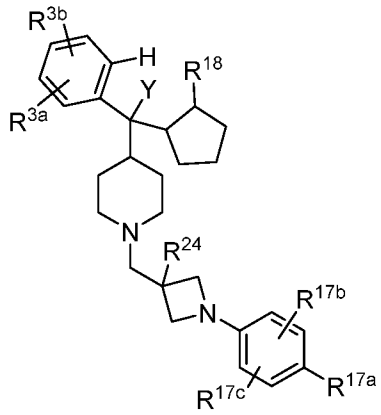
.

70. The compound of claims 68 or 69, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein:

X-Y is $-CH_2N(R^{1c})-CH_2-$; and

R^{1c} is selected from the group consisting of hydrogen and C_{1-6} alkyl.

71. The compound of claim 68, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, having Formula **Xi**:



Xi,

wherein:

Y is selected from the group consisting of cyano and $-CH_2-R^{12}$;

R^{12} is selected from the group consisting of amino and heteroaryl;

R^{17a} is selected from the group consisting of chloro, cyano, alkylsulfonyl, haloalkylsulfonyl, cycloalkylsulfonyl, arylsulfonyl, and heteroarylsulfonyl;

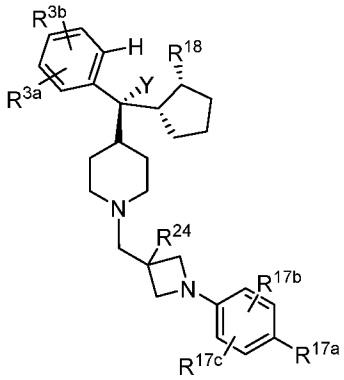
R^{17b} and R^{17c} are independently selected from the group consisting of hydrogen and halo;

R^{18} is selected from the group consisting of -OC(=O)-amino and -NHC(=O)-R^{19b};

R^{19b} is selected from the group consisting of amino, alkoxy, alkyl, and optionally substituted aryl; and

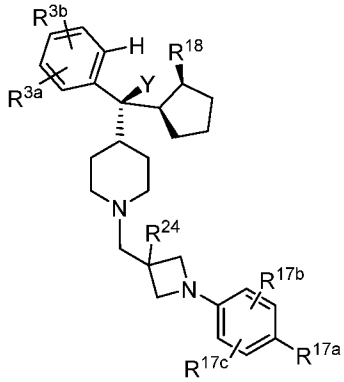
R^{24} is selected from the group consisting of hydrogen and fluoro.

72. The compound of claim 71, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, having any one or more of the following formulae:

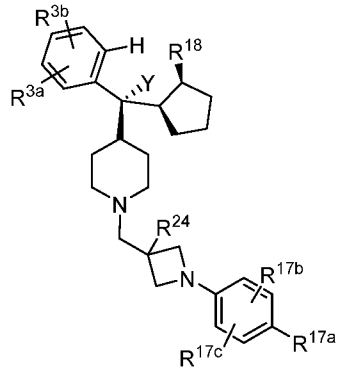


Formula **Xi-A**

,

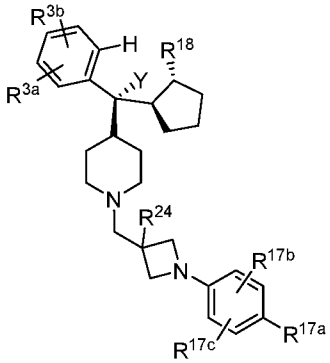


Formula **Xi-B**

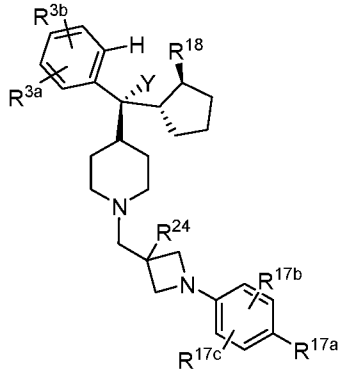


Formula **Xi-D**

,

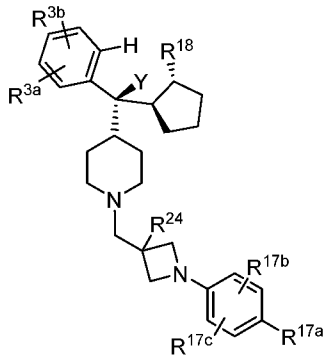


Formula **Xi-E**



Formula **Xi-G**

and



Formula **Xi-H**

73. The compound of claim 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, selected from one or more of the compounds of Table 1.

74. The compound of claim 73, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, selected from one or more of the compounds of Table 2 or Table 5.

75. A pharmaceutical composition comprising the compound of any one of claims 1-74, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, and a pharmaceutically acceptable carrier.

76. A method of treating a patient, the method comprising administering to the patient a therapeutically effective amount of the compound of any one of claims 1-74, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein the patient has cancer, a chronic autoimmune disorder, an inflammatory condition, a proliferative disorder, sepsis, or a viral infection.

77. The method claim 76, wherein the patient has cancer.

78. The method of claim 77, wherein the cancer is selected from the group consisting of adrenal cancer, acinic cell carcinoma, acoustic neuroma, acral lentigious melanoma, acrospiroma, acute eosinophilic leukemia, acute erythroid leukemia, acute lymphoblastic leukemia, acute megakaryoblastic leukemia, acute monocytic leukemia, acute promyelocytic leukemia, adenocarcinoma, adenoid cystic carcinoma, adenoma, adenomatoid odontogenic tumor, adenosquamous carcinoma, adipose tissue neoplasm, adrenocortical carcinoma, adult T-cell leukemia/lymphoma, aggressive NK-cell leukemia, AIDS-related lymphoma, alveolar rhabdomyosarcoma, alveolar soft part sarcoma, ameloblastic fibroma, anaplastic large cell lymphoma, anaplastic thyroid cancer, angioimmunoblastic T-cell lymphoma, angiomyolipoma, angiosarcoma, astrocytoma, atypical teratoid rhabdoid tumor, B-cell chronic lymphocytic leukemia, B-cell prolymphocytic leukemia, B-cell lymphoma, basal cell carcinoma, biliary tract cancer, bladder cancer, blastoma, bone cancer, Brenner tumor, Brown tumor, Burkitt's lymphoma, breast cancer, brain cancer, carcinoma, carcinoma in situ, carcinosarcoma, cartilage tumor, cementoma, myeloid sarcoma, chondroma, chordoma, choriocarcinoma, choroid plexus papilloma, clear-cell sarcoma of the kidney, craniopharyngioma, cutaneous T-cell lymphoma, cervical cancer, colorectal cancer, Degos disease, desmoplastic small round cell tumor, diffuse large B-cell lymphoma, dysembryoplastic neuroepithelial tumor, dysgerminoma, embryonal carcinoma, endocrine gland neoplasm, endodermal sinus tumor, enteropathy-associated T-cell

