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Office de la Propriété Intellectuelle du Canada

Innovation, Science and Economic Development Canada
Canadian Intellectual Property Office

CA 2894228 C 2021/08/17

(11)(21) 2 894 228

(12) BREVET CANADIEN
CANADIAN PATENT

(13) C

(86) Date de dépôt PCT/PCT Filing Date: 2013/12/20
(87) Date publication PCT/PCT Publication Date: 2014/06/26
(45) Date de délivrance/Issue Date: 2021/08/17
(85) Entrée phase nationale/National Entry: 2015/06/05
(86) N° demande PCT/PCT Application No.: US 2013/077235
(87) N° publication PCT/PCT Publication No.: 2014/100719
(30) Priorités/Priorities: 2012/12/21 (US61/745,485); 2013/03/15 (US61/790,525)

(51) Cl.Int./Int.Cl. *C07D 217/12* (2006.01), *A61K 31/472* (2006.01), *A61K 31/4725* (2006.01), *A61P 3/04* (2006.01), *A61P 3/10* (2006.01), *A61P 35/00* (2006.01), *A61P 7/06* (2006.01), *C07D 401/12* (2006.01), *C07D 405/12* (2006.01)

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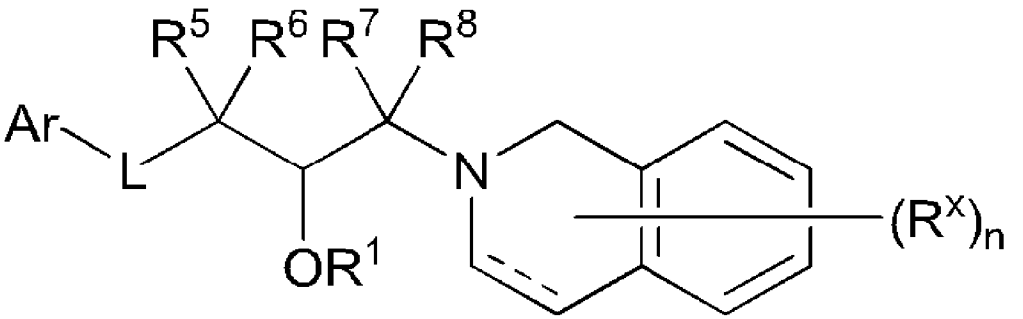
(54) Titre : INHIBITEURS DE PRMT5 ET LEURS UTILISATIONS
(54) Title: PRMT5 INHIBITORS AND USES THEREOF



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(57) Abrégé/Abstract:
Described herein are compounds of Formula (A), pharmaceutically acceptable salts thereof, and pharmaceutical compositions thereof. Compounds of the present invention are useful for inhibiting PRMT5 activity. Methods of using the compounds for treating PRMT5 mediated disorders are also described.

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
26 June 2014 (26.06.2014)

WIPO | PCT

(10) International Publication Number
WO 2014/100719 A3

(51) International Patent Classification:
C07D 217/12 (2006.01) *A61P 35/00* (2006.01)
A61K 31/472 (2006.01) *A61P 3/04* (2006.01)
A61K 31/4725 (2006.01) *A61P 3/10* (2006.01)
C07D 401/12 (2006.01) *A61P 7/06* (2006.01)
C07D 405/12 (2006.01)

(21) International Application Number:
PCT/US2013/077235

(22) International Filing Date:
20 December 2013 (20.12.2013)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/745,485 21 December 2012 (21.12.2012) US
61/790,525 15 March 2013 (15.03.2013) US

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(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, 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, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, 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, 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).

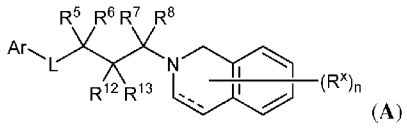
Published:

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

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

(88) Date of publication of the international search report:
14 August 2014

(54) Title: TEATRAHYDRO- AND DIHYDRO-ISOQUINOLINE PRMT5 INHIBITORS AND USES THEREOF



(A)

(57) Abstract: Described herein are compounds of Formula (A), pharmaceutically acceptable salts thereof, and pharmaceutical compositions thereof. Compounds of the present invention are useful for inhibiting PRMT5 activity. Methods of using the compounds for treating PRMT5 mediated disorders are also described.

WO 2014/100719 A3

DEMANDES OU BREVETS VOLUMINEUX

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THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE THAN ONE VOLUME.

THIS IS VOLUME __1___ OF __2___

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PRMT5 Inhibitors and Uses Thereof

Background of the Invention

[0002] Epigenetic regulation of gene expression is an important biological determinant of protein production and cellular differentiation and plays a significant pathogenic role in a number of human diseases.

[0003] Epigenetic regulation involves heritable modification of genetic material without changing its nucleotide sequence. Typically, epigenetic regulation is mediated by selective and reversible modification (*e.g.*, methylation) of DNA and proteins (*e.g.*, histones) that control the conformational transition between transcriptionally active and inactive states of chromatin. These covalent modifications can be controlled by enzymes such as methyltransferases (*e.g.*, PRMT5), many of which are associated with specific genetic alterations that can cause human disease.

[0004] Disease-associated chromatin-modifying enzymes (*e.g.*, PRMT5) play a role in diseases such as proliferative disorders, metabolic disorders, and blood disorders. Thus, there is a need for the development of small molecules that are capable of inhibiting the activity of PRMT5.

Detailed Description of Certain Embodiments

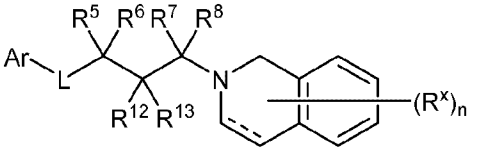
[0005] Protein arginine methyltransferase 5 (PRMT5) catalyzes the addition of two methyl groups to the two ω-guanidino nitrogen atoms of arginine, resulting in ω-NG, N′G symmetric dimethylation of arginine (sDMA) of the target protein. PRMT5 functions in the nucleus as well as in the cytoplasm, and its substrates include histones, spliceosomal proteins, transcription factors (See *e.g.*, Sun et al., *PNAS* (2011), 108: 20538-20543). PRMT5 generally functions as part of a molecule weight protein complex. While the protein complexes of PRMT5 can have a variety of components, they generally include the protein

Date Reçue/Date Received 2020-04-17

MEP50 (methylosome protein 50). In addition, PRMT5 acts in conjunction with cofactor SAM (S-adenosyl methionine).

[0006] PRMT5 is an attractive target for modulation given its role in the regulation of diverse biological processes. It has now been found that compounds described herein, and pharmaceutically acceptable salts and compositions thereof, are effective as inhibitors of PRMT5.

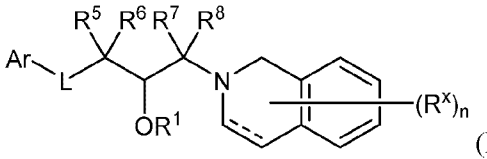
[0007] Such compounds have the general Formula (**A**):



(**A**)

or a pharmaceutically acceptable salt thereof, wherein R^1, R^5, R^6, R^7, R^8, R^x, R^{12}, R^{13}, n, L, and Ar are as defined herein.

[0008] In some embodiments, the inhibitors of PRMT5 have the general Formula (**I**):



(**I**)

or a pharmaceutically acceptable salt thereof, wherein R^1, R^5, R^6, R^7, R^8, R^x, n, L, and Ar are as defined herein.

[0009] In some embodiments, pharmaceutical compositions are provided which comprise a compound described herein (*e.g.*, a compound of Formula (**A**), *e.g.*, Formula (**I**)), or a pharmaceutically acceptable salt thereof, and optionally a pharmaceutically acceptable excipient.

[0010] In certain embodiments, compounds described herein inhibit activity of PRMT5. In certain embodiments, methods of inhibiting PRMT5 are provided which comprise contacting PRMT5 with an effective amount of a compound of Formula (**A**), *e.g.*, Formula (**I**), or a pharmaceutically acceptable salt thereof. The PRMT5 may be purified or crude, and may be present in a cell, tissue, or a subject. Thus, such methods encompass inhibition of PRMT5 activity both *in vitro* and *in vivo*. In certain embodiments, the PRMT5 is wild-type PRMT5. In certain embodiments, the PRMT5 is overexpressed. In certain embodiments, the PRMT5 is a mutant. In certain embodiments, the PRMT5 is in a cell. In certain embodiments, the PRMT5 is in an animal, *e.g.*, a human. In some embodiments, the PRMT5 is in a subject that is susceptible to normal levels of PRMT5 activity due to one or more mutations associated with a PRMT5 substrate. In some embodiments, the PRMT5 is in a

subject known or identified as having abnormal PRMT5 activity (*e.g.*, overexpression). In some embodiments, a provided compound is selective for PRMT5 over other methyltransferases. In certain embodiments, a provided compound is at least about 10-fold selective, at least about 20-fold selective, at least about 30-fold selective, at least about 40-fold selective, at least about 50-fold selective, at least about 60-fold selective, at least about 70-fold selective, at least about 80-fold selective, at least about 90-fold selective, or at least about 100-fold selective relative to one or more other methyltransferases.

[0011] In certain embodiments, methods of altering gene expression in a cell are provided which comprise contacting a cell with an effective amount of a compound of Formula (**A**), *e.g.*, Formula (**I**), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof. In certain embodiments, the cell in culture *in vitro*. In certain embodiments, cell is in an animal, *e.g.*, a human.

[0012] In certain embodiments, methods of altering transcription in a cell are provided which comprise contacting a cell with an effective amount of a compound of Formula (**A**), *e.g.*, Formula (**I**), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof. In certain embodiments, the cell in culture *in vitro*. In certain embodiments, the cell is in an animal, *e.g.*, a human.

[0013] In some embodiments, methods of treating a PRMT5-mediated disorder are provided which comprise administering to a subject suffering from a PRMT5-mediated disorder an effective amount of a compound described herein (*e.g.*, a compound of Formula (**A**), *e.g.*, Formula (**I**)), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof. In certain embodiments, the PRMT5-mediated disorder is a proliferative disorder, a metabolic disorder, or a blood disorder. In certain embodiments, compounds described herein are useful for treating cancer. In certain embodiments, compounds described herein are useful for treating hematopoietic cancer, lung cancer, prostate cancer, melanoma, or pancreatic cancer. In certain embodiments, compounds described herein are useful for treating a hemoglobinopathy. In certain embodiments, compounds described herein are useful for treating sickle cell anemia. In certain embodiments, compounds described herein are useful for treating diabetes or obesity. In certain embodiments, a provided compound is useful in treating inflammatory and autoimmune disease.

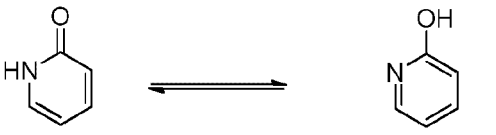
[0014] Compounds described herein are also useful for the study of PRMT5 in biological and pathological phenomena, the study of intracellular signal transduction pathways mediated by PRMT5, and the comparative evaluation of new PRMT5 inhibitors.

[0015] This application refers to various issued patent, published patent applications, journal articles, and other publications, all of which are incorporated herein by reference.

[0016] Definitions of specific functional groups and chemical terms are described in more detail below. The chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, *Handbook of Chemistry and Physics*, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in Thomas Sorrell, *Organic Chemistry*, University Science Books, Sausalito, 1999; Smith and March, *March's Advanced Organic Chemistry*, 5th Edition, John Wiley & Sons, Inc., New York, 2001; Larock, *Comprehensive Organic Transformations*, VCH Publishers, Inc., New York, 1989; and Carruthers, *Some Modern Methods of Organic Synthesis*, 3rd Edition, Cambridge University Press, Cambridge, 1987.

[0017] Compounds described herein can comprise one or more asymmetric centers, and thus can exist in various isomeric forms, *e.g.*, enantiomers and/or diastereomers. For example, the compounds described herein can be in the form of an individual enantiomer, diastereomer or geometric isomer, or can be in the form of a mixture of stereoisomers, including racemic mixtures and mixtures enriched in one or more stereoisomer. Isomers can be isolated from mixtures by methods known to those skilled in the art, including chiral high pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts; or preferred isomers can be prepared by asymmetric syntheses. See, for example, Jacques *et al.*, *Enantiomers, Racemates and Resolutions* (Wiley Interscience, New York, 1981); Wilen *et al.*, *Tetrahedron* 33:2725 (1977); Eliel, *Stereochemistry of Carbon Compounds* (McGraw–Hill, NY, 1962); and Wilen, *Tables of Resolving Agents and Optical Resolutions* p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN 1972). The present disclosure additionally encompasses compounds described herein as individual isomers substantially free of other isomers, and alternatively, as mixtures of various isomers.

[0018] It is to be understood that the compounds of the present invention may be depicted as different tautomers. It should also be understood that when compounds have tautomeric forms, all tautomeric forms are intended to be included in the scope of the present invention, and the naming of any compound described herein does not exclude any tautomer form.



pyridin-2(1*H*)-one pyridin-2-ol

[0019] Unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of hydrogen by deuterium or tritium, replacement of ^{19}F with ^{18}F, or the replacement of a carbon by a ^{13}C- or ^{14}C-enriched carbon are within the scope of the disclosure. Such compounds are useful, for example, as analytical tools or probes in biological assays.

[0020] The term "aliphatic," as used herein, includes both saturated and unsaturated, nonaromatic, straight chain (*i.e.*, unbranched), branched, acyclic, and cyclic (*i.e.*, carbocyclic) hydrocarbons. In some embodiments, an aliphatic group is optionally substituted with one or more functional groups. As will be appreciated by one of ordinary skill in the art, "aliphatic" is intended herein to include alkyl, alkenyl, alkynyl, cycloalkyl, and cycloalkenyl moieties.

[0021] When a range of values is listed, it is intended to encompass each value and sub–range within the range. For example "C_{1-6} alkyl" is intended to encompass, C_1, C_2, C_3, C_4, C_5, C_6, C_{1-6}, C_{1-5}, C_{1-4}, C_{1-3}, C_{1-2}, C_{2-6}, C_{2-5}, C_{2-4}, C_{2-3}, C_{3-6}, C_{3-5}, C_{3-4}, C_{4-6}, C_{4-5}, and C_{5-6} alkyl.

[0022] "Alkyl" refers to a radical of a straight–chain or branched saturated hydrocarbon group having from 1 to 20 carbon atoms ("C_{1-20} alkyl"). In some embodiments, an alkyl group has 1 to 10 carbon atoms ("C_{1-10} alkyl"). In some embodiments, an alkyl group has 1 to 9 carbon atoms ("C_{1-9} alkyl"). In some embodiments, an alkyl group has 1 to 8 carbon atoms ("C_{1-8} alkyl"). In some embodiments, an alkyl group has 1 to 7 carbon atoms ("C_{1-7} alkyl"). In some embodiments, an alkyl group has 1 to 6 carbon atoms ("C_{1-6} alkyl"). In some embodiments, an alkyl group has 1 to 5 carbon atoms ("C_{1-5} alkyl"). In some embodiments, an alkyl group has 1 to 4 carbon atoms ("C_{1-4} alkyl"). In some embodiments, an alkyl group has 1 to 3 carbon atoms ("C_{1-3} alkyl"). In some embodiments, an alkyl group has 1 to 2 carbon atoms ("C_{1-2} alkyl"). In some embodiments, an alkyl group has 1 carbon atom ("C_1 alkyl"). In some embodiments, an alkyl group has 2 to 6 carbon atoms ("C_{2-6} alkyl"). Examples of C_{1-6} alkyl groups include methyl (C_1), ethyl (C_2), n–propyl (C_3), isopropyl (C_3), n–butyl (C_4), tert–butyl (C_4), sec–butyl (C_4), iso–butyl (C_4), n–pentyl (C_5), 3–pentanyl (C_5), amyl (C_5), neopentyl (C_5), 3–methyl–2–butanyl (C_5), tertiary amyl (C_5), and n–hexyl (C_6). Additional examples of alkyl groups include n–heptyl (C_7), n–octyl (C_8) and the like. In certain embodiments, each instance of an alkyl group is independently optionally substituted, *e.g.*, unsubstituted (an "unsubstituted alkyl") or substituted (a "substituted alkyl") with one or more substituents. In certain embodiments, the alkyl group is unsubstituted C_{1-10} alkyl (*e.g.*, $–CH_3$). In certain embodiments, the alkyl group is substituted C_{1-10} alkyl.

[0023] In some embodiments, an alkyl group is substituted with one or more halogens. "Perhaloalkyl" is a substituted alkyl group as defined herein wherein all of the hydrogen atoms are independently replaced by a halogen, *e.g.,* fluoro, bromo, chloro, or iodo. In some embodiments, the alkyl moiety has 1 to 8 carbon atoms ("C_{1-8} perhaloalkyl"). In some embodiments, the alkyl moiety has 1 to 6 carbon atoms ("C_{1-6} perhaloalkyl"). In some embodiments, the alkyl moiety has 1 to 4 carbon atoms ("C_{1-4} perhaloalkyl"). In some embodiments, the alkyl moiety has 1 to 3 carbon atoms ("C_{1-3} perhaloalkyl"). In some embodiments, the alkyl moiety has 1 to 2 carbon atoms ("C_{1-2} perhaloalkyl"). In some embodiments, all of the hydrogen atoms are replaced with fluoro. In some embodiments, all of the hydrogen atoms are replaced with chloro. Examples of perhaloalkyl groups include –CF_3, –CF_2CF_3, –$CF_2CF_2CF_3$, –CCl_3, –$CFCl_2$, –CF_2Cl, and the like.

[0024] "Alkenyl" refers to a radical of a straight–chain or branched hydrocarbon group having from 2 to 20 carbon atoms, one or more carbon–carbon double bonds, and no triple bonds ("C_{2-20} alkenyl"). In some embodiments, an alkenyl group has 2 to 10 carbon atoms ("C_{2-10} alkenyl"). In some embodiments, an alkenyl group has 2 to 9 carbon atoms ("C_{2-9} alkenyl"). In some embodiments, an alkenyl group has 2 to 8 carbon atoms ("C_{2-8} alkenyl"). In some embodiments, an alkenyl group has 2 to 7 carbon atoms ("C_{2-7} alkenyl"). In some embodiments, an alkenyl group has 2 to 6 carbon atoms ("C_{2-6} alkenyl"). In some embodiments, an alkenyl group has 2 to 5 carbon atoms ("C_{2-5} alkenyl"). In some embodiments, an alkenyl group has 2 to 4 carbon atoms ("C_{2-4} alkenyl"). In some embodiments, an alkenyl group has 2 to 3 carbon atoms ("C_{2-3} alkenyl"). In some embodiments, an alkenyl group has 2 carbon atoms ("C_2 alkenyl"). The one or more carbon–carbon double bonds can be internal (such as in 2–butenyl) or terminal (such as in 1–butenyl). Examples of C_{2-4} alkenyl groups include ethenyl (C_2), 1–propenyl (C_3), 2–propenyl (C_3), 1–butenyl (C_4), 2–butenyl (C_4), butadienyl (C_4), and the like. Examples of C_{2-6} alkenyl groups include the aforementioned C_{2-4} alkenyl groups as well as pentenyl (C_5), pentadienyl (C_5), hexenyl (C_6), and the like. Additional examples of alkenyl include heptenyl (C_7), octenyl (C_8), octatrienyl (C_8), and the like. In certain embodiments, each instance of an alkenyl group is independently optionally substituted, *e.g.*, unsubstituted (an "unsubstituted alkenyl") or substituted (a "substituted alkenyl") with one or more substituents. In certain embodiments, the alkenyl group is unsubstituted C_{2-10} alkenyl. In certain embodiments, the alkenyl group is substituted C_{2-10} alkenyl.

[0025] "Alkynyl" refers to a radical of a straight–chain or branched hydrocarbon group having from 2 to 20 carbon atoms, one or more carbon–carbon triple bonds, and optionally

one or more double bonds ("C_{2-20} alkynyl"). In some embodiments, an alkynyl group has 2 to 10 carbon atoms ("C_{2-10} alkynyl"). In some embodiments, an alkynyl group has 2 to 9 carbon atoms ("C_{2-9} alkynyl"). In some embodiments, an alkynyl group has 2 to 8 carbon atoms ("C_{2-8} alkynyl"). In some embodiments, an alkynyl group has 2 to 7 carbon atoms ("C_{2-7} alkynyl"). In some embodiments, an alkynyl group has 2 to 6 carbon atoms ("C_{2-6} alkynyl"). In some embodiments, an alkynyl group has 2 to 5 carbon atoms ("C_{2-5} alkynyl"). In some embodiments, an alkynyl group has 2 to 4 carbon atoms ("C_{2-4} alkynyl"). In some embodiments, an alkynyl group has 2 to 3 carbon atoms ("C_{2-3} alkynyl"). In some embodiments, an alkynyl group has 2 carbon atoms ("C_2 alkynyl"). The one or more carbon–carbon triple bonds can be internal (such as in 2–butynyl) or terminal (such as in 1–butynyl). Examples of C_{2-4} alkynyl groups include, without limitation, ethynyl (C_2), 1–propynyl (C_3), 2–propynyl (C_3), 1–butynyl (C_4), 2–butynyl (C_4), and the like. Examples of C_{2-6} alkenyl groups include the aforementioned C_{2-4} alkynyl groups as well as pentynyl (C_5), hexynyl (C_6), and the like. Additional examples of alkynyl include heptynyl (C_7), octynyl (C_8), and the like. In certain embodiments, each instance of an alkynyl group is independently optionally substituted, *e.g.*, unsubstituted (an "unsubstituted alkynyl") or substituted (a "substituted alkynyl") with one or more substituents. In certain embodiments, the alkynyl group is unsubstituted C_{2-10} alkynyl. In certain embodiments, the alkynyl group is substituted C_{2-10} alkynyl.

[0026] "Carbocyclyl" or "carbocyclic" refers to a radical of a non–aromatic cyclic hydrocarbon group having from 3 to 14 ring carbon atoms ("C_{3-14} carbocyclyl") and zero heteroatoms in the non–aromatic ring system. In some embodiments, a carbocyclyl group has 3 to 10 ring carbon atoms ("C_{3-10} carbocyclyl"). In some embodiments, a carbocyclyl group has 3 to 8 ring carbon atoms ("C_{3-8} carbocyclyl"). In some embodiments, a carbocyclyl group has 3 to 6 ring carbon atoms ("C_{3-6} carbocyclyl"). In some embodiments, a carbocyclyl group has 3 to 6 ring carbon atoms ("C_{3-6} carbocyclyl"). In some embodiments, a carbocyclyl group has 5 to 10 ring carbon atoms ("C_{5-10} carbocyclyl"). Exemplary C_{3-6} carbocyclyl groups include, without limitation, cyclopropyl (C_3), cyclopropenyl (C_3), cyclobutyl (C_4), cyclobutenyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), cyclohexadienyl (C_6), and the like. Exemplary C_{3-8} carbocyclyl groups include, without limitation, the aforementioned C_{3-6} carbocyclyl groups as well as cycloheptyl (C_7), cycloheptenyl (C_7), cycloheptadienyl (C_7), cycloheptatrienyl (C_7), cyclooctyl (C_8), cyclooctenyl (C_8), bicyclo[2.2.1]heptanyl (C_7), bicyclo[2.2.2]octanyl (C_8), and the like. Exemplary C_{3-10} carbocyclyl groups include, without limitation, the

aforementioned C_{3-8} carbocyclyl groups as well as cyclononyl (C_9), cyclononenyl (C_9), cyclodecyl (C_{10}), cyclodecenyl (C_{10}), octahydro–1*H*–indenyl (C_9), decahydronaphthalenyl (C_{10}), spiro[4.5]decanyl (C_{10}), and the like. As the foregoing examples illustrate, in certain embodiments, the carbocyclyl group is either monocyclic ("monocyclic carbocyclyl") or is a fused, bridged or spiro-fused ring system such as a bicyclic system ("bicyclic carbocyclyl") and can be saturated or can be partially unsaturated. "Carbocyclyl" also includes ring systems wherein the carbocyclyl ring, as defined above, is fused with one or more aryl or heteroaryl groups wherein the point of attachment is on the carbocyclyl ring, and in such instances, the number of carbons continue to designate the number of carbons in the carbocyclic ring system. In certain embodiments, each instance of a carbocyclyl group is independently optionally substituted, *e.g.*, unsubstituted (an "unsubstituted carbocyclyl") or substituted (a "substituted carbocyclyl") with one or more substituents. In certain embodiments, the carbocyclyl group is unsubstituted C_{3-10} carbocyclyl. In certain embodiments, the carbocyclyl group is a substituted C_{3-10} carbocyclyl.

[0027] In some embodiments, "carbocyclyl" is a monocyclic, saturated carbocyclyl group having from 3 to 14 ring carbon atoms ("C_{3-14} cycloalkyl"). In some embodiments, a cycloalkyl group has 3 to 10 ring carbon atoms ("C_{3-10} cycloalkyl"). In some embodiments, a cycloalkyl group has 3 to 8 ring carbon atoms ("C_{3-8} cycloalkyl"). In some embodiments, a cycloalkyl group has 3 to 6 ring carbon atoms ("C_{3-6} cycloalkyl"). In some embodiments, a cycloalkyl group has 5 to 6 ring carbon atoms ("C_{5-6} cycloalkyl"). In some embodiments, a cycloalkyl group has 5 to 10 ring carbon atoms ("C_{5-10} cycloalkyl"). Examples of C_{5-6} cycloalkyl groups include cyclopentyl (C_5) and cyclohexyl (C_5). Examples of C_{3-6} cycloalkyl groups include the aforementioned C_{5-6} cycloalkyl groups as well as cyclopropyl (C_3) and cyclobutyl (C_4). Examples of C_{3-8} cycloalkyl groups include the aforementioned C_{3-6} cycloalkyl groups as well as cycloheptyl (C_7) and cyclooctyl (C_8). In certain embodiments, each instance of a cycloalkyl group is independently unsubstituted (an "unsubstituted cycloalkyl") or substituted (a "substituted cycloalkyl") with one or more substituents. In certain embodiments, the cycloalkyl group is unsubstituted C_{3-10} cycloalkyl. In certain embodiments, the cycloalkyl group is substituted C_{3-10} cycloalkyl.

[0028] "Heterocyclyl" or "heterocyclic" refers to a radical of a 3– to 14–membered non–aromatic ring system having ring carbon atoms and 1 to 4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("3–14 membered heterocyclyl"). In certain embodiments, heterocyclyl or heterocyclic refers to a radical of a 3–10 membered non–aromatic ring system having ring carbon atoms and 1–4 ring

heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("3–10 membered heterocyclyl"). In heterocyclyl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. A heterocyclyl group can either be monocyclic ("monocyclic heterocyclyl") or a fused, bridged or spiro-fused ring system such as a bicyclic system ("bicyclic heterocyclyl"), and can be saturated or can be partially unsaturated. Heterocyclyl bicyclic ring systems can include one or more heteroatoms in one or both rings. "Heterocyclyl" also includes ring systems wherein the heterocyclyl ring, as defined above, is fused with one or more carbocyclyl groups wherein the point of attachment is either on the carbocyclyl or heterocyclyl ring, or ring systems wherein the heterocyclyl ring, as defined above, is fused with one or more aryl or heteroaryl groups, wherein the point of attachment is on the heterocyclyl ring, and in such instances, the number of ring members continue to designate the number of ring members in the heterocyclyl ring system. In certain embodiments, each instance of heterocyclyl is independently optionally substituted, *e.g.*, unsubstituted (an "unsubstituted heterocyclyl") or substituted (a "substituted heterocyclyl") with one or more substituents. In certain embodiments, the heterocyclyl group is unsubstituted 3–10 membered heterocyclyl. In certain embodiments, the heterocyclyl group is substituted 3–10 membered heterocyclyl.

[0029] In some embodiments, a heterocyclyl group is a 5–10 membered non–aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5–10 membered heterocyclyl"). In some embodiments, a heterocyclyl group is a 5–8 membered non–aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5–8 membered heterocyclyl"). In some embodiments, a heterocyclyl group is a 5–6 membered non–aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5–6 membered heterocyclyl"). In some embodiments, the 5–6 membered heterocyclyl has 1–3 ring heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5–6 membered heterocyclyl has 1–2 ring heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5–6 membered heterocyclyl has one ring heteroatom selected from nitrogen, oxygen, and sulfur.

[0030] Exemplary 3–membered heterocyclyl groups containing one heteroatom include, without limitation, azirdinyl, oxiranyl, and thiorenyl. Exemplary 4–membered heterocyclyl

groups containing one heteroatom include, without limitation, azetidinyl, oxetanyl, and thietanyl. Exemplary 5–membered heterocyclyl groups containing one heteroatom include, without limitation, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothiophenyl, dihydrothiophenyl, pyrrolidinyl, dihydropyrrolyl, and pyrrolyl–2,5–dione. Exemplary 5–membered heterocyclyl groups containing two heteroatoms include, without limitation, dioxolanyl, oxasulfuranyl, disulfuranyl, and oxazolidin-2-one. Exemplary 5–membered heterocyclyl groups containing three heteroatoms include, without limitation, triazolinyl, oxadiazolinyl, and thiadiazolinyl. Exemplary 6–membered heterocyclyl groups containing one heteroatom include, without limitation, piperidinyl, tetrahydropyranyl, dihydropyridinyl, and thianyl. Exemplary 6–membered heterocyclyl groups containing two heteroatoms include, without limitation, piperazinyl, morpholinyl, dithianyl, and dioxanyl. Exemplary 6–membered heterocyclyl groups containing three heteroatoms include, without limitation, triazinanyl, oxadiazinanyl, thiadiazinanyl, oxathiazinanyl, and dioxazinanyl. Exemplary 7–membered heterocyclyl groups containing one heteroatom include, without limitation, azepanyl, oxepanyl and thiepanyl. Exemplary 8–membered heterocyclyl groups containing one heteroatom include, without limitation, azocanyl, oxecanyl, and thiocanyl. Exemplary 5-membered heterocyclyl groups fused to a C_6 aryl ring (also referred to herein as a 5,6-bicyclic heterocyclic ring) include, without limitation, indolinyl, isoindolinyl, dihydrobenzofuranyl, dihydrobenzothienyl, benzoxazolinonyl, and the like. Exemplary 6-membered heterocyclyl groups fused to an aryl ring (also referred to herein as a 6,6-bicyclic heterocyclic ring) include, without limitation, tetrahydroquinolinyl, tetrahydroisoquinolinyl, and the like.

[0031] "Aryl" refers to a radical of a monocyclic or polycyclic (*e.g.*, bicyclic or tricyclic) 4n+2 aromatic ring system (*e.g.*, having 6, 10, or 14 π electrons shared in a cyclic array) having 6–14 ring carbon atoms and zero heteroatoms provided in the aromatic ring system ("C_{6-14} aryl"). In some embodiments, an aryl group has six ring carbon atoms ("C_6 aryl"; *e.g.*, phenyl). In some embodiments, an aryl group has ten ring carbon atoms ("C_{10} aryl"; *e.g.*, naphthyl such as 1–naphthyl and 2–naphthyl). In some embodiments, an aryl group has fourteen ring carbon atoms ("C_{14} aryl"; *e.g.*, anthracyl). "Aryl" also includes ring systems wherein the aryl ring, as defined above, is fused with one or more carbocyclyl or heterocyclyl groups wherein the radical or point of attachment is on the aryl ring, and in such instances, the number of carbon atoms continue to designate the number of carbon atoms in the aryl ring system. In certain embodiments, each instance of an aryl group is independently optionally substituted, *e.g.*, unsubstituted (an "unsubstituted aryl") or substituted (a "substituted aryl")

with one or more substituents. In certain embodiments, the aryl group is unsubstituted C_{6-14} aryl. In certain embodiments, the aryl group is substituted C_{6-14} aryl.

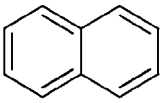
[0032] "Heteroaryl" refers to a radical of a 5–14 membered monocyclic or polycyclic (*e.g.,* bicyclic or tricyclic) 4n+2 aromatic ring system (*e.g.,* having 6 or 10 π electrons shared in a cyclic array) having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5–14 membered heteroaryl"). In certain embodiments, heteroaryl refers to a radical of a 5–10 membered monocyclic or bicyclic 4n+2 aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen and sulfur ("5–10 membered heteroaryl"). In heteroaryl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. Heteroaryl bicyclic ring systems can include one or more heteroatoms in one or both rings. "Heteroaryl" includes ring systems wherein the heteroaryl ring, as defined above, is fused with one or more carbocyclyl or heterocyclyl groups wherein the point of attachment is on the heteroaryl ring, and in such instances, the number of ring members continue to designate the number of ring members in the heteroaryl ring system. "Heteroaryl" also includes ring systems wherein the heteroaryl ring, as defined above, is fused with one or more aryl groups wherein the point of attachment is either on the aryl or heteroaryl ring, and in such instances, the number of ring members designates the number of ring members in the fused (aryl/heteroaryl) ring system. Bicyclic heteroaryl groups wherein one ring does not contain a heteroatom (*e.g.,* indolyl, quinolinyl, carbazolyl, and the like) the point of attachment can be on either ring, *e.g.,* either the ring bearing a heteroatom (*e.g.,* 2–indolyl) or the ring that does not contain a heteroatom (*e.g.,* 5–indolyl).

[0033] In some embodiments, a heteroaryl group is a 5–14 membered aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5–14 membered heteroaryl"). In some embodiments, a heteroaryl group is a 5–10 membered aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5–10 membered heteroaryl"). In some embodiments, a heteroaryl group is a 5–8 membered aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is

independently selected from nitrogen, oxygen, and sulfur ("5–8 membered heteroaryl"). In some embodiments, a heteroaryl group is a 5–6 membered aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5–6 membered heteroaryl"). In some embodiments, the 5–6 membered heteroaryl has 1–3 ring heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5–6 membered heteroaryl has 1–2 ring heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5–6 membered heteroaryl has 1 ring heteroatom selected from nitrogen, oxygen, and sulfur. In certain embodiments, each instance of a heteroaryl group is independently optionally substituted, *e.g.*, unsubstituted ("unsubstituted heteroaryl") or substituted ("substituted heteroaryl") with one or more substituents. In certain embodiments, the heteroaryl group is unsubstituted 5–14 membered heteroaryl. In certain embodiments, the heteroaryl group is substituted 5–14 membered heteroaryl.

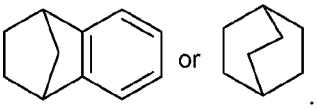
[0034] Exemplary 5–membered heteroaryl groups containing one heteroatom include, without limitation, pyrrolyl, furanyl and thiophenyl. Exemplary 5–membered heteroaryl groups containing two heteroatoms include, without limitation, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, and isothiazolyl. Exemplary 5–membered heteroaryl groups containing three heteroatoms include, without limitation, triazolyl, oxadiazolyl, and thiadiazolyl. Exemplary 5–membered heteroaryl groups containing four heteroatoms include, without limitation, tetrazolyl. Exemplary 6–membered heteroaryl groups containing one heteroatom include, without limitation, pyridinyl. Exemplary 6–membered heteroaryl groups containing two heteroatoms include, without limitation, pyridazinyl, pyrimidinyl, and pyrazinyl. Exemplary 6–membered heteroaryl groups containing three or four heteroatoms include, without limitation, triazinyl and tetrazinyl, respectively. Exemplary 7–membered heteroaryl groups containing one heteroatom include, without limitation, azepinyl, oxepinyl, and thiepinyl. Exemplary 5,6–bicyclic heteroaryl groups include, without limitation, indolyl, isoindolyl, indazolyl, benzotriazolyl, benzothiophenyl, isobenzothiophenyl, benzofuranyl, benzoisofuranyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzoxadiazolyl, benzthiazolyl, benzisothiazolyl, benzthiadiazolyl, indolizinyl, and purinyl. Exemplary 6,6–bicyclic heteroaryl groups include, without limitation, naphthyridinyl, pteridinyl, quinolinyl, isoquinolinyl, cinnolinyl, quinoxalinyl, phthalazinyl, and quinazolinyl.

[0035] "Fused" or "ortho-fused" are used interchangeably herein, and refer to two rings that have two atoms and one bond in common, *e.g.*,

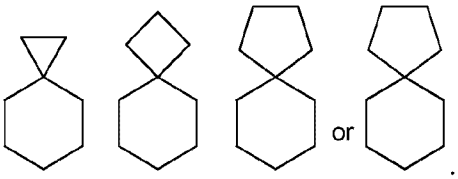


napthalene.

[0036] "Bridged" refers to a ring system containing (1) a bridgehead atom or group of atoms which connect two or more non-adjacent positions of the same ring; or (2) a bridgehead atom or group of atoms which connect two or more positions of different rings of a ring system and does not thereby form an ortho-fused ring, *e.g.*,



[0037] "Spiro" or "Spiro-fused" refers to a group of atoms which connect to the same atom of a carbocyclic or heterocyclic ring system (geminal attachment), thereby forming a ring, *e.g.*,



Spiro-fusion at a bridgehead atom is also contemplated.

[0038] "Partially unsaturated" refers to a group that includes at least one double or triple bond. The term "partially unsaturated" is intended to encompass rings having multiple sites of unsaturation, but is not intended to include aromatic groups (*e.g.*, aryl or heteroaryl groups) as herein defined. Likewise, "saturated" refers to a group that does not contain a double or triple bond, *i.e.*, contains all single bonds.

[0039] In some embodiments, aliphatic, alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl groups, as defined herein, are optionally substituted (*e.g.*, "substituted" or "unsubstituted" aliphatic, "substituted" or "unsubstituted" alkyl, "substituted" or "unsubstituted" alkenyl, "substituted" or "unsubstituted" alkynyl, "substituted" or "unsubstituted" carbocyclyl, "substituted" or "unsubstituted" heterocyclyl, "substituted" or "unsubstituted" aryl or "substituted" or "unsubstituted" heteroaryl group). In general, the term "substituted", whether preceded by the term "optionally" or not, means that at least one hydrogen present on a group (*e.g.*, a carbon or nitrogen atom) is replaced with a permissible substituent, *e.g.*, a substituent which upon substitution results in a stable compound, *e.g.*, a

compound which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, or other reaction. Unless otherwise indicated, a "substituted" group has a substituent at one or more substitutable positions of the group, and when more than one position in any given structure is substituted, the substituent is either the same or different at each position. The term "substituted" is contemplated to include substitution with all permissible substituents of organic compounds, including any of the substituents described herein that results in the formation of a stable compound. The present disclosure contemplates any and all such combinations in order to arrive at a stable compound. For purposes of this disclosure, heteroatoms such as nitrogen may have hydrogen substituents and/or any suitable substituent as described herein which satisfy the valencies of the heteroatoms and results in the formation of a stable moiety.