lymphoma, esophageal cancer, fetus in fetu, fibroma, fibrosarcoma, follicular lymphoma, follicular thyroid cancer, ganglioneuroma, gastrointestinal cancer, germ cell tumor, gestational choriocarcinoma, giant cell fibroblastoma, giant cell tumor of the bone, glial tumor, glioblastoma multiforme, glioma, gliomatosis cerebri, glucagonoma, gonadoblastoma, granulosa cell tumor, gynandroblastoma, gallbladder cancer, gastric cancer, hairy cell leukemia, hemangioblastoma, head and neck cancer, hemangiopericytoma, hematological malignancy, hepatoblastoma, hepatosplenic T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, invasive lobular carcinoma, intestinal cancer, kidney cancer, laryngeal cancer, lentigo maligna, lethal midline carcinoma, leukemia, leydig cell tumor, liposarcoma, lung cancer, lymphangioma, lymphangiosarcoma, lymphoepithelioma, lymphoma, acute lymphocytic leukemia, acute myelogeous leukemia, chronic lymphocytic leukemia, liver cancer, small cell lung cancer, non-small cell lung cancer, MALT lymphoma, malignant fibrous histiocytoma, malignant peripheral nerve sheath tumor, malignant triton tumor, mantle cell lymphoma, marginal zone B-cell lymphoma, mast cell leukemia, mediastinal germ cell tumor, medullary carcinoma of the breast, medullary thyroid cancer, medulloblastoma, melanoma, meningioma, merkel cell cancer, mesothelioma, metastatic urothelial carcinoma, mixed Mullerian tumor, mucinous tumor, multiple myeloma, muscle tissue neoplasm, mycosis fungoides, myxoid liposarcoma, myxoma, myxosarcoma, nasopharyngeal carcinoma, neurinoma, neuroblastoma, neurofibroma, neuroma, nodular melanoma, ocular cancer, oligoastrocytoma, oligodendroglioma, oncocytoma, optic nerve sheath meningioma, optic nerve tumor, oral cancer, osteosarcoma, ovarian cancer, Pancoast tumor, papillary thyroid cancer, paraganglioma, pinealoblastoma, pineocytoma, pituicytoma, pituitary adenoma, pituitary tumor, plasmacytoma, polyembryoma, precursor T-lymphoblastic lymphoma, primary central nervous system lymphoma, primary effusion lymphoma, preimary peritoneal cancer, prostate cancer, pancreatic cancer, pharyngeal cancer, pseudomyxoma periotonei, renal cell carcinoma, renal medullary carcinoma, retinoblastoma, rhabdomyoma, rhabdomyosarcoma, Richter's transformation, rectal cancer, sarcoma, Schwannomatosis, seminoma, Sertoli cell tumor, sex cord-gonadal stromal tumor, signet ring cell carcinoma, skin cancer, small blue round cell tumors, small cell carcinoma, soft tissue sarcoma, somatostatinoma, soot wart, spinal tumor,

splenic marginal zone lymphoma, squamous cell carcinoma, synovial sarcoma, Sezary's disease, small intestine cancer, squamous carcinoma, stomach cancer, T-cell lymphoma, testicular cancer, thecoma, thyroid cancer, transitional cell carcinoma, throat cancer, urachal cancer, urogenital cancer, urothelial carcinoma, uveal melanoma, uterine cancer, verrucous carcinoma, visual pathway glioma, vulvar cancer, vaginal cancer, Waldenstrom's macroglobulinemia, Warthin's tumor, and Wilms' tumor.

79. The method of claim 77, wherein the cancer is selected from the group consisting of acute monocytic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia mixed lineage leukaemia, NUT-midline carcinoma, multiple myeloma, small cell lung cancer (SCLC), neuroblastoma, Burkitt's lymphoma, cervical cancer, esophageal cancer, ovarian cancer, colorectal cancer, prostate cancer, and breast cancer.

80. The method of any one of claims 76-79 further comprising administering a therapeutically effective amount of a second therapeutic agent useful in the treatment of the disease or condition.

81. The pharmaceutical composition of claim 75 for use in treating cancer, a chronic autoimmune disorder, an inflammatory condition, a proliferative disorder, sepsis, or a viral infection.

82. The pharmaceutical composition of claim 81 for use in treating cancer.

83. The pharmaceutical composition of claim 82, wherein the cancer is selected from the group consisting of adrenal cancer, acinic cell carcinoma, acoustic neuroma, acral lentigious melanoma, acrospiroma, acute eosinophilic leukemia, acute erythroid leukemia, acute lymphoblastic leukemia, acute megakaryoblastic leukemia, acute monocytic leukemia, acute promyelocytic leukemia, adenocarcinoma, adenoid cystic carcinoma, adenoma, adenomatoid odontogenic tumor, adenosquamous carcinoma, adipose tissue neoplasm, adrenocortical carcinoma, adult T-cell leukemia/lymphoma, aggressive NK-cell leukemia, AIDS-related lymphoma, alveolar

rhabdomyosarcoma, alveolar soft part sarcoma, ameloblastic fibroma, anaplastic large cell lymphoma, anaplastic thyroid cancer, angioimmunoblastic T-cell lymphoma, angiomyolipoma, angiosarcoma, astrocytoma, atypical teratoid rhabdoid tumor, B-cell chronic lymphocytic leukemia, B-cell prolymphocytic leukemia, B-cell lymphoma, basal cell carcinoma, biliary tract cancer, bladder cancer, blastoma, bone cancer, Brenner tumor, Brown tumor, Burkitt's lymphoma, breast cancer, brain cancer, carcinoma, carcinoma in situ, carcinosarcoma, cartilage tumor, cementoma, myeloid sarcoma, chondroma, chordoma, choriocarcinoma, choroid plexus papilloma, clear-cell sarcoma of the kidney, craniopharyngioma, cutaneous T-cell lymphoma, cervical cancer, colorectal cancer, Degos disease, desmoplastic small round cell tumor, diffuse large B-cell lymphoma, dysembryoplastic neuroepithelial tumor, dysgerminoma, embryonal carcinoma, endocrine gland neoplasm, endodermal sinus tumor, enteropathy-associated T-cell lymphoma, esophageal cancer, fetus in fetu, fibroma, fibrosarcoma, follicular lymphoma, follicular thyroid cancer, ganglioneuroma, gastrointestinal cancer, germ cell tumor, gestational choriocarcinoma, giant cell fibroblastoma, giant cell tumor of the bone, glial tumor, glioblastoma multiforme, glioma, gliomatosis cerebri, glucagonoma, gonadoblastoma, granulosa cell tumor, gynandroblastoma, gallbladder cancer, gastric cancer, hairy cell leukemia, hemangioblastoma, head and neck cancer, hemangiopericytoma, hematological malignancy, hepatoblastoma, hepatosplenic T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, invasive lobular carcinoma, intestinal cancer, kidney cancer, laryngeal cancer, lentigo maligna, lethal midline carcinoma, leukemia, leydig cell tumor, liposarcoma, lung cancer, lymphangioma, lymphangiosarcoma, lymphoepithelioma, lymphoma, acute lymphocytic leukemia, acute myelogeous leukemia, chronic lymphocytic leukemia, liver cancer, small cell lung cancer, non-small cell lung cancer, MALT lymphoma, malignant fibrous histiocytoma, malignant peripheral nerve sheath tumor, malignant triton tumor, mantle cell lymphoma, marginal zone B-cell lymphoma, mast cell leukemia, mediastinal germ cell tumor, medullary carcinoma of the breast, medullary thyroid cancer, medulloblastoma, melanoma, meningioma, merkel cell cancer, mesothelioma, metastatic urothelial carcinoma, mixed Mullerian tumor, mucinous tumor, multiple myeloma, muscle tissue neoplasm, mycosis fungoides, myxoid liposarcoma, myxoma, myxosarcoma, nasopharyngeal carcinoma,