[0040] Exemplary carbon atom substituents include, but are not limited to, halogen, $-CN$, $-NO_2$, $-N_3$, $-SO_2H$, $-SO_3H$, $-OH$, $-OR^{aa}$, $-ON(R^{bb})_2$, $-N(R^{bb})_2$, $-N(R^{bb})_3^+X^-$, $-N(OR^{cc})R^{bb}$, $-SH$, $-SR^{aa}$, $-SSR^{cc}$, $-C(=O)R^{aa}$, $-CO_2H$, $-CHO$, $-C(OR^{cc})_2$, $-CO_2R^{aa}$, $-OC(=O)R^{aa}$, $-OCO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, $-OC(=O)N(R^{bb})_2$, $-NR^{bb}C(=O)R^{aa}$, $-NR^{bb}CO_2R^{aa}$, $-NR^{bb}C(=O)N(R^{bb})_2$, $-C(=NR^{bb})R^{aa}$, $-C(=NR^{bb})OR^{aa}$, $-OC(=NR^{bb})R^{aa}$, $-OC(=NR^{bb})OR^{aa}$, $-C(=NR^{bb})N(R^{bb})_2$, $-OC(=NR^{bb})N(R^{bb})_2$, $-NR^{bb}C(=NR^{bb})N(R^{bb})_2$, $-C(=O)NR^{bb}SO_2R^{aa}$, $-NR^{bb}SO_2R^{aa}$, $-SO_2N(R^{bb})_2$, $-SO_2R^{aa}$, $-SO_2OR^{aa}$, $-OSO_2R^{aa}$, $-S(=O)R^{aa}$, $-OS(=O)R^{aa}$, $-Si(R^{aa})_3$, $-OSi(R^{aa})_3$ $-C(=S)N(R^{bb})_2$, $-C(=O)SR^{aa}$, $-C(=S)SR^{aa}$, $-SC(=S)SR^{aa}$, $-SC(=O)SR^{aa}$, $-OC(=O)SR^{aa}$, $-SC(=O)OR^{aa}$, $-SC(=O)R^{aa}$, $-P(=O)_2R^{aa}$, $-OP(=O)_2R^{aa}$, $-P(=O)(R^{aa})_2$, $-OP(=O)(R^{aa})_2$, $-OP(=O)(OR^{cc})_2$, $-P(=O)_2N(R^{bb})_2$, $-OP(=O)_2N(R^{bb})_2$, $-P(=O)(NR^{bb})_2$, $-OP(=O)(NR^{bb})_2$, $-NR^{bb}P(=O)(OR^{cc})_2$, $-NR^{bb}P(=O)(NR^{bb})_2$, $-P(R^{cc})_2$, $-P(R^{cc})_3$, $-OP(R^{cc})_2$, $-OP(R^{cc})_3$, $-B(R^{aa})_2$, $-B(OR^{cc})_2$, $-BR^{aa}(OR^{cc})$, C_{1-10} alkyl, C_{1-10} perhaloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} carbocyclyl, 3–14 membered heterocyclyl, C_{6-14} aryl, and 5–14 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

or two geminal hydrogens on a carbon atom are replaced with the group $=O$, $=S$, $=NN(R^{bb})_2$, $=NNR^{bb}C(=O)R^{aa}$, $=NNR^{bb}C(=O)OR^{aa}$, $=NNR^{bb}S(=O)_2R^{aa}$, $=NR^{bb}$, or $=NOR^{cc}$;

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

each instance of R^{bb} is, independently, selected from hydrogen, –OH, $–OR^{aa}$, $–N(R^{cc})_2$, –CN, $–C(=O)R^{aa}$, $–C(=O)N(R^{cc})_2$, $–CO_2R^{aa}$, $–SO_2R^{aa}$, $–C(=NR^{cc})OR^{aa}$, $–C(=NR^{cc})N(R^{cc})_2$, $–SO_2N(R^{cc})_2$, $–SO_2R^{cc}$, $–SO_2OR^{cc}$, $–SOR^{aa}$, $–C(=S)N(R^{cc})_2$, $–C(=O)SR^{cc}$, $–C(=S)SR^{cc}$, $–P(=O)_2R^{aa}$, $–P(=O)(R^{aa})_2$, $–P(=O)_2N(R^{cc})_2$, $–P(=O)(NR^{cc})_2$, $C_{1–10}$ alkyl, $C_{1–10}$ perhaloalkyl, $C_{2–10}$ alkenyl, $C_{2–10}$ alkynyl, $C_{3–10}$ carbocyclyl, 3–14 membered heterocyclyl, $C_{6–14}$ aryl, and 5–14 membered heteroaryl, or two R^{bb} groups are joined to form a 3–14 membered heterocyclyl or 5–14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

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

each instance of R^{dd} is, independently, selected from halogen, –CN, $–NO_2$, $–N_3$, $–SO_2H$, $–SO_3H$, –OH, $–OR^{ee}$, $–ON(R^{ff})_2$, $–N(R^{ff})_2$, $–N(R^{ff})_3{}^+X^-$, $–N(OR^{ee})R^{ff}$, –SH, $–SR^{ee}$, $–SSR^{ee}$, $–C(=O)R^{ee}$, $–CO_2H$, $–CO_2R^{ee}$, $–OC(=O)R^{ee}$, $–OCO_2R^{ee}$, $–C(=O)N(R^{ff})_2$, $–OC(=O)N(R^{ff})_2$, $–NR^{ff}C(=O)R^{ee}$, $–NR^{ff}CO_2R^{ee}$, $–NR^{ff}C(=O)N(R^{ff})_2$, $–C(=NR^{ff})OR^{ee}$, $–OC(=NR^{ff})R^{ee}$, $–OC(=NR^{ff})OR^{ee}$, $–C(=NR^{ff})N(R^{ff})_2$, $–OC(=NR^{ff})N(R^{ff})_2$, $–NR^{ff}C(=NR^{ff})N(R^{ff})_2$, $–NR^{ff}SO_2R^{ee}$, $–SO_2N(R^{ff})_2$, $–SO_2R^{ee}$, $–SO_2OR^{ee}$, $–OSO_2R^{ee}$, $–S(=O)R^{ee}$, $–Si(R^{ee})_3$, $–OSi(R^{ee})_3$, $–C(=S)N(R^{ff})_2$, $–C(=O)SR^{ee}$, $–C(=S)SR^{ee}$, $–SC(=S)SR^{ee}$, $–P(=O)_2R^{ee}$, $–P(=O)(R^{ee})_2$, $–OP(=O)(R^{ee})_2$, $–OP(=O)(OR^{ee})_2$, $C_{1–6}$ alkyl, $C_{1–6}$ perhaloalkyl, $C_{2–6}$ alkenyl, $C_{2–6}$ alkynyl, $C_{3–10}$ carbocyclyl, 3–10 membered heterocyclyl, $C_{6–10}$ aryl, 5–10 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups, or two geminal R^{dd} substituents can be joined to form =O or =S;

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

each instance of R^{ff} is, independently, selected from hydrogen, $C_{1–6}$ alkyl, $C_{1–6}$ perhaloalkyl, $C_{2–6}$ alkenyl, $C_{2–6}$ alkynyl, $C_{3–10}$ carbocyclyl, 3–10 membered heterocyclyl, $C_{6–10}$ aryl and 5–10 membered heteroaryl, or two R^{ff} groups are joined to form a 3–14 membered

heterocyclyl or 5–14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups; and

each instance of R^{gg} is, independently, halogen, –CN, $–NO_2$, $–N_3$, $–SO_2H$, $–SO_3H$, –OH, $–OC_{1–6}$ alkyl, $–ON(C_{1–6}$ alkyl$)_2$, $–N(C_{1–6}$ alkyl$)_2$, $–N(C_{1–6}$ alkyl$)_3^+X^–$, $–NH(C_{1–6}$ alkyl$)_2^+X^–$, $–NH_2(C_{1–6}$ alkyl$)^+X^–$, $–NH_3^+X^–$, $–N(OC_{1–6}$ alkyl$)(C_{1–6}$ alkyl), $–N(OH)(C_{1–6}$ alkyl), –NH(OH), –SH, $–SC_{1–6}$ alkyl, $–SS(C_{1–6}$ alkyl), $–C(=O)(C_{1–6}$ alkyl), $–CO_2H$, $–CO_2(C_{1–6}$ alkyl), $–OC(=O)(C_{1–6}$ alkyl), $–OCO_2(C_{1–6}$ alkyl), $–C(=O)NH_2$, $–C(=O)N(C_{1–6}$ alkyl$)_2$, $–OC(=O)NH(C_{1–6}$ alkyl), $–NHC(=O)(C_{1–6}$ alkyl), $–N(C_{1–6}$ alkyl$)C(=O)(C_{1–6}$ alkyl), $–NHCO_2(C_{1–6}$ alkyl), $–NHC(=O)N(C_{1–6}$ alkyl$)_2$, $–NHC(=O)NH(C_{1–6}$ alkyl), $–NHC(=O)NH_2$, $–C(=NH)O(C_{1–6}$ alkyl), $–OC(=NH)(C_{1–6}$ alkyl), $–OC(=NH)OC_{1–6}$ alkyl, $–C(=NH)N(C_{1–6}$ alkyl$)_2$, $–C(=NH)NH(C_{1–6}$ alkyl), $–C(=NH)NH_2$, $–OC(=NH)N(C_{1–6}$ alkyl$)_2$, $–OC(NH)NH(C_{1–6}$ alkyl), $–OC(NH)NH_2$, $–NHC(NH)N(C_{1–6}$ alkyl$)_2$, $–NHC(=NH)NH_2$, $–NHSO_2(C_{1–6}$ alkyl), $–SO_2N(C_{1–6}$ alkyl$)_2$, $–SO_2NH(C_{1–6}$ alkyl), $–SO_2NH_2$, $–SO_2C_{1–6}$ alkyl, $–SO_2OC_{1–6}$ alkyl, $–OSO_2C_{1–6}$ alkyl, $–SOC_{1–6}$ alkyl, $–Si(C_{1–6}$ alkyl$)_3$, $–OSi(C_{1–6}$ alkyl$)_3$ – $C(=S)N(C_{1–6}$ alkyl$)_2$, $C(=S)NH(C_{1–6}$ alkyl), $C(=S)NH_2$, $–C(=O)S(C_{1–6}$ alkyl), $–C(=S)SC_{1–6}$ alkyl, $–SC(=S)SC_{1–6}$ alkyl, $–P(=O)_2(C_{1–6}$ alkyl), $–P(=O)(C_{1–6}$ alkyl$)_2$, $–OP(=O)(C_{1–6}$ alkyl$)_2$, $–OP(=O)(OC_{1–6}$ alkyl$)_2$, $C_{1–6}$ alkyl, $C_{1–6}$ perhaloalkyl, $C_{2–6}$ alkenyl, $C_{2–6}$ alkynyl, $C_{3–10}$ carbocyclyl, $C_{6–10}$ aryl, 3–10 membered heterocyclyl, 5–10 membered heteroaryl; or two geminal R^{gg} substituents can be joined to form =O or =S; wherein $X^–$ is a counterion.

[0041] A "counterion" or "anionic counterion" is a negatively charged group associated with a cationic quaternary amino group in order to maintain electronic neutrality. Exemplary counterions include halide ions (*e.g.*, $F^–$, $Cl^–$, $Br^–$, $I^–$), $NO_3^–$, $ClO_4^–$, $OH^–$, $H_2PO_4^–$, $HSO_4^–$, sulfonate ions (*e.g.*, methansulfonate, trifluoromethanesulfonate, p–toluenesulfonate, benzenesulfonate, 10–camphor sulfonate, naphthalene–2–sulfonate, naphthalene–1–sulfonic acid–5–sulfonate, ethan–1–sulfonic acid–2–sulfonate, and the like), and carboxylate ions (*e.g.*, acetate, ethanoate, propanoate, benzoate, glycerate, lactate, tartrate, glycolate, and the like).

[0042] "Halo" or "halogen" refers to fluorine (fluoro, –F), chlorine (chloro, –Cl), bromine (bromo, –Br), or iodine (iodo, –I).

[0043] Nitrogen atoms can be substituted or unsubstituted as valency permits, and include primary, secondary, tertiary, and quarternary nitrogen atoms. Exemplary nitrogen atom substitutents include, but are not limited to, hydrogen, –OH, $–OR^{aa}$, $–N(R^{cc})_2$, –CN, $–C(=O)R^{aa}$, $–C(=O)N(R^{cc})_2$, $–CO_2R^{aa}$, $–SO_2R^{aa}$, $–C(=NR^{bb})R^{aa}$, $–C(=NR^{cc})OR^{aa}$, –

$C(=NR^{cc})N(R^{cc})_2$, $-SO_2N(R^{cc})_2$, $-SO_2R^{cc}$, $-SO_2OR^{cc}$, $-SOR^{aa}$, $-C(=S)N(R^{cc})_2$, $-C(=O)SR^{cc}$, $-C(=S)SR^{cc}$, $-P(=O)_2R^{aa}$, $-P(=O)(R^{aa})_2$, $-P(=O)_2N(R^{cc})_2$, $-P(=O)(NR^{cc})_2$, C_{1-10} alkyl, C_{1-10} perhaloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} carbocyclyl, 3–14 membered heterocyclyl, C_{6-14} aryl, and 5–14 membered heteroaryl, or two R^{cc} groups attached to a nitrogen atom are joined to form a 3–14 membered heterocyclyl or 5–14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups, and wherein R^{aa}, R^{bb}, R^{cc} and R^{dd} are as defined above.

[0044] In certain embodiments, the substituent present on a nitrogen atom is a nitrogen protecting group (also referred to as an amino protecting group). Nitrogen protecting groups include, but are not limited to, –OH, $-OR^{aa}$, $-N(R^{cc})_2$, $-C(=O)R^{aa}$, $-C(=O)N(R^{cc})_2$, $-CO_2R^{aa}$, $-SO_2R^{aa}$, $-C(=NR^{cc})R^{aa}$, $-C(=NR^{cc})OR^{aa}$, $-C(=NR^{cc})N(R^{cc})_2$, $-SO_2N(R^{cc})_2$, $-SO_2R^{cc}$, $-SO_2OR^{cc}$, $-SOR^{aa}$, $-C(=S)N(R^{cc})_2$, $-C(=O)SR^{cc}$, $-C(=S)SR^{cc}$, C_{1-10} alkyl (*e.g.*, aralkyl, heteroaralkyl), C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} carbocyclyl, 3–14 membered heterocyclyl, C_{6-14} aryl, and 5–14 membered heteroaryl groups, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aralkyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups, and wherein R^{aa}, R^{bb}, R^{cc}, and R^{dd} are as defined herein. Nitrogen protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999.

[0045] Amide nitrogen protecting groups (*e.g.*, $-C(=O)R^{aa}$) include, but are not limited to, formamide, acetamide, chloroacetamide, trichloroacetamide, trifluoroacetamide, phenylacetamide, 3–phenylpropanamide, picolinamide, 3–pyridylcarboxamide, *N*–benzoylphenylalanyl derivative, benzamide, *p*–phenylbenzamide, *o*–nitophenylacetamide, *o*–nitrophenoxyacetamide, acetoacetamide, (*N'*–dithiobenzyloxyacylamino)acetamide, 3–(*p*–hydroxyphenyl)propanamide, 3–(*o*–nitrophenyl)propanamide, 2–methyl–2–(*o*–nitrophenoxy)propanamide, 2–methyl–2–(*o*–phenylazophenoxy)propanamide, 4–chlorobutanamide, 3–methyl–3–nitrobutanamide, *o*–nitrocinnamide, *N*–acetylmethionine, *o*–nitrobenzamide, and *o*–(benzoyloxymethyl)benzamide.

[0046] Carbamate nitrogen protecting groups (*e.g.*, $-C(=O)OR^{aa}$) include, but are not limited to, methyl carbamate, ethyl carbamante, 9–fluorenylmethyl carbamate (Fmoc), 9–(2–sulfo)fluorenylmethyl carbamate, 9–(2,7–dibromo)fluoroenylmethyl carbamate, 2,7–di–*t*–butyl–[9–(10,10–dioxo–10,10,10,10–tetrahydrothioxanthyl)]methyl carbamate (DBD–Tmoc), 4–methoxyphenacyl carbamate (Phenoc), 2,2,2–trichloroethyl carbamate (Troc), 2–

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

[0047] Sulfonamide nitrogen protecting groups (*e.g.*, $-S(=O)_2R^{aa}$) include, but are not limited to, *p*–toluenesulfonamide (Ts), benzenesulfonamide, 2,3,6,–trimethyl–4–

methoxybenzenesulfonamide (Mtr), 2,4,6–trimethoxybenzenesulfonamide (Mtb), 2,6–dimethyl–4–methoxybenzenesulfonamide (Pme), 2,3,5,6–tetramethyl–4–methoxybenzenesulfonamide (Mte), 4–methoxybenzenesulfonamide (Mbs), 2,4,6–trimethylbenzenesulfonamide (Mts), 2,6–dimethoxy–4–methylbenzenesulfonamide (iMds), 2,2,5,7,8–pentamethylchroman–6–sulfonamide (Pmc), methanesulfonamide (Ms), β–trimethylsilylethanesulfonamide (SES), 9–anthracenesulfonamide, 4–(4',8'–dimethoxynaphthylmethyl)benzenesulfonamide (DNMBS), benzylsulfonamide, trifluoromethylsulfonamide, and phenacylsulfonamide.

[0048] Other nitrogen protecting groups include, but are not limited to, phenothiazinyl–(10)–acyl derivative, *N'*–*p*–toluenesulfonylaminoacyl derivative, *N'*–phenylaminothioacyl derivative, *N*–benzoylphenylalanyl derivative, *N*–acetylmethionine derivative, 4,5–diphenyl–3–oxazolin–2–one, *N*–phthalimide, *N*–dithiasuccinimide (Dts), *N*–2,3–diphenylmaleimide, *N*–2,5–dimethylpyrrole, *N*–1,1,4,4–tetramethyldisilylazacyclopentane adduct (STABASE), 5–substituted 1,3–dimethyl–1,3,5–triazacyclohexan–2–one, 5–substituted 1,3–dibenzyl–1,3,5–triazacyclohexan–2–one, 1–substituted 3,5–dinitro–4–pyridone, *N*–methylamine, *N*–allylamine, *N*–[2–(trimethylsilyl)ethoxy]methylamine (SEM), *N*–3–acetoxypropylamine, *N*–(1–isopropyl–4–nitro–2–oxo–3–pyroolin–3–yl)amine, quaternary ammonium salts, *N*–benzylamine, *N*–di(4–methoxyphenyl)methylamine, *N*–5–dibenzosuberylamine, *N*–triphenylmethylamine (Tr), *N*–[(4–methoxyphenyl)diphenylmethyl]amine (MMTr), *N*–9–phenylfluorenylamine (PhF), *N*–2,7–dichloro–9–fluorenylmethyleneamine, *N*–ferrocenylmethylamino (Fcm), *N*–2–picolylamino *N'*–oxide, *N*–1,1–dimethylthiomethyleneamine, *N*–benzylideneamine, *N*–*p*–methoxybenzylideneamine, *N*–diphenylmethyleneamine, *N*–[(2–pyridyl)mesityl]methyleneamine, *N*–(*N',N'*–dimethylaminomethylene)amine, *N,N'*–isopropylidenediamine, *N*–*p*–nitrobenzylideneamine, *N*–salicylideneamine, *N*–5–chlorosalicylideneamine, *N*–(5–chloro–2–hydroxyphenyl)phenylmethyleneamine, *N*–cyclohexylideneamine, *N*–(5,5–dimethyl–3–oxo–1–cyclohexenyl)amine, *N*–borane derivative, *N*–diphenylborinic acid derivative, *N*–[phenyl(pentaacylchromium– or tungsten)acyl]amine, *N*–copper chelate, *N*–zinc chelate, *N*–nitroamine, *N*–nitrosoamine, amine *N*–oxide, diphenylphosphinamide (Dpp), dimethylthiophosphinamide (Mpt), diphenylthiophosphinamide (Ppt), dialkyl phosphoramidates, dibenzyl phosphoramidate, diphenyl phosphoramidate, benzenesulfenamide, *o*–nitrobenzenesulfenamide (Nps), 2,4–dinitrobenzenesulfenamide, pentachlorobenzenesulfenamide, 2–nitro–4–methoxybenzenesulfenamide, triphenylmethylsulfenamide, and 3–nitropyridinesulfenamide (Npys).

[0049] In certain embodiments, the substituent present on an oxygen atom is an oxygen protecting group (also referred to as a hydroxyl protecting group). Oxygen protecting groups include, but are not limited to, $-R^{aa}$, $-N(R^{bb})_2$, $-C(=O)SR^{aa}$, $-C(=O)R^{aa}$, $-CO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, $-C(=NR^{bb})R^{aa}$, $-C(=NR^{bb})OR^{aa}$, $-C(=NR^{bb})N(R^{bb})_2$, $-S(=O)R^{aa}$, $-SO_2R^{aa}$, $-Si(R^{aa})_3$, $-P(R^{cc})_2$, $-P(R^{cc})_3$, $-P(=O)_2R^{aa}$, $-P(=O)(R^{aa})_2$, $-P(=O)(OR^{cc})_2$, $-P(=O)_2N(R^{bb})_2$, and $-P(=O)(NR^{bb})_2$, wherein R^{aa}, R^{bb}, and R^{cc} are as defined herein. Oxygen protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999.

[0050] Exemplary oxygen protecting groups include, but are not limited to, methyl, methoxylmethyl (MOM), methylthiomethyl (MTM), *t*–butylthiomethyl, (phenyldimethylsilyl)methoxymethyl (SMOM), benzyloxymethyl (BOM), *p*–methoxybenzyloxymethyl (PMBM), (4–methoxyphenoxy)methyl (*p*–AOM), guaiacolmethyl (GUM), *t*–butoxymethyl, 4–pentenyloxymethyl (POM), siloxymethyl, 2–methoxyethoxymethyl (MEM), 2,2,2–trichloroethoxymethyl, bis(2–chloroethoxy)methyl, 2–(trimethylsilyl)ethoxymethyl (SEMOR), tetrahydropyranyl (THP), 3–bromotetrahydropyranyl, tetrahydrothiopyranyl, 1–methoxycyclohexyl, 4–methoxytetrahydropyranyl (MTHP), 4–methoxytetrahydrothiopyranyl, 4–methoxytetrahydrothiopyranyl S,S–dioxide, 1–[(2–chloro–4–methyl)phenyl]–4–methoxypiperidin–4–yl (CTMP), 1,4–dioxan–2–yl, tetrahydrofuranyl, tetrahydrothiofuranyl, 2,3,3a,4,5,6,7,7a–octahydro–7,8,8–trimethyl–4,7–methanobenzofuran–2–yl, 1–ethoxyethyl, 1–(2–chloroethoxy)ethyl, 1–methyl–1–methoxyethyl, 1–methyl–1–benzyloxyethyl, 1–methyl–1–benzyloxy–2–fluoroethyl, 2,2,2–trichloroethyl, 2–trimethylsilylethyl, 2–(phenylselenyl)ethyl, *t*–butyl, allyl, *p*–chlorophenyl, *p*–methoxyphenyl, 2,4–dinitrophenyl, benzyl (Bn), *p*–methoxybenzyl, 3,4–dimethoxybenzyl, *o*–nitrobenzyl, *p*–nitrobenzyl, *p*–halobenzyl, 2,6–dichlorobenzyl, *p*–cyanobenzyl, *p*–phenylbenzyl, 2–picolyl, 4–picolyl, 3–methyl–2–picolyl *N*–oxido, diphenylmethyl, *p,p'*–dinitrobenzhydryl, 5–dibenzosuberyl, triphenylmethyl, α–naphthyldiphenylmethyl, *p*–methoxyphenyldiphenylmethyl, di(*p*–methoxyphenyl)phenylmethyl, tri(*p*–methoxyphenyl)methyl, 4–(4′–bromophenacyloxyphenyl)diphenylmethyl, 4,4′,4″–tris(4,5–dichlorophthalimidophenyl)methyl, 4,4′,4″–tris(levulinoyloxyphenyl)methyl, 4,4′,4″–tris(benzoyloxyphenyl)methyl, 3–(imidazol–1–yl)bis(4′,4″–dimethoxyphenyl)methyl, 1,1–bis(4–methoxyphenyl)–1′–pyrenylmethyl, 9–anthryl, 9–(9–phenyl)xanthenyl, 9–(9–phenyl–10–oxo)anthryl, 1,3–benzodisulfuran–2–yl, benzisothiazolyl S,S–dioxido, trimethylsilyl

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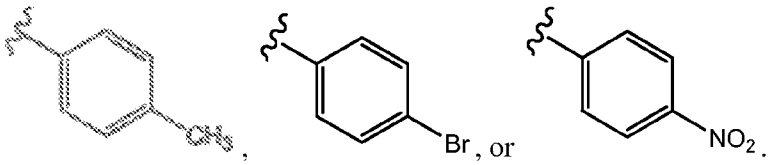
(TMS), triethylsilyl (TES), triisopropylsilyl (TIPS), dimethylisopropylsilyl (IPDMS), diethylisopropylsilyl (DEIPS), dimethylthexylsilyl, *t*–butyldimethylsilyl (TBDMS), *t*–butyldiphenylsilyl (TBDPS), tribenzylsilyl, tri–*p*–xylylsilyl, triphenylsilyl, diphenylmethylsilyl (DPMS), *t*–butylmethoxyphenylsilyl (TBMPS), formate, benzoylformate, acetate, chloroacetate, dichloroacetate, trichloroacetate, trifluoroacetate, methoxyacetate, triphenylmethoxyacetate, phenoxyacetate, *p*–chlorophenoxyacetate, 3–phenylpropionate, 4–oxopentanoate (levulinate), 4,4–(ethylenedithio)pentanoate (levulinoyldithioacetal), pivaloate, adamantoate, crotonate, 4–methoxycrotonate, benzoate, *p*–phenylbenzoate, 2,4,6–trimethylbenzoate (mesitoate), t–butyl carbonate (BOC), alkyl methyl carbonate, 9–fluorenylmethyl carbonate (Fmoc), alkyl ethyl carbonate, alkyl 2,2,2–trichloroethyl carbonate (Troc), 2–(trimethylsilyl)ethyl carbonate (TMSEC), 2–(phenylsulfonyl) ethyl carbonate (Psec), 2–(triphenylphosphonio) ethyl carbonate (Peoc), alkyl isobutyl carbonate, alkyl vinyl carbonate alkyl allyl carbonate, alkyl *p*–nitrophenyl carbonate, alkyl benzyl carbonate, alkyl *p*–methoxybenzyl carbonate, alkyl 3,4–dimethoxybenzyl carbonate, alkyl *o*–nitrobenzyl carbonate, alkyl *p*–nitrobenzyl carbonate, alkyl *S*–benzyl thiocarbonate, 4–ethoxy–1–napththyl carbonate, methyl dithiocarbonate, 2–iodobenzoate, 4–azidobutyrate, 4–nitro–4–methylpentanoate, *o*–(dibromomethyl)benzoate, 2–formylbenzenesulfonate, 2–(methylthiomethoxy)ethyl, 4–(methylthiomethoxy)butyrate, 2–(methylthiomethoxymethyl)benzoate, 2,6–dichloro–4–methylphenoxyacetate, 2,6–dichloro–4–(1,1,3,3–tetramethylbutyl)phenoxyacetate, 2,4–bis(1,1–dimethylpropyl)phenoxyacetate, chlorodiphenylacetate, isobutyrate, monosuccinoate, (*E*)–2–methyl–2–butenoate, *o*–(methoxyacyl)benzoate, α–naphthoate, nitrate, alkyl *N,N,N',N'*–tetramethylphosphorodiamidate, alkyl *N*–phenylcarbamate, borate, dimethylphosphinothioyl, alkyl 2,4–dinitrophenylsulfenate, sulfate, methanesulfonate (mesylate), benzylsulfonate, and tosylate (Ts).

[0051] In certain embodiments, the substituent present on a sulfur atom is a sulfur protecting group (also referred to as a thiol protecting group). Sulfur protecting groups include, but are not limited to, $-R^{aa}$, $-N(R^{bb})_2$, $-C(=O)SR^{aa}$, $-C(=O)R^{aa}$, $-CO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, $-C(=NR^{bb})R^{aa}$, $-C(=NR^{bb})OR^{aa}$, $-C(=NR^{bb})N(R^{bb})_2$, $-S(=O)R^{aa}$, $-SO_2R^{aa}$, $-Si(R^{aa})_3$, $-P(R^{cc})_2$, $-P(R^{cc})_3$, $-P(=O)_2R^{aa}$, $-P(=O)(R^{aa})_2$, $-P(=O)(OR^{cc})_2$, $-P(=O)_2N(R^{bb})_2$, and $-P(=O)(NR^{bb})_2$, wherein R^{aa}, R^{bb}, and R^{cc} are as defined herein. Sulfur protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, incorporated herein by reference.

[0052] As used herein, a "leaving group", or "LG", is a term understood in the art to refere to a molecular fragment that departs with a pair of electrons upon heterolytic bond cleavage, wherein the molecular fragment is an anion or neutral molecule. See, for example, Smith, March *Advanced Organic Chemistry* 6th ed. (501–502). Examples of suitable leaving groups include, but are not limited to, halides (such as chloride, bromide, or iodide), alkoxycarbonyloxy, aryloxycarbonyloxy, alkanesulfonyloxy, arenesulfonyloxy, alkyl-carbonyloxy (*e.g.*, acetoxy), arylcarbonyloxy, aryloxy, methoxy, N,O-dimethylhydroxylamino, pixyl, haloformates, $-NO_2$, trialkylammonium, and aryliodonium salts. In some embodiments, the leaving group is a sulfonic acid ester. In some embodiments, the sulfonic acid ester comprises the formula $-OSO_2R^{LG1}$ wherein R^{LG1} is selected from the group consisting alkyl optionally, alkenyl optionally substituted, heteroalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, arylalkyl optionally substituted, and heterarylalkyl optionally substituted. In some embodiments, R^{LG1} is substituted or unsubstituted C_1-C_6 alkyl. In some embodiments, R^{LG1} is methyl. In some embodiments, R^{LG1} is $-CF_3$. In some embodiments, R^{LG1} is substituted or unsubstituted aryl. In some embodiments, R^{LG1} is substituted or unsubstituted phenyl. In some embodiments R^{LG1} is:



[0053] In some cases, the leaving group is toluenesulfonate (tosylate, Ts), methanesulfonate (mesylate, Ms), *p*-bromobenzenesulfonyl (brosylate, Bs), or trifluoromethanesulfonate (triflate, Tf). In some cases, the leaving group is a brosylate (*p*-bromobenzenesulfonyl). In some cases, the leaving group is a nosylate (2-nitrobenzenesulfonyl). In some embodiments, the leaving group is a sulfonate-containing group. In some embodiments, the leaving group is a tosylate group. The leaving group may also be a phosphineoxide (*e.g.*, formed during a Mitsunobu reaction) or an internal leaving group such as an epoxide or cyclic sulfate.

[0054] These and other exemplary substituents are described in more detail in the Detailed Description, Examples, and claims. The present disclosure is not intended to be limited in any manner by the above exemplary listing of substituents.

[0055] "Pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and other

animals without undue toxicity, irritation, allergic response, and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, Berge *et al.* describe pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences* (1977) 66:1–19. Pharmaceutically acceptable salts of the compounds describe herein include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid, or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2–hydroxy–ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2–naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3–phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, *p*–toluenesulfonate, undecanoate, valerate salts, and the like. Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4}alkyl)_4$ salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, quaternary salts.

[0056] A "subject" to which administration is contemplated includes, but is not limited to, humans (*e.g.,* a male or female of any age group, *e.g.,* a pediatric subject (*e.g,* infant, child, adolescent) or adult subject (*e.g.,* young adult, middle–aged adult or senior adult)) and/or other non–human animals, for example, non-human mammals (*e.g.*, primates (*e.g.,* cynomolgus monkeys, rhesus monkeys); commercially relevant mammals such as cattle, pigs, horses, sheep, goats, cats, and/or dogs), birds (*e.g.*, commercially relevant birds such as chickens, ducks, geese, and/or turkeys), rodents (*e.g.*, rats and/or mice), reptiles, amphibians, and fish. In certain embodiments, the non–human animal is a mammal. The non–human animal may be a male or female at any stage of development. A non–human animal may be a transgenic animal.

[0057] "Condition," "disease," and "disorder" are used interchangeably herein.

[0058] "Treat," "treating" and "treatment" encompasses an action that occurs while a subject is suffering from a condition which reduces the severity of the condition or retards or slows the progression of the condition ("therapeutic treatment"). "Treat," "treating" and "treatment" also encompasses an action that occurs before a subject begins to suffer from the condition and which inhibits or reduces the severity of the condition ("prophylactic treatment").

[0059] An "effective amount" of a compound refers to an amount sufficient to elicit the desired biological response, *e.g.*, treat the condition. As will be appreciated by those of ordinary skill in this art, the effective amount of a compound described herein may vary depending on such factors as the desired biological endpoint, the pharmacokinetics of the compound, the condition being treated, the mode of administration, and the age and health of the subject. An effective amount encompasses therapeutic and prophylactic treatment.

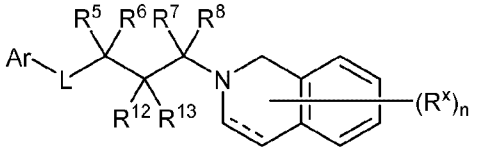
[0060] A "therapeutically effective amount" of a compound is an amount sufficient to provide a therapeutic benefit in the treatment of a condition or to delay or minimize one or more symptoms associated with the condition. A therapeutically effective amount of a compound means an amount of therapeutic agent, alone or in combination with other therapies, which provides a therapeutic benefit in the treatment of the condition. The term "therapeutically effective amount" can encompass an amount that improves overall therapy, reduces or avoids symptoms or causes of the condition, or enhances the therapeutic efficacy of another therapeutic agent.

[0061] A "prophylactically effective amount" of a compound is an amount sufficient to prevent a condition, or one or more symptoms associated with the condition or prevent its recurrence. A prophylactically effective amount of a compound means an amount of a therapeutic agent, alone or in combination with other agents, which provides a prophylactic benefit in the prevention of the condition. The term "prophylactically effective amount" can encompass an amount that improves overall prophylaxis or enhances the prophylactic efficacy of another prophylactic agent.

[0062] As used herein, the term "methyltransferase" represents transferase class enzymes that are able to transfer a methyl group from a donor molecule to an acceptor molecule, *e.g.*, an amino acid residue of a protein or a nucleic base of a DNA molecule. Methytransferases typically use a reactive methyl group bound to sulfur in S-adenosyl methionine (SAM) as the methyl donor. In some embodiments, a methyltransferase described herein is a protein methyltransferase. In some embodiments, a methyltransferase described herein is a histone methyltransferase. Histone methyltransferases (HMT) are histone-modifying enzymes,

(including histone-lysine N-methyltransferase and histone-arginine N-methyltransferase), that catalyze the transfer of one or more methyl groups to lysine and arginine residues of histone proteins. In certain embodiments, a methyltransferase described herein is a histone-arginine N-methyltransferase.

[0063] As generally described above, provided herein are compounds useful as PRMT5 inhibitors. In some embodiments, the present disclosure provides a compound of Formula (**A**):



(**A**)

or a pharmaceutically acceptable salt thereof,

wherein:

------ represents a single or double bond;

R^{12} is hydrogen, halogen, or optionally substituted C_{1-3}alkyl;

R^{13} is hydrogen, halogen, optionally substituted C_{1-3}alkyl, $-NR^{A1}R^{A2}$, or $-OR^1$;

R^{A1} and R^{A2} are each independently hydrogen, optionally substituted C_{1-3} alkyl, optionally substituted acyl, or a nitrogen protecting group, or R^{A1} and R^{A2} are taken together with the intervening nitrogen atom to form an optionally substituted 3-6 membered heterocyclic ring;

R^1 is hydrogen, R^z, or $-C(O)R^z$, wherein R^z is optionally substituted C_{1-6} alkyl;

L is –N(R)C(O)–, –C(O)N(R)–, –N(R)C(O)N(R)–,–N(R)C(O)O–, or –OC(O)N(R)–;

each R is independently hydrogen or optionally substituted C_{1-6} aliphatic;

Ar is a monocyclic or bicyclic aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Ar is substituted with 0, 1, 2, 3, 4, or 5 R^y groups, as valency permits; or

Ar is a monocyclic or bicyclic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Ar is substituted with 0, 1, 2, 3, 4, or 5 R^y groups, as valency permits;

each R^y is independently selected from the group consisting of halo, -CN, $-NO_2$, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, $-OR^A$, $-N(R^B)_2$, $-SR^A$, $-C(=O)R^A$, $-C(O)OR^A$, $-C(O)SR^A$, $-C(O)N(R^B)_2$, $-C(O)N(R^B)N(R^B)_2$, $-OC(O)R^A$, $-OC(O)N(R^B)_2$, $-NR^BC(O)R^A$, $-NR^BC(O)N(R^B)_2$, $-NR^BC(O)N(R^B)N(R^B)_2$, $-NR^BC(O)OR^A$, -

$SC(O)R^A$, $-C(=NR^B)R^A$, $-C(=NNR^B)R^A$, $-C(=NOR^A)R^A$, $-C(=NR^B)N(R^B)_2$, $-NR^BC(=NR^B)R^B$, $-C(=S)R^A$, $-C(=S)N(R^B)_2$, $-NR^BC(=S)R^A$, $-S(O)R^A$, $-OS(O)_2R^A$, $-SO_2R^A$, $-NR^BSO_2R^A$, or $-SO_2N(R^B)_2$;

each R^A is independently selected from the group consisting of hydrogen, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

each R^B is independently selected from the group consisting of hydrogen, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, or two R^B groups are taken together with their intervening atoms to form an optionally substituted heterocyclic ring;

R^5, R^6, R^7, and R^8 are each independently hydrogen, halo, or optionally substituted aliphatic;

each R^x is independently selected from the group consisting of halo, -CN, optionally substituted aliphatic, -OR', and $-N(R'')_2$;

R' is hydrogen or optionally substituted aliphatic;

each R" is independently hydrogen or optionally substituted aliphatic, or two R" are taken together with their intervening atoms to form a heterocyclic ring; and

n is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, as valency permits.

[0064] In some embodiments, the provided compound is of a free base form. In some embodiments, the provided compound is in the form of a pharmaceutically acceptable salt as generally defined herein. In some embodiments, the provided compound is a hydrochloride salt thereof. In some embodiments, the provided compound is a tartrate salt thereof. In some embodiments, the provided compound is a monotartrate salt thereof. In some embodiments, the provided compound is a bitartrate salt thereof.

[0065] In some embodiments, the carbon attached to R^{12} has (*S*)-stereochemistry. In some embodiments, the carbon attached to R^{12} has (*R*)-stereochemistry. In some embodiments, the carbon attached to R^{13} has (*S*)-stereochemistry. In some embodiments, the carbon attached to R^{13} has (*R*)-stereochemistry.

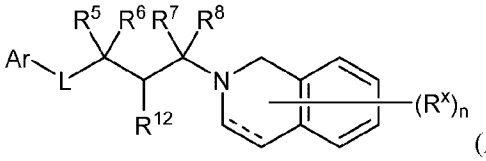
[0066] As generally defined above, R^{12} is hydrogen, halogen, or optionally substituted C_{1-3}alkyl. In certain embodiments, R^{12} is hydrogen. In certain embodiments, R^{12} is optionally substituted C_{1-3}alkyl, *e.g.*, optionally substituted with halogen. In certain embodiments, R^{12} is optionally substituted C_1alkyl, *e.g.*, methyl or trifluoromethyl. In certain embodiments, R^{12} is optionally substituted C_2 alkyl, *e.g.*, ethyl. In certain embodiments, R^{12} is optionally substituted C_3 alkyl, *e.g.*, propyl. In certain embodiments, R^{12} is fluoro, provided that R^{13} is

not $-OR^1$. In certain embodiments, R^{12} is chloro, provided that R^{13} is not $-OR^1$. In certain embodiments, R^{12} is bromo, provided that R^{13} is not $-OR^1$. In certain embodiments, R^{12} is iodo, provided that R^{13} is not $-OR^1$.

[0067] As generally defined above, R^{13} is hydrogen, halogen, optionally substituted C_{1-3}alkyl, $-NR^{A1}R^{A2}$, or $-OR^1$. In certain embodiments, R^{13} is hydrogen. In certain embodiments, R^{13} is optionally substituted C_{1-3}alkyl, *e.g.*, optionally substituted with halogen. In certain embodiments, R^{13} is optionally substituted C_1alkyl, *e.g.*, methyl or trifluoromethyl. In certain embodiments, R^{13} is optionally substituted C_2 alkyl, *e.g.*, ethyl. In certain embodiments, R^{13} is optionally substituted C_3 alkyl, *e.g.*, propyl. In certain embodiments, R^{13} is fluoro. In certain embodiments, R^{13} is chloro. In certain embodiments, R^{13} is bromo. In certain embodiments, R^{13} is iodo.

[0068] In some embodiments, both R^{12} and R^{13} are optionally substituted C_{1-3}alkyl. In some embodiments, R^{12} is halogen *e.g.*, fluoro, bromo, chloro, or iodo, provided that R^{13} is not $-OR^1$. In some embodiments, R^{13} is halogen *e.g.*, fluoro, bromo, chloro, or iodo. In some embodiments, both R^{12} and R^{13} are halogen *e.g.*, fluoro, bromo, chloro, or iodo. In some embodiments, R^{12} is halogen *e.g.*, fluoro, bromo, chloro, or iodo and R^{13} is optionally substituted C_{1-3}alkyl. In some embodiments, R^{12} is optionally substituted C_{1-3}alkyl and R^{13} is halogen *e.g.*, fluoro, bromo, chloro, or iodo. In some embodiments, R^{13} is $-OR^1$. In some embodiments, R^{12} is optionally substituted C_{1-3}alkyl and R^{13} is $-OR^1$. In some embodiments, R^{12} is hydrogen and R^{13} is $-OR^1$. In some embodiments, R^{12} is hydrogen and R^{13} optionally substituted C_{1-3}alkyl. In some embodiments, R^{12} is optionally substituted C_{1-3}alkyl and R^{13} is hydrogen. In some embodiments, R^{12} is halogen *e.g.*, fluoro, bromo, chloro, or iodo and R^{13} is hydrogen. In some embodiments, R^{12} is hydrogen and R^{13} is halogen *e.g.*, fluoro, bromo, chloro, or iodo.

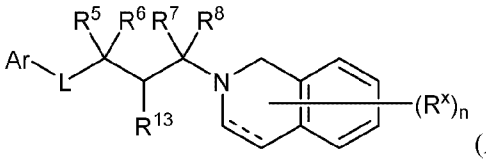
[0069] For example, in some embodiments of Formula (**A**), wherein R^{13} is hydrogen, the present disclosure provides a compound of Formula (**A-1**):



(A-1)

or a pharmaceutically acceptable salt thereof, wherein R^5, R^6, R^7, R^8, R^x, R^{12}, n, L, and Ar are as described herein.

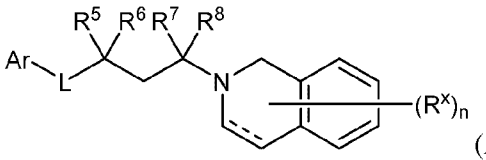
[0070] In some embodiments of Formula (**A**), wherein R^{12} is hydrogen, the present disclosure provides a compound of Formula (**A-2**):



(**A-2**)

or a pharmaceutically acceptable salt thereof, wherein R^5, R^6, R^7, R^8, R^x, R^{13}, n, L, and Ar are as described herein.

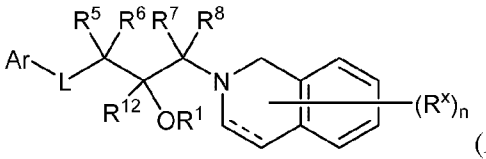
[0071] In some embodiments of Formula (**A**), wherein both R^{12} and R^{13} are hydrogen, the present disclosure provides a compound of Formula (**A-3**):



(**A-3**)

or a pharmaceutically acceptable salt thereof, wherein R^5, R^6, R^7, R^8, R^x, n, L, and Ar are as described herein.

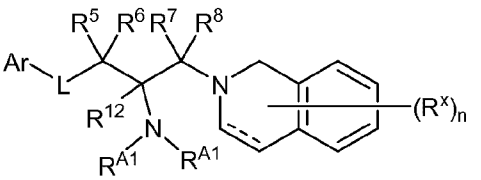
[0072] In some embodiments of Formula (**A**), wherein R^{13} is $-OR^1$, the present disclosure provides a compound of Formula (**A-4**):



(**A-4**)

or a pharmaceutically acceptable salt thereof, wherein R^1, R^5, R^6, R^7, R^8, R^x, R^{12}, n, L, and Ar are as described herein.

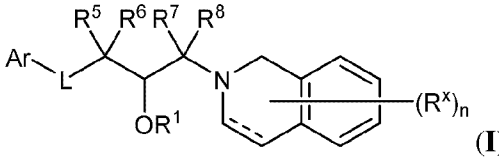
[0073] In some embodiments of Formula (**A**), wherein R^{13} is $-OR^1$, the present disclosure provides a compound of Formula (**A-5**):



(**A-5**)

or a pharmaceutically acceptable salt thereof, wherein R^1, R^5, R^6, R^7, R^8, R^x, R^{12}, R^{A1}, R^{A2}, n, L, and Ar are as described herein.

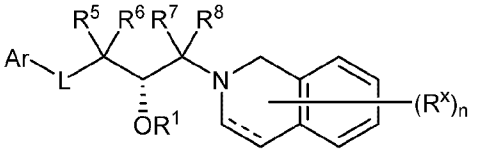
[0074] In some embodiments of Formula (**A**), wherein R^{12} is hydrogen, and R^{13} is $-OR^1$, the present disclosure provides a compound of Formula (**I**):



(**I**)

or a pharmaceutically acceptable salt thereof, wherein R^1, R^5, R^6, R^7, R^8, R^x, n, L, and Ar are as described herein.

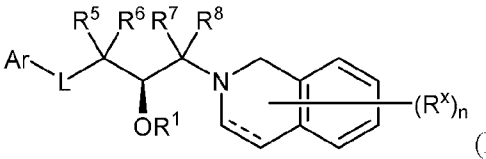
[0075] In certain embodiments, a provided compound is of Formula (**I-a**):



(**I-a**)

or a pharmaceutically acceptable salt thereof, wherein R^1, R^5, R^6, R^7, R^8, R^x, n, L, and Ar are as described herein.

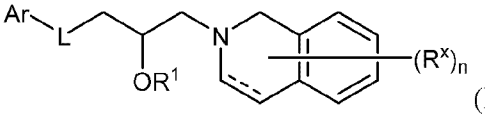
[0076] In certain embodiments, a provided compound is of Formula (**I-b**):



(**I-b**)

or a pharmaceutically acceptable salt thereof, wherein R^1, R^5, R^6, R^7, R^8, R^x, n, L, and Ar are as described herein.

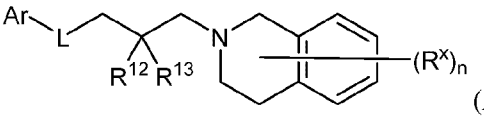
[0077] In certain embodiments, a provided compound is of Formula (**I-c**):



(**I-c**)

or a pharmaceutically acceptable salt thereof, wherein R^1, R^x, n, L, and Ar are as described herein.

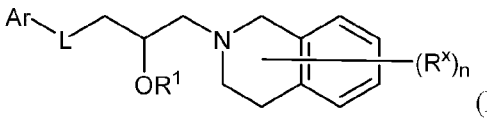
[0078] In certain embodiments, a provided compound is of Formula (**A-6**):



(**A-6**)

or a pharmaceutically acceptable salt thereof, wherein R^1, R^x, R^{12}, R^{13}, n, L, and Ar are as described herein.

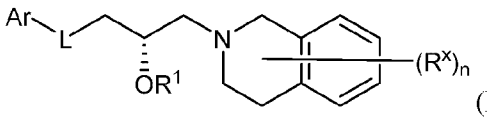
[0079] In certain embodiments, a provided compound is of Formula (**I'**):



(**I'**)

or a pharmaceutically acceptable salt thereof, wherein R^1, R^x, n, L, and Ar are as described herein.

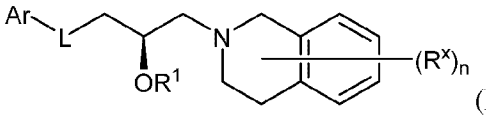
[0080] In certain embodiments, a provided compound is of Formula (**I'-a**):



(**I'-a**)

or a pharmaceutically acceptable salt thereof, wherein R^1, R^x, n, L, and Ar are as described herein.

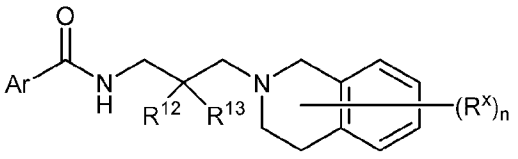
[0081] In certain embodiments, a provided compound is of Formula (**I'-b**):



(**I'-b**)

or a pharmaceutically acceptable salt thereof, wherein R^1, R^x, n, L, and Ar are as described herein.

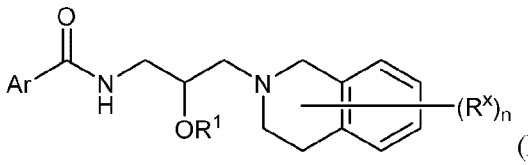
[0082] In some embodiments of Formula (**A**), the present disclosure provides a compound of Formula (**A-7**):



(**A-7**)

or a pharmaceutically acceptable salt thereof, wherein R^x, R^{12}, R^{13}, n, and Ar are as described herein.

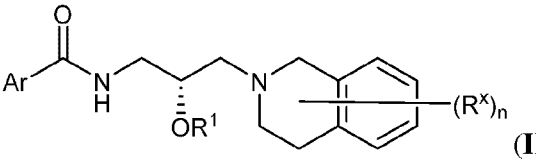
[0083] In certain embodiments, a provided compound is of Formula (**II**):



(**II**)

or a pharmaceutically acceptable salt thereof, wherein R^1, R^x, n, and Ar are as described herein.

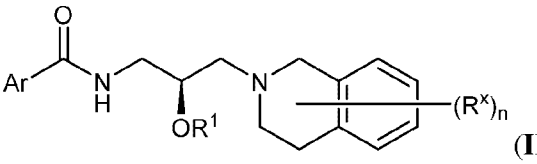
[0084] In certain embodiments, a provided compound is of Formula (**II-a**):



(**II-a**)

or a pharmaceutically acceptable salt thereof, wherein R^1, R^x, n, and Ar are as described herein.

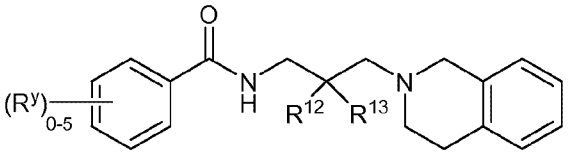
[0085] In certain embodiments, a provided compound is of Formula (**II-b**):



(**II-b**)

or a pharmaceutically acceptable salt thereof, wherein R^1, R^x, n, and Ar are as described herein.

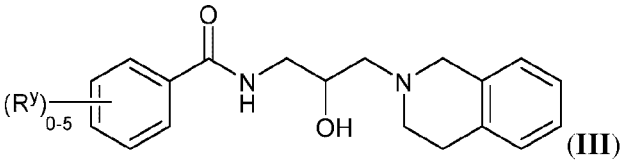
[0086] In some embodiments of Formula (**A**), the present disclosure provides a compound of Formula (**A-8**):



(**A-8**)

or a pharmaceutically acceptable salt thereof, wherein R^{12}, R^{13}, and R^y are described herein.

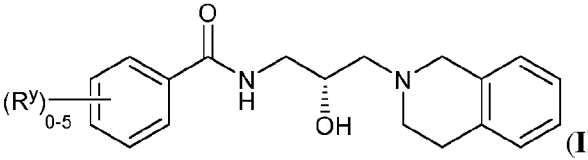
[0087] In certain embodiments, a provided compound is of Formula (**III**):



(**III**)

or a pharmaceutically acceptable salt thereof, wherein R^y is as described herein.

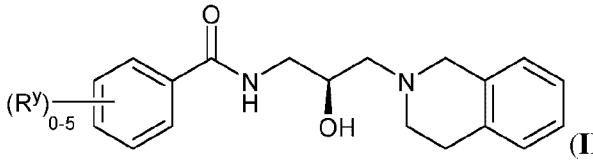
[0088] In certain embodiments, a provided compound is of Formula (**III-a**):



(**III-a**)

or a pharmaceutically acceptable salt thereof, wherein R^y is as described herein.

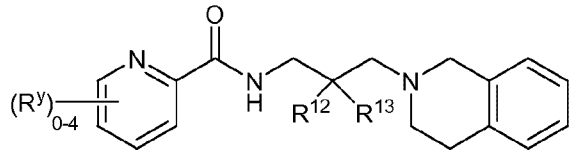
[0089] In certain embodiments, a provided compound is of Formula (**III-b**):



(**III-b**)

or a pharmaceutically acceptable salt thereof, wherein R^y is as described herein.

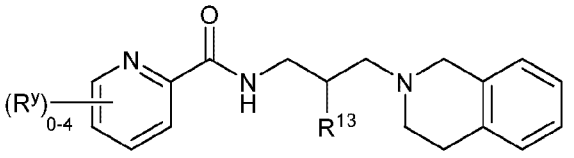
[0090] In some embodiments of Formula (**A**), the present disclosure provides a compound of Formula (**A-9**):



(**A-9**)

or a pharmaceutically acceptable salt thereof, wherein R^{12}, R^{13}, and R^y are described herein.

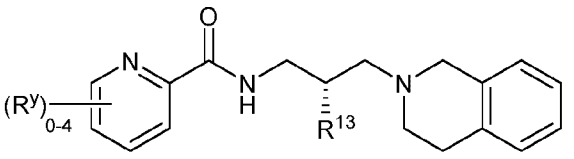
[0091] In some embodiments of Formula (**A**), the present disclosure provides a compound of Formula (**A-9-a**):



(**A-9-a**)

or a pharmaceutically acceptable salt thereof, wherein R^{13}, and R^y are described herein.

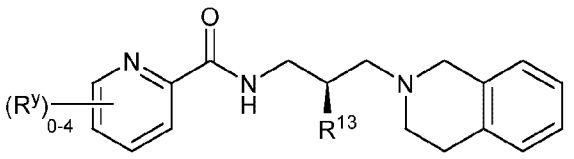
[0092] In some embodiments of Formula (**A**), the present disclosure provides a compound of Formula (**A-9-b**):



(**A-9-b**)

or a pharmaceutically acceptable salt thereof, wherein R^{13}, and R^y are described herein.

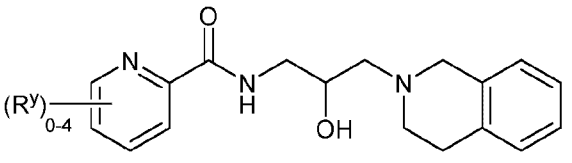
[0093] In some embodiments of Formula (**A**), the present disclosure provides a compound of Formula (**A-9-c**):



(**A-9-c**)

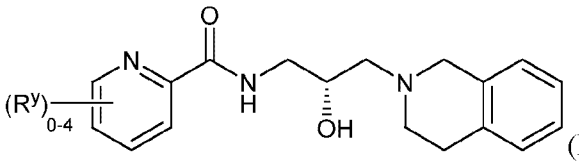
or a pharmaceutically acceptable salt thereof, wherein R^{13}, and R^y are described herein.

[0094] In certain embodiments, a provided compound is of Formula (**IV**):


(**IV**)

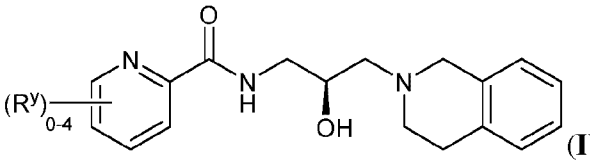
or a pharmaceutically acceptable salt thereof, wherein R^y is as described herein.

[0095] In certain embodiments, a provided compound is of Formula (**IV-a**):


(**IV-a**)

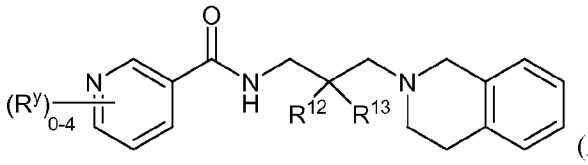
or a pharmaceutically acceptable salt thereof, wherein R^y is as described herein.

[0096] In certain embodiments, a provided compound is of Formula (**IV-b**):


(**IV-b**)

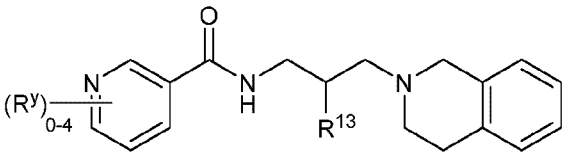
or a pharmaceutically acceptable salt thereof, wherein R^y is as described herein.

[0097] In some embodiments of Formula (**A**), the present disclosure provides a compound of Formula (**A-10**):


(**A-10**)

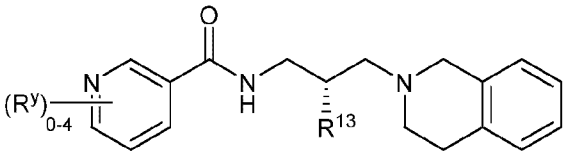
or a pharmaceutically acceptable salt thereof, wherein R^{12}, R^{13}, and R^y are described herein.

[0098] In some embodiments of Formula (**A**), the present disclosure provides a compound of Formula (**A-10-a**):


(**A-10-a**)

or a pharmaceutically acceptable salt thereof, wherein R^{13}, and R^y are described herein.

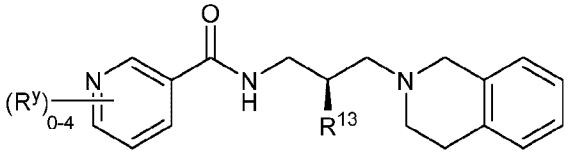
[0099] In some embodiments of Formula (**A**), the present disclosure provides a compound of Formula (**A-10-b**):



(**A-10-b**)

or a pharmaceutically acceptable salt thereof, wherein R^{13}, and R^y are described herein.

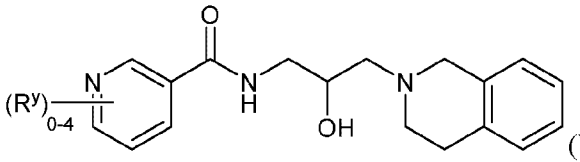
[00100] In some embodiments of Formula (**A**), the present disclosure provides a compound of Formula (**A-10-c**):



(**A-10-c**)

or a pharmaceutically acceptable salt thereof, wherein R^{13}, and R^y are described herein.

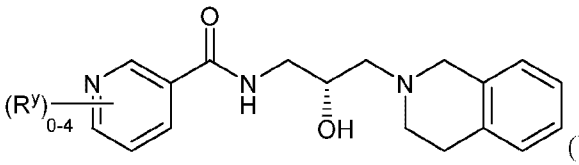
[00101] In certain embodiments, a provided compound is of Formula (**V**):



(**V**)

or a pharmaceutically acceptable salt thereof, wherein R^y is as described herein.

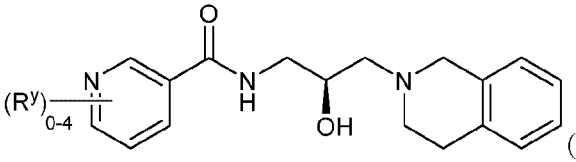
[00102] In certain embodiments, a provided compound is of Formula (**V-a**):



(**V-a**)

or a pharmaceutically acceptable salt thereof, wherein R^y is as described herein.

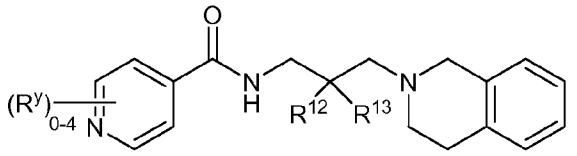
[00103] In certain embodiments, a provided compound is of Formula (**V-b**):



(**V-b**)

or a pharmaceutically acceptable salt thereof, wherein R^y is as described herein.

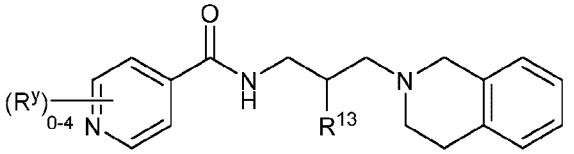
[00104] In some embodiments of Formula (**A**), the present disclosure provides a compound of Formula (**A-11**):



(**A-11**)

or a pharmaceutically acceptable salt thereof, wherein R^{12}, R^{13}, and R^{y} are described herein.

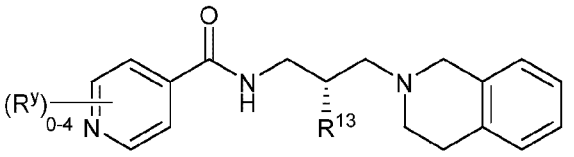
[00105] In some embodiments of Formula (**A**), the present disclosure provides a compound of Formula (**A-11-a**):



(**A-11-a**)

or a pharmaceutically acceptable salt thereof, wherein R^{13}, and R^{y} are described herein.

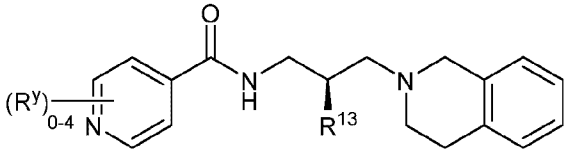
[00106] In some embodiments of Formula (**A**), the present disclosure provides a compound of Formula (**A-11-b**):



(**A-11-b**)

or a pharmaceutically acceptable salt thereof, wherein R^{13}, and R^{y} are described herein.

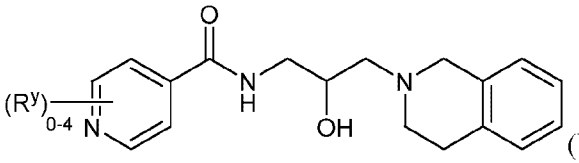
[00107] In some embodiments of Formula (**A**), the present disclosure provides a compound of Formula (**A-11-c**):



(**A-11-c**)

or a pharmaceutically acceptable salt thereof, wherein R^{13}, and R^{y} are described herein.

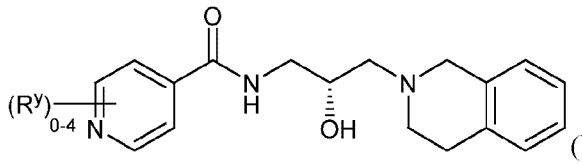
[00108] In certain embodiments, a provided compound is of Formula (**VI**):



(**VI**)

or a pharmaceutically acceptable salt thereof, wherein R^{y} is as described herein.

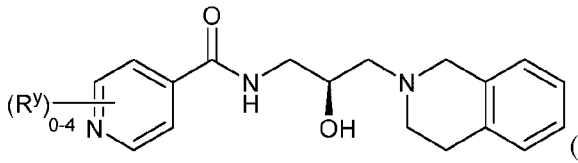
[00109] In certain embodiments, a provided compound is of Formula (**VI-a**):



(**VI-a**)

or a pharmaceutically acceptable salt thereof, wherein R^y is as described herein.

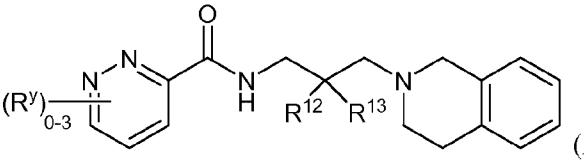
[00110] In certain embodiments, a provided compound is of Formula (**VI-b**):



(**VI-b**)

or a pharmaceutically acceptable salt thereof, wherein R^y is as described herein.

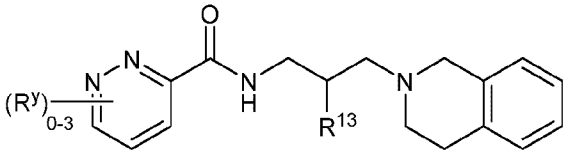
[00111] In some embodiments of Formula (**A**), the present disclosure provides a compound of Formula (**A-12**):



(**A-12**)

or a pharmaceutically acceptable salt thereof, wherein R^y is described herein.

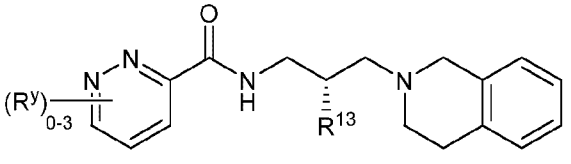
[00112] In some embodiments of Formula (**A**), the present disclosure provides a compound of Formula (**A-12-a**):



(**A-12-a**)

or a pharmaceutically acceptable salt thereof, wherein R^{13} and R^y is described herein.

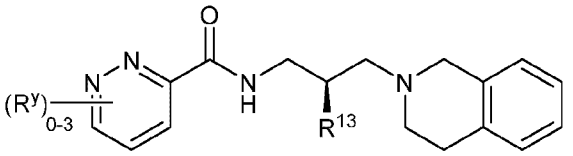
[00113] In some embodiments of Formula (**A**), the present disclosure provides a compound of Formula (**A-12-b**):



(**A-12-b**)

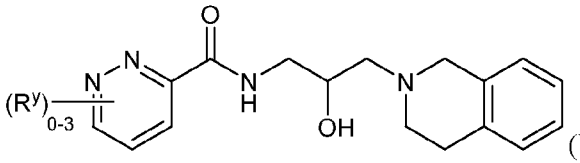
or a pharmaceutically acceptable salt thereof, wherein R^{13} and R^y is described herein.

[00114] In some embodiments of Formula (**A**), the present disclosure provides a compound of Formula (**A-12-c**):


(**A-12-c**)

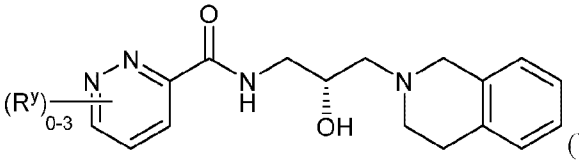
or a pharmaceutically acceptable salt thereof, wherein R^{13} and R^{y} is described herein.

[00115] In certain embodiments, a provided compound is of Formula (**VII**):


(**VII**)

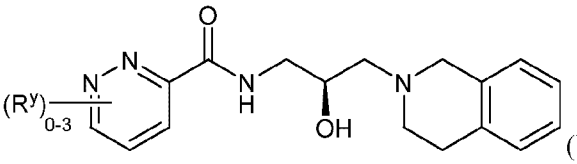
or a pharmaceutically acceptable salt thereof, wherein R^{y} is as described herein.

[00116] In certain embodiments, a provided compound is of Formula (**VII-a**):


(**VII-a**)

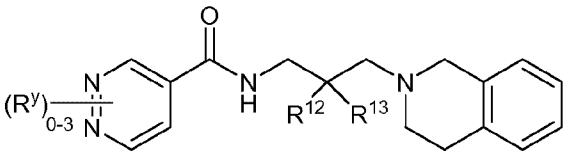
or a pharmaceutically acceptable salt thereof, wherein R^{y} is as described herein.

[00117] In certain embodiments, a provided compound is of Formula (**VII-b**):


(**VII-b**)

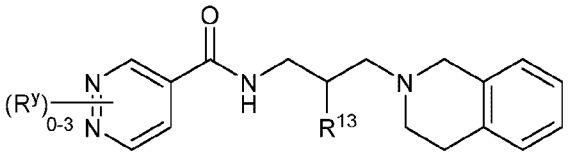
or a pharmaceutically acceptable salt thereof, wherein R^{y} is as described herein.

[00118] In some embodiments of Formula (**A**), the present disclosure provides a compound of Formula (**A-13**):


(**A-13**)

or a pharmaceutically acceptable salt thereof, wherein R^{12}, R^{13}, and R^{y} are described herein.

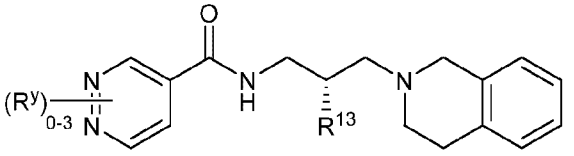
[00119] In some embodiments of Formula (**A**), the present disclosure provides a compound of Formula (**A-13-a**):



(**A-13-a**)

or a pharmaceutically acceptable salt thereof, wherein R^{13}, and R^y are described herein.

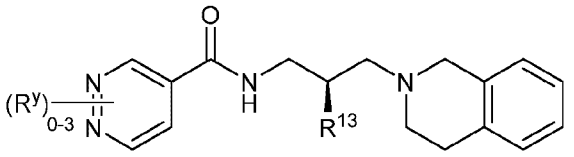
[00120] In some embodiments of Formula (**A**), the present disclosure provides a compound of Formula (**A-13-b**):



(**A-13-b**)

or a pharmaceutically acceptable salt thereof, wherein R^{13}, and R^y are described herein.

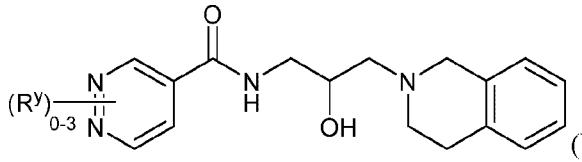
[00121] In some embodiments of Formula (**A**), the present disclosure provides a compound of Formula (**A-13-c**):



(**A-13-c**)

or a pharmaceutically acceptable salt thereof, wherein R^{13}, and R^y are described herein.

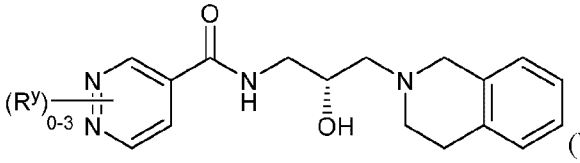
[00122] In certain embodiments, a provided compound is of Formula (**VIII**):



(**VIII**)

or a pharmaceutically acceptable salt thereof, wherein R^y is as described herein.

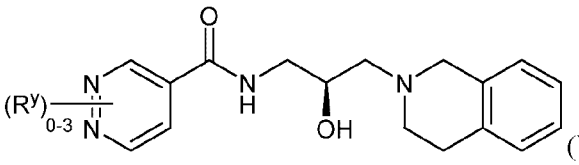
[00123] In certain embodiments, a provided compound is of Formula (**VIII-a**):



(**VIII-a**)

or a pharmaceutically acceptable salt thereof, wherein R^y is as described herein.

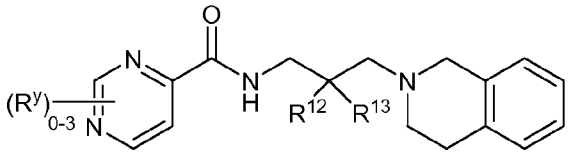
[00124] In certain embodiments, a provided compound is of Formula (**VIII-b**):



(**VIII-b**)

or a pharmaceutically acceptable salt thereof, wherein R^y is as described herein.

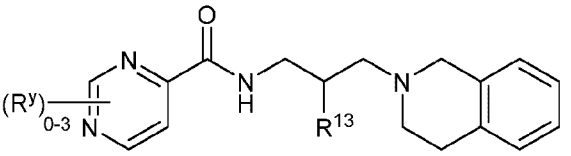
[00125] In some embodiments of Formula (**A**), the present disclosure provides a compound of Formula (**A-14**):



(**A-14**)

or a pharmaceutically acceptable salt thereof, wherein R^{12}, R^{13}, and R^y are described herein.

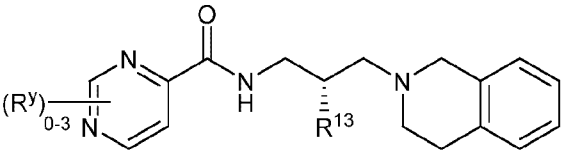
[00126] In some embodiments of Formula (**A**), the present disclosure provides a compound of Formula (**A-14-a**):



(**A-14-a**)

or a pharmaceutically acceptable salt thereof, wherein R^{13}, and R^y are described herein.

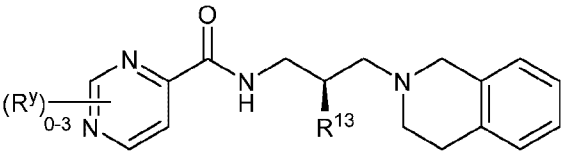
[00127] In some embodiments of Formula (**A**), the present disclosure provides a compound of Formula (**A-14-b**):



(**A-14-b**)

or a pharmaceutically acceptable salt thereof, wherein R^{13}, and R^y are described herein.

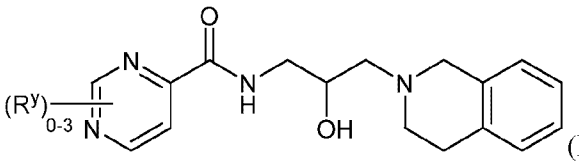
[00128] In some embodiments of Formula (**A**), the present disclosure provides a compound of Formula (**A-14-c**):



(**A-14-c**)

or a pharmaceutically acceptable salt thereof, wherein R^{13}, and R^y are described herein.

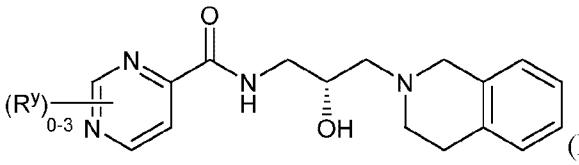
[00129] In certain embodiments, a provided compound is of Formula (**IX**):



(**IX**)

or a pharmaceutically acceptable salt thereof, wherein R^y is as described herein.

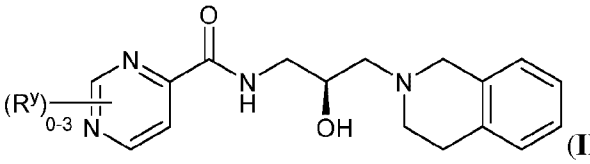
[00130] In certain embodiments, a provided compound is of Formula (**IX-a**):



(**IX-a**)

or a pharmaceutically acceptable salt thereof, wherein R^y is as described herein.

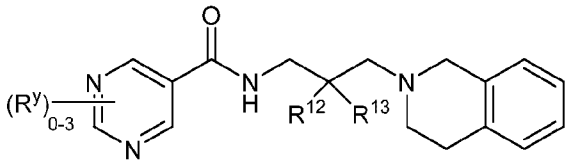
[00131] In certain embodiments, a provided compound is of Formula (**IX-b**):



(**IX-b**)

or a pharmaceutically acceptable salt thereof, wherein R^y is as described herein.

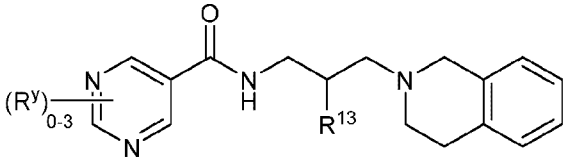
[00132] In some embodiments of Formula (**A**), the present disclosure provides a compound of Formula (**A-15**):



(**A-15**)

or a pharmaceutically acceptable salt thereof, wherein R^y is described herein.

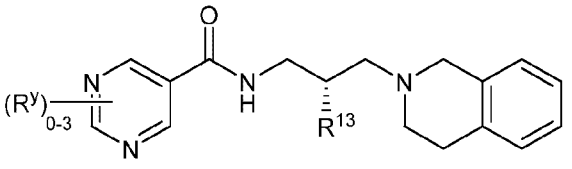
[00133] In some embodiments of Formula (**A**), the present disclosure provides a compound of Formula (**A-15-a**):



(**A-15-a**)

or a pharmaceutically acceptable salt thereof, wherein R^{13} and R^y is described herein.

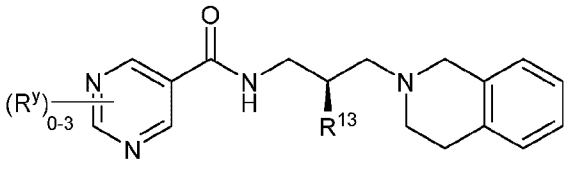
[00134] In some embodiments of Formula (**A**), the present disclosure provides a compound of Formula (**A-15-b**):



(**A-15-b**)

or a pharmaceutically acceptable salt thereof, wherein R^{13} and R^y is described herein.

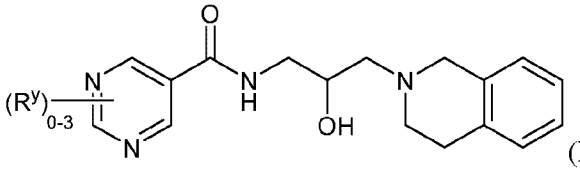
[00135] In some embodiments of Formula (**A**), the present disclosure provides a compound of Formula (**A-15-c**):



(**A-15-c**)

or a pharmaceutically acceptable salt thereof, wherein R^{13} and R^y is described herein.

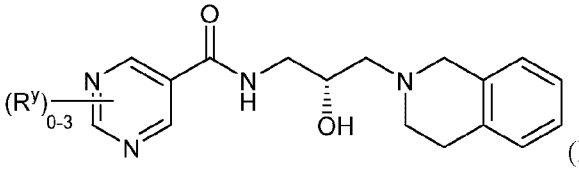
[00136] In certain embodiments, a provided compound is of Formula (**X**):



(**X**)

or a pharmaceutically acceptable salt thereof, wherein R^y is as described herein.

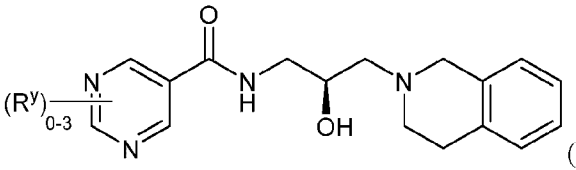
[00137] In certain embodiments, a provided compound is of Formula (**X-a**):



(**X-a**)

or a pharmaceutically acceptable salt thereof, wherein R^y is as described herein.

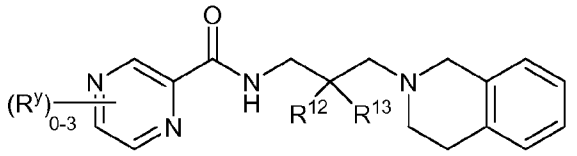
[00138] In certain embodiments, a provided compound is of Formula (**X-b**):



(**X-b**)

or a pharmaceutically acceptable salt thereof, wherein R^y is as described herein.