neurinoma, neuroblastoma, neurofibroma, neuroma, nodular melanoma, ocular cancer, oligoastrocytoma, oligodendroglioma, oncocytoma, optic nerve sheath meningioma, optic nerve tumor, oral cancer, osteosarcoma, ovarian cancer, Pancoast tumor, papillary thyroid cancer, paraganglioma, pinealoblastoma, pineocytoma, pituicytoma, pituitary adenoma, pituitary tumor, plasmacytoma, polyembryoma, precursor T-lymphoblastic lymphoma, primary central nervous system lymphoma, primary effusion lymphoma, preimary peritoneal cancer, prostate cancer, pancreatic cancer, pharyngeal cancer, pseudomyxoma periotonei, renal cell carcinoma, renal medullary carcinoma, retinoblastoma, rhabdomyoma, rhabdomyosarcoma, Richter's transformation, rectal cancer, sarcoma, Schwannomatosis, seminoma, Sertoli cell tumor, sex cord-gonadal stromal tumor, signet ring cell carcinoma, skin cancer, small blue round cell tumors, small cell carcinoma, soft tissue sarcoma, somatostatinoma, soot wart, spinal tumor, splenic marginal zone lymphoma, squamous cell carcinoma, synovial sarcoma, Sezary's disease, small intestine cancer, squamous carcinoma, stomach cancer, T-cell lymphoma, testicular cancer, thecoma, thyroid cancer, transitional cell carcinoma, throat cancer, urachal cancer, urogenital cancer, urothelial carcinoma, uveal melanoma, uterine cancer, verrucous carcinoma, visual pathway glioma, vulvar cancer, vaginal cancer, Waldenstrom's macroglobulinemia, Warthin's tumor, and Wilms' tumor.

84. The pharmaceutical composition of claim 82, wherein the cancer is selected from the group consisting of acute monocytic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia mixed lineage leukaemia, NUT-midline carcinoma, multiple myeloma, small cell lung cancer (SCLC), neuroblastoma, Burkitt's lymphoma, cervical cancer, esophageal cancer, ovarian cancer, colorectal cancer, prostate cancer, and breast cancer.

85. A compound of any one of claims 1-74, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, for use in treatment of cancer, a chronic autoimmune disorder, an inflammatory condition, a proliferative disorder, sepsis, or a viral infection.

86. The compound of claim 85 for use in treating cancer.

87. The compound of claim 86, wherein the cancer is selected from the group consisting of adrenal cancer, acinic cell carcinoma, acoustic neuroma, acral lentigious melanoma, acrospiroma, acute eosinophilic leukemia, acute erythroid leukemia, acute lymphoblastic leukemia, acute megakaryoblastic leukemia, acute monocytic leukemia, acute promyelocytic leukemia, adenocarcinoma, adenoid cystic carcinoma, adenoma, adenomatoid odontogenic tumor, adenosquamous carcinoma, adipose tissue neoplasm, adrenocortical carcinoma, adult T-cell leukemia/lymphoma, aggressive NK-cell leukemia, AIDS-related lymphoma, alveolar rhabdomyosarcoma, alveolar soft part sarcoma, ameloblastic fibroma, anaplastic large cell lymphoma, anaplastic thyroid cancer, angioimmunoblastic T-cell lymphoma, angiomyolipoma, angiosarcoma, astrocytoma, atypical teratoid rhabdoid tumor, B-cell chronic lymphocytic leukemia, B-cell prolymphocytic leukemia, B-cell lymphoma, basal cell carcinoma, biliary tract cancer, bladder cancer, blastoma, bone cancer, Brenner tumor, Brown tumor, Burkitt's lymphoma, breast cancer, brain cancer, carcinoma, carcinoma in situ, carcinosarcoma, cartilage tumor, cementoma, myeloid sarcoma, chondroma, chordoma, choriocarcinoma, choroid plexus papilloma, clear-cell sarcoma of the kidney, craniopharyngioma, cutaneous T-cell lymphoma, cervical cancer, colorectal cancer, Degos disease, desmoplastic small round cell tumor, diffuse large B-cell lymphoma, dysembryoplastic neuroepithelial tumor, dysgerminoma, embryonal carcinoma, endocrine gland neoplasm, endodermal sinus tumor, enteropathy-associated T-cell lymphoma, esophageal cancer, fetus in fetu, fibroma, fibrosarcoma, follicular lymphoma, follicular thyroid cancer, ganglioneuroma, gastrointestinal cancer, germ cell tumor, gestational choriocarcinoma, giant cell fibroblastoma, giant cell tumor of the bone, glial tumor, glioblastoma multiforme, glioma, gliomatosis cerebri, glucagonoma, gonadoblastoma, granulosa cell tumor, gynandroblastoma, gallbladder cancer, gastric cancer, hairy cell leukemia, hemangioblastoma, head and neck cancer, hemangiopericytoma, hematological malignancy, hepatoblastoma, hepatosplenic T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, invasive lobular carcinoma, intestinal cancer, kidney cancer, laryngeal cancer, lentigo maligna, lethal midline carcinoma, leukemia, leydig cell tumor, liposarcoma, lung cancer, lymphangioma, lymphangiosarcoma, lymphoepithelioma, lymphoma, acute

lymphocytic leukemia, acute myelogeous leukemia, chronic lymphocytic leukemia, liver cancer, small cell lung cancer, non-small cell lung cancer, MALT lymphoma, malignant fibrous histiocytoma, malignant peripheral nerve sheath tumor, malignant triton tumor, mantle cell lymphoma, marginal zone B-cell lymphoma, mast cell leukemia, mediastinal germ cell tumor, medullary carcinoma of the breast, medullary thyroid cancer, medulloblastoma, melanoma, meningioma, merkel cell cancer, mesothelioma, metastatic urothelial carcinoma, mixed Mullerian tumor, mucinous tumor, multiple myeloma, muscle tissue neoplasm, mycosis fungoides, myxoid liposarcoma, myxoma, myxosarcoma, nasopharyngeal carcinoma, neurinoma, neuroblastoma, neurofibroma, neuroma, nodular melanoma, ocular cancer, oligoastrocytoma, oligodendroglioma, oncocytoma, optic nerve sheath meningioma, optic nerve tumor, oral cancer, osteosarcoma, ovarian cancer, Pancoast tumor, papillary thyroid cancer, paraganglioma, pinealoblastoma, pineocytoma, pituicytoma, pituitary adenoma, pituitary tumor, plasmacytoma, polyembryoma, precursor T-lymphoblastic lymphoma, primary central nervous system lymphoma, primary effusion lymphoma, preimary peritoneal cancer, prostate cancer, pancreatic cancer, pharyngeal cancer, pseudomyxoma periotonei, renal cell carcinoma, renal medullary carcinoma, retinoblastoma, rhabdomyoma, rhabdomyosarcoma, Richter's transformation, rectal cancer, sarcoma, Schwannomatosis, seminoma, Sertoli cell tumor, sex cord-gonadal stromal tumor, signet ring cell carcinoma, skin cancer, small blue round cell tumors, small cell carcinoma, soft tissue sarcoma, somatostatinoma, soot wart, spinal tumor, splenic marginal zone lymphoma, squamous cell carcinoma, synovial sarcoma, Sezary's disease, small intestine cancer, squamous carcinoma, stomach cancer, T-cell lymphoma, testicular cancer, thecoma, thyroid cancer, transitional cell carcinoma, throat cancer, urachal cancer, urogenital cancer, urothelial carcinoma, uveal melanoma, uterine cancer, verrucous carcinoma, visual pathway glioma, vulvar cancer, vaginal cancer, Waldenstrom's macroglobulinemia, Warthin's tumor, and Wilms' tumor.

88. The compound of claim 86, wherein the cancer is selected from the group consisting of acute monocytic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia mixed lineage leukaemia, NUT-midline carcinoma, multiple myeloma, small cell lung cancer (SCLC), neuroblastoma,

Burkitt's lymphoma, cervical cancer, esophageal cancer, ovarian cancer, colorectal cancer, prostate cancer, and breast cancer.

89. Use of a compound of any one of claims 1-74, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, for the manufacture of a medicament for treatment of cancer, a chronic autoimmune disorder, an inflammatory condition, a proliferative disorder, sepsis, or a viral infection.

90. The use of claim 89 for treatment of cancer.

91. The use of claim 90, wherein the cancer is selected from the group consisting of adrenal cancer, acinic cell carcinoma, acoustic neuroma, acral lentigious melanoma, acrospiroma, acute eosinophilic leukemia, acute erythroid leukemia, acute lymphoblastic leukemia, acute megakaryoblastic leukemia, acute monocytic leukemia, acute promyelocytic leukemia, adenocarcinoma, adenoid cystic carcinoma, adenoma, adenomatoid odontogenic tumor, adenosquamous carcinoma, adipose tissue neoplasm, adrenocortical carcinoma, adult T-cell leukemia/lymphoma, aggressive NK-cell leukemia, AIDS-related lymphoma, alveolar rhabdomyosarcoma, alveolar soft part sarcoma, ameloblastic fibroma, anaplastic large cell lymphoma, anaplastic thyroid cancer, angioimmunoblastic T-cell lymphoma, angiomyolipoma, angiosarcoma, astrocytoma, atypical teratoid rhabdoid tumor, B-cell chronic lymphocytic leukemia, B-cell prolymphocytic leukemia, B-cell lymphoma, basal cell carcinoma, biliary tract cancer, bladder cancer, blastoma, bone cancer, Brenner tumor, Brown tumor, Burkitt's lymphoma, breast cancer, brain cancer, carcinoma, carcinoma in situ, carcinosarcoma, cartilage tumor, cementoma, myeloid sarcoma, chondroma, chordoma, choriocarcinoma, choroid plexus papilloma, clear-cell sarcoma of the kidney, craniopharyngioma, cutaneous T-cell lymphoma, cervical cancer, colorectal cancer, Degos disease, desmoplastic small round cell tumor, diffuse large B-cell lymphoma, dysembryoplastic neuroepithelial tumor, dysgerminoma, embryonal carcinoma, endocrine gland neoplasm, endodermal sinus tumor, enteropathy-associated T-cell lymphoma, esophageal cancer, fetus in fetu, fibroma, fibrosarcoma, follicular lymphoma, follicular thyroid cancer, ganglioneuroma, gastrointestinal cancer, germ cell

tumor, gestational choriocarcinoma, giant cell fibroblastoma, giant cell tumor of the bone, glial tumor, glioblastoma multiforme, glioma, gliomatosis cerebri, glucagonoma, gonadoblastoma, granulosa cell tumor, gynandroblastoma, gallbladder cancer, gastric cancer, hairy cell leukemia, hemangioblastoma, head and neck cancer, hemangiopericytoma, hematological malignancy, hepatoblastoma, hepatosplenic T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, invasive lobular carcinoma, intestinal cancer, kidney cancer, laryngeal cancer, lentigo maligna, lethal midline carcinoma, leukemia, leydig cell tumor, liposarcoma, lung cancer, lymphangioma, lymphangiosarcoma, lymphoepithelioma, lymphoma, acute lymphocytic leukemia, acute myelogeous leukemia, chronic lymphocytic leukemia, liver cancer, small cell lung cancer, non-small cell lung cancer, MALT lymphoma, malignant fibrous histiocytoma, malignant peripheral nerve sheath tumor, malignant triton tumor, mantle cell lymphoma, marginal zone B-cell lymphoma, mast cell leukemia, mediastinal germ cell tumor, medullary carcinoma of the breast, medullary thyroid cancer, medulloblastoma, melanoma, meningioma, merkel cell cancer, mesothelioma, metastatic urothelial carcinoma, mixed Mullerian tumor, mucinous tumor, multiple myeloma, muscle tissue neoplasm, mycosis fungoides, myxoid liposarcoma, myxoma, myxosarcoma, nasopharyngeal carcinoma, neurinoma, neuroblastoma, neurofibroma, neuroma, nodular melanoma, ocular cancer, oligoastrocytoma, oligodendroglioma, oncocytoma, optic nerve sheath meningioma, optic nerve tumor, oral cancer, osteosarcoma, ovarian cancer, Pancoast tumor, papillary thyroid cancer, paraganglioma, pinealoblastoma, pineocytoma, pituicytoma, pituitary adenoma, pituitary tumor, plasmacytoma, polyembryoma, precursor T-lymphoblastic lymphoma, primary central nervous system lymphoma, primary effusion lymphoma, preimary peritoneal cancer, prostate cancer, pancreatic cancer, pharyngeal cancer, pseudomyxoma periotonei, renal cell carcinoma, renal medullary carcinoma, retinoblastoma, rhabdomyoma, rhabdomyosarcoma, Richter's transformation, rectal cancer, sarcoma, Schwannomatosis, seminoma, Sertoli cell tumor, sex cord-gonadal stromal tumor, signet ring cell carcinoma, skin cancer, small blue round cell tumors, small cell carcinoma, soft tissue sarcoma, somatostatinoma, soot wart, spinal tumor, splenic marginal zone lymphoma, squamous cell carcinoma, synovial sarcoma, Sezary's disease, small intestine cancer, squamous carcinoma, stomach cancer, T-cell

lymphoma, testicular cancer, thecoma, thyroid cancer, transitional cell carcinoma, throat cancer, urachal cancer, urogenital cancer, urothelial carcinoma, uveal melanoma, uterine cancer, verrucous carcinoma, visual pathway glioma, vulvar cancer, vaginal cancer, Waldenstrom's macroglobulinemia, Warthin's tumor, and Wilms' tumor.

92. The use of claim 90, wherein the cancer is selected from the group consisting of acute monocytic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia mixed lineage leukaemia, NUT-midline carcinoma, multiple myeloma, small cell lung cancer (SCLC), neuroblastoma, Burkitt's lymphoma, cervical cancer, esophageal cancer, ovarian cancer, colorectal cancer, prostate cancer, and breast cancer.

93. A kit comprising the compound of any one of claims 1-74, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, and instructions for administering the compound, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, to a patient having cancer, a chronic autoimmune disorder, an inflammatory condition, a proliferative disorder, sepsis, or a viral infection.

94. The kit of claim 93, wherein the patient has cancer.

95. The kit of claim 94, wherein the cancer is selected from the group consisting of adrenal cancer, acinic cell carcinoma, acoustic neuroma, acral lentigious melanoma, acrospiroma, acute eosinophilic leukemia, acute erythroid leukemia, acute lymphoblastic leukemia, acute megakaryoblastic leukemia, acute monocytic leukemia, acute promyelocytic leukemia, adenocarcinoma, adenoid cystic carcinoma, adenoma, adenomatoid odontogenic tumor, adenosquamous carcinoma, adipose tissue neoplasm, adrenocortical carcinoma, adult T-cell leukemia/lymphoma, aggressive NK-cell leukemia, AIDS-related lymphoma, alveolar rhabdomyosarcoma, alveolar soft part sarcoma, ameloblastic fibroma, anaplastic large cell lymphoma, anaplastic thyroid cancer, angioimmunoblastic T-cell lymphoma, angiomyolipoma, angiosarcoma, astrocytoma, atypical teratoid rhabdoid tumor, B-cell chronic lymphocytic leukemia, B-cell prolymphocytic leukemia, B-cell lymphoma, basal cell carcinoma, biliary tract