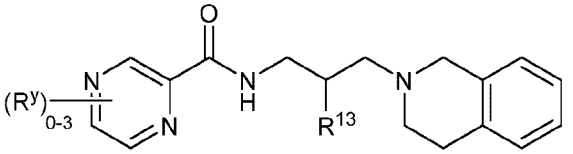
[00139] In some embodiments of Formula (**A**), the present disclosure provides a compound of Formula (**A-16**):



(**A-16**)

or a pharmaceutically acceptable salt thereof, wherein R^{12}, R^{13}, and R^y are described herein.

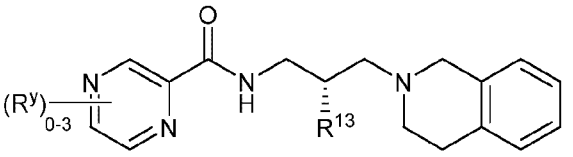
[00140] In some embodiments of Formula (**A**), the present disclosure provides a compound of Formula (**A-16-a**):



(**A-16-a**)

or a pharmaceutically acceptable salt thereof, wherein R^{13}, and R^y are described herein.

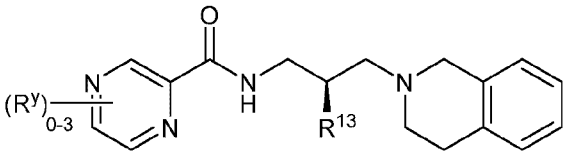
[00141] In some embodiments of Formula (**A**), the present disclosure provides a compound of Formula (**A-16-b**):



(**A-16-b**)

or a pharmaceutically acceptable salt thereof, wherein R^{13}, and R^y are described herein.

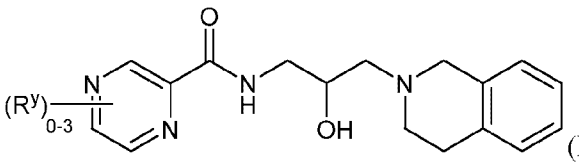
[00142] In some embodiments of Formula (**A**), the present disclosure provides a compound of Formula (**A-16-c**):



(**A-16-c**)

or a pharmaceutically acceptable salt thereof, wherein R^{13}, and R^y are described herein.

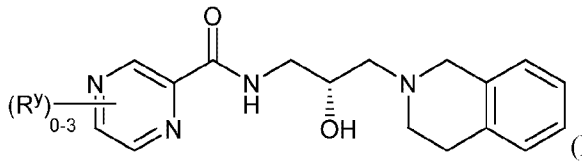
[00143] In certain embodiments, a provided compound is of Formula (**XI**):



(**XI**)

or a pharmaceutically acceptable salt thereof, wherein R^y is as described herein.

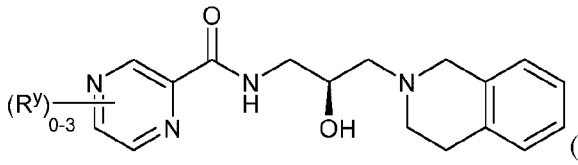
[00144] In certain embodiments, a provided compound is of Formula (**XI-a**):



(**XI-a**)

or a pharmaceutically acceptable salt thereof, wherein R^y is as described herein.

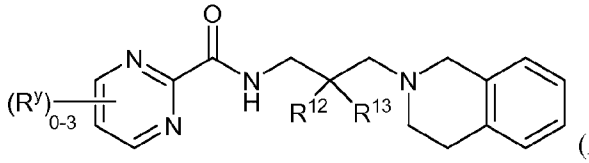
[00145] In certain embodiments, a provided compound is of Formula (**XI-b**):



(**XI-b**)

or a pharmaceutically acceptable salt thereof, wherein R^y is as described herein.

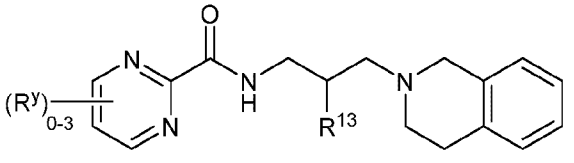
[00146] In some embodiments of Formula (**A**), the present disclosure provides a compound of Formula (**A-17**):



(**A-17**)

or a pharmaceutically acceptable salt thereof, wherein R^{12}, R^{13}, and R^y are described herein.

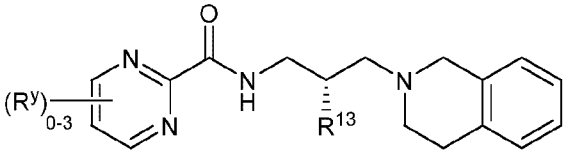
[00147] In some embodiments of Formula (**A**), the present disclosure provides a compound of Formula (**A-17-a**):



(**A-17-a**)

or a pharmaceutically acceptable salt thereof, wherein R^{13} and R^y are described herein.

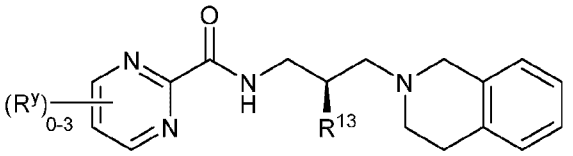
[00148] In some embodiments of Formula (**A**), the present disclosure provides a compound of Formula (**A-17-b**):



(**A-17-b**)

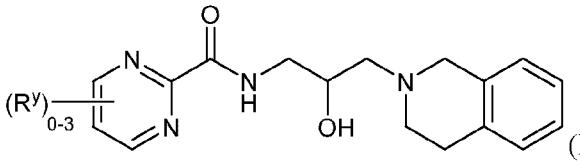
or a pharmaceutically acceptable salt thereof, wherein R^{13} and R^y are described herein.

[00149] In some embodiments of Formula (**A**), the present disclosure provides a compound of Formula (**A-17-c**):


(**A-17-c**)

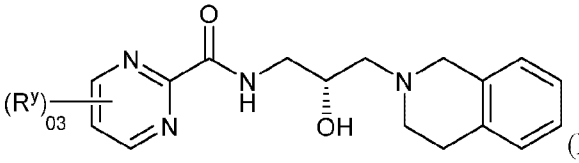
or a pharmaceutically acceptable salt thereof, wherein R^{13} and R^y are described herein.

[00150] In certain embodiments, a provided compound is of Formula (**XII**):


(**XII**)

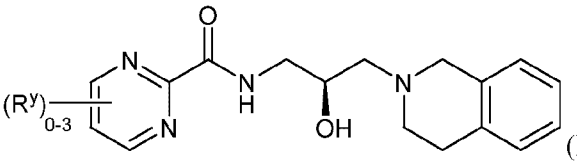
or a pharmaceutically acceptable salt thereof, wherein R^y is as described herein.

[00151] In certain embodiments, a provided compound is of Formula (**XII-a**):


(**XII-a**)

or a pharmaceutically acceptable salt thereof, wherein R^y is as described herein.

[00152] In certain embodiments, a provided compound is of Formula (**XII-b**):


(**XII-b**)

or a pharmaceutically acceptable salt thereof, wherein R^y is as described herein.

[00153] In some embodiments, ------ represents a single bond. In some embodiments, ------ represents a double bond.

[00154] As defined generally above, R^1 is hydrogen, R^z, or $-C(O)R^z$, wherein R^z is optionally substituted C_{1-6} alkyl. In certain embodiments, R^1 is hydrogen. In some embodiments, R^1 is optionally substituted C_{1-6} alkyl. In certain embodiments, R^1 is unsubstituted C_{1-6} alkyl. In certain embodiments, R^1 is methyl, ethyl, or propyl. In some embodiments, R^1 is $-C(O)R^z$, wherein R^z is optionally substituted C_{1-6} alkyl. In certain embodiments, R^1 is $-C(O)R^z$, wherein R^z is unsubstituted C_{1-6} alkyl. In certain embodiments, R^1 is acetyl.

[00155] As defined generally above, R^5, R^6, R^7, and R^8 are each independently hydrogen, halo, or optionally substituted aliphatic. In some embodiments, R^5, R^6, R^7, and R^8 are

hydrogen. In some embodiments, R^6, R^7, and $R^8$are hydrogen, and R^5 is optionally substituted aliphatic. In some embodiments, R^6, R^7, and $R^8$are hydrogen, and R^5 is optionally substituted C_{1-6} aliphatic. In some embodiments, R^6, R^7, and $R^8$are hydrogen, and R^5 is optionally substituted C_{1-3} aliphatic. In some embodiments, R^6, R^7, and $R^8$are hydrogen, and R^5 is methyl. In some embodiments, R^5, R^7, and $R^8$are hydrogen, and R^6 is optionally substituted aliphatic. In some embodiments, R^5, R^7, and $R^8$are hydrogen, and R^6 is optionally substituted C_{1-6} aliphatic. In some embodiments, R^5, R^7, and $R^8$are hydrogen, and R^6 is optionally substituted C_{1-3} aliphatic. In some embodiments, R^5, R^7, and $R^8$are hydrogen, and R^6 is methyl. In some embodiments, R^5, R^6, and $R^8$are hydrogen, and R^7 is optionally substituted aliphatic. In some embodiments, R^5, R^6, and $R^8$are hydrogen, and R^7 is optionally substituted C_{1-6} aliphatic. In some embodiments, R^5, R^6, and $R^8$are hydrogen, and R^7 is optionally substituted C_{1-3} aliphatic. In some embodiments, R^5, R^6, and $R^8$are hydrogen, and R^7 is methyl. In some embodiments, R^5, R^6, and R^7 are hydrogen, and R^8 is optionally substituted aliphatic. In some embodiments, R^5, R^6, and R^7 are hydrogen, and R^8 is optionally substituted C_{1-6} aliphatic. In some embodiments, R^5, R^6, and R^7 are hydrogen, and R^8 is optionally substituted C_{1-3} aliphatic. In some embodiments, R^5, R^6, and R^7 are hydrogen, and R^8 is methyl. In some embodiments, R^5 is hydrogen. In some embodiments, R^5 is halo. In certain embodiments, R^5 is fluoro. In some embodiments, R^5 is optionally substituted C_{1-6} aliphatic. In some embodiments, R^5 is optionally substituted C_{1-3} alkyl. In certain embodiments, R^5 is methyl. In some embodiments, R^6 is hydrogen. In some embodiments, R^6 is halo. In certain embodiments, R^6 is fluoro. In some embodiments, R^6 is optionally substituted C_{1-6} aliphatic. In some embodiments, R^6 is optionally substituted C_{1-3} alkyl. In certain embodiments, R^6 is methyl. In some embodiments, R^7 is hydrogen. In some embodiments, R^7 is halo. In certain embodiments, R^7 is fluoro. In some embodiments, R^7 is optionally substituted C_{1-6} aliphatic. In some embodiments, R^7 is optionally substituted C_{1-3} alkyl. In certain embodiments, R^7 is methyl. In some embodiments, R^8 is hydrogen. In some embodiments, R^8 is halo. In certain embodiments, R^8 is fluoro. In some embodiments, R^8 is optionally substituted C_{1-6} aliphatic. In some embodiments, R^8 is optionally substituted C_{1-3} alkyl. In certain embodiments, R^8 is methyl.

[00156] As defined generally above, L is –N(R)C(O)–, –C(O)N(R)–, –N(R)C(O)N(R)–, –N(R)C(O)O–, or –OC(O)N(R)–, wherein R is as described herein. In some embodiments, L is –N(R)C(O)–. In some embodiments, L is –NHC(O)–. In some embodiments, L is –N(C_{1-6} alkyl)C(O)–. In some embodiments, L is –N(CH_3)C(O)–. In some embodiments, L is –C(O)N(R)–. In some embodiments, L is –C(O)NH–. In some embodiments, L is –

$C(O)N(C_{1-6}$ alkyl)–. In some embodiments, L is $–C(O)N(CH_3)–$. In some embodiments, L is –N(R)C(O)N(R)–. In some embodiments, L is –NHC(O)NH–. In some embodiments, L is –NHC(O)N(R)–. In some embodiments, L is –N(R)C(O)NH–. In some embodiments, L is $–N(CH_3)C(O)N(R)–$. In some embodiments, L is $–N(R)C(O)N(CH_3)–$. In some embodiments, L is $–N(CH_3)C(O)N(CH_3)–$. In some embodiments, L is –N(R)C(O)O–. In some embodiments, L is –NHC(O)O–. In some embodiments, L is $–N(C_{1-6}$ alkyl)C(O)O–. In some embodiments, L is $–N(CH_3)C(O)O–$. In some embodiments, L is –OC(O)N(R)–. In some embodiments, L is –OC(O)NH–. In some embodiments, L is $–OC(O)N(C_{1-6}$ alkyl)–. In some embodiments, L is $–OC(O)N(CH_3)–$.

[00157] As defined generally above, each R is independently hydrogen or optionally substituted C_{1-6} aliphatic. In certain embodiments, R is hydrogen. In some embodiments, R is optionally substituted C_{1-6} aliphatic. In some embodiments, R is substituted C_{1-6} aliphatic. In some embodiments, R is unsubstituted C_{1-6} aliphatic. In some embodiments, R is optionally substituted C_{1-6} alkyl. In some embodiments, R is substituted C_{1-6} alkyl. In some embodiments, R is unsubstituted C_{1-6} alkyl. In some embodiments, R is methyl, ethyl, or propyl.

[00158] For avoidance of confusion, though Ar is sometimes used to denote the element argon, as used herein Ar denotes a monocyclic or bicyclic aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Ar is substituted with 0, 1, 2, 3, 4, or 5 R^y groups, as valency permits, and various embodiments thereof as described herein, or Ar is a monocyclic or bicyclic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Ar is substituted with 0, 1, 2, 3, 4, or 5 R^y groups, as valency permits, and various embodiments thereof as described herein. In certain embodiments, Ar is unsubstituted. In certain embodiments, Ar is substituted with one or two R^y groups. In certain embodiments, Ar is substituted with one R^y group. In certain embodiments, Ar is substituted with two R^y groups. In certain embodiments, Ar is substituted with three R^y groups. In certain embodiments, Ar is substituted with four R^y groups. In certain embodiments, Ar is substituted with five R^y groups.

[00159] In certain embodiments, Ar is phenyl substituted with 0, 1, 2, 3, 4, or 5 R^y groups. In certain embodiments, Ar is phenyl substituted with one or two R^y groups. In certain embodiments, Ar is unsubstituted phenyl. In certain embodiments, Ar is phenyl substituted with one R^y group. In certain embodiments, Ar is phenyl substituted with two R^y groups. In certain embodiments, Ar is phenyl substituted with three R^y groups. In certain embodiments,

Ar is phenyl substituted with four R^y groups. In certain embodiments, Ar is phenyl substituted with five R^y groups.

[00160] In certain embodiments, Ar is heteroaryl substituted with 0, 1, 2, 3, 4, or 5 R^y groups, as valency permits. In certain embodiments, Ar is a 5- to 6-membered heteroaryl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and is substituted with 0, 1, 2, 3, or 4 R^y groups. In certain embodiments, Ar is an unsubstituted 5- to 6-membered heteroaryl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, Ar is a 5- to 6-membered heteroaryl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and is substituted with one or two R^y groups. In certain embodiments, Ar is a 5- to 6-membered heteroaryl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and is substituted with one R^y group. In certain embodiments, Ar is a 5-membered heteroaryl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur (*e.g.*, furanyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, imidazolyl, pyrazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl), and is substituted with 0, 1, 2, or 3 R^y groups. In certain embodiments, Ar is a 6-membered heteroaryl having 1-3 nitrogens (*e.g.*, pyridyl, pyrimidyl, pyridazinyl, pyrazinyl, triazinyl), and is substituted with 0, 1, 2, 3, or 4 R^y groups. In certain embodiments, Ar is pyridyl, and is substituted with 0, 1, 2, 3, or 4 R^y groups. In certain embodiments, Ar is pyridyl, and is substituted with one R^y group. In certain embodiments, Ar is pyridyl, and is substituted with two R^y groups. In certain embodiments, Ar is a 6-membered heteroaryl having two nitrogens (*e.g.*, pyrimidyl, pyridazinyl, pyrazinyl), and is substituted with 0, 1, 2, or 3 R^y groups. In certain embodiments, Ar is a 6-membered heteroaryl having two nitrogens (*e.g.*, pyrimidyl, pyridazinyl, pyrazinyl), and is substituted with one R^y group. In certain embodiments, Ar is a 6-membered heteroaryl having two nitrogens (*e.g.*, pyrimidyl, pyridazinyl, pyrazinyl), and is substituted with two R^y groups.

[00161] In certain embodiments, Ar is a bicyclic aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Ar is substituted with 0, 1, 2, 3, or 4 R^y groups. In certain embodiments, Ar is an 8- to 12-membered bicyclic aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Ar is substituted with 0, 1, 2, 3, or 4 R^y groups. In certain embodiments, Ar is an unsubstituted bicyclic aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, Ar is a bicyclic aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Ar is substituted with one or two R^y groups. In certain embodiments, Ar is a bicyclic aromatic ring

having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Ar is substituted with one R^y group. In certain embodiments, Ar is a bicyclic aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Ar is substituted with two R^y groups. In certain embodiments, Ar is a bicyclic aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Ar is substituted with three R^y groups. In certain embodiments, Ar is a bicyclic aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Ar is substituted with four R^y groups. In certain embodiments, Ar is a bicyclic aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Ar is substituted with five R^y groups. In certain embodiments, Ar is naphthalene substituted with 0, 1, 2, 3, 4, or 5 R^y groups.

[00162] In certain embodiments, Ar is an 8- to 10-membered bicyclic heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Ar is substituted with 0, 1, 2, 3, or 4 R^y groups. In certain embodiments, Ar is a 9-membered bicyclic heteroaryl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur (*e.g.*, indolyl, isoindolyl, indazolyl, benzotriazolyl, benzothiophenyl, isobenzothiophenyl, benzofuranyl, benzoisofuranyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzoxadiazolyl, benzthiazolyl, benzisothiazolyl, benzthiadiazolyl, indolizinyl), wherein Ar is substituted with 0, 1, 2, 3, 4, or 5 R^y groups. In certain embodiments, Ar is a 10-membered bicyclic heteroaryl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur (*e.g.*, naphthyridinyl, quinolinyl, isoquinolinyl, quinoxalinyl, quinazolinyl), wherein Ar is substituted with 0, 1, 2, 3, 4, or 5 R^y groups. In certain embodiments, Ar is selected from the group consisting of quinoline, benzimidazole, benzopyrazole, quinoxaline, tetrahydroquinoline, tetrahydroisoquinoline, naphthalene, tetrahydronaphthalene, 2,3-dihydrobenzo[*b*][1,4]dioxine, isoindole, 2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one, 3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine, and quinoxalin-2(1*H*)-one, wherein Ar is substituted with 0, 1, 2, 3, or 4 R^y groups. In some embodiments, Ar is quinoline, wherein Ar is substituted with 0, 1, 2, 3, or 4 R^y groups.

[00163] As generally defined above, in certain embodiments, Ar is a monocyclic or bicyclic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Ar is substituted with 0, 1, 2, 3, 4, or 5 R^y groups, as valency permits. In certain embodiments, Ar is a monocyclic heterocyclic ring, e.g., a monocyclic 5-membered or 6-membered heterocyclic ring substituted with 0, 1, 2, 3, 4, or 5 R^y groups, as valency permits. In certain embodiments, Ar is a bicyclic heterocyclic ring, e.g., a 6,6-

bicyclic or 5,6-bicyclic heterocyclic ring substituted with 0, 1, 2, 3, 4, or 5 R^y groups, as valency permits. In certain embodiments, Ar is a 5,6-bicyclic heterocyclic ring wherein the point of attachment is on the 6-membered ring. In certain embodiments, wherein Ar is a 5,6-bicyclic heterocyclic ring, Ar is an optionally substituted dihydroimidazo pyrimidinyl ring.

[00164] As defined generally above, each R^y is independently selected from the group consisting of halo, -CN, -NO_2, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, -OR^A, -$N(R^B)_2$, -SR^A, -$C(=O)R^A$, -$C(O)OR^A$, -$C(O)SR^A$, -$C(O)N(R^B)_2$, -$C(O)N(R^B)N(R^B)_2$, -$OC(O)R^A$, -$OC(O)N(R^B)_2$, -$NR^BC(O)R^A$, -$NR^BC(O)N(R^B)_2$, -$NR^BC(O)N(R^B)N(R^B)_2$, -$NR^BC(O)OR^A$, -$SC(O)R^A$, -$C(=NR^B)R^A$, -$C(=NNR^B)R^A$, -$C(=NOR^A)R^A$, -$C(=NR^B)N(R^B)_2$, -$NR^BC(=NR^B)R^B$, -$C(=S)R^A$, -$C(=S)N(R^B)_2$, -$NR^BC(=S)R^A$, -$S(O)R^A$, -$OS(O)_2R^A$, -SO_2R^A, -$NR^BSO_2R^A$, and -$SO_2N(R^B)_2$, wherein R^A and R^B are described herein.

[00165] In some embodiments, at least one R^y is halo. In certain embodiments, at least one R^y is fluoro. In certain embodiments, at least one R^y is chloro. In some embodiments, at least one R^y is –CN. In some embodiments, at least one R^y is –OR^A, wherein R^A is optionally substituted aliphatic. In some embodiments, at least one R^y is –OR^A, wherein R^A is unsubstituted C_{1-6} alkyl. In certain embodiments, at least one R^y is methoxy, ethoxy, or propoxy. In certain embodiments, at least one R^y is methoxy. In some embodiments, at least one R^y is –OR^A, wherein R^A is substituted C_{1-6} alkyl. In certain embodiments, at least one R^y is –$OCH_2CH_2N(CH_3)_2$. In some embodiments, at least one R^y is –OR^A, wherein R^A is optionally substituted heterocyclyl. In some embodiments, at least one R^y is –OR^A, wherein R^A is an optionally subsituted 4- to 7-membered heterocyclyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, at least one R^y is –OR^A, wherein R^A is oxetanyl, tetrahydrofuranyl, or tetrahydropyranyl. In some embodiments, at least one R^y is –$N(R^B)_2$, wherein each R^B is independently hydrogen,optionally substituted alkyl, optionally substituted heterocyclyl, optionally substituted carbocyclyl, or optionally substituted aryl. In some embodiments, at least one R^y is –NHR^B, wherein each R^B is independently hydrogen,optionally substituted alkyl, optionally substituted heterocyclyl, optionally substituted carbocyclyl, or optionally substituted aryl. In some embodiments, at least one R^y is –$N(CH_3)R^B$, wherein each R^B is independently hydrogen,optionally substituted alkyl, optionally substituted heterocyclyl, optionally substituted carbocyclyl, or optionally substituted aryl. In some embodiments, at least one R^y is –$N(R^B)_2$, wherein each R^B is independently hydrogen or C_{1-6} alkyl. In some

embodiments, at least one R^y is $-NHR^B$. In some embodiments, at least one R^y is $-N(C_{1-6}$ alkyl$)_2$, $-NH(C_{1-6}$ alkyl), or $-NH_2$. In certain embodiments, at least one R^y is $-NH_2$. In certain embodiments, at least one R^y is $-NHCH_3$. In certain embodiments, at least one R^y is $-N(CH_3)_2$. In some embodiments, at least one R^y is $-N(R^B)_2$, $-NHR^B$, or $-N(CH_3)R^B$, wherein at least one R^B is –(optionally substituted C_{1-6} alkyl)-(C_{1-6} alkyl heterocyclyl). In some embodiments, at least one R^y is $-N(R^B)_2$ or $-NHR^B$, wherein at least one R^B is optionally substituted heterocyclyl. In some embodiments, at least one R^y is $-N(R^B)_2$ or $-NHR^B$, wherein at least one R^B is an optionally subsituted 4- to 7-membered heterocyclyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, at least one R^y is $-N(R^B)_2$ or $-NHR^B$, wherein at least one R^B is oxetanyl, tetrahydropyranyl, or tetrahydrofuranyl. In some embodiments, at least one R^y is $-N(R^B)_2$ or $-NHR^B$, wherein at least one R^B is optionally substituted piperidinyl or optionally substituted piperazinyl.

[00166] In some embodiments, at least one R^y is optionally substituted aliphatic. In certain embodiments, at least one R^y is substituted aliphatic. In certain embodiments, at least one R^y is unsubstituted aliphatic. In some embodiments, at least one R^y is optionally substituted C_{1-6} alkyl. In certain embodiments, at least one R^y is unsubstituted C_{1-6} alkyl. In certain embodiments, at least one R^y is substituted C_{1-6} alkyl. In certain embodiments, at least one R^y is methyl, ethyl, or propyl. In certain embodiments, at least one R^y is methyl. In certain embodiments, at least one R^y is $-CF_3$, CHF_2, or CH_2F. In certain embodiments, at least one R^y is C_{1-6} alkyl substituted with aryl, heteroaryl, or heterocyclyl. In certain embodiments, at least one R^y is benzyl. In certain embodiments, at least one R^y is $-(C_{1-6}$ alkyl)-aryl. In certain embodiments, at least one R^y is $-(C_{1-6}$ alkyl)-heteroaryl. In certain embodiments, at least one R^y is $-(C_{1-6}$ alkyl)-heterocyclyl. In certain embodiments, at least one R^y is $-CH_2$-aryl. In certain embodiments, at least one R^y is $-CH_2$-heteroaryl. In certain embodiments, at least one R^y is $-CH_2$-heterocyclyl.

[00167] In some embodiments, at least one R^y is $-C(O)N(R^B)_2$. In certain embodiments, at least one R^y is $-C(O)NHR^B$. In certain embodiments, at least one R^y is $-C(O)NH_2$. In certain embodiments, at least one R^y is $-C(O)N(R^B)_2$, wherein the R^B groups are taken together with their intervening atoms to form an optionally substituted 5- to 6-membered heterocyclyl. In certain embodiments, at least one R^y is $-C(O)N(R^B)_2$, wherein the R^B groups are taken together with their intervening atoms to form an optionally substituted morpholinyl.

[00168] In some embodiments, at least one R^y is $-SO_2N(R^B)_2$. In certain embodiments, at least one R^y is $-SO_2NHR^B$. In certain embodiments, at least one R^y is $-SO_2NH_2$. In certain

embodiments, at least one R^y is $-SO_2N(R^B)_2$, wherein neither R^B is hydrogen. In certain embodiments, at least one R^y is $-SO_2NH(C_{1-6}$ alkyl) or $-SO_2N(C_{1-6}$ alkyl)$_2$. In certain embodiments, at least one R^y is $-SO_2N(CH_3)_2$. In certain embodiments, at least one R^y is $-SO_2N(R^B)_2$, wherein the R^B groups are taken together with their intervening atoms to form an optionally substituted 5- to 6-membered heterocyclyl. In certain embodiments, at least one R^y is $-SO_2$-morpholinyl. In certain embodiments, at least one R^y is $-SO_2$-piperidinyl, $-SO_2$-piperazinyl, or $-SO_2$-piperidinyl.

[00169] In some embodiments, at least one R^y is $-SO_2R^A$. In some embodiments, at least one R^y is $-SO_2R^A$, wherein R^A is optionally substituted aliphatic. In some embodiments, at least one R^y is $-SO_2(C_{1-6}$ alkyl). In some embodiments, at least one R^y is $-SO_2CH_3$. In some embodiments, at least one R^y is $-C(O)R^A$. In some embodiments, at least one R^y is $-C(O)R^A$, wherein R^A is optionally substituted aliphatic. In some embodiments, at least one R^y is $-C(O)(C_{1-6}$ alkyl). In some embodiments, at least one R^y is $-C(O)CH_3$.

[00170] In some embodiments, at least one R^y is $-N(R^B)C(O)R^A$. In certain embodiments, at least one R^y is $-NHC(O)R^A$. In certain embodiments, at least one R^y is $-NHC(O)(C_{1-6}$ alkyl). In certain embodiments, at least one R^y is $-NHC(O)CH_3$.

[00171] In some embodiments, at least one R^y is $-N(R^B)SO_2R^A$. In some embodiments, at least one R^y is $-NHSO_2R^A$. In some embodiments, at least one R^y is $-N(C_{1-6}$ alkyl)SO_2R^A. In certain embodiments, at least one R^y is $-NHSO_2(C_{1-6}$ alkyl) or $-N(C_{1-6}$ alkyl)$SO_2(C_{1-6}$ alkyl). In certain embodiments, at least one R^y is $-NHSO_2CH_3$. In certain embodiments, at least one R^y is $-N(CH_3)SO_2CH_3$.

[00172] In some embodiments, at least one R^y is optionally substituted heterocyclyl, optionally substituted carbocyclyl, optionally substituted aryl, or optionally substituted heteroaryl. In certain embodiments, at least one R^y is an optionally substituted 5- to 6-membered heterocyclyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, at least one R^y is an optionally substituted 5-membered heterocyclyl having one heteroatom selected from nitrogen, oxygen, and sulfur. In certain embodiments, at least one R^y is optionally substituted pyrrolidinyl. In certain embodiments, at least one R^y is pyrroldinyl, hydroxypyrrolidinyl, or methylpyrrolidinyl. In certain embodiments, at least one R^y is an optionally substituted 6-membered heterocyclyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, at least one R^y is an optionally substituted 6-membered heterocyclyl having one heteroatom selected from nitrogen, oxygen, and sulfur. In certain embodiments, at least one R^y is optionally substituted piperidinyl. In certain embodiments, at least one R^y is an

optionally substituted 6-membered heterocyclyl having two heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, at least one R^y is optionally substituted piperdinyl, optionally substituted piperazinyl, or optionally substituted morpholinyl. In certain embodiments, at least one R^y is morpholinyl, tetrahydropyranyl, piperidinyl, methylpiperidinyl, piperazinyl, methylpiperazinyl, acetylpiperazinyl, methylsulfonylpiperazinyl, aziridinyl, or methylaziridinyl. In some embodiments, at least one R^y is an optionally substituted 5- to 6-membered heteroaryl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, at least one R^y is an optionally substituted 5-membered heteroaryl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, at least one R^y is an optionally substituted 5-membered heteroaryl having one heteroatom selected from nitrogen, oxygen, and sulfur. In certain embodiments, at least one R^y is an optionally substituted 5-membered heteroaryl having two heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, at least one R^y is an optionally substituted 6-membered heteroaryl having 1-3 nitrogens. In certain embodiments, at least one R^y is an optionally substituted pyrazolyl. In certain embodiments, at least one R^y is an optionally substituted imidazolyl. In certain embodiments, at least one R^y is an optionally substituted pyridyl. In certain embodiments, at least one R^y is an optionally substituted pyrimidyl. In certain embodiments, at least one R^y is pyrazolyl, methylpyrazolyl, imidazolyl, or methylimidazolyl.

[00173] In some embodiments, R^y is $-OR^A$. In some embodiments, R^y is $-OR^A$, wherein R^A is optionally substituted heterocyclyl. In some embodiments, R^y is $-OR^A$, wherein R^A is optionally substituted heteroaryl. In some embodiments, R^y is $-OR^A$, wherein R^A is optionally substituted cycloalkyl. In some embodiments, R^y is $-N(R^B)_2$. In some embodiments, R^y is $-NHR^B$. In some embodiments, R^y is $-NHR^B$, wherein R^B is optionally substituted heterocyclyl. In some embodiments, R^y is $-NHR^B$, wherein R^B is optionally substituted heteroaryl. In some embodiments, R^y is $-NHR^B$, wherein R^B is optionally substituted cycloalkyl. In some embodiments, R^y is $-N(R^B)_2$, wherein one R^B is optionally substituted heterocyclyl, and the other R^B is C_{1-4} alkyl. In some embodiments, R^y is $-N(R^B)_2$, wherein one R^B is optionally substituted heteroaryl, and the other R^B is C_{1-4} alkyl. In some embodiments, R^y is $-N(R^B)_2$, wherein one R^B is optionally substituted cycloalkyl, and the other R^B is C_{1-4} alkyl.

[00174] In some embodiments of Formula (**A**), when L is $-C(O)N(R)-$; R^{12} is hydrogen; and R^{13} is hydrogen or $-OR_1$; then Ar is not optionally substituted five-membered heteroaryl,

optionally substituted five-membered heterocyclyl, an optionally substituted bicyclic aromatic ring, an optionally substituted bicyclic heterocyclic ring, or optionally substituted phenyl. In some embodiments of Formula (**A**), when L is –C(O)N(R)-; R^{12} is hydrogen; and R^{13} is hydrogen or $–OR_1$, then Ar is substituted six-membered heteroaryl with at least one R^y at the beta-position of the point of the attachment to L. In some embodiments of Formula (**A**), when L is –C(O)NH-; R^{12} is hydrogen; and R^{13} is hydrogen or –OH, then Ar is substituted six-membered heteroaryl with at least one R^y at the beta-position of the point of the attachment to L. In some embodiments of Formula (**A**), when L is –C(O)N(R)-; R^{12} is hydrogen; R^{13} is hydrogen or $–OR_1$; and Ar is substituted six-membered heteroaryl, then R^y is not halo (e.g., F or Cl) or optionally substituted alkyl. In some embodiments of Formula (**A**), when L is –C(O)N(R)-; R^{12} is hydrogen; and R^{13} is hydrogen or $–OR_1$; and Ar is substituted six-membered heteroaryl, then R^y is not halo (e.g., F or Cl) or C_{1-3} alkyl (e.g., methyl, ethyl, n-propyl, or iso-propyl). In some embodiments of Formula (**A**), when L is –C(O)NH-; R^{12} is hydrogen; and R^{13} is hydrogen or $–OR_1$; and Ar is substituted six-membered heteroaryl, then R^y is not halo (e.g., F or Cl) or C_{1-3} alkyl (e.g., methyl, ethyl, n-propyl, or iso-propyl). In some embodiments of Formula (**A**), when L is –C(O)NH-; R^{12} is hydrogen; and R^{13} is hydrogen or –OH; and Ar is substituted six-membered heteroaryl, then R^y is not halo (e.g., F or Cl) or C_{1-3} alkyl (e.g., methyl, ethyl, n-propyl, or iso-propyl). In some embodiments of Formula (**A**), when L is –C(O)N(R)-; R^{12} is hydrogen; and R^{13} is hydrogen or $–OR_1$; and Ar is optionally substituted pyridine or pyrimidine, then R^y is not halo (e.g., F or Cl) or optionally substituted alkyl. In some embodiments of Formula (**A**), when L is –C(O)N(R)-; R^{12} is hydrogen; and R^{13} is hydrogen or $–OR_1$; and Ar is optionally substituted pyridine or pyrimidine, then R^y is not halo (e.g., F or Cl) or C_{1-3} alkyl (e.g., methyl, ethyl, n-propyl, or iso-propyl). In some embodiments of Formula (**A**), when L is –C(O)NH-; R^{12} is hydrogen; and R^{13} is hydrogen or $–OR_1$; and Ar is optionally substituted pyridine or pyrimidine, then R^y is not halo (e.g., F or Cl) or C_{1-3} alkyl (e.g., methyl, ethyl, n-propyl, or iso-propyl). In some embodiments of Formula (**A**), when L is –C(O)NH-; R^{12} is hydrogen; and R^{13} is hydrogen or –OH; and Ar is optionally substituted pyridine or pyrimidine, then R^y is not halo (e.g., F or Cl) or C_{1-3} alkyl (e.g., methyl, ethyl, n-propyl, or iso-propyl). In some embodiments of Formula (**A**), when L is –C(O)NH-; R^{12} is hydrogen; and R^{13} is hydrogen or –OH; and Ar is pyridine or pyrimidine substituted with one R^y, then R^y is not halo (e.g., F or Cl) or C_{1-3} alkyl (e.g., methyl, ethyl, n-propyl, or iso-propyl).

[00175] In some embodiments of Formula (**A**), when L is –C(O)N(R)-; R^{12} is hydrogen; R^{13} is hydrogen or $–OR_1$; and Ar is monocyclic or bicyclic heteroaryl, then Ar is substituted

with 1, 2, 3, 4, or 5 R^y, as valency permits, and each instance of R^y is not halo (e.g., F or Cl), optionally substituted alkyl (e.g., methyl), optionally substituted heteroaryl (e.g., thiazolyl, isoxazolyl, or thiadiazolyl), optionally substituted carbocyclyl, or $-SO_2N(R^B)_2$, wherein R^B is as generally defined herein. In some embodiments of Formula (**A**), when L is –C(O)N(R)-; R^{12} is hydrogen; R^{13} is hydrogen or $-OR_1$; and Ar is monocyclic heteroaryl, then Ar is substituted with 1, 2, 3, 4, or 5 R^y, as valency permits, and each instance of R^y is not halo (e.g., F or Cl) or optionally substituted alkyl (e.g., methyl or ethyl).

[00176] In some embodiments of Formula (**A**), when L is –C(O)N(R)-; R^{12} is hydrogen; R^{13} is–OR_1; and Ar is substituted six-membered heteroaryl, then R^y is not halo (e.g., F or Cl) or optionally substituted alkyl. In some embodiments of Formula (**A**), when L is –C(O)NH-; R^{12} is hydrogen; R^{13} is–OH; and Ar is substituted six-membered heteroaryl, then R^y is not halo (e.g., F or Cl) or optionally substituted alkyl. In some embodiments of Formula (**A**), when L is –C(O)N(R)-; R^{12} is hydrogen; R^{13} is–OR_1; and Ar is substituted five-membered heteroaryl, then each R^y is not halo (e.g., F or Cl) or optionally substituted alkyl. In some embodiments of Formula (**A**), when L is –C(O)N(R)-; R^{12} and R^{13} are both hydrogen; and Ar is six-membered heteroaryl, then Ar is substituted with 1, 2, 3, 4, or 5 R^y, as valency permits, and each instance of R^y is not halo, optionally substituted alkyl, or optionally substituted heteroaryl.