cancer, bladder cancer, blastoma, bone cancer, Brenner tumor, Brown tumor, Burkitt's lymphoma, breast cancer, brain cancer, carcinoma, carcinoma in situ, carcinosarcoma, cartilage tumor, cementoma, myeloid sarcoma, chondroma, chordoma, choriocarcinoma, choroid plexus papilloma, clear-cell sarcoma of the kidney, craniopharyngioma, cutaneous T-cell lymphoma, cervical cancer, colorectal cancer, Degos disease, desmoplastic small round cell tumor, diffuse large B-cell lymphoma, dysembryoplastic neuroepithelial tumor, dysgerminoma, embryonal carcinoma, endocrine gland neoplasm, endodermal sinus tumor, enteropathy-associated T-cell lymphoma, esophageal cancer, fetus in fetu, fibroma, fibrosarcoma, follicular lymphoma, follicular thyroid cancer, ganglioneuroma, gastrointestinal cancer, germ cell tumor, gestational choriocarcinoma, giant cell fibroblastoma, giant cell tumor of the bone, glial tumor, glioblastoma multiforme, glioma, gliomatosis cerebri, glucagonoma, gonadoblastoma, granulosa cell tumor, gynandroblastoma, gallbladder cancer, gastric cancer, hairy cell leukemia, hemangioblastoma, head and neck cancer, hemangiopericytoma, hematological malignancy, hepatoblastoma, hepatosplenic T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, invasive lobular carcinoma, intestinal cancer, kidney cancer, laryngeal cancer, lentigo maligna, lethal midline carcinoma, leukemia, leydig cell tumor, liposarcoma, lung cancer, lymphangioma, lymphangiosarcoma, lymphoepithelioma, lymphoma, acute lymphocytic leukemia, acute myelogeous leukemia, chronic lymphocytic leukemia, liver cancer, small cell lung cancer, non-small cell lung cancer, MALT lymphoma, malignant fibrous histiocytoma, malignant peripheral nerve sheath tumor, malignant triton tumor, mantle cell lymphoma, marginal zone B-cell lymphoma, mast cell leukemia, mediastinal germ cell tumor, medullary carcinoma of the breast, medullary thyroid cancer, medulloblastoma, melanoma, meningioma, merkel cell cancer, mesothelioma, metastatic urothelial carcinoma, mixed Mullerian tumor, mucinous tumor, multiple myeloma, muscle tissue neoplasm, mycosis fungoides, myxoid liposarcoma, myxoma, myxosarcoma, nasopharyngeal carcinoma, neurinoma, neuroblastoma, neurofibroma, neuroma, nodular melanoma, ocular cancer, oligoastrocytoma, oligodendroglioma, oncocytoma, optic nerve sheath meningioma, optic nerve tumor, oral cancer, osteosarcoma, ovarian cancer, Pancoast tumor, papillary thyroid cancer, paraganglioma, pinealoblastoma, pineocytoma, pituicytoma, pituitary

adenoma, pituitary tumor, plasmacytoma, polyembryoma, precursor T-lymphoblastic lymphoma, primary central nervous system lymphoma, primary effusion lymphoma, preimary peritoneal cancer, prostate cancer, pancreatic cancer, pharyngeal cancer, pseudomyxoma periotonei, renal cell carcinoma, renal medullary carcinoma, retinoblastoma, rhabdomyoma, rhabdomyosarcoma, Richter's transformation, rectal cancer, sarcoma, Schwannomatosis, seminoma, Sertoli cell tumor, sex cord-gonadal stromal tumor, signet ring cell carcinoma, skin cancer, small blue round cell tumors, small cell carcinoma, soft tissue sarcoma, somatostatinoma, soot wart, spinal tumor, splenic marginal zone lymphoma, squamous cell carcinoma, synovial sarcoma, Sezary's disease, small intestine cancer, squamous carcinoma, stomach cancer, T-cell lymphoma, testicular cancer, thecoma, thyroid cancer, transitional cell carcinoma, throat cancer, urachal cancer, urogenital cancer, urothelial carcinoma, uveal melanoma, uterine cancer, verrucous carcinoma, visual pathway glioma, vulvar cancer, vaginal cancer, Waldenstrom's macroglobulinemia, Warthin's tumor, and Wilms' tumor.

96. The kit of claim 94, wherein the cancer is selected from the group consisting of acute monocytic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia mixed lineage leukemia, NUT-midline carcinoma, multiple myeloma, small cell lung cancer (SCLC), neuroblastoma, Burkitt's lymphoma, cervical cancer, esophageal cancer, ovarian cancer, colorectal cancer, prostate cancer, and breast cancer.

97. The kit of any one of claims 93-96 further comprising one or more additional therapeutic agents.

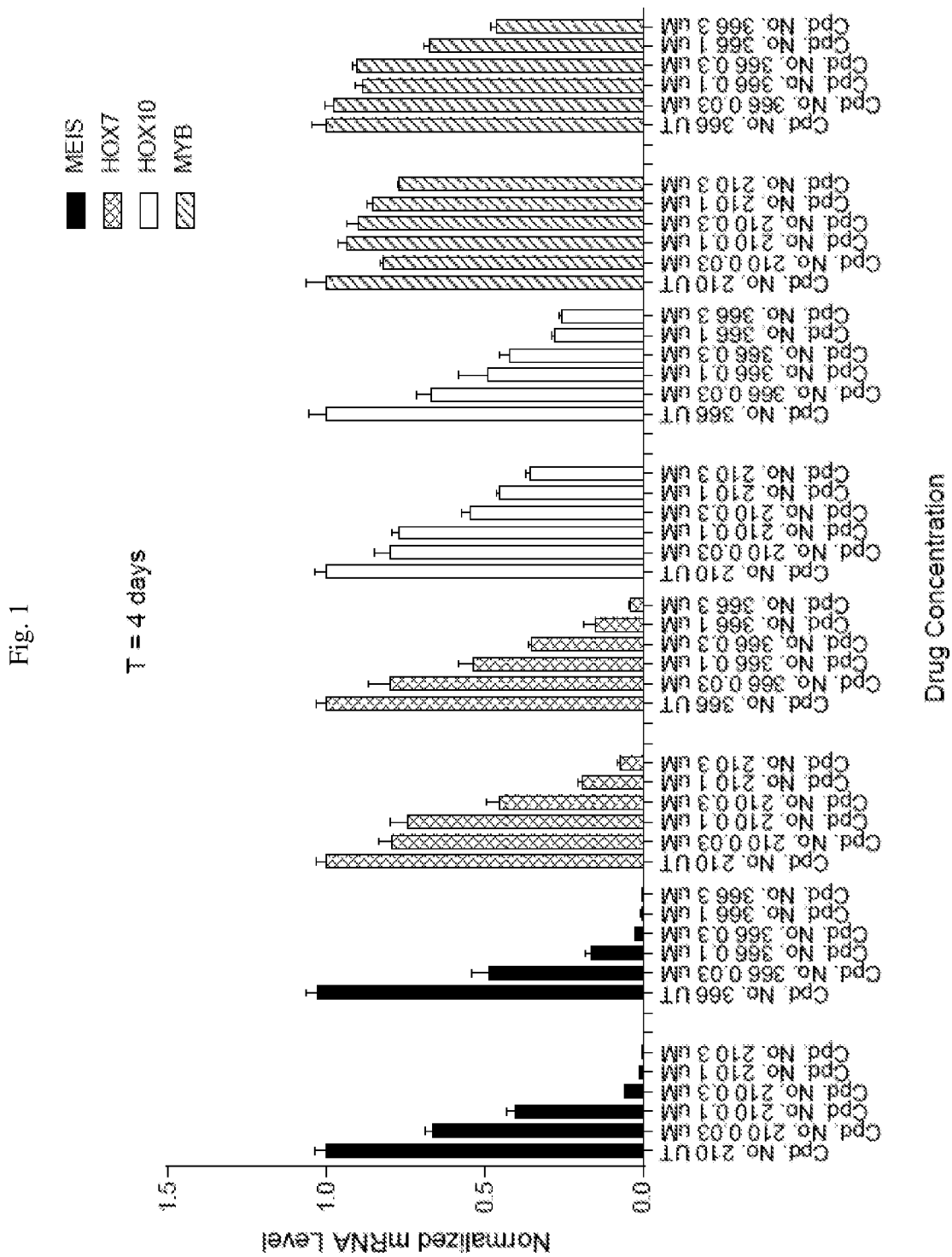

MEIS
HOX7
HOX10
MYB
T = 4 days
Normalized mRNA Level
1.5
1.0
0.5
0.0
Cpd. No. 210 UT
Cpd. No. 210 0.03 uM
Cpd. No. 210 0.1 uM
Cpd. No. 210 0.3 uM
Cpd. No. 210 1 uM
Cpd. No. 210 3 uM
Cpd. No. 366 UT
Cpd. No. 366 0.03 uM
Cpd. No. 366 0.1 uM
Cpd. No. 366 0.3 uM
Cpd. No. 366 1 uM
Cpd. No. 366 3 uM
Drug Concentration

Fig. 1

Fig. 2

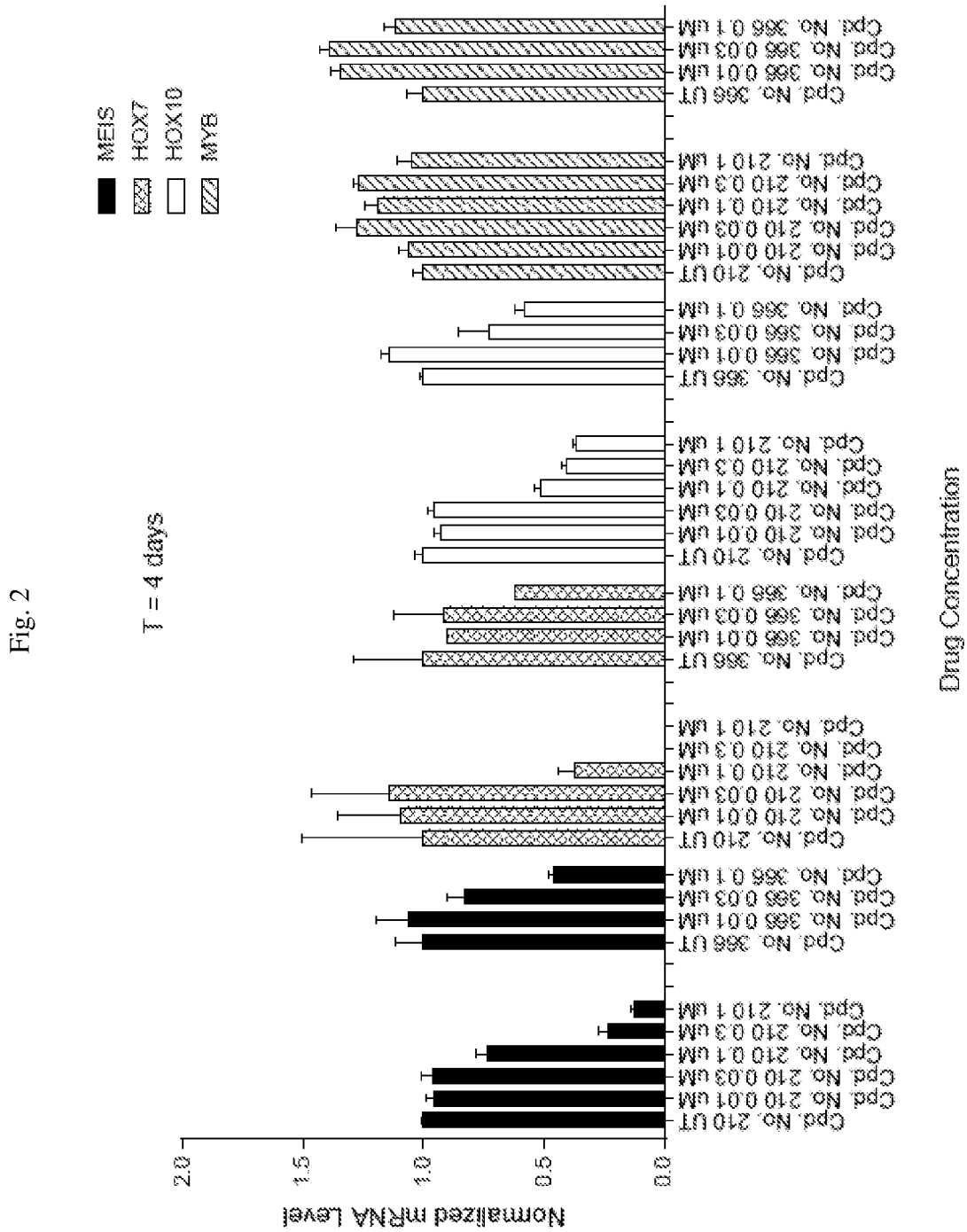

T = 4 days
MEIS
HOX7
HOX10
MYB
Normalized mRNA Level
2.0
1.5
1.0
0.5
0.0
Drug Concentration
Cpd. No. 210 UT
Cpd. No. 210 0.01 uM
Cpd. No. 210 0.03 uM
Cpd. No. 210 0.1 uM
Cpd. No. 210 0.3 uM
Cpd. No. 210 1 uM
Cpd. No. 366 UT
Cpd. No. 366 0.01 uM
Cpd. No. 366 0.03 uM
Cpd. No. 366 0.1 uM