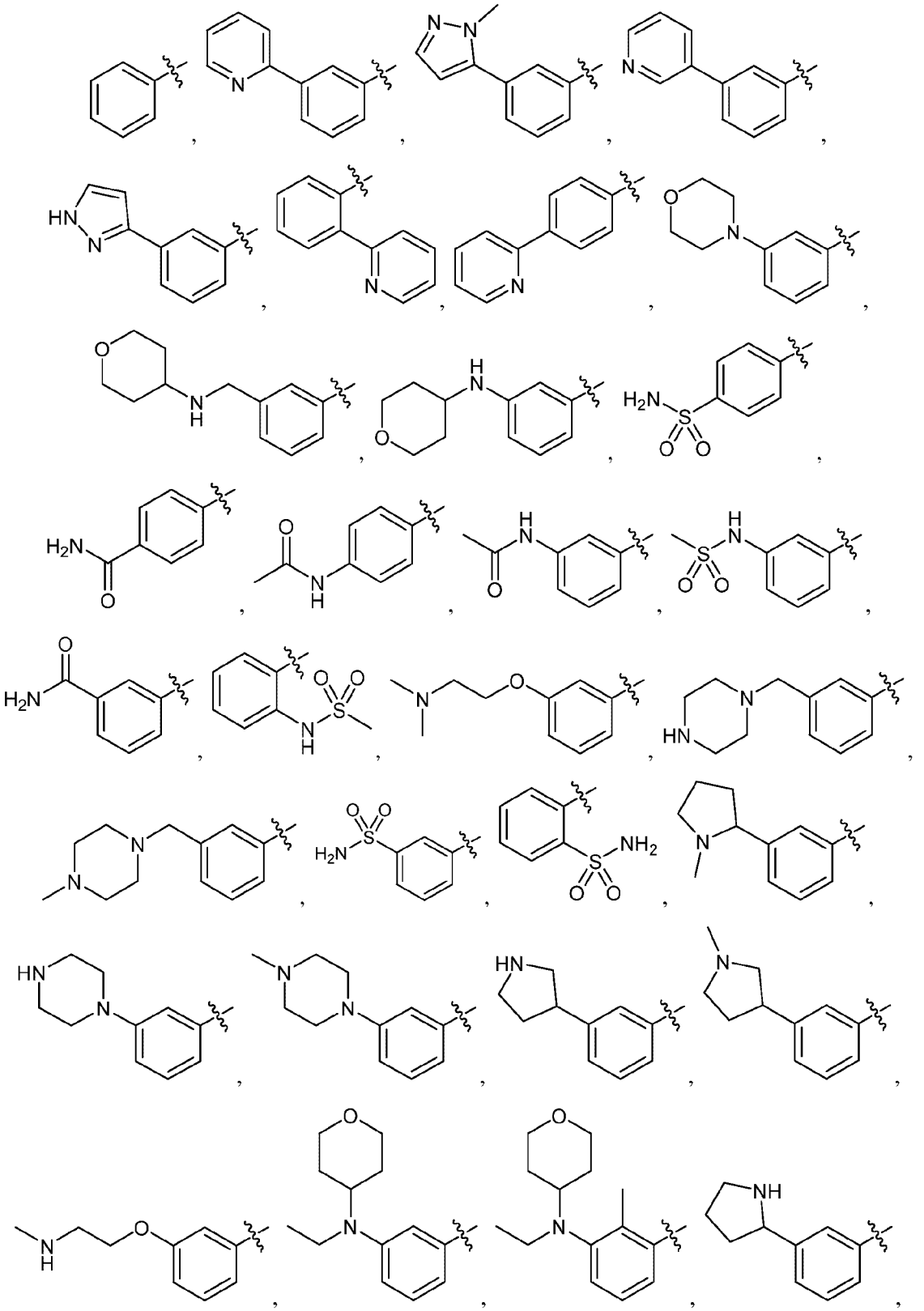
[00177] In some embodiments of Formula (**I**), when L is –C(O)N(R)-, then Ar is not optionally substituted five-membered heteroaryl, optionally substituted five-membered heterocyclyl, an optionally substituted bicyclic aromatic ring, an optionally substituted bicyclic heterocyclic ring, or optionally substituted phenyl. In some embodiments of Formula (**I**), when L is –C(O)NH-, then Ar is not optionally substituted five-membered heteroaryl, optionally substituted five-membered heterocyclyl, an optionally substituted bicyclic aromatic ring, an optionally substituted bicyclic heterocyclic ring, or optionally substituted phenyl. In some embodiments of Formula (**I**), when L is –C(O)N(R)-, then Ar is six-membered heteroaryl with at least one R^y substituted at the beta-position of the point of the attachment to L. In some embodiments of Formula (**I**), when L is –C(O)NH- and R^1 is hydrogen, then Ar is six-membered heteroaryl with at least one R^y substituted at the beta-position of the point of the attachment to L.

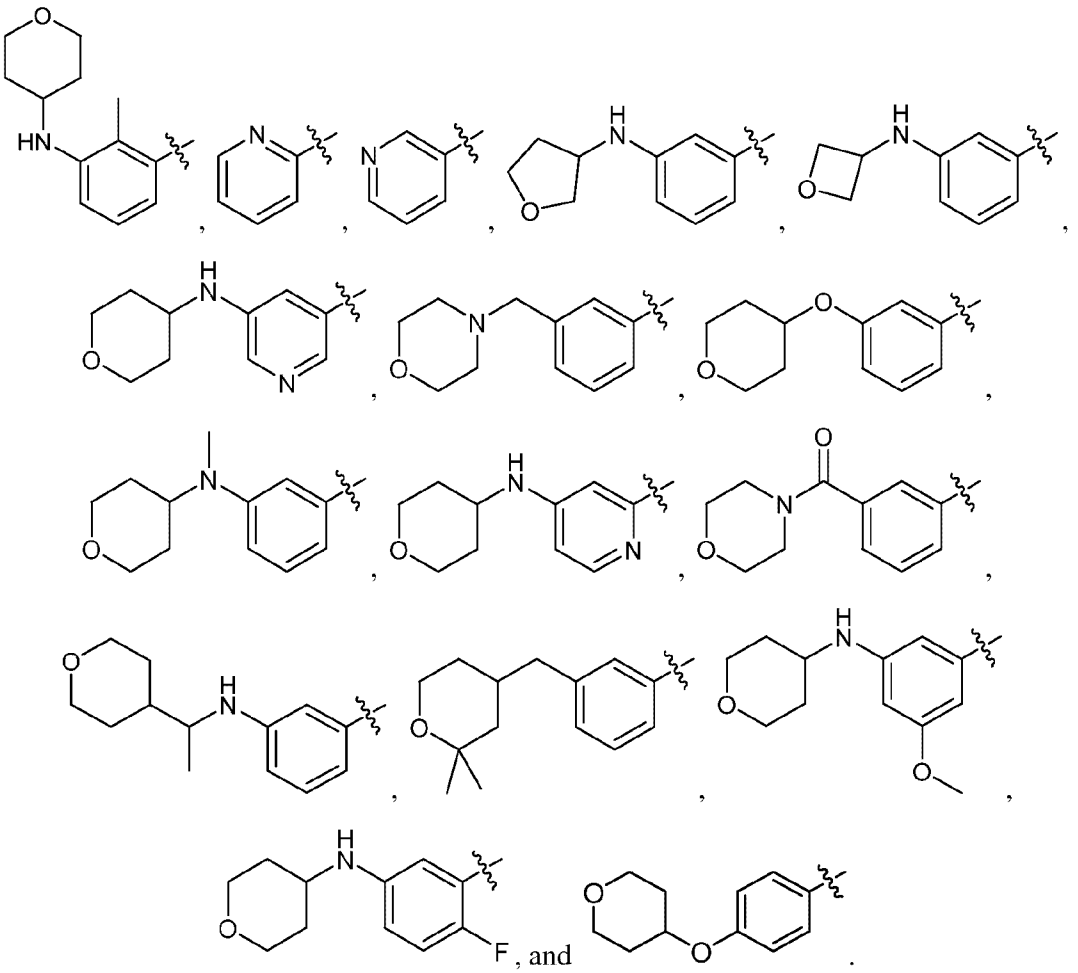
[00178] In some embodiments of Formula (**I**), when L is –C(O)N(R)- and Ar is substituted six-membered heteroaryl, then each instance of R^y is not halo (e.g., F or Cl) or optionally substituted alkyl. In some embodiments of Formula (**I**), when L is –C(O)N(R)- and Ar is substituted six-membered heteroaryl, then each instance of R^y is not halo (e.g., F or Cl) or C_1-

$_3$ alkyl (e.g., methyl, ethyl, n-propyl, or iso-propyl). In some embodiments of Formula (**I**), when L is –C(O)NH-; R^1 is hydrogen; and Ar is substituted six-membered heteroaryl, then each instance of R^y is not halo (e.g., F or Cl) or C_{1-3} alkyl (e.g., methyl, ethyl, n-propyl, or iso-propyl). In some embodiments of Formula (**A**), when L is –C(O)N(R)- and R^1 is hydrogen, then Ar is substituted pyridine or pyrimidine , then each instance of R^y is not halo (e.g., F or Cl) or optionally substituted alkyl. In some embodiments of Formula (**A**), when L is –C(O)N(R)- and R^1 is hydrogen, then Ar is substituted pyridine or pyrimidine and R^y is not halo (e.g., F or Cl) or C_{1-3} alkyl (e.g., methyl, ethyl, n-propyl, or iso-propyl). In some embodiments of Formula (**A**), when L is –C(O)NH- and R^1 is hydrogen, then Ar is substituted pyridine or pyrimidine and R^y is not halo (e.g., F or Cl) or C_{1-3} alkyl (e.g., methyl, ethyl, n-propyl, or iso-propyl).

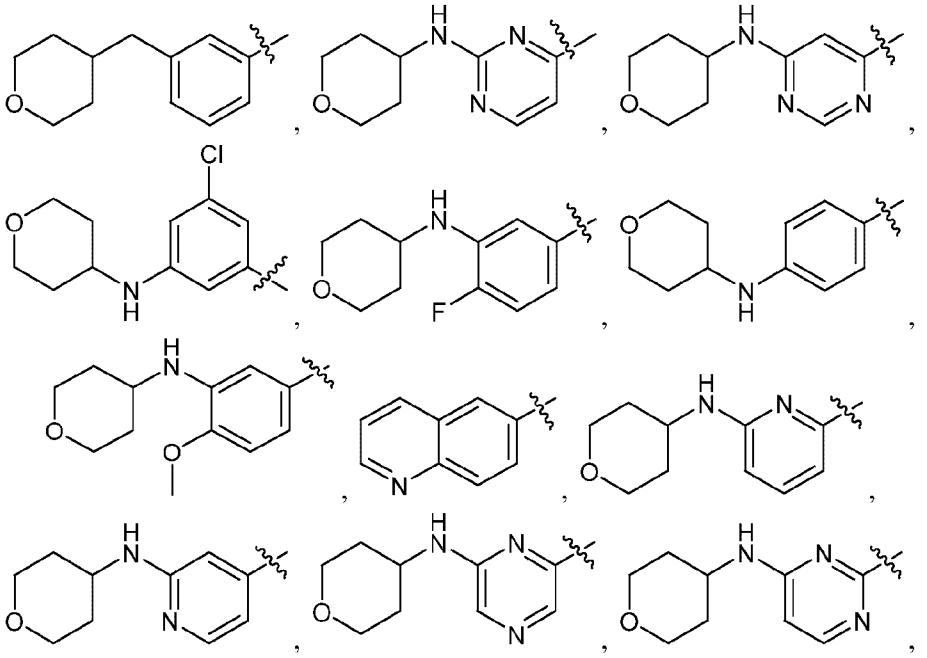
[00179] In some embodiments of Formula (**I**), when L is –C(O)N(R)- and Ar is monocyclic or bicyclic heteroaryl, then Ar is substituted with 1, 2, 3, 4, or 5 R^y, as valency permits, and each instance of R^y is not halo (e.g., F or Cl) or optionally substituted alkyl. In some embodiments of Formula (**I**), when L is –C(O)N(R)-, and Ar is six-membered heteroaryl, then Ar is substituted with 1, 2, 3, 4, or 5 R^y, as valency permits, and each instance of R^y is not halo or optionally substituted alkyl. In some embodiments of Formula (**I**), when L is –C(O)NH-, and Ar is six-membered heteroaryl, then Ar is substituted with 1, 2, 3, 4, or 5 R^y, as valency permits, and each instance of R^y is not halo or optionally substituted alkyl. In some embodiments of Formula (**I**), when L is –C(O)N(R)- and Ar is pyridine or pyrimidine; then Ar is substituted with 1, 2, 3, 4, or 5 R^y, as valency permits, and each instance of R^y is not halo or optionally substituted alkyl. In some embodiments of Formula (**I**), when L is –C(O)NH- and Ar is pyridine or pyrimidine; then Ar is substituted with 1, 2, 3, 4, or 5 R^y, as valency permits, and each instance of R^y is not halo or optionally substituted alkyl. In some embodiments of Formula (**I**), when L is –C(O)N(R)- and Ar is pyridine, then Ar is substituted with 1, 2, 3, 4, or 5 R^y, as valency permits, and each instance of R^y is not halo or optionally substituted alkyl. In some embodiments of Formula (**I**), when L is –C(O)N(R)- and Ar is pyridine substituted with one R^y, and R^y is not halo or C_{1-3} alkyl (e.g., methyl, ethyl, n-propyl, or iso-propyl). In some embodiments of Formula (**I**), when L is –C(O)N(R)- and Ar is pyrimidine substituted with one R^y, then R^y is not halo or optionally substituted alkyl (e.g., methyl). In some embodiments of Formula (**I**), when L is –C(O)N(R)- and Ar is pyrimidine substituted with one R^y, then R^y is not optionally substituted alkyl. In some embodiments of Formula (**I**), when L is –C(O)N(R)- and Ar is pyrimidine substituted with one R^y, then R^y is not C_{1-3} alkyl.

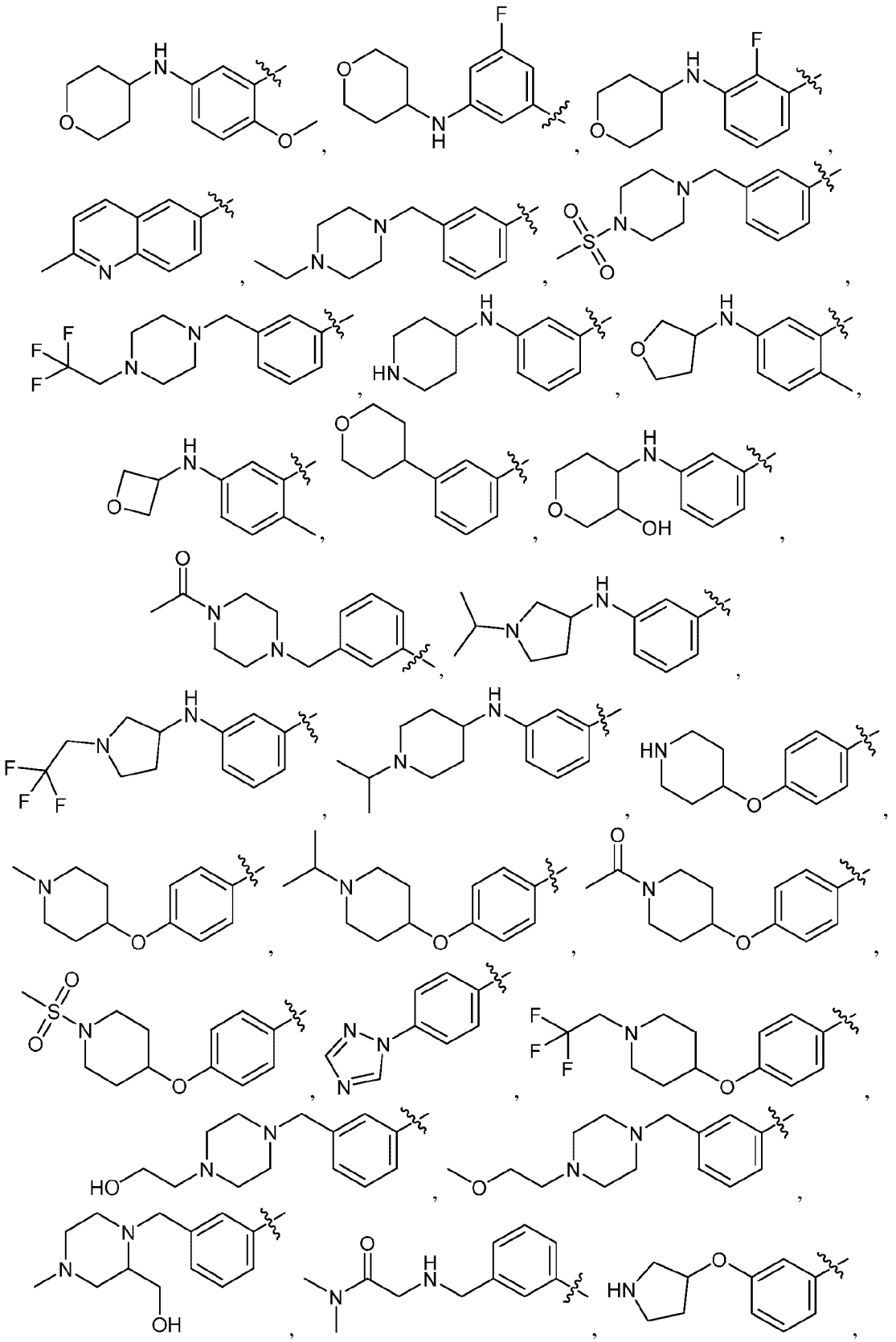
[00180] In certain embodiments, Ar is selected from the group consisting of:

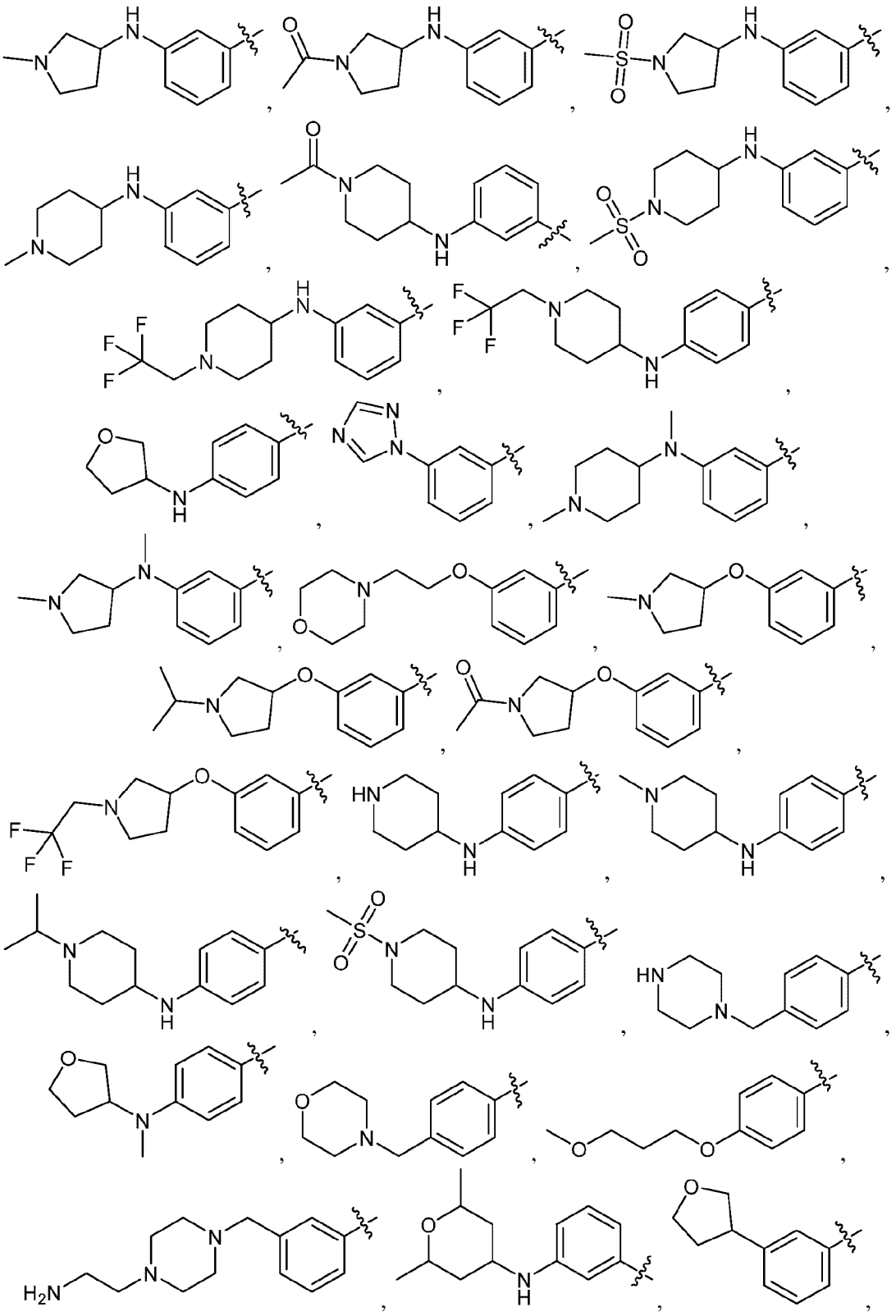


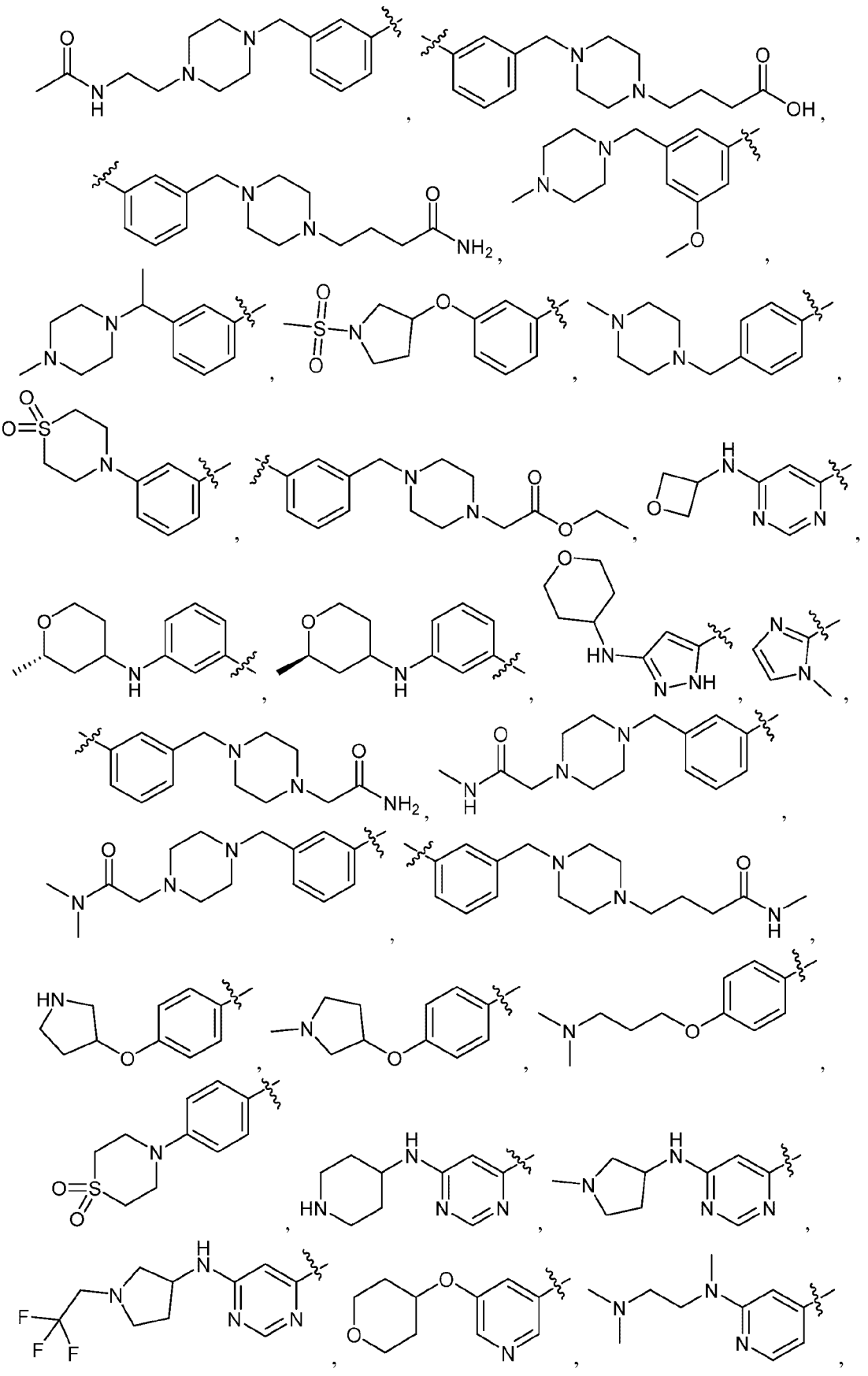


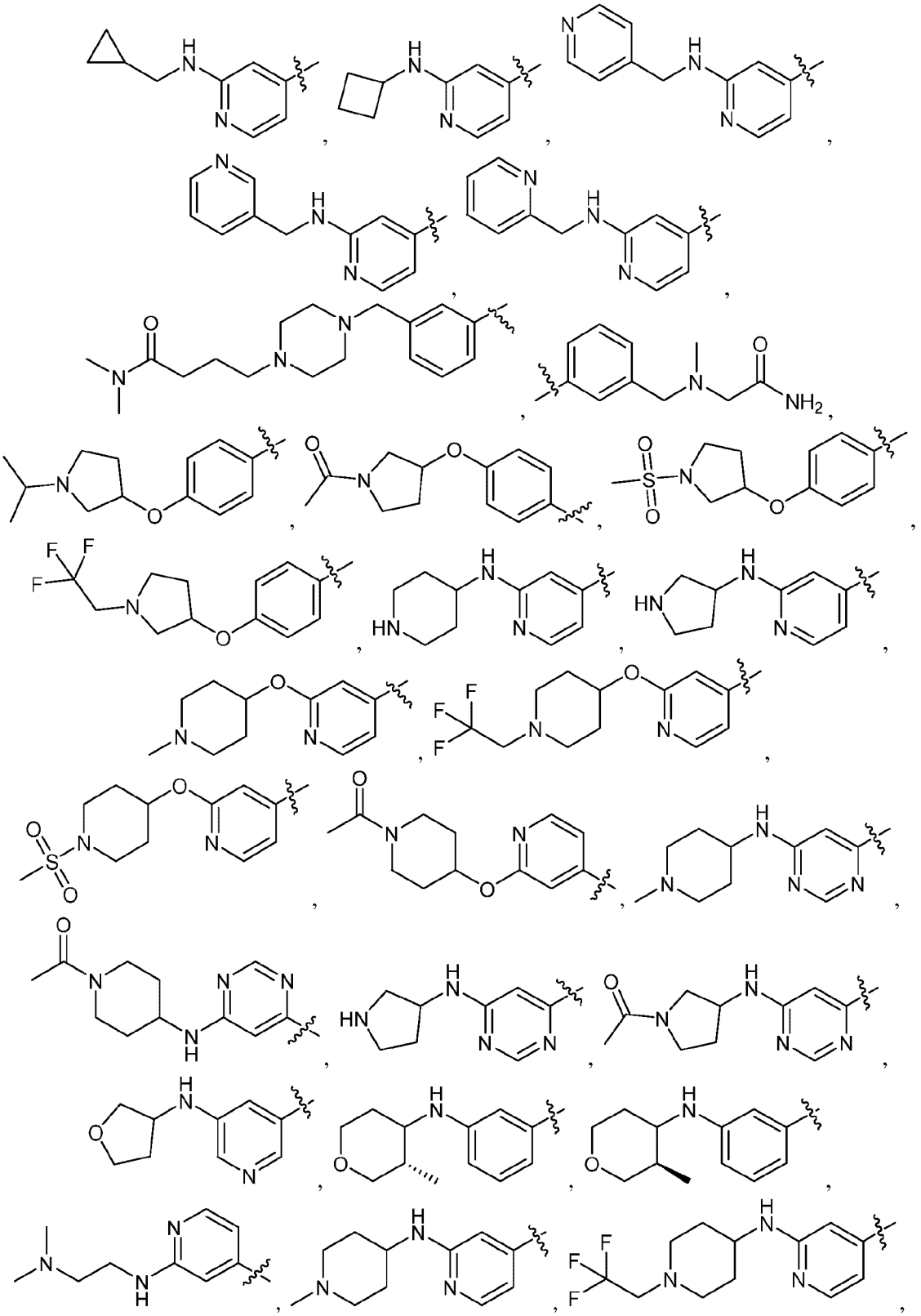
[00181] In certain embodiments, Ar is selected from the group consisting of:

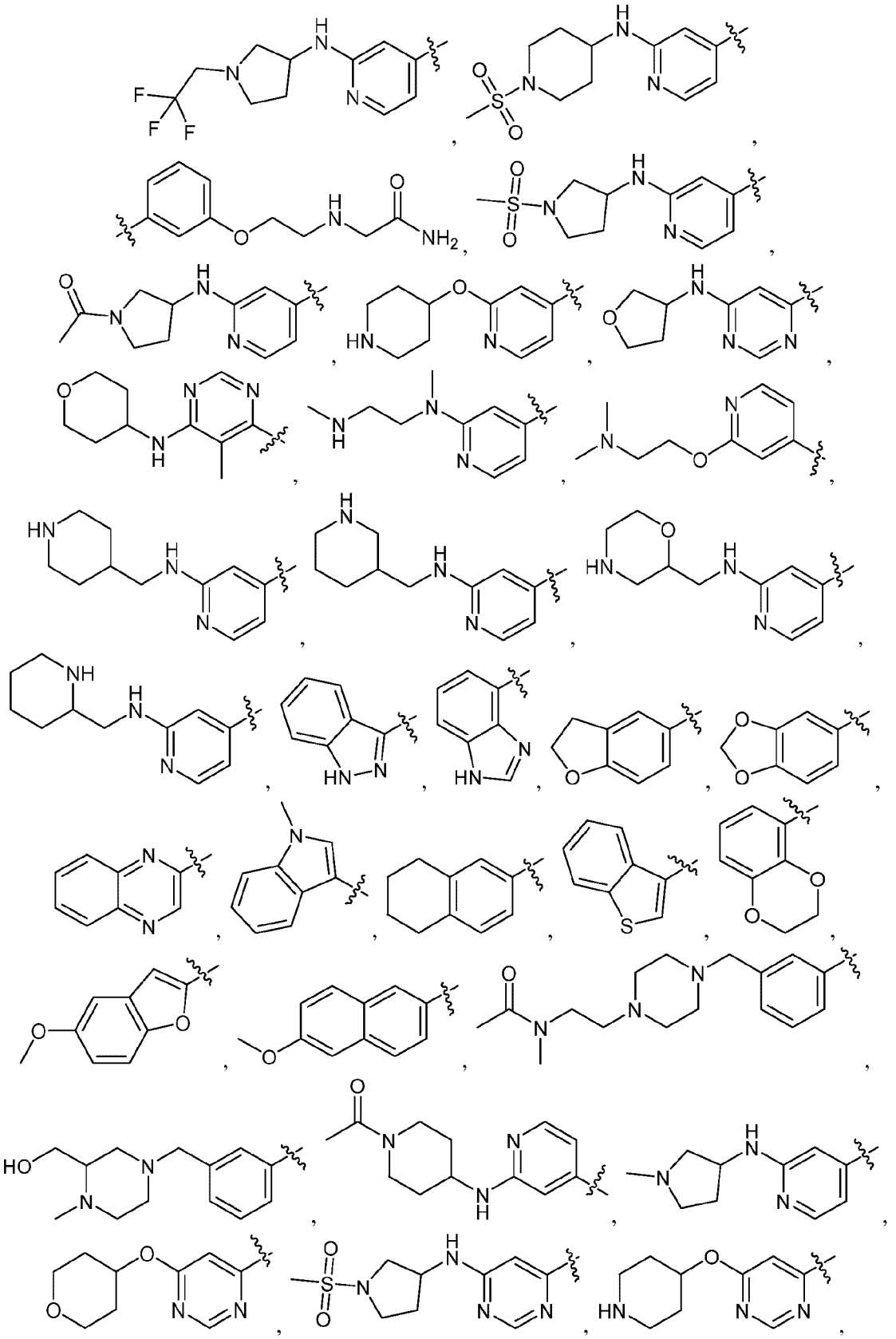


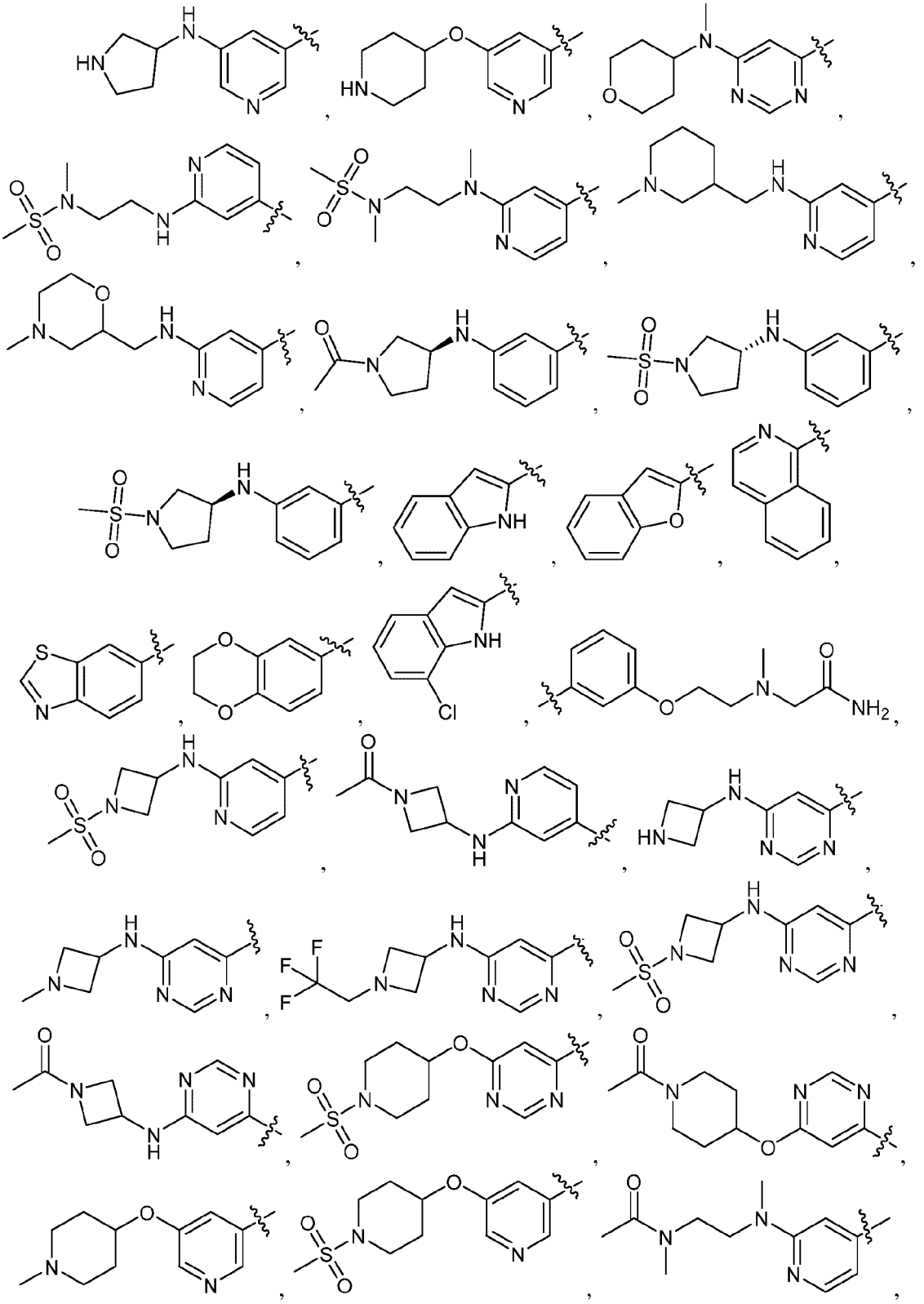


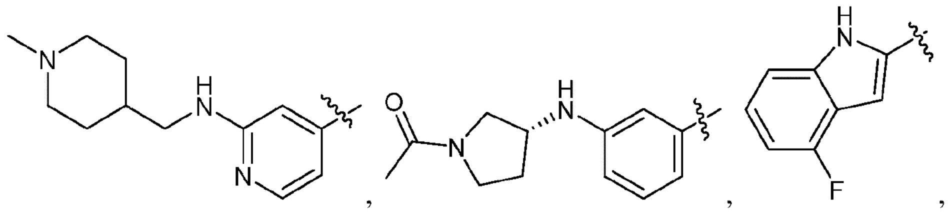


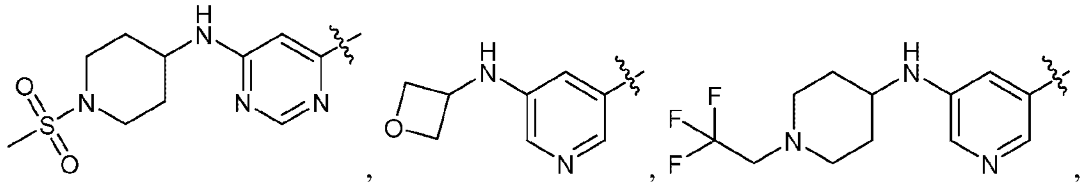


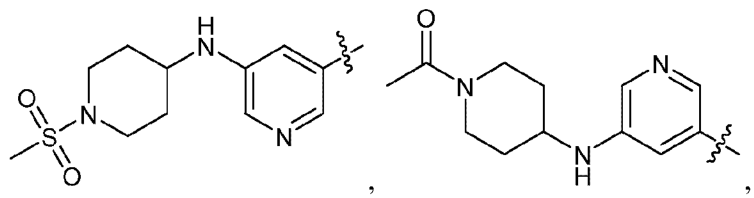


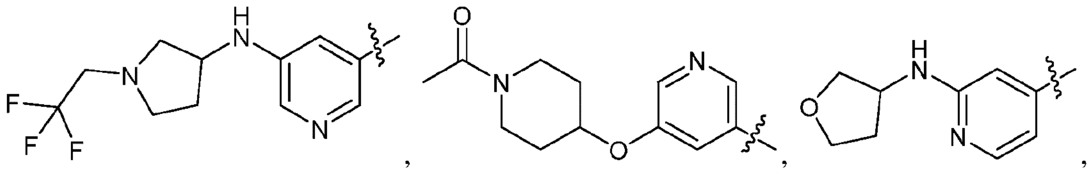


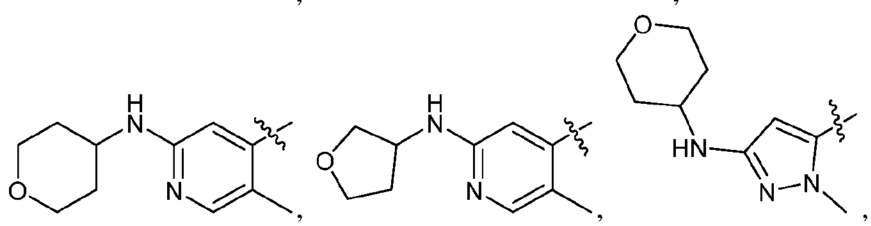


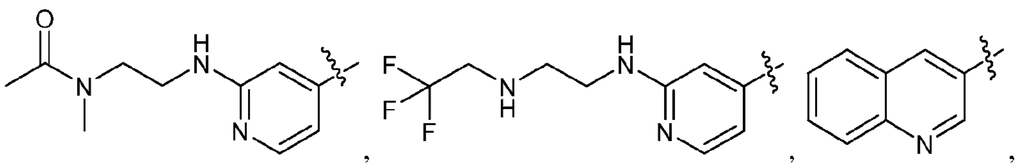


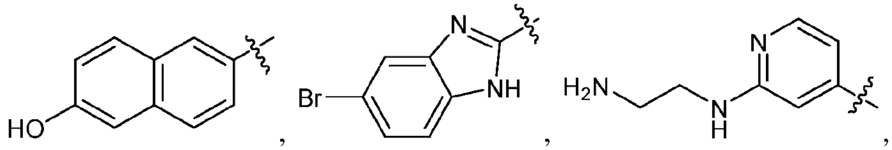


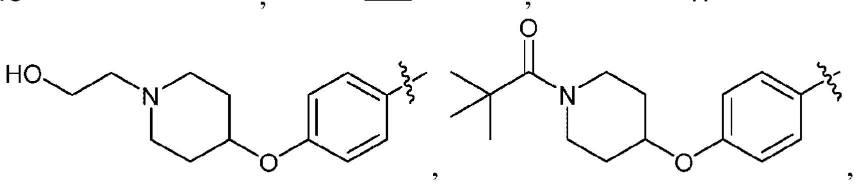


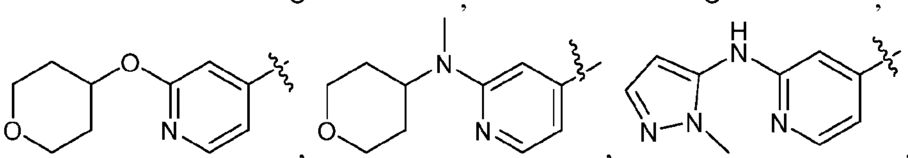


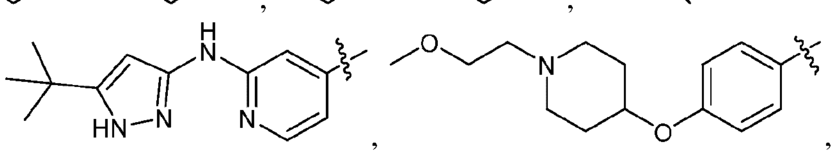


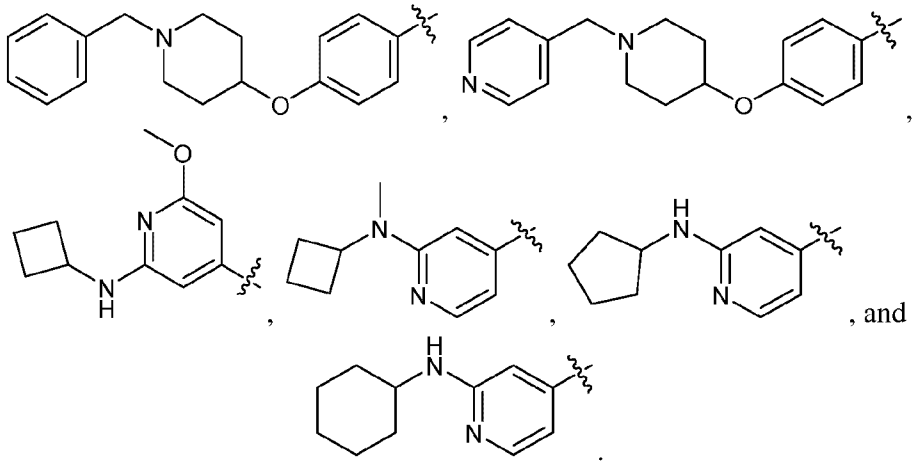






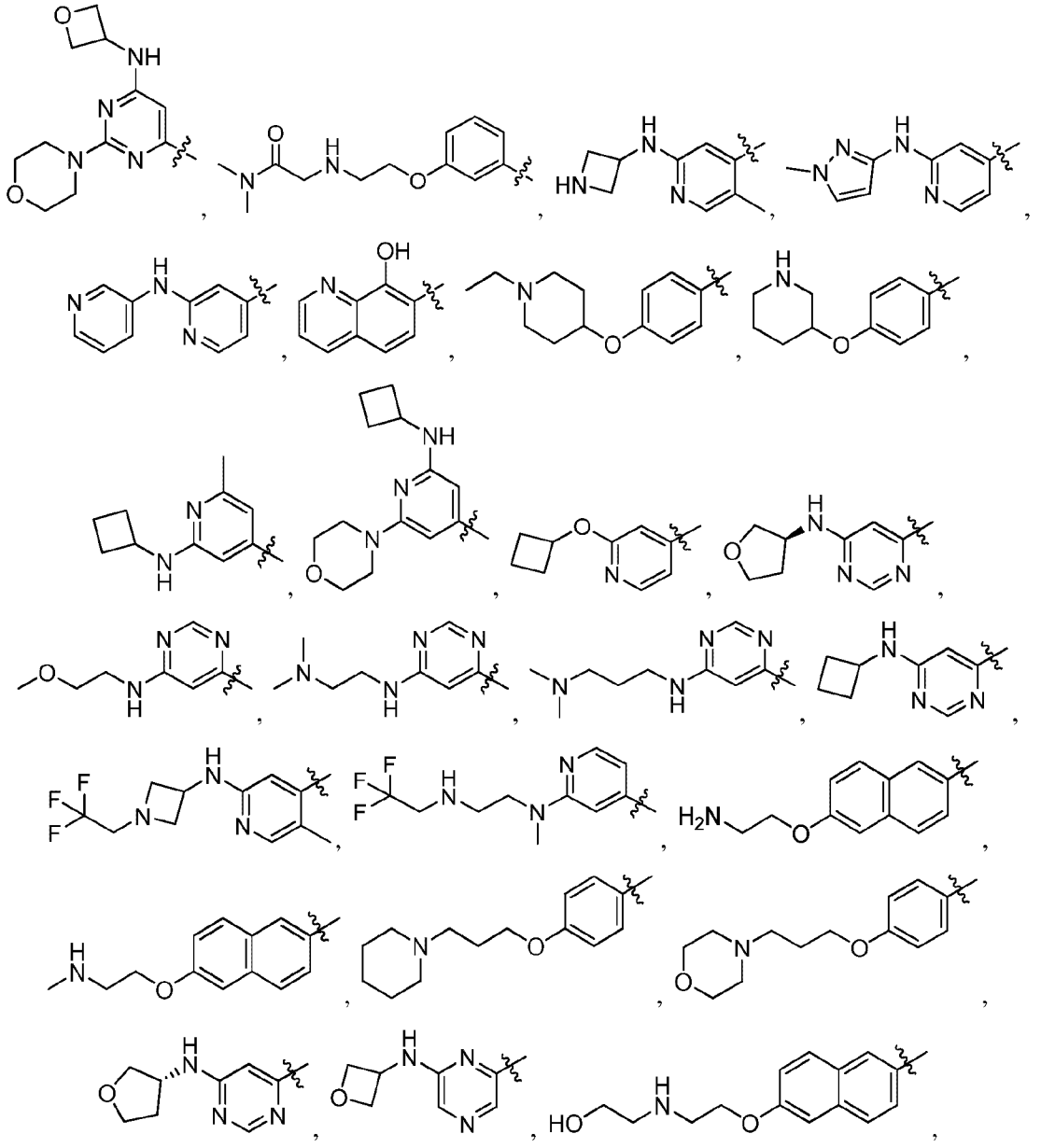


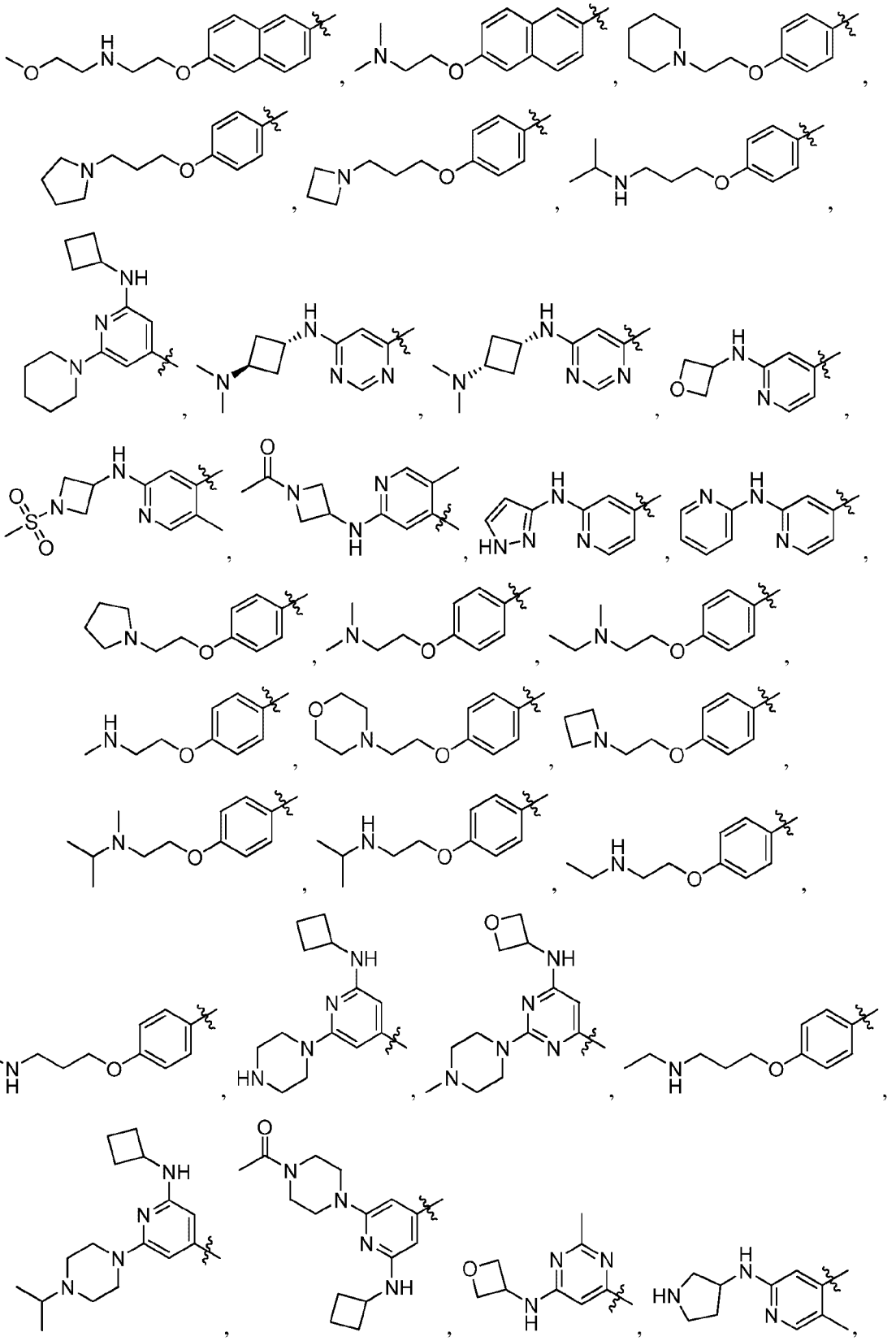


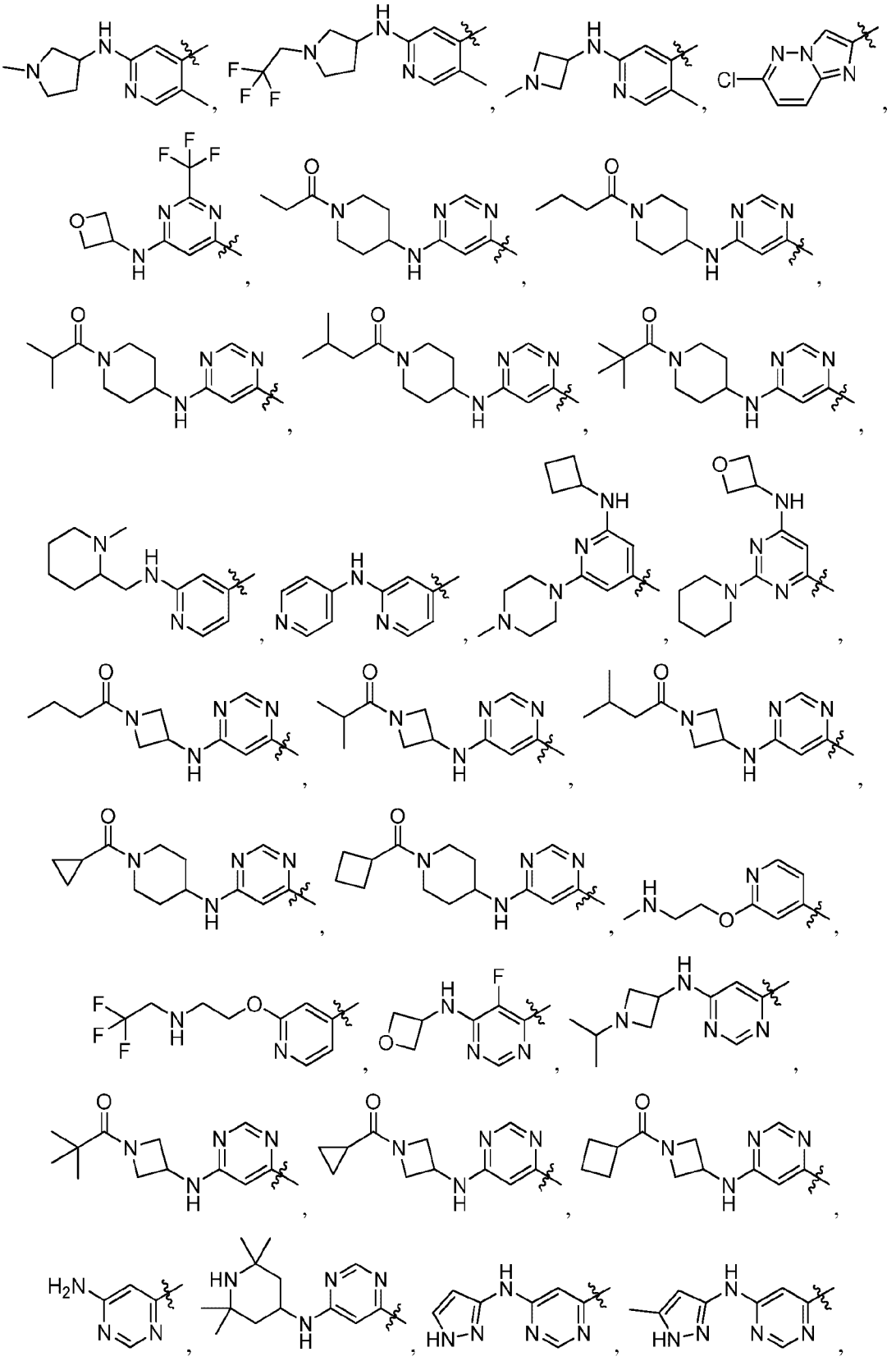


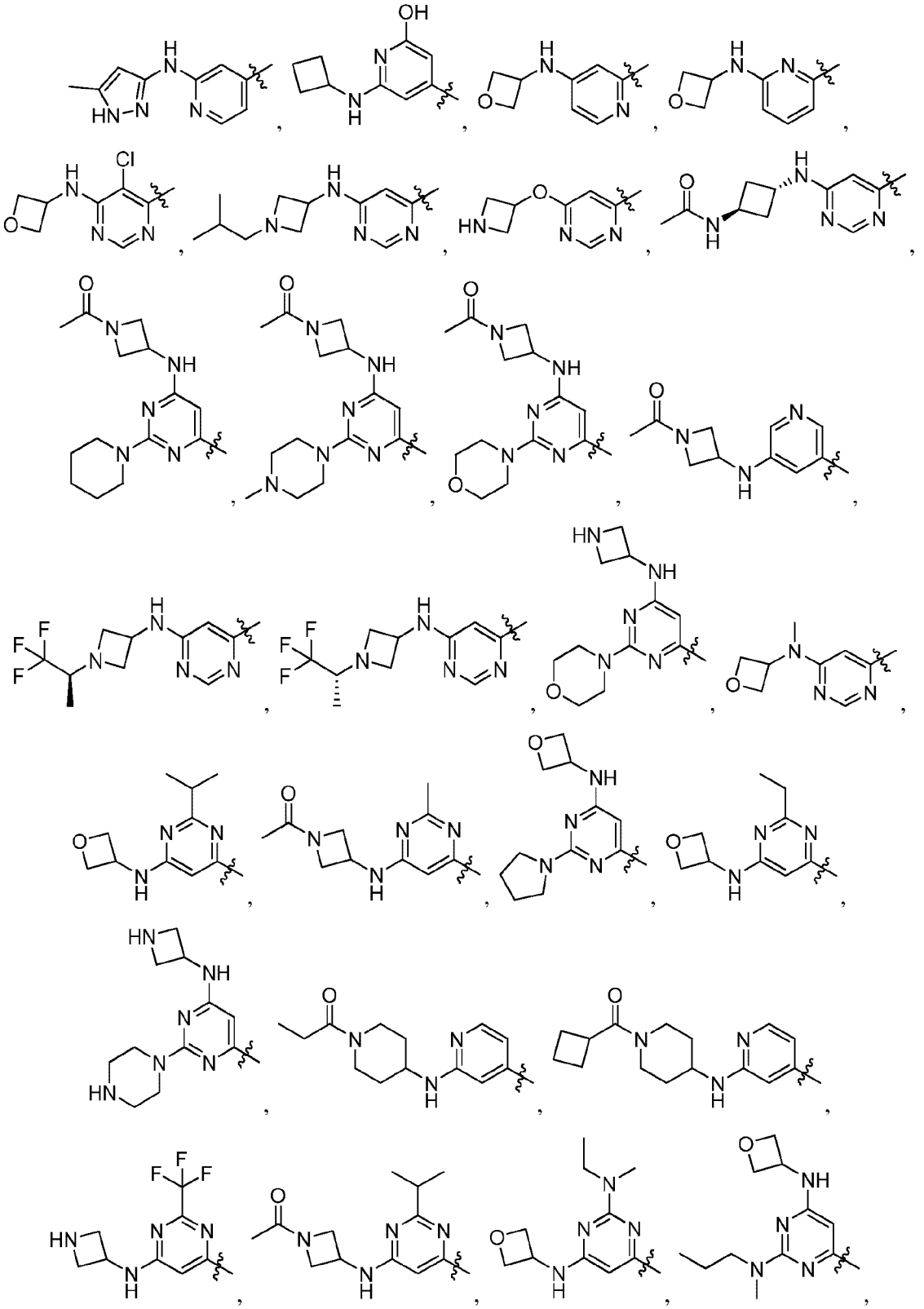
, and

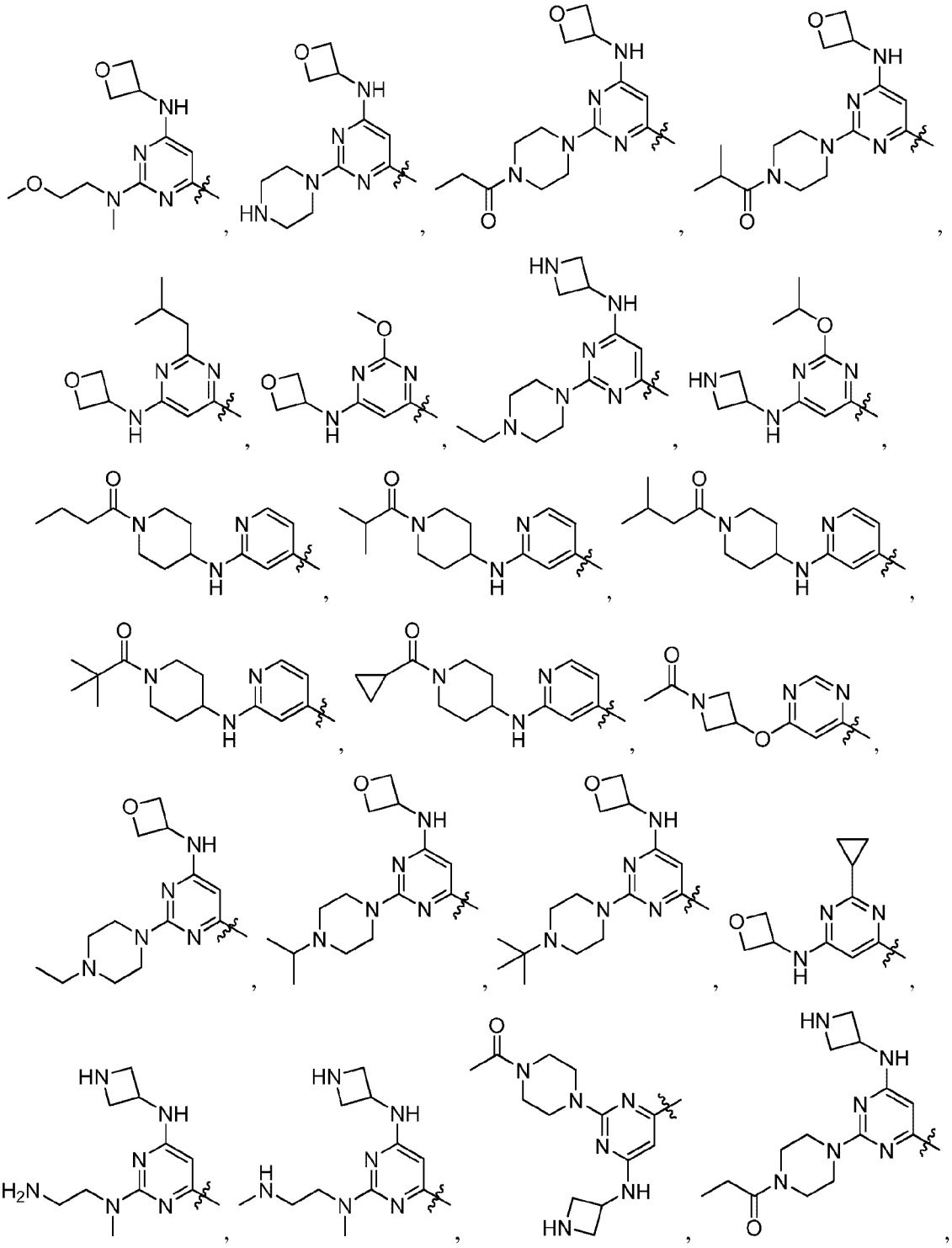
[00182] In certain embodiments, Ar is selected from the group consisting of:

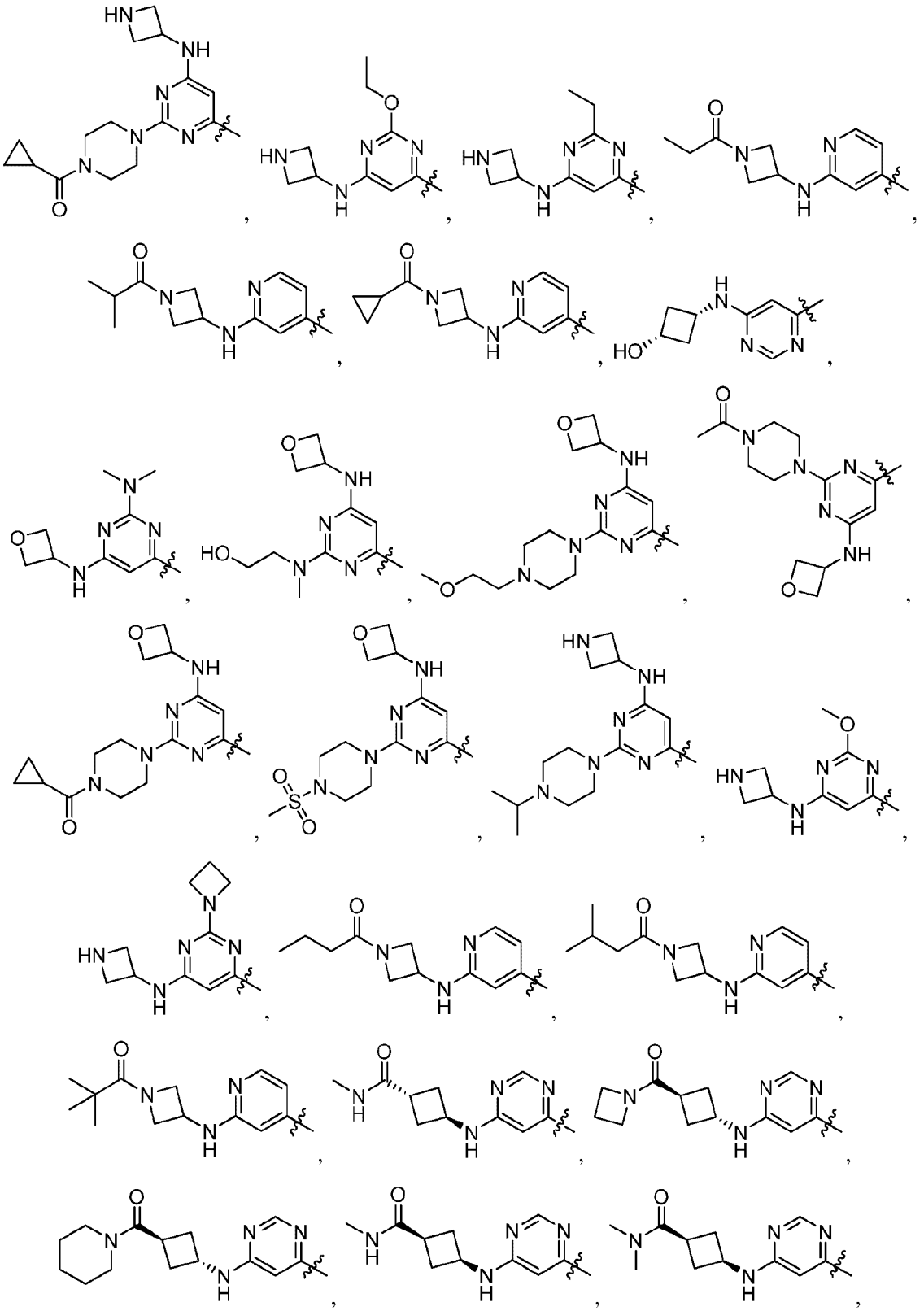


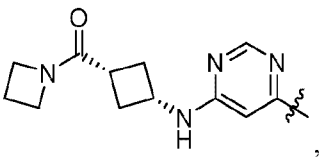








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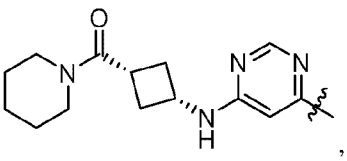
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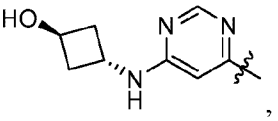
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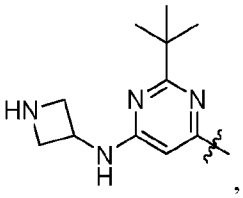
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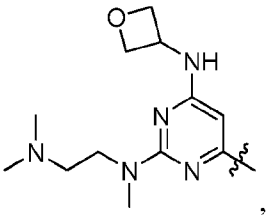
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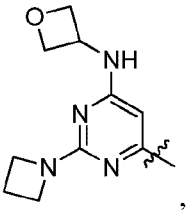
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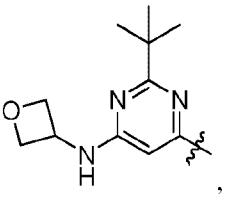
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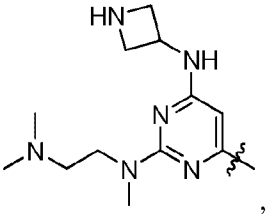
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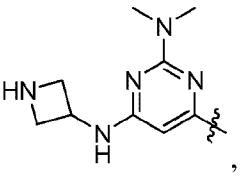
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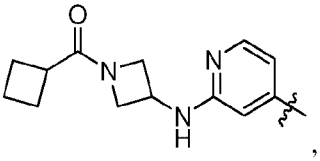
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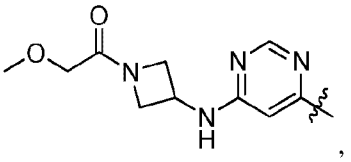
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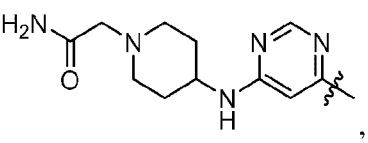
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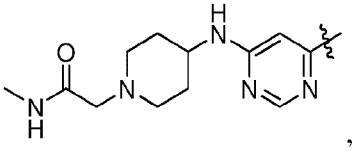
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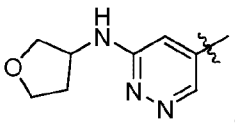
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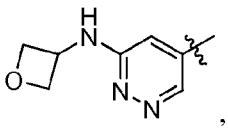
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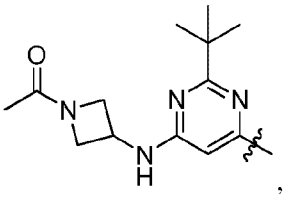
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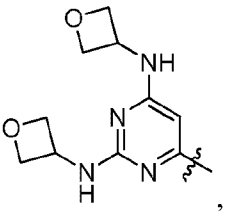
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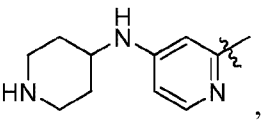
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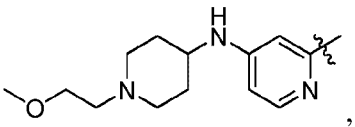
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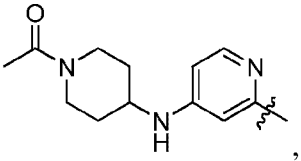
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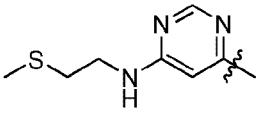
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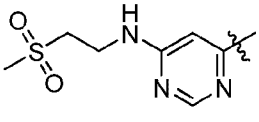
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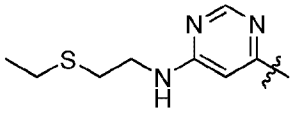
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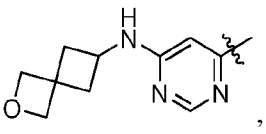
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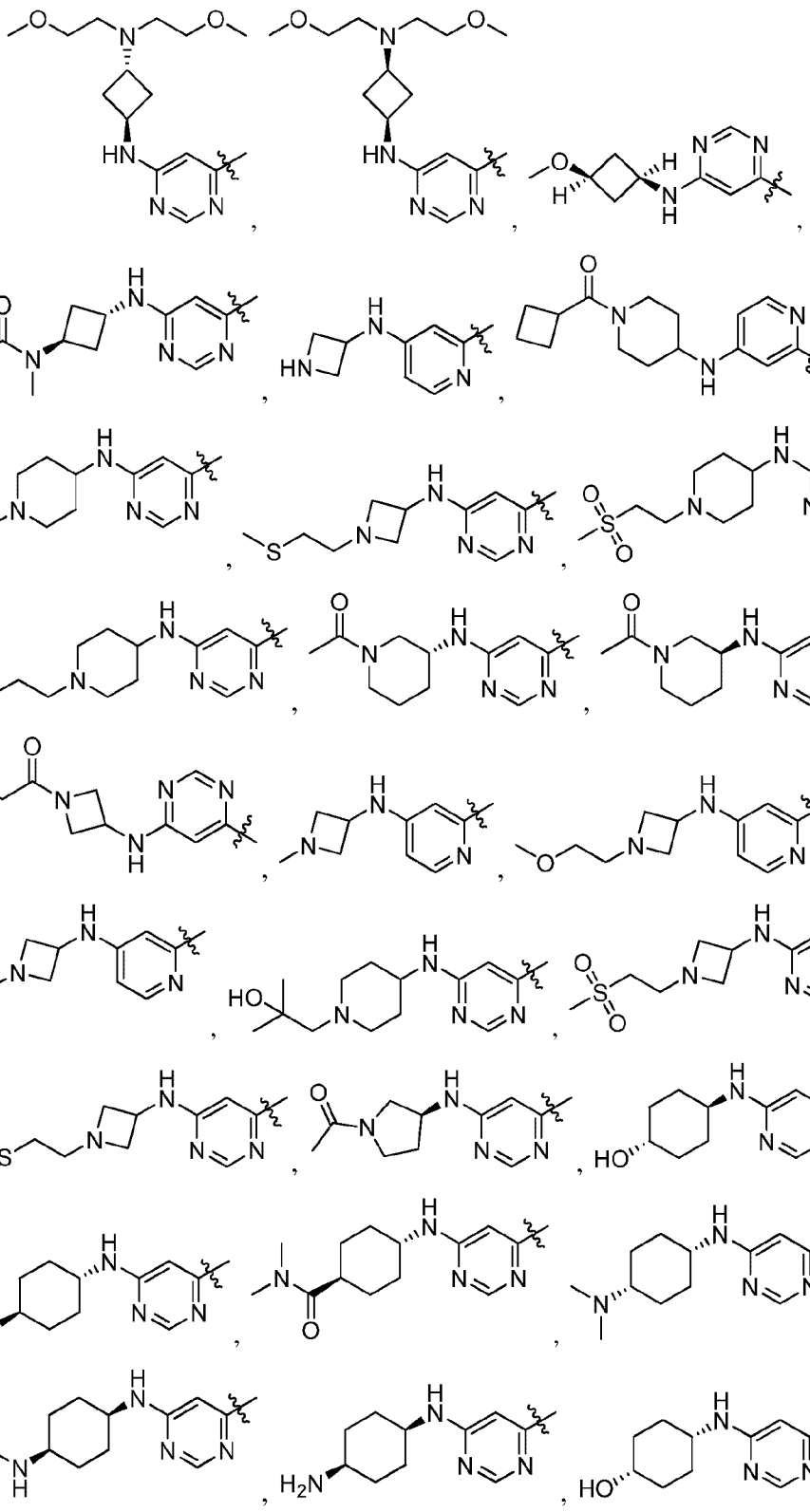

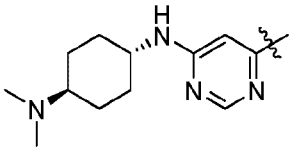
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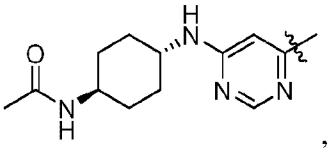
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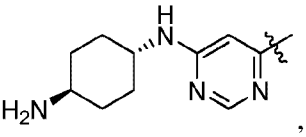
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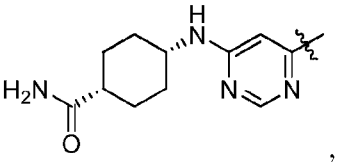
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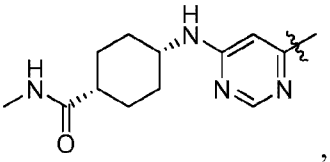
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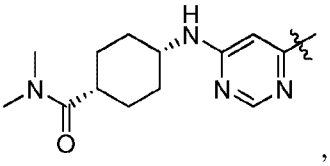
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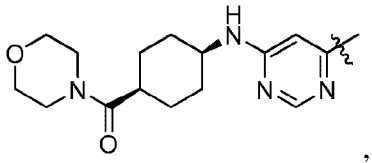
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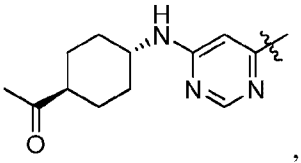
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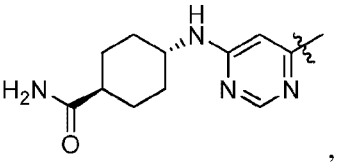
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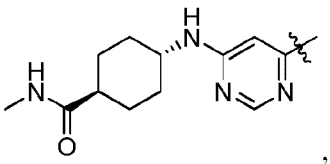
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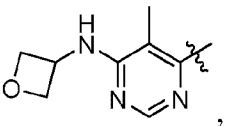
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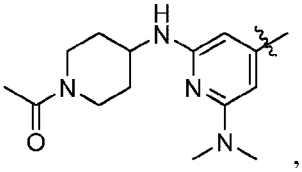
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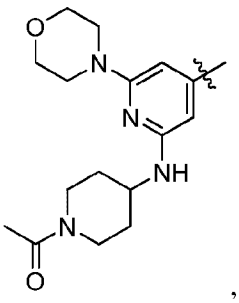
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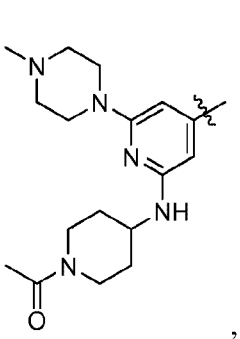
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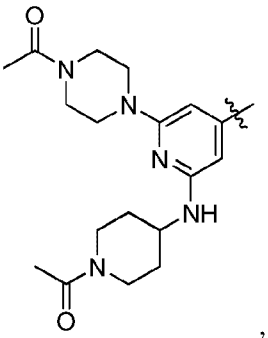
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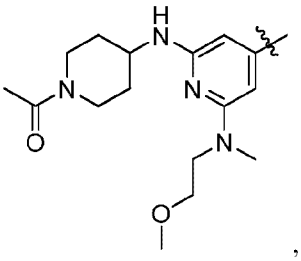
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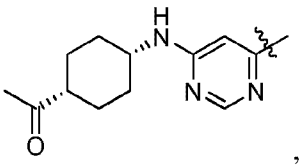
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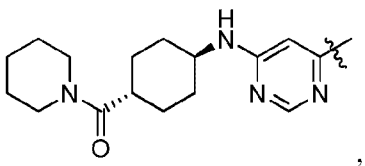
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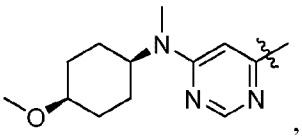
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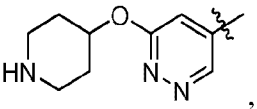
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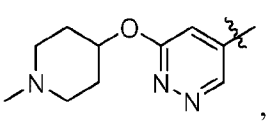
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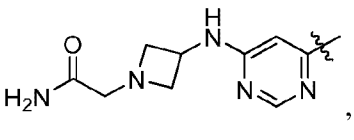
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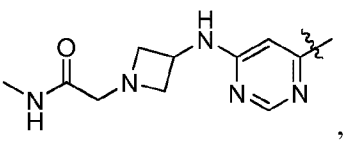
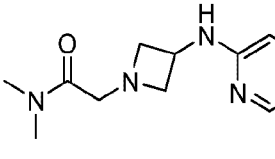