Fig. 3

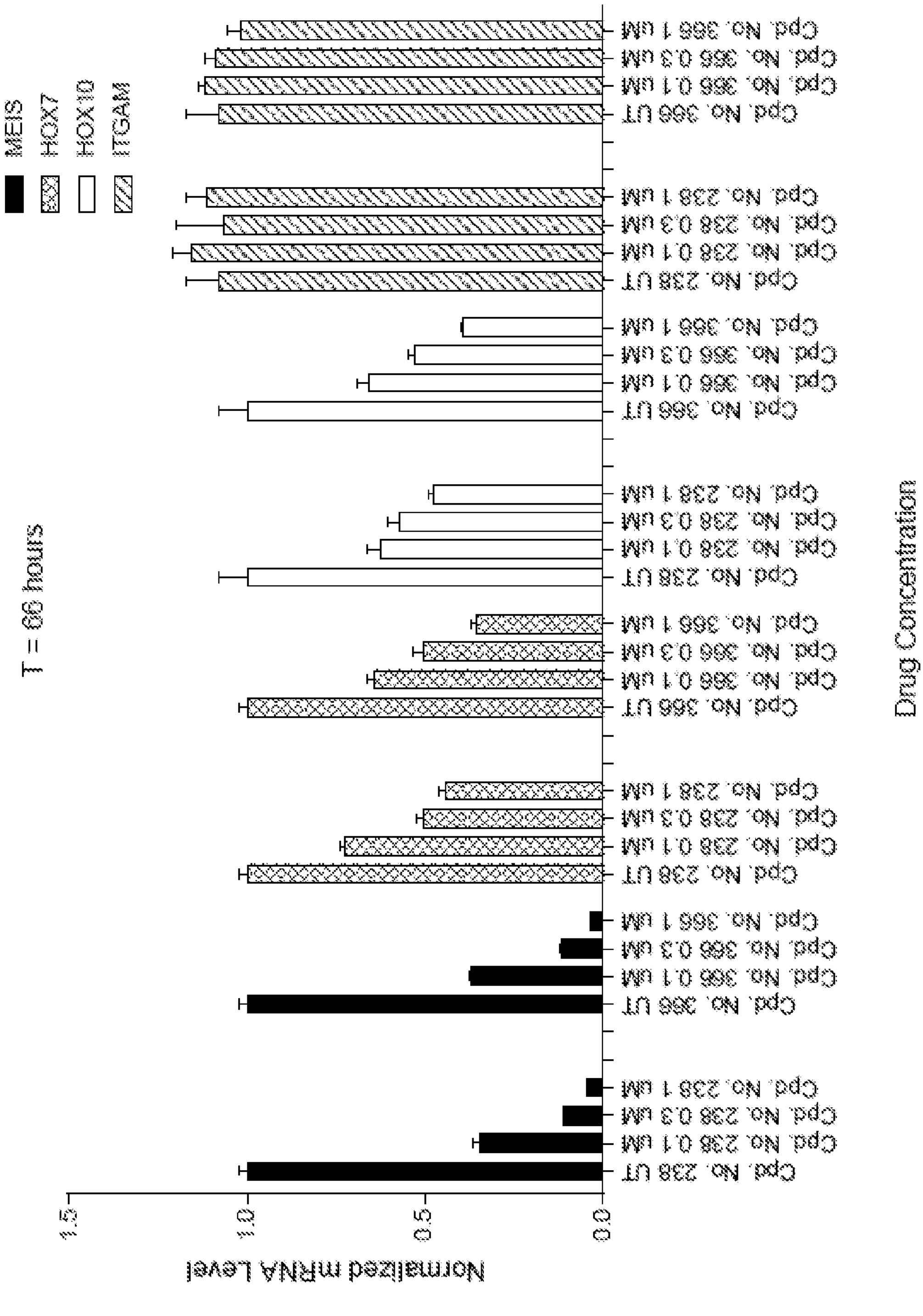

T = 66 hours
MEIS
HOX7
HOX10
ITGAM
Normalized mRNA Level
0.0
0.5
1.0
1.5
Drug Concentration
Cpd. No. 238 UT
Cpd. No. 238 0.1 uM
Cpd. No. 238 0.3 uM
Cpd. No. 238 1 uM
Cpd. No. 366 UT
Cpd. No. 366 0.1 uM
Cpd. No. 366 0.3 uM
Cpd. No. 366 1 uM

Fig. 4

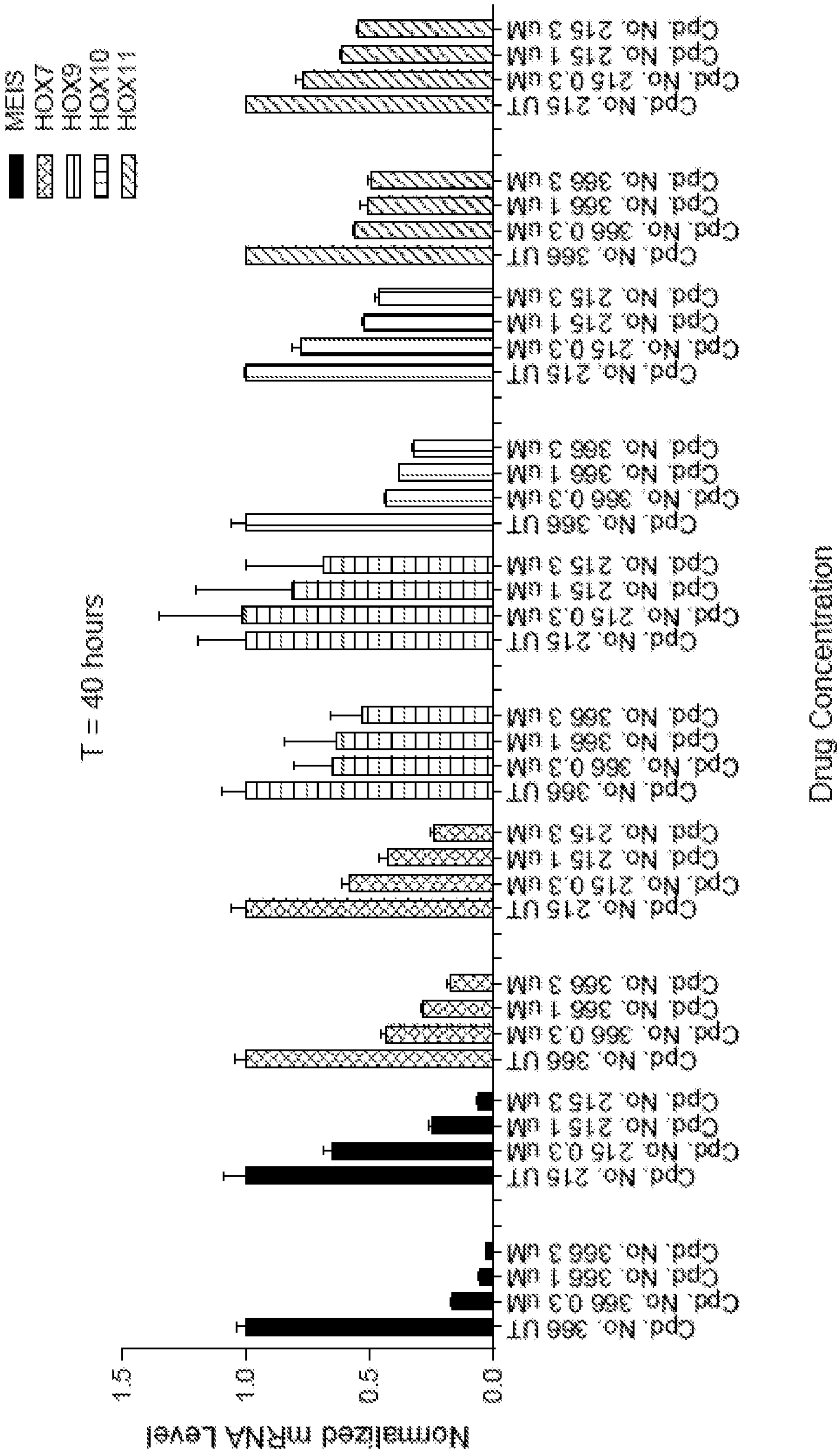
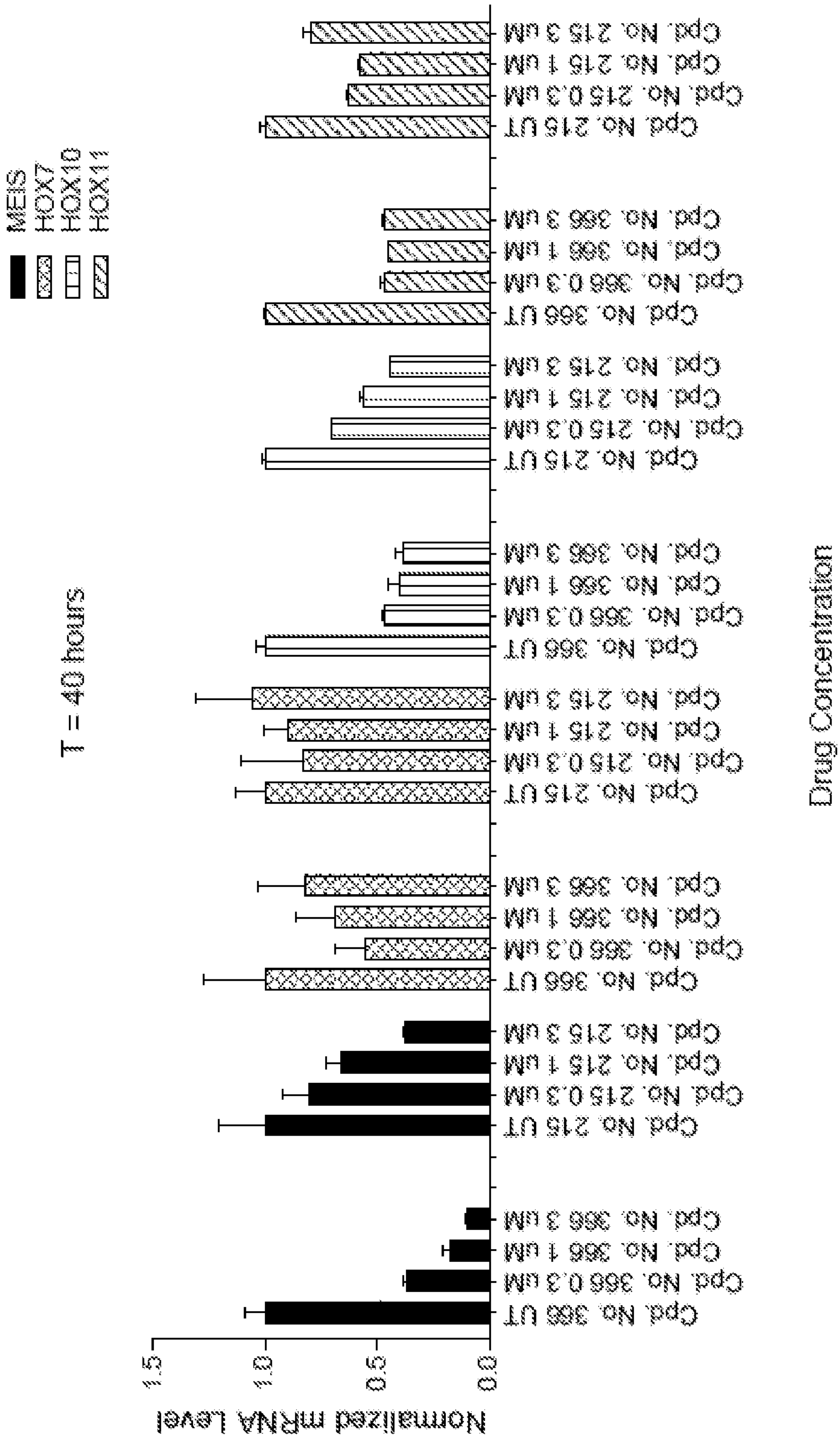

T = 40 hours
MEIS
HOX7
HOX9
HOX10
HOX11
Normalized mRNA Level
0.0
0.5
1.0
1.5
Drug Concentration
Cpd. No. 366 UT
Cpd. No. 366 0.3 uM
Cpd. No. 366 1 uM
Cpd. No. 366 3 uM
Cpd. No. 215 UT
Cpd. No. 215 0.3 uM
Cpd. No. 215 1 uM
Cpd. No. 215 3 uM

Fig. 5


T = 40 hours
MEIS
HOX7
HOX10
HOX11
Normalized mRNA Level
0.0
0.5
1.0
1.5
Cpd. No. 366 UT
Cpd. No. 366 0.3 uM
Cpd. No. 366 1 uM
Cpd. No. 366 3 uM
Cpd. No. 215 UT
Cpd. No. 215 0.3 uM
Cpd. No. 215 1 uM
Cpd. No. 215 3 uM
Drug Concentration

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2017/030577

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/04 C07D401/14 C07D405/04 C07D211/34 A61K31/4523
A61K31/454 A61K31/4545 A61P35/00
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	XU Y. ET AL.: "Discovery of novel inhibitors targeting the menin-mixed lineage leukemia interface using pharmacophore- and docking-based virtual screening", JOURNAL OF CHEMICAL INFORMATION AND MODELING, vol. 56, 11 August 2016 (2016-08-11), pages 1847-1855, XP002771197, figure 1, compound MIV-6 -----	1-43, 46-67, 73-97
X	WO 2014/200479 A1 (UNIV MICHIGAN [US]; UNIV VANDERBILT [US]) 18 December 2014 (2014-12-18) claim 1 examples ----- -/--	1-43, 46-67, 73-97

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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

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

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 June 2017	30/06/2017

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Bérillon, Laurent

1

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2017/030577

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-43, 46-67, 73-97(all partially)
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: 1-43, 46-67, 73-97(all partially)

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claims 1-43, 46-67 and 73-97 may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, the search was performed taking into consideration the non-compliance in determining the extent of the search. A full search was only carried out for claims 44, 45 and 68-72.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guidelines C-IV, 7.2), should the problems which led to the Article 17(2) declaration be overcome.

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2014/371239 A1 (GREMBECKA JOLANTA [US] ET AL) 18 December 2014 (2014-12-18) claim 1 examples -----	1-43, 46-67, 73-97
X	SENTER T. ET AL.: "Progress towards small molecule menin-mixed lineage leukemia (MLL) interaction inhibitors with in vivo utility", BIOORGANIC AND MEDICINAL CHEMISTRY LETTERS, vol. 25, 25 April 2015 (2015-04-25), pages 2720-2725, XP002771198, tables 1-3 -----	1-43, 46-67, 73-97
X	HE S. ET AL.: "High-affinity small molecule inhibitors of the menin-mixed lineage leukemia (MLL) interaction closely mimic a natural protein-protein interaction", JOURNAL OF MEDICINAL CHEMISTRY, vol. 57, 28 January 2014 (2014-01-28), pages 1543-1556, XP002771199, table 1 -----	1-43, 46-67, 73-97
X	PITTA B. R. ET AL.: "Metalated nitrile and enolate chlorinations", ORGANIC LETTERS, vol. 12, no. 12, 18 May 2010 (2010-05-18), pages 2810-2813, XP002771200, compound 7h -----	1-43, 46-67, 73-97
X	PRAT L. ET AL.: "Synthesis of N-methyl-4-pyridyl-1,2,3,4-tetrahydroisoquinolines via a Pictet-Spengler cyclisation", JOURNAL OF HETEROCYCLIC CHEMISTRY, vol. 37, 1 July 2000 (2000-07-01), pages 767-771, XP002771201, compounds 2c and 3c -----	1-43, 46-67, 73-97
X	BURM BRIGITTE E A ET AL: "Synthesis of new bridged tetrahydro-[beta]-carbolines andspiro-fused quinuclidines", TETRAHEDRON, vol. 57, no. 10, 1 January 2001 (2001-01-01), pages 2039-2049, XP085040496, ISSN: 0040-4020, DOI: 10.1016/S0040-4020(01)00023-0 compound 2 -----	1-43, 46-67, 73-97

-/--

1

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KITA Y. ET AL.: "Enhancing effects of salt formation on catalytic activity and enantioselectivity for asymetric hydrogenation of isoquinolinium salts by dinuclear halide-bridged iridium complexes bearing chiral diphosphine ligands", CHEMISTRY - A EUROPEAN JOURNAL, vol. 21, 28 November 2014 (2014-11-28), pages 1915-1927, XP002771202, compound 3q -----	1-43, 46-67, 73-97

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2017/030577

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2014200479 A1	18-12-2014	NONE	
US 2014371239 A1	18-12-2014	NONE	