,

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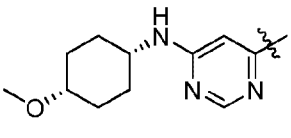
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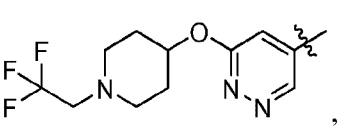
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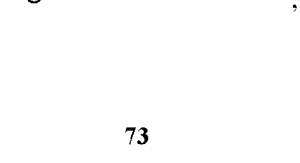
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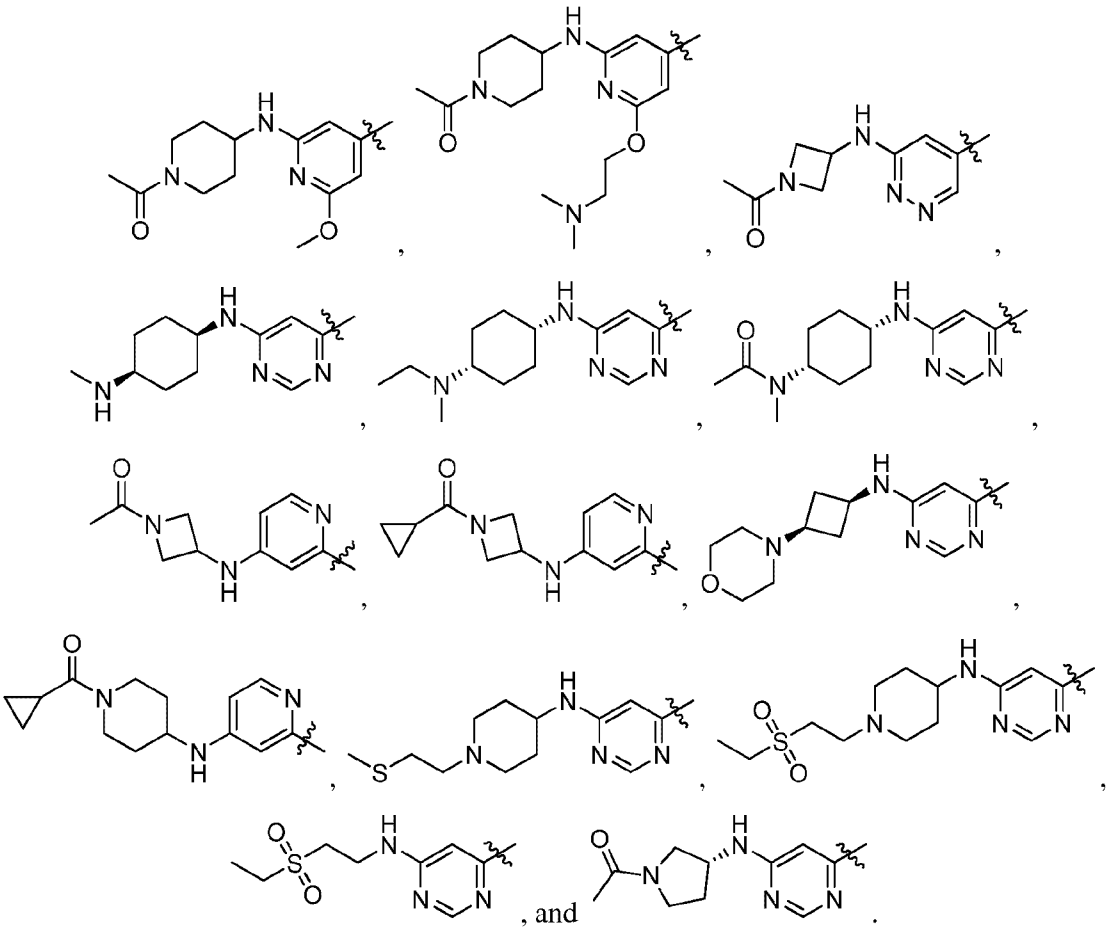
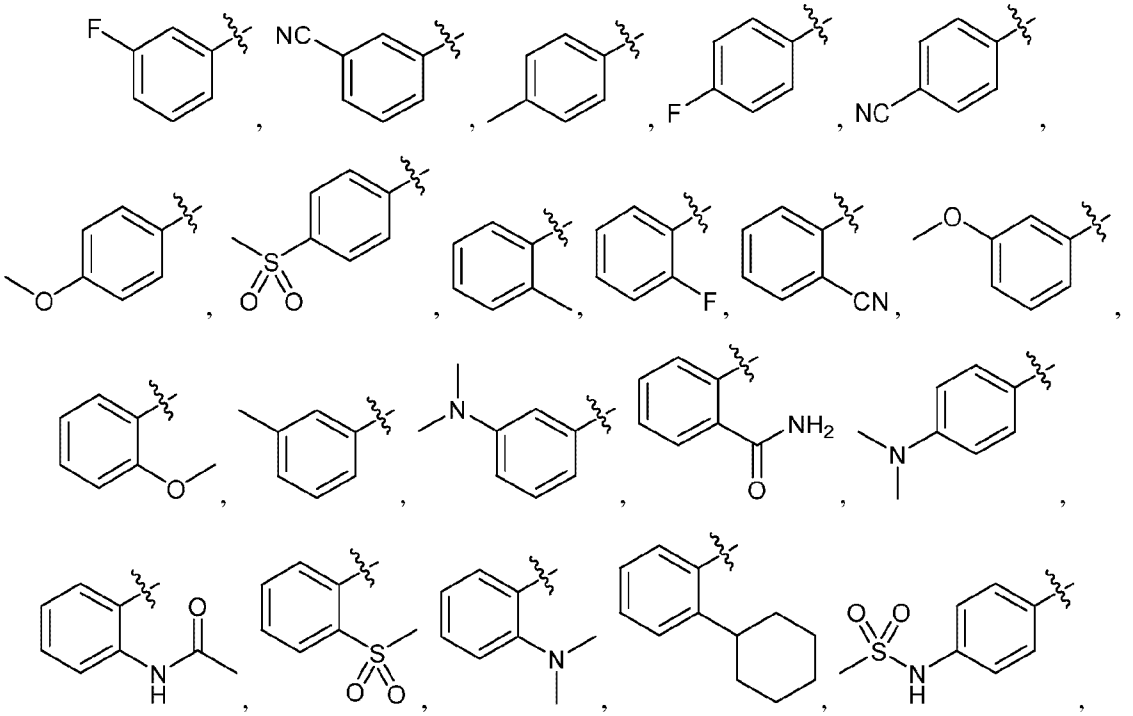
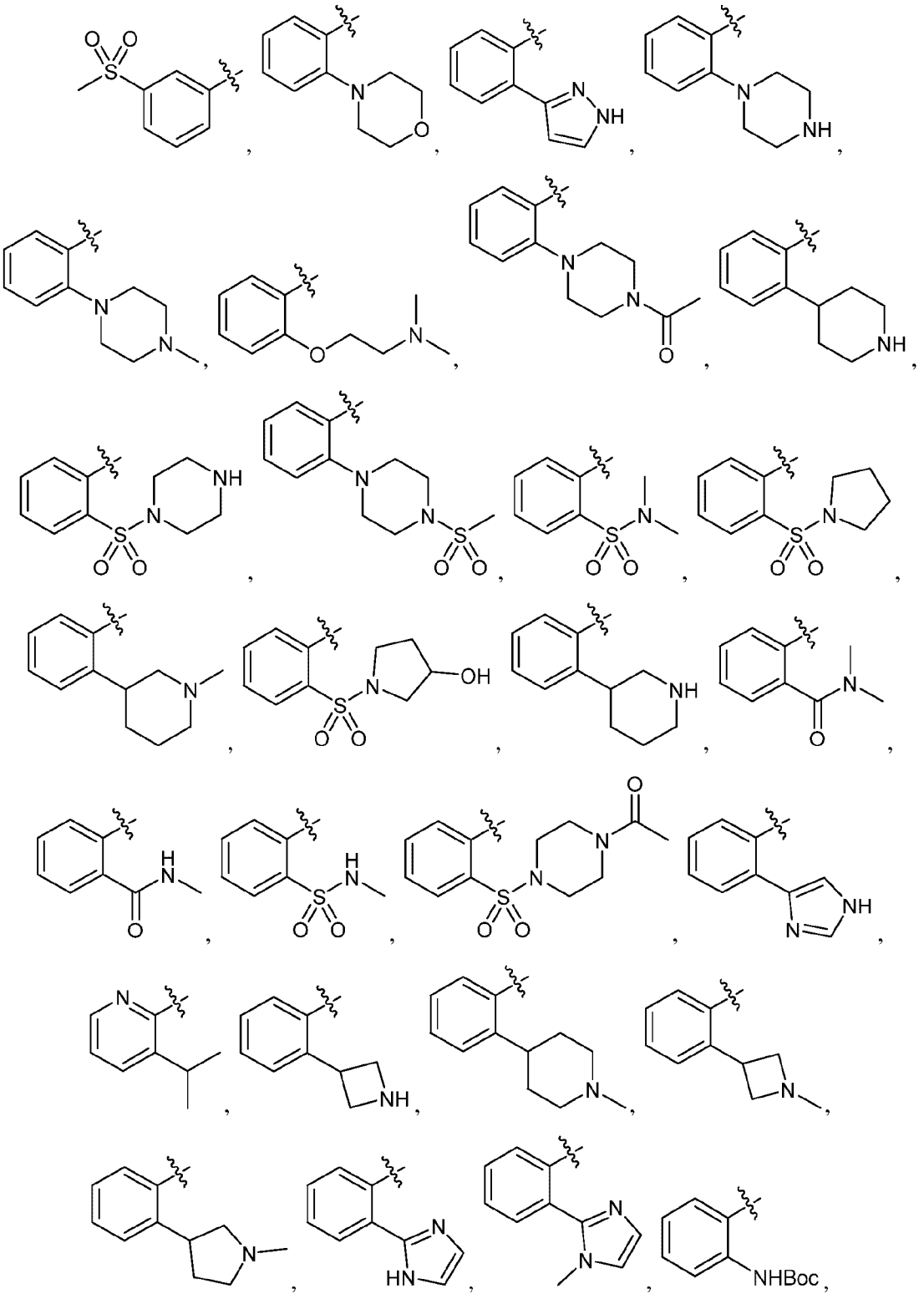
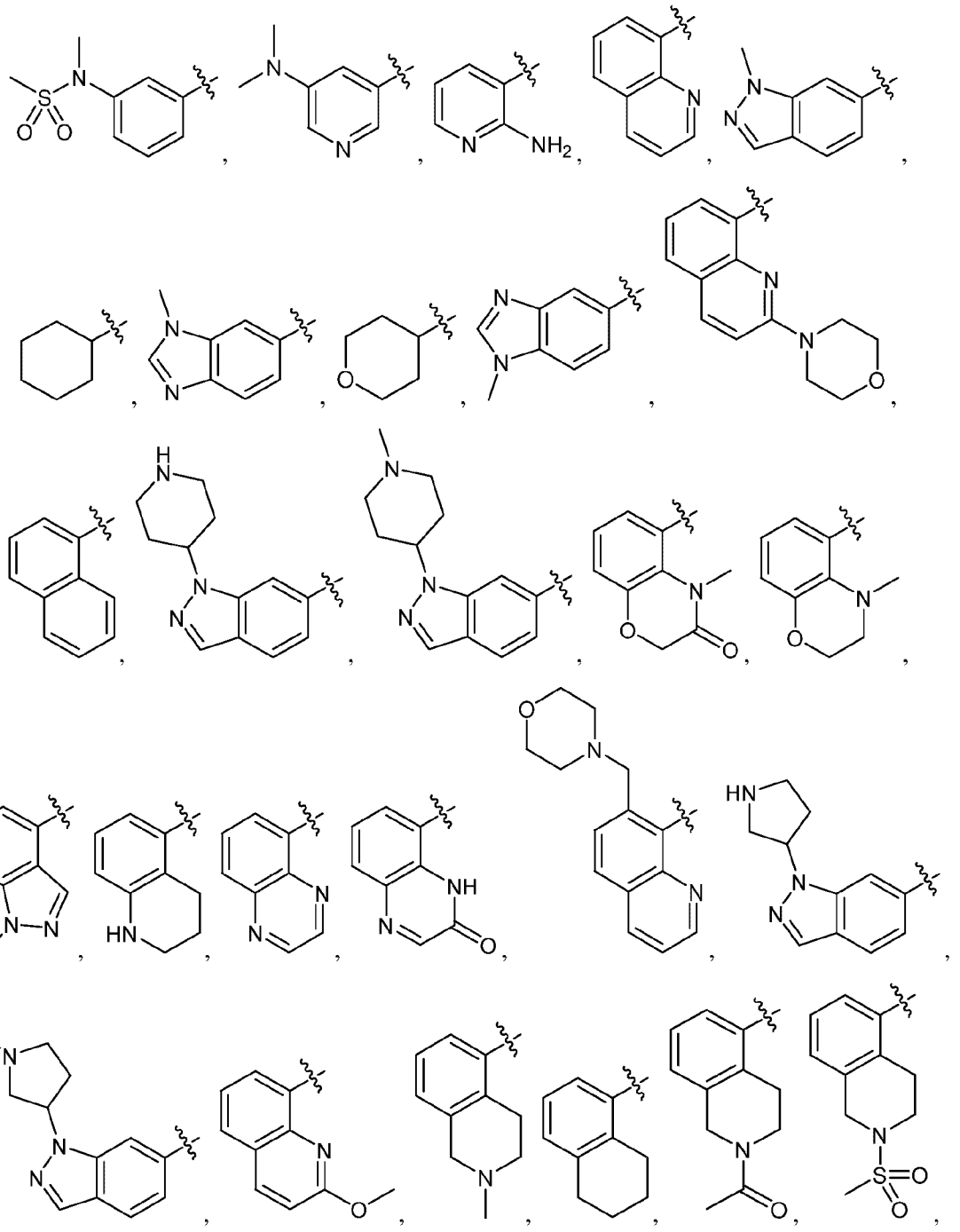
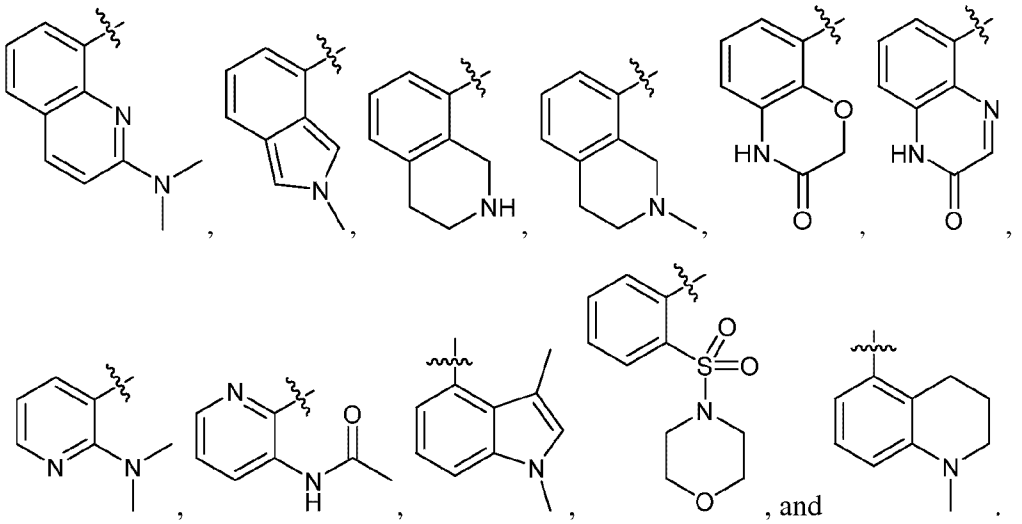


[00183] In certain embodiments, Ar is selected from the group consisting of:

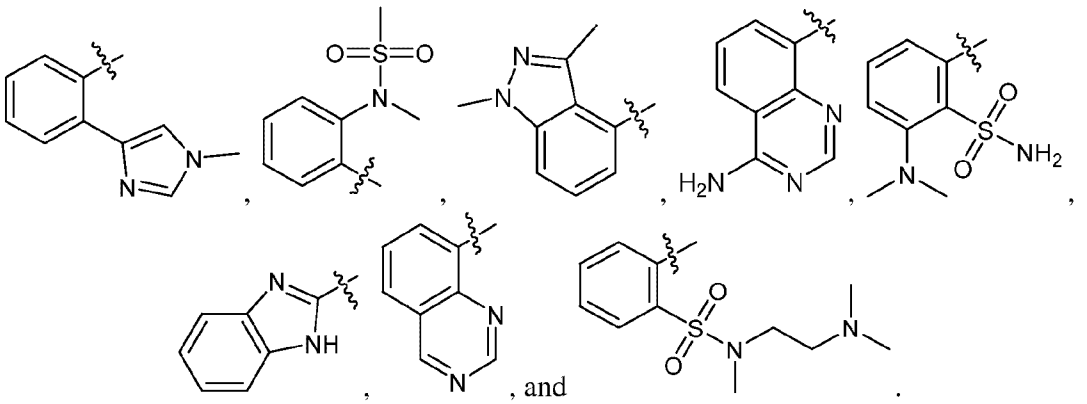




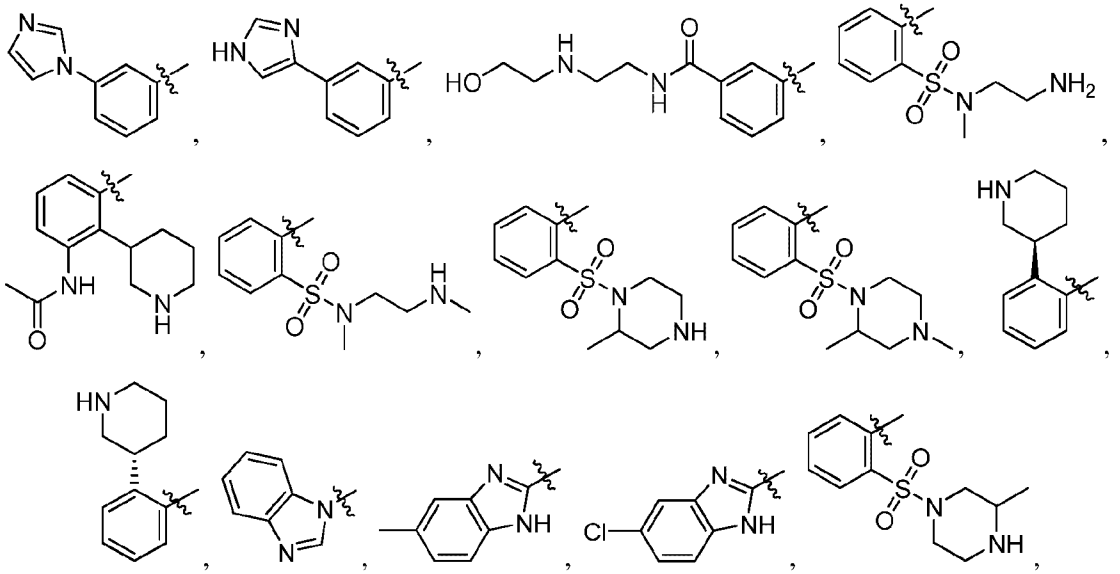


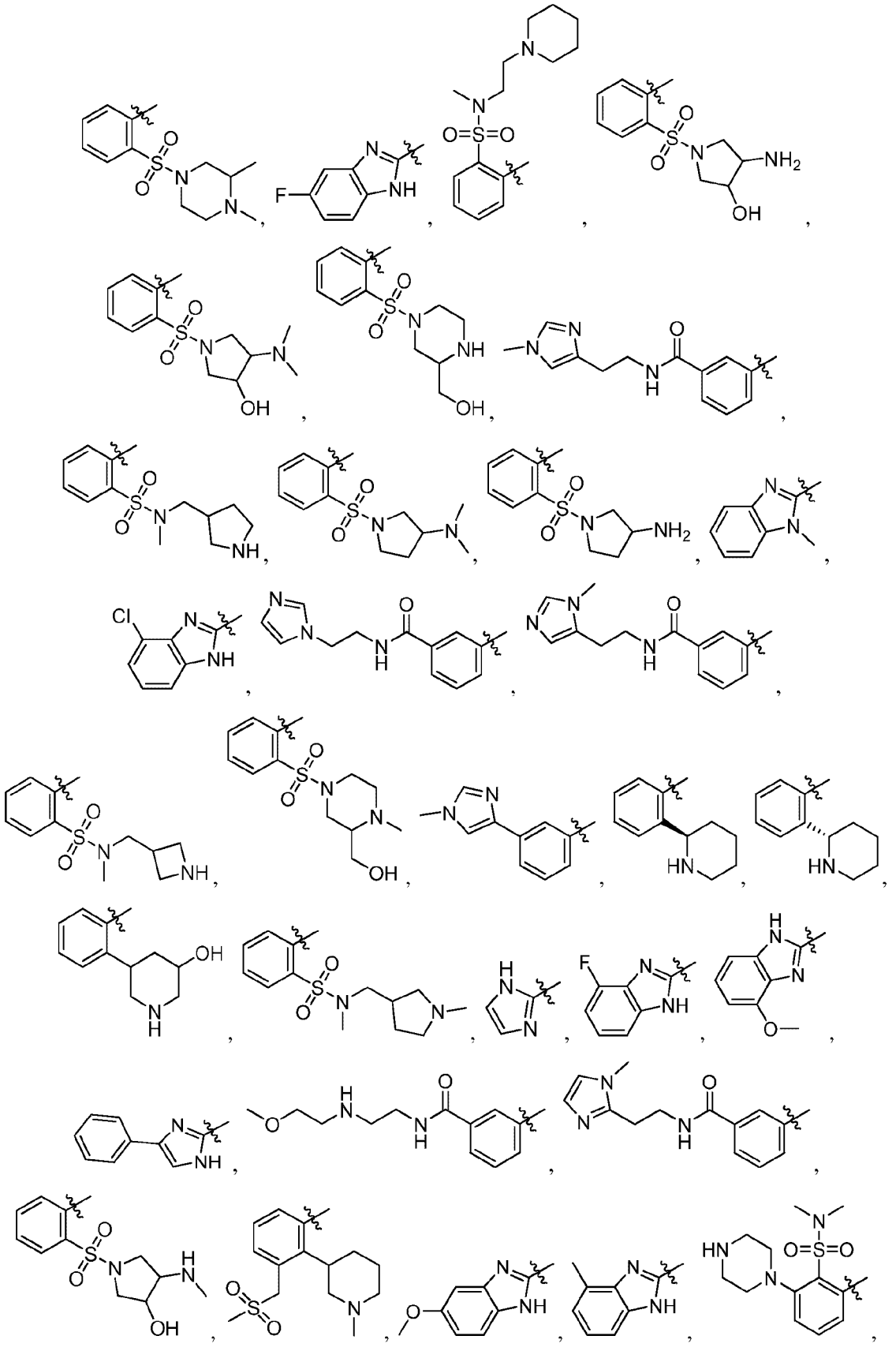


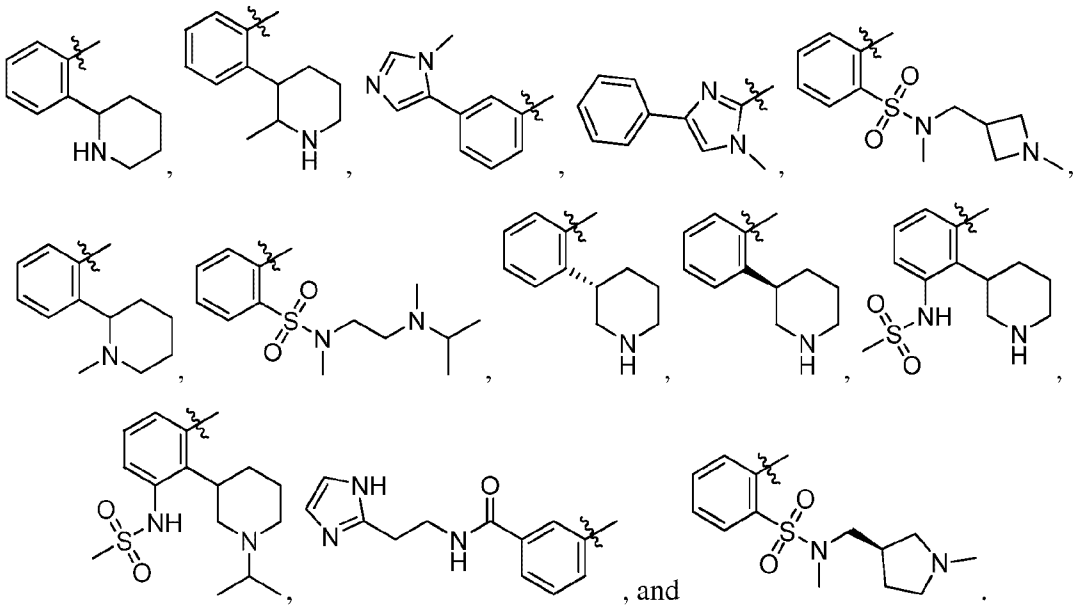
[00184] In some embodiments, Ar is selected from the group consisting of:



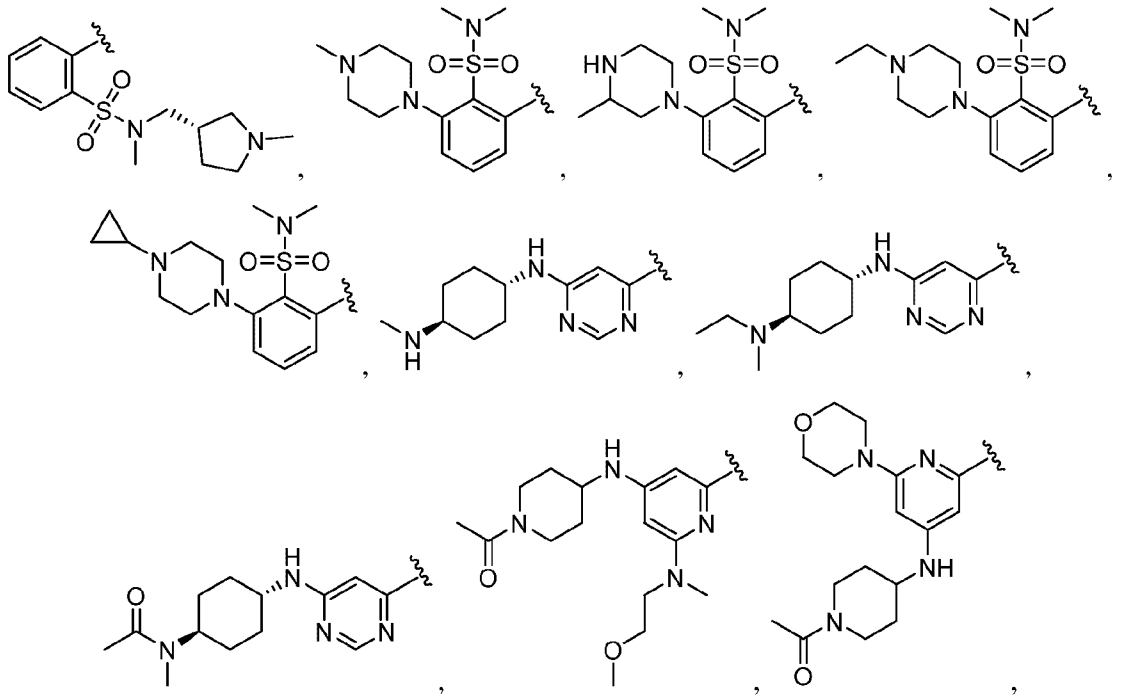
[00185] In some embodiments, Ar is selected from the group consisting of:

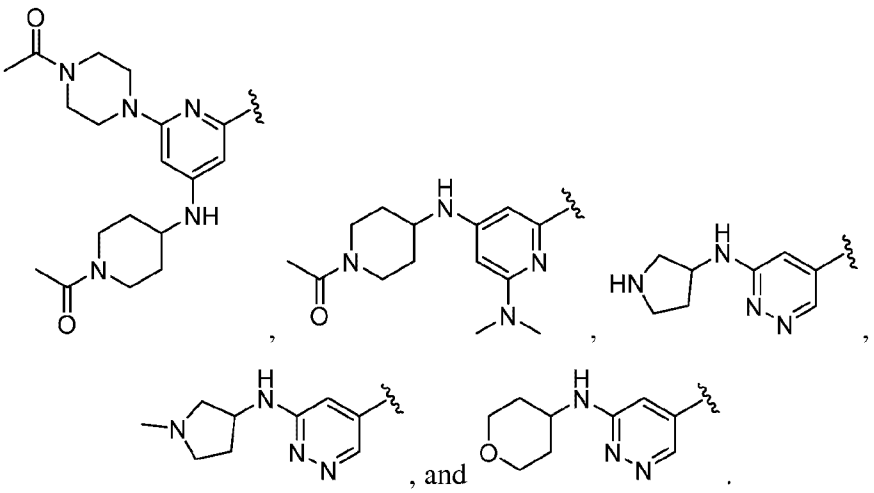




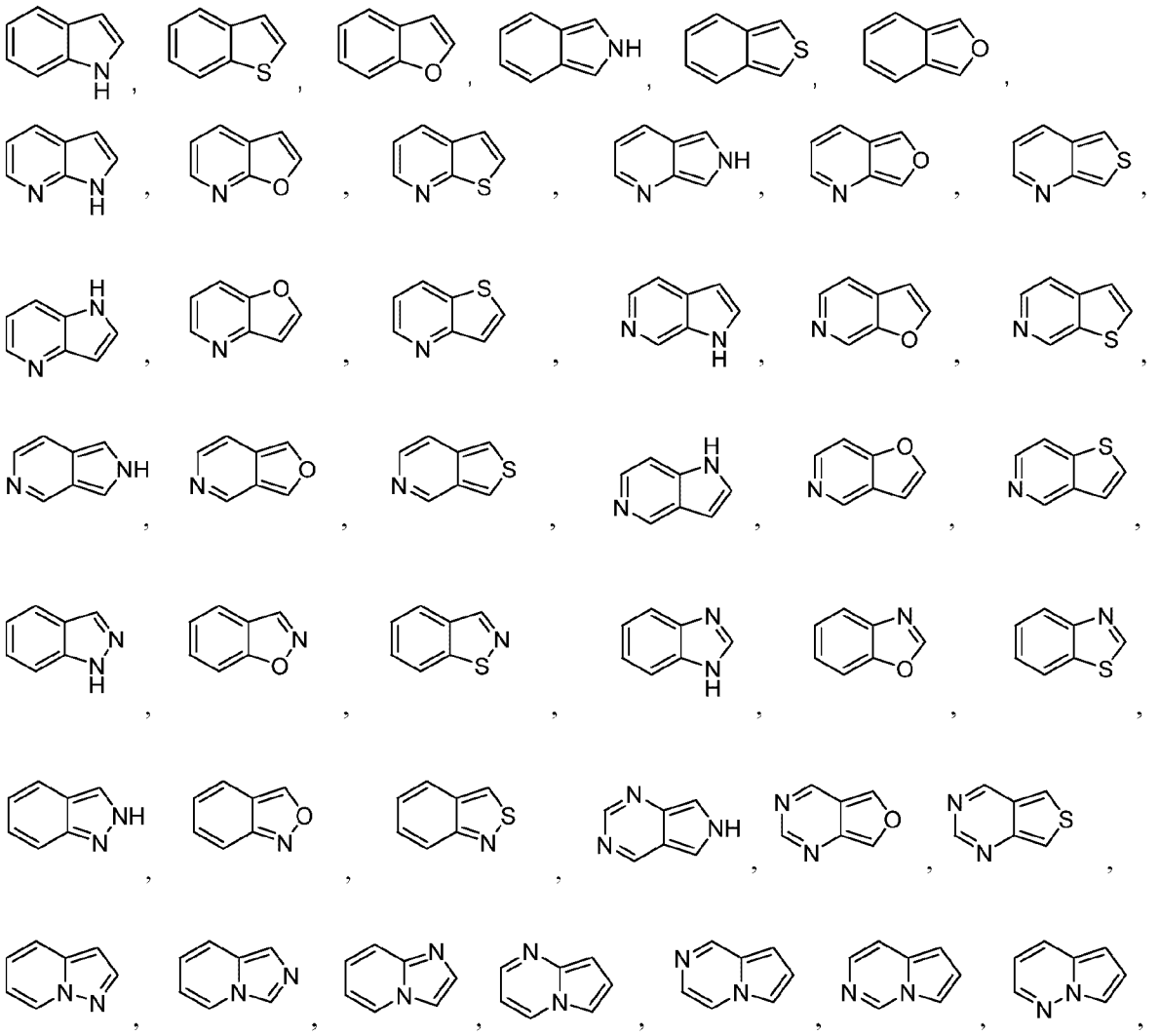


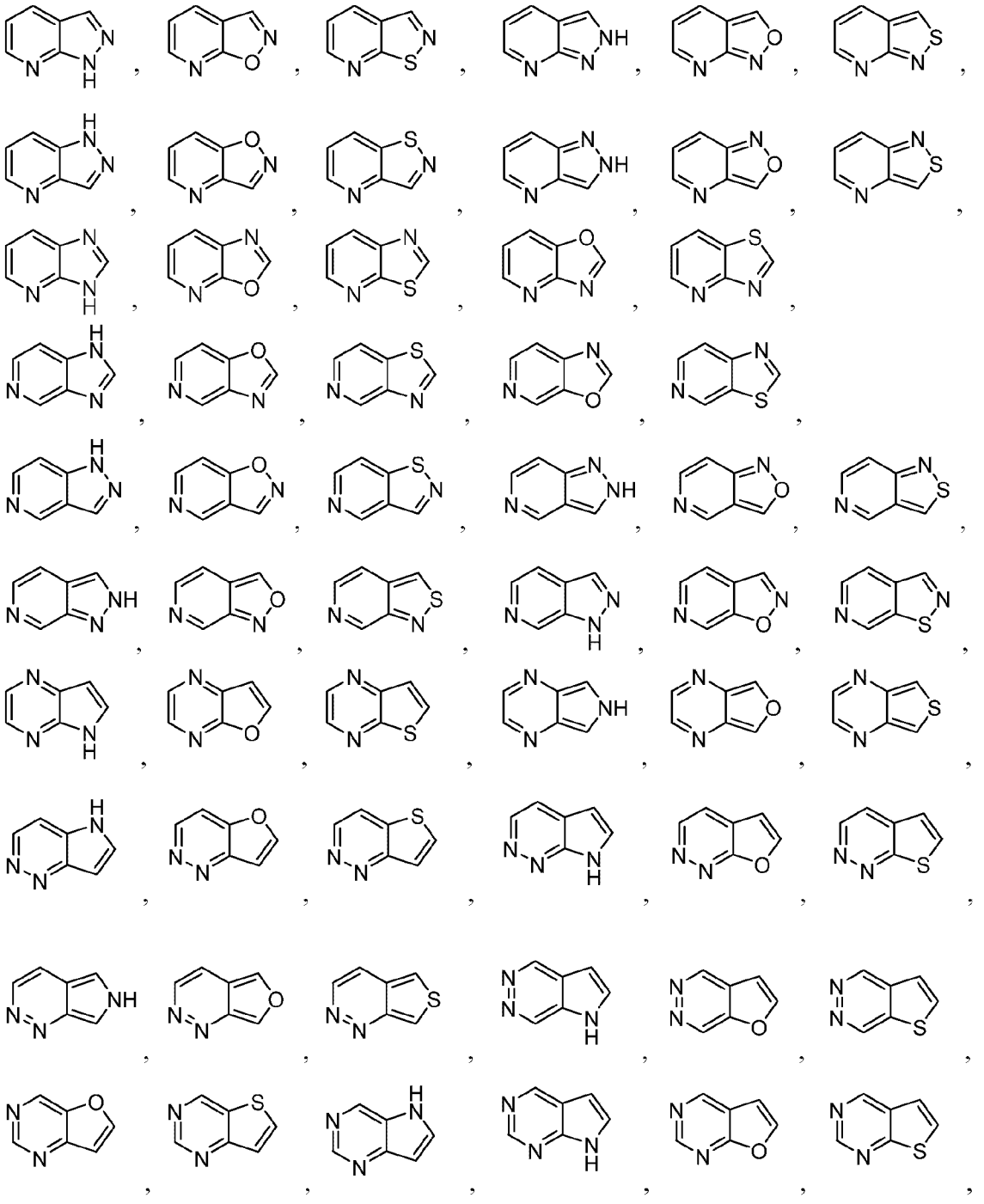
[00186] In certain embodiments, Ar is selected from the group consisting of:

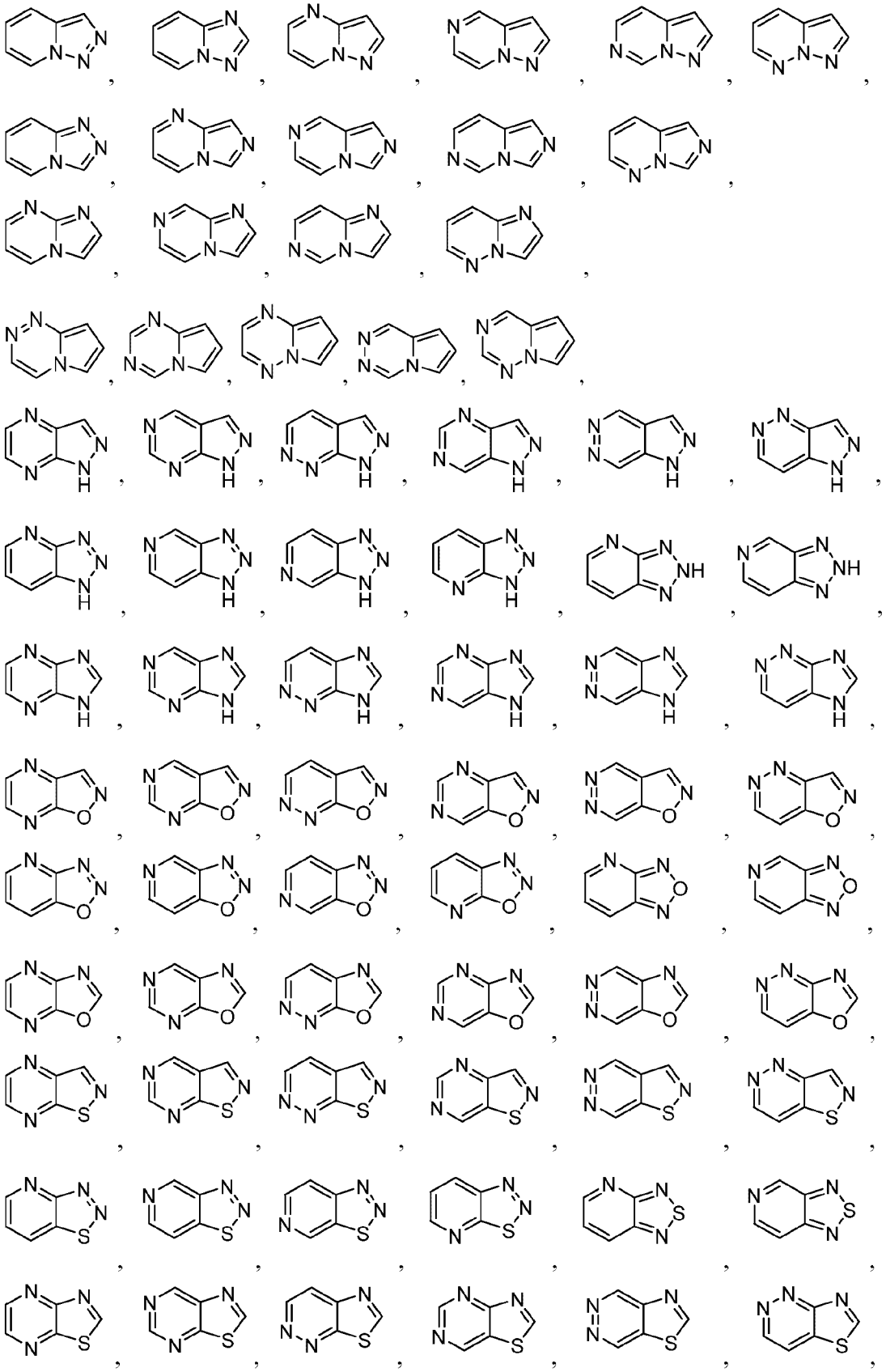


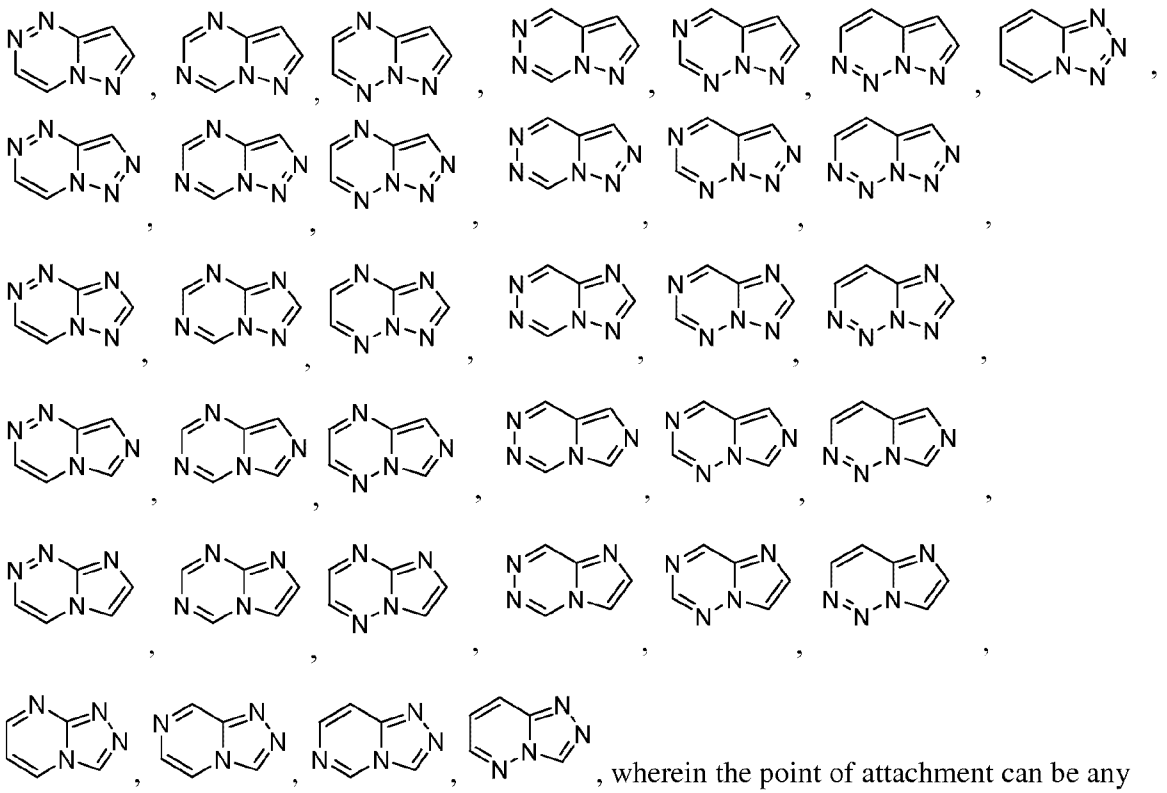


[00187] In certain embodiments, Ar is a 5,6-fused bicyclic heteroaryl ring system such as one of the following:



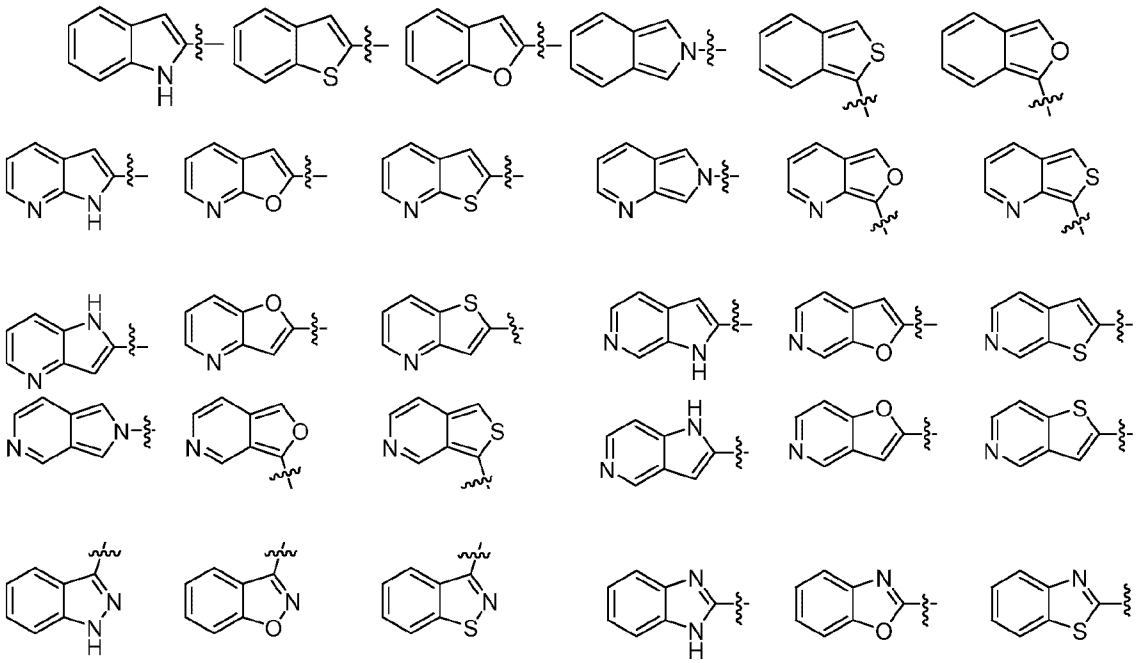


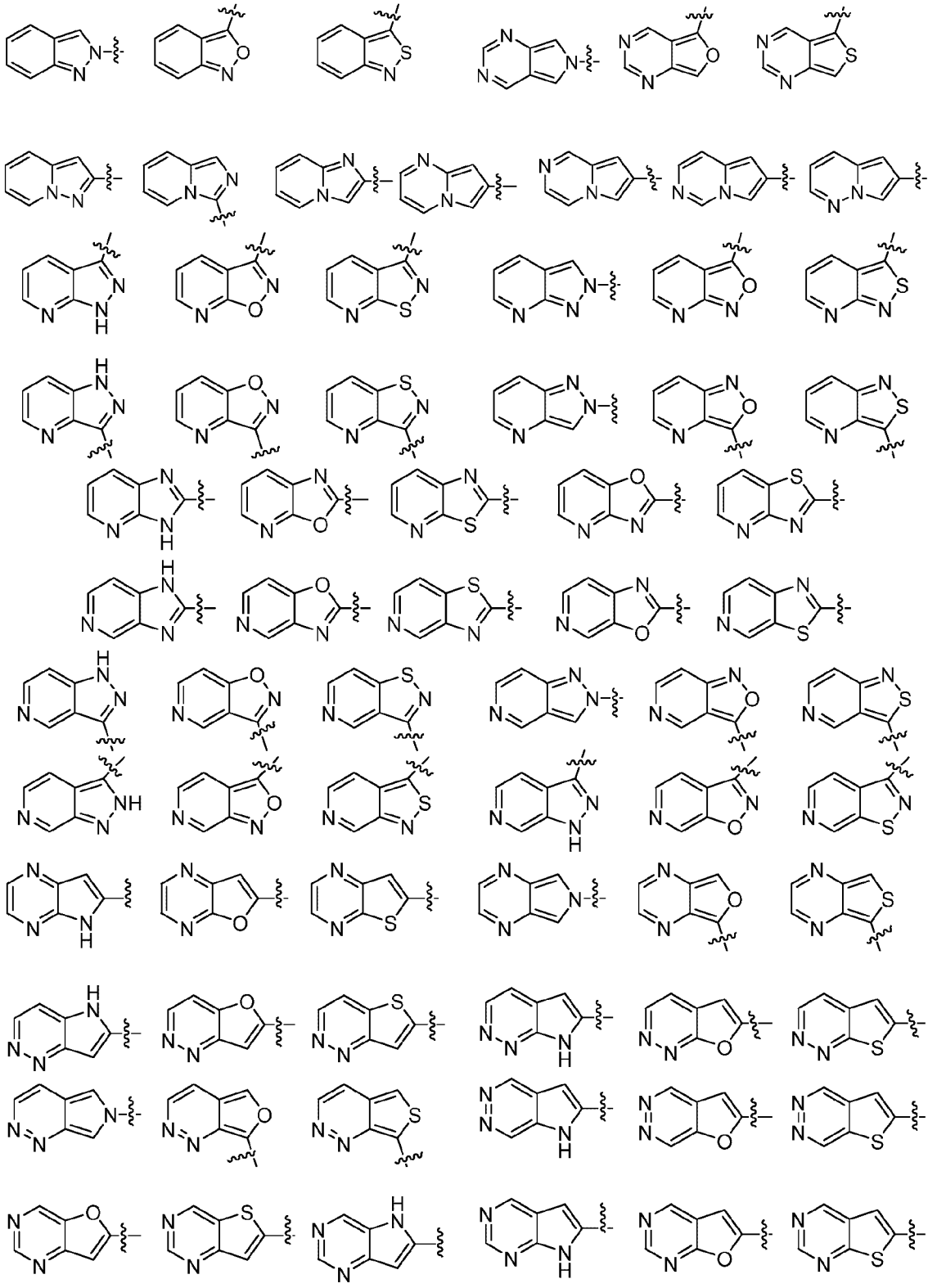


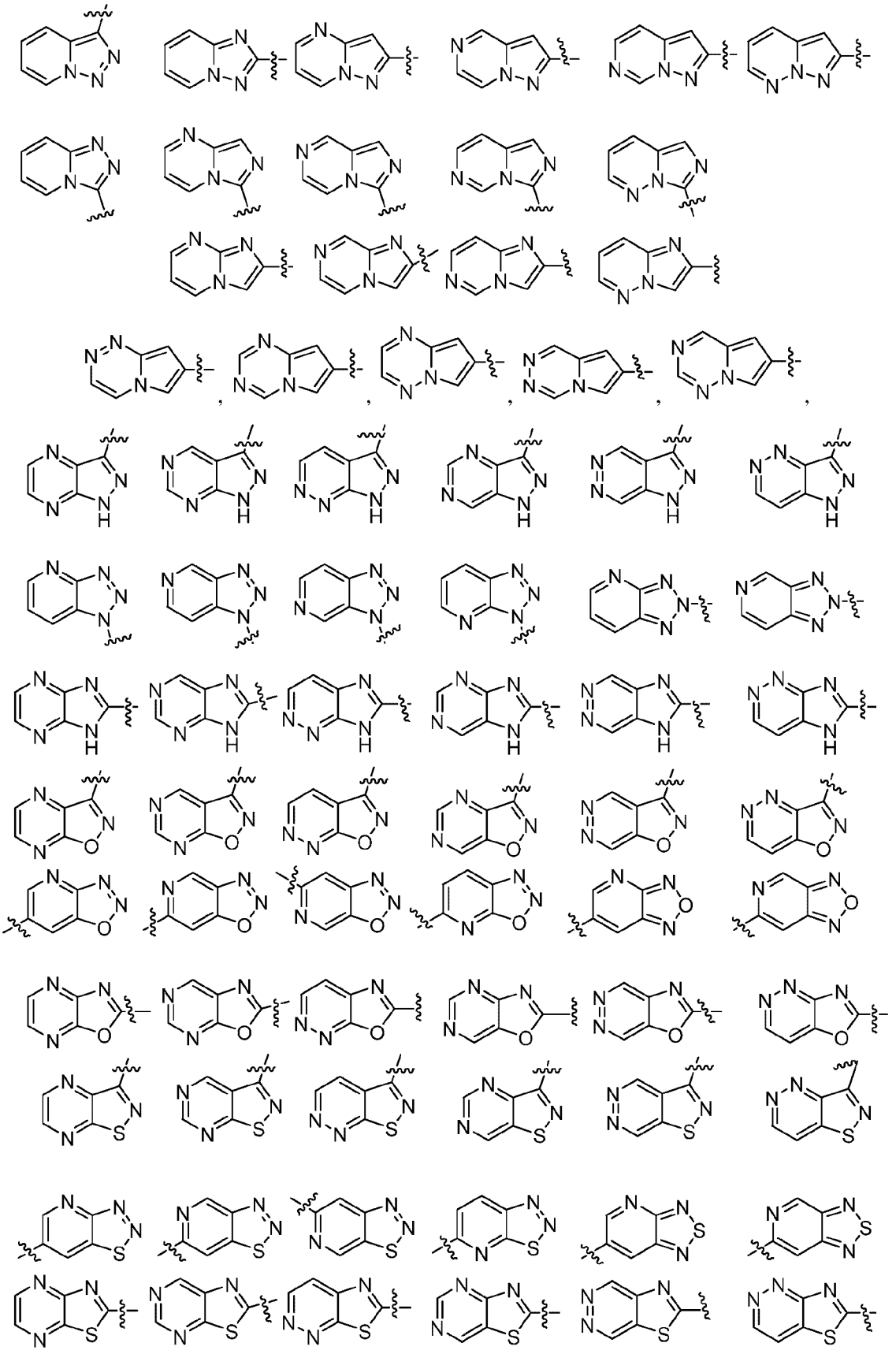


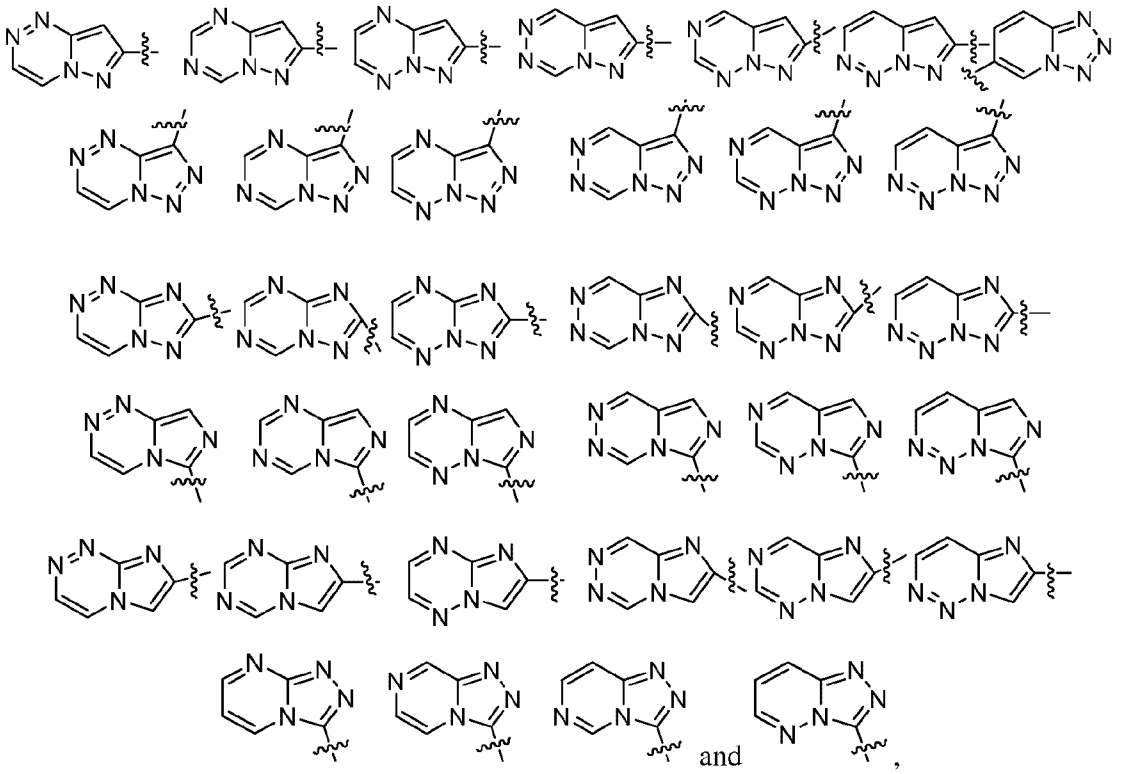
, wherein the point of attachment can be any carbon or nitrogen atom, as valency permits, and the ring may be substituted with 0, 1, 2, 3, 4, or 5 R^y groups, as valency permits.

[00188] In some embodiments, Ar is selected from the group consisting of:



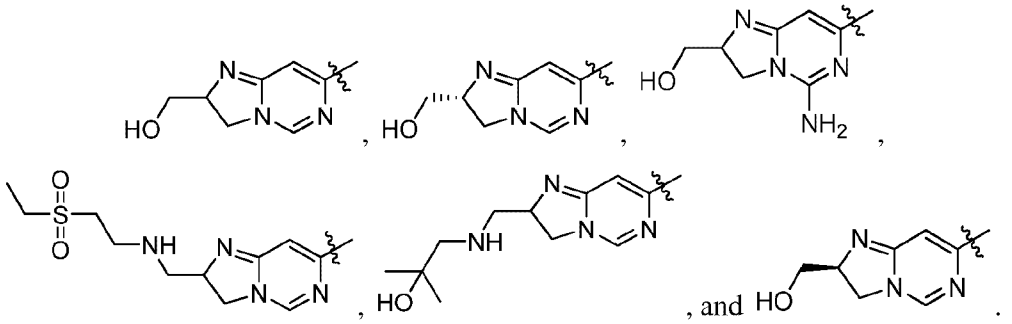




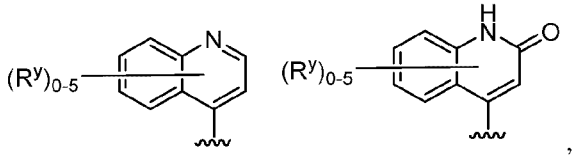


each of which may be optionally substituted with 1, 2, 3, 4, or 5 R^y groups as valency permits.

[00189] In certain embodiments, Ar is an optionally substituted heterocyclyl (*i.e.*, an optionally substituted dihydroimidazo pyrimidinyl) selected from the group consisting of:



[00190] In certain embodiments, Ar is not any one of the following formulae:

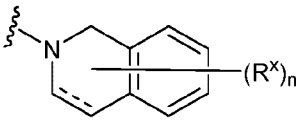


, wherein R^y is as generally defined herein.

[00191] As defined generally above, each R^x is independently selected from the group consisting of halo, -CN, optionally substituted aliphatic, -OR', and -N(R'')$_2$. In certain embodiments, at least one R^x is halo. In certain embodiments, at least one R^x is fluoro. In certain embodiments, at least one R^x is –CN. In certain embodiments, at least one R^x is

optionally substituted aliphatic. In certain embodiments, at least one R^x is optionally substituted C_{1-6} alkyl. In certain embodiments, at least one R^x is methyl. In certain embodiments, at least one R^x is $-CF_3$. In certain embodiments, at least one R^x is -OR' or -$N(R'')_2$. In certain embodiments, R^x is not -OR' or -$N(R'')_2$. In certain embodiments, at least one R^x is $-OCH_3$. In certain embodiments, R^x is not $-OCH_3$.

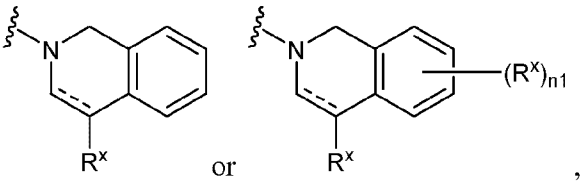
[00192] As is generally understood from the above disclosure, the ring system:



is a fused bicyclic ring system, *i.e.*, a phenyl ring fused to a nitrogen containing ring, wherein the point of attachment to the parent moiety is on the nitrogen, and wherein the fused bicyclic system is optionally substituted with $(R^x)_n$, wherein n and R^x are as defined herein. As is generally understood, each of the atoms of the phenyl ring and the nitrogen-containing ring can be independently optionally substituted with R^x, as valency permits.

[00193] In certain embodiments, the fused bicyclic ring system is optionally substituted with one or more R^x, with the proviso that when the nitrogen-containing ring is substituted at one of the positions alpha to the nitrogen, R^x is not–$C(=O)R^{x1}$, wherein R^{x1} is optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, -OR^A, -$N(R^B)_2$, or -SR^A, wherein R^A and R^B are as generally defined herein.. In certain embodiments, the nitrogen-containing ring does not comprise an R^x substituent. In certain embodiments, only atoms of the phenyl ring are optionally substituted with one or more R^x.

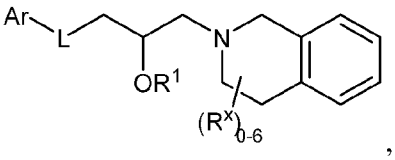
[00194] In certain embodiments, the nitrogen-containing ring is optionally substituted, and the fused bicyclic ring system is of the formula:



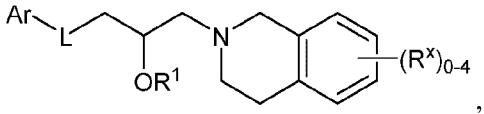
wherein R^x is as defined herein, and n1 is 0, 1, 2, 3, or 4.

[00195] Thus, one of ordinary skill in the art will appreciate that an R^x group can be attached anywhere on the tetrahydroisoquinoline or dihydroisoquinoline ring. In certain embodiments, an R^x group is attached to the phenyl of the tetrahydroisoquinoline or dihydroisoquinoline ring. In certain embodiments, an R^x group is attached to the

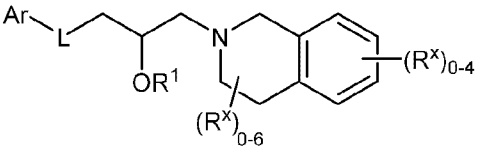
tetrahydropyridine or dihydropyridine portion of the tetrahydroisoquinoline or dihydroisoquinoline ring. In certain embodiments, R^x groups are attached to both the phenyl portion and the tetrahydropyridine (or dihydropyridine) portion of the tetrahydroisoquinoline (or dihydroisoquinoline) ring. See, for example, the structures shown below:



,

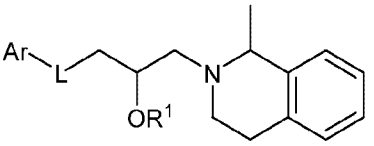


, and



.

[00196] In certain embodiments, a provided compound is of Formula (**XIV**):

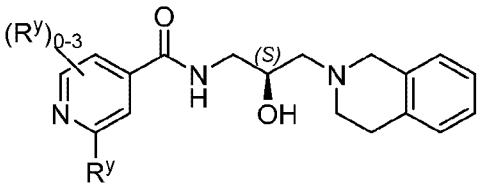


XIV

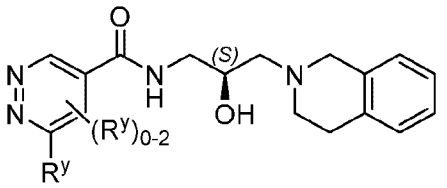
or a pharmaceutically acceptable salt thereof.

[00197] As defined generally above, n is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10. In certain embodiments, n is 0. In certain embodiments, n is 1. In certain embodiments, n is 2.

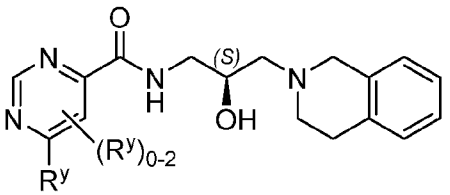
[00198] In certain embodiments, a provided compound is of Formula (**XV**), (**XVI**), (**XVII**), or (**XVIII**):



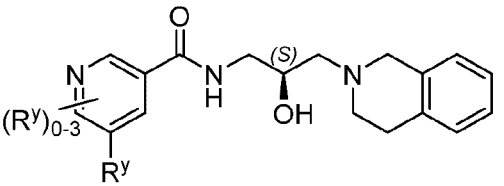
XV



XVI



XVII

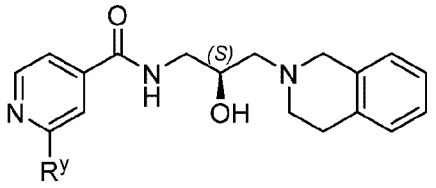


XVIII

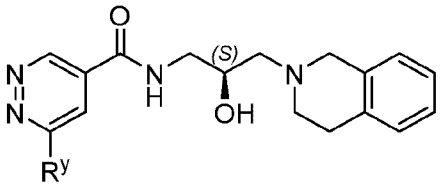
or a pharmaceutically acceptable salt thereof, wherein each R^y for Formula (**XV**), (**XVI**), (**XVII**), or (**XVIII**) is independently as described herein.

[00199] In some embodiments of Formula (**XV**), (**XVI**), (**XVII**), or (**XVIII**), it is understood that when the nitrogen-containing heteroaryl moiety has only one substituent R^y, R^y is not halo (e.g., F or Cl) or optionally substituted alkyl. In some embodiments of Formula (**XV**), (**XVI**), (**XVII**), or (**XVIII**), when the nitrogen-containing heteroaryl moiety has only one substituent R^y, R^y is not halo (e.g., F or Cl) or C_{1-3} alkyl (e.g. methyl, ethyl, n-propyl, or iso-propyl). In some embodiments of Formula (**XV**), (**XVI**), (**XVII**), or (**XVIII**), when the nitrogen-containing heteroaryl has only one substituent R^y, R^y is $-N(R^B)_2$, wherein R^B is as generally defined herein. In some embodiments of Formula (**XV**), (**XVI**), (**XVII**), or (**XVIII**), when the nitrogen-containing heteroaryl has only one substituent R^y, R^y is $-N(R^B)_2$, and at least one R^B is optionally substituted heterocyclyl. In some embodiments of Formula (**XV**), (**XVI**), (**XVII**), or (**XVIII**), when the nitrogen-containing heteroaryl has only one substituent R^y, R^y is $-NHR^B$, wherein R^B is as generally defined herein. In some embodiments of Formula (**XV**), (**XVI**), (**XVII**), or (**XVIII**), when the nitrogen-containing heteroaryl has only one substituent R^y, R^y is $-NHR^B$, wherein R^B is optionally substituted heterocyclyl.

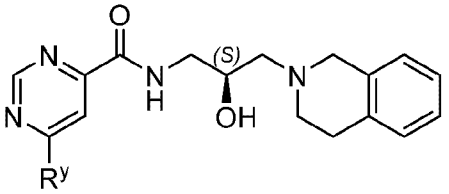
[00200] In certain embodiments, a provided compound is of Formula (**XV-a**), (**XVI-a**), (**XVII-a**), or (**XVIII-a**):



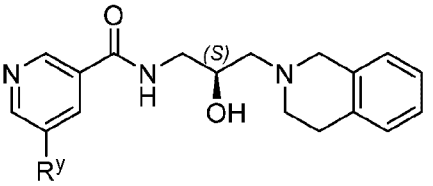
XV-a



XVI-a



XVII-a



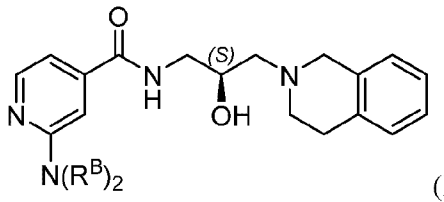
XVIII-a

or a pharmaceutically acceptable salt thereof, wherein R^y for Formula (**XV-a**), (**XVI-a**), (**XVII-a**), or (**XVIII-a**) is as generally described herein. In some embodiments, *e.g.* for Formula (**XV-a**), (**XVI-a**), (**XVII-a**), or (**XVIII-a**), R^y is $-OR^A$, wherein R^A is optionally

substituted alkyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl. In some embodiments, *e.g.* for Formula (**XV-a**), (**XVI-a**), (**XVII-a**), or (**XVIII-a**), R^y is $-OR^A$, wherein R^A is -(optionally substituted alkyl)-(optionally substituted carbocyclyl), -(optionally substituted alkyl)-(optionally substituted heterocyclyl), or -(optionally substituted alkyl)-(optionally substituted heteroaryl). In some embodiments, *e.g.* for Formula (**XV-a**), (**XVI-a**), (**XVII-a**), or (**XVIII-a**), R^y is $-OR^A$, wherein R^A is optionally substituted heterocyclyl. In some embodiments, *e.g.* for Formula (**XV-a**), (**XVI-a**), (**XVII-a**), or (**XVIII-a**), R^y is $-OR^A$, wherein R^A is optionally substituted heteroaryl. In some embodiments, *e.g.* for Formula (**XV-a**), (**XVI-a**), (**XVII-a**), or (**XVIII-a**), R^y is $-OR^A$, wherein R^A is optionally substituted carbocyclyl. In some embodiments, *e.g.* for Formula (**XV-a**), (**XVI-a**), (**XVII-a**), or (**XVIII-a**), R^y is $-N(R^B)_2$, wherein R^B is hydrogen, optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl. In some embodiments, *e.g.* for Formula (**XV-a**), (**XVI-a**), (**XVII-a**), or (**XVIII-a**), R^y is $-NHR^B$. In some embodiments, *e.g.* for Formula (**XV-a**), (**XVI-a**), (**XVII-a**), or (**XVIII-a**), R^y is $-NHR^B$, wherein R^B is optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl. In some embodiments, *e.g.* for Formula (**XV-a**), (**XVI-a**), (**XVII-a**), or (**XVIII-a**), R^y is $-NHR^B$, wherein R^B is -(optionally substituted alkyl)-(optionally substituted carbocyclyl)-, -(optionally substituted alkyl)-(optionally substituted heterocyclyl)-, or -(optionally substituted alkyl)-(optionally substituted heteroaryl)-. In some embodiments, *e.g.* for Formula (**XV-a**), (**XVI-a**), (**XVII-a**), or (**XVIII-a**), R^y is $-NHR^B$, wherein R^B is optionally substituted heterocyclyl. In some embodiments, *e.g.* for Formula (**XV-a**), (**XVI-a**), (**XVII-a**), or (**XVIII-a**), R^y is $-NHR^B$, wherein R^B is optionally substituted heteroaryl. In some embodiments, *e.g.* for Formula (**XV-a**), (**XVI-a**), (**XVII-a**), or (**XVIII-a**), R^y is $-NHR^B$, wherein R^B is optionally substituted cycloalkyl. In some embodiments, *e.g.* for Formula (**XV-a**), (**XVI-a**), (**XVII-a**), or (**XVIII-a**), R^y is $-N(CH_3)R^B$. In some embodiments, *e.g.* for Formula (**XV-a**), (**XVI-a**), (**XVII-a**), or (**XVIII-a**), R^y is $-N(CH_3)R^B$, wherein R^B is optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl. In some embodiments, *e.g.* for Formula (**XV-a**), (**XVI-a**), (**XVII-a**), or (**XVIII-a**), R^y is $-N(CH_3)R^B$, wherein R^B is -(optionally substituted alkyl)-(optionally substituted carbocyclyl)-, -(optionally substituted alkyl)-(optionally substituted heterocyclyl)-, or -(optionally substituted alkyl)-(optionally substituted heteroaryl)-. In some embodiments, *e.g.* for

Formula (**XV-a**), (**XVI-a**), (**XVII-a**), or (**XVIII-a**), R^y is $-N(R^B)_2$, wherein one R^B is optionally substituted heterocyclyl, and the other R^B is C_{1-4} alkyl. In some embodiments, *e.g.* for Formula (**XV-a**), (**XVI-a**), (**XVII-a**), or (**XVIII-a**), R^y is $-N(R^B)_2$, wherein one R^B is optionally substituted heteroaryl, and the other R^B is C_{1-4} alkyl. In some embodiments, *e.g.* for Formula (**XV-a**), (**XVI-a**), (**XVII-a**), or (**XVIII-a**), R^y is $-N(R^B)_2$, wherein one R^B is optionally substituted cycloalkyl, and the other R^B is C_{1-4} alkyl.

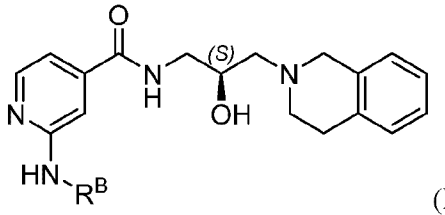
[00201] In certain embodiments of Formula (**XV-a**), wherein R^y is $-N(R^B)_2$, provided is a compound of Formula (**XV-a-1**):



(**XV-a-1**)

or a pharmaceutically acceptable salt thereof, wherein R^B is as generally defined herein. In certain embodiments, at least one R^B is an optionally substituted carbocyclic ring or optionally substituted heterocyclic ring, *e.g.,* a 4- to 6-membered optionally substituted carbocyclic ring or a 4- to 6-membered optionally substituted heterocyclic ring.

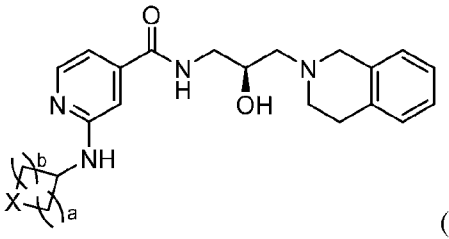
[00202] In certain embodiments of Formula (**XV-a-1**), wherein at least one R^B is a hydrogen, provided is a compound of Formula (**XV-a-2**):



(**XV-a-2**)

or a pharmaceutically acceptable salt thereof, wherein R^B is as generally defined herein. In certain embodiments of Formula (**XV-a-2**), R^B is an optionally substituted carbocyclic ring or optionally substituted heterocyclic ring. In certain embodiments of Formula (**XV-a-2**), R^B is an optionally substituted carbocyclic ring, *e.g.,* a 4- to 6-membered optionally substituted carbocyclic ring. In certain embodiments of Formula (**XV-a-2**), R^B is an optionally substituted heterocyclic ring, *e.g.,* or a 4- to 6-membered optionally substituted heterocyclic ring.

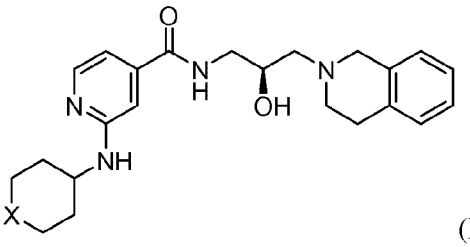
[00203] In certain embodiments of Formula (**XV-a-2**), wherein R^B is an optionally substituted heterocyclic ring, provided is a compound of Formula (**XV-a-3**):



(**XV-a-3**)

or a pharmaceutically acceptable salt thereof, wherein each instance of a and b is independently 1 or 2, and X is $-C(R^{XC})_2-$, –O-, -S-, or $-NR^{XN}-$, wherein each instance of R^{XC} is independently hydrogen, optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl; R^{XN} is independently hydrogen, optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, $-C(=O)R^{XA}$, or a nitrogen protecting group; R^{XA} is optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl. In certain embodiments, a and b are both 1. In certain embodiments, a and b are both 2. In certain embodiments, X is –O-. In certain embodiments, X is $-NR^{XN}-$, wherein R^{XN} is as generally defined above. In certain embodiments, X is $-NR^{XN}-$, wherein R^{XN} is optionally substituted alkyl, $-C(=O)R^{XA}$, or a nitrogen protecting group. In certain embodiments, X is $-NR^{XN}-$, wherein R^{XN} is $-C(=O)R^{XA}$, wherein R^{XA} is optionally substituted alkyl or optionally substituted carbocyclyl. In certain embodiments, X is $-NR^{XN}-$, wherein R^{XN} is $-C(=O)R^{XA}$, wherein R^{XA} is methyl, ethyl, n-propyl, iso-propyl, cyclopropyl, or cyclobutyl. In certain embodiments, a and b are each independently 1 or 2; and X is–O- or $-NR^{XN}-$, wherein R^{XN} is as generally defined above. In certain embodiments, a and b are each independently 1 or 2; and X is–O- or $-NC(=O)R^{XA}$, wherein R^{XA} is as generally defined above. In certain embodiments, a and b are both 1; and X is–O- or $-NR^{XN}-$, wherein R^{XN} is as generally defined above. In certain embodiments, a and b are both 1; and X is–O- or $-NC(=O)R^{XA}$, wherein R^{XA} is as generally defined above. In certain embodiments, a and b are both 1; and X is–O- or $-NC(=O)CH_3$. In certain embodiments, a and b are both 1; and X is–O- . In certain embodiments, a and b are both 2; and X is–O- or $-NC(=O)CH_3$. In certain embodiments, a and b are both 2; and X is $-NC(=O)CH_3$.

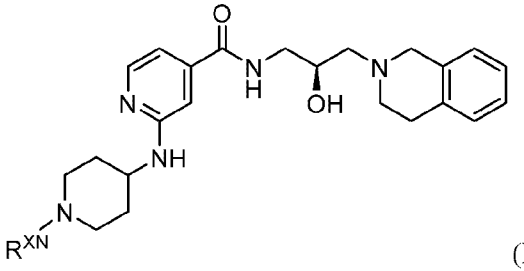
[00204] In certain embodiments of Formula (**XV-a-3**), wherein a and b are 2, provided is a compound of Formula (**XV-a-4**):



(**XV-a-4**)

or a pharmaceutically acceptable salt thereof, wherein X is $–C(R^{XC})_2$-, –O-, -S-, or $-NR^{XN}$-; each instance of R^{XC} is independently hydrogen, optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl; R^{XN} is independently hydrogen, optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, $-C(=O)R^{XA}$, or a nitrogen protecting group; R^{XA} is optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl. In certain embodiments, X is –O-. In certain embodiments, X is $–NR^{XN}$-, wherein R^{XN} is as generally defined above. In certain embodiments, X is $–NR^{XN}$-, wherein R^{XN} is optionally substituted alkyl, $-C(=O)R^{XA}$, or a nitrogen protecting group. In certain embodiments, X is $–NR^{XN}$-, wherein R^{XN} is $-C(=O)R^{XA}$, wherein R^{XA} is optionally substituted alkyl or optionally substituted carbocyclyl. In certain embodiments, X is $–NR^{XN}$-, wherein R^{XN} is $-C(=O)R^{XA}$, wherein R^{XA} is methyl, ethyl, n-propyl, iso-propyl, cyclopropyl, or cyclobutyl. In certain embodiments, X is $–NC(=O)CH_3$.

[00205] In certain embodiments of Formula (**XV-a-4**), wherein X is $-NR^{XN}$-, provided is a compound of Formula (**XV-a-5**):

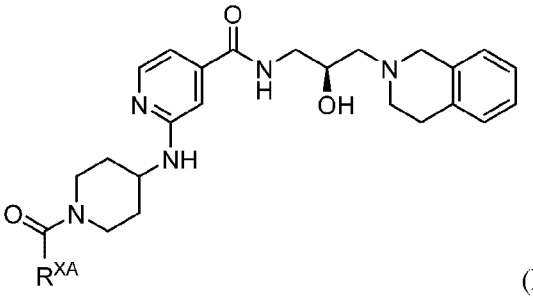


(**XV-a-5**)

or a pharmaceutically acceptable salt thereof, wherein R^{XN} is independently hydrogen, optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, $-C(=O)R^{XA}$, or a nitrogen protecting group; R^{XA} is optionally substituted alkyl, optionally substituted

carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl. In certain embodiments, R^{XN} is optionally substituted alkyl, -$C(=O)R^{XA}$, or a nitrogen protecting group. In certain embodiments, R^{XN} is -$C(=O)R^{XA}$, wherein R^{XA} is optionally substituted alkyl or optionally substituted carbocyclyl. In certain embodiments, R^{XN} is -$C(=O)R^{XA}$, wherein R^{XA} is methyl, ethyl, n-propyl, iso-propyl, cyclopropyl, or cyclobutyl. In certain embodiments, R^{XN} is -$C(=O)R^{XA}$, wherein R^{XA} is methyl.

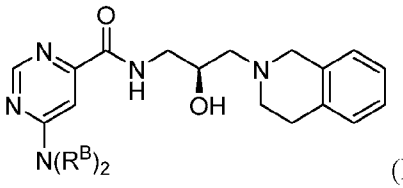
[00206] In certain embodiments of Formula (**XV-a-5**), wherein -NR^{XN}- is -$C(=O)R^{XA}$, provided is a compound of Formula (**XV-a-6**):



(**XV-a-6**)

or a pharmaceutically acceptable salt thereof, wherein R^{XA} is optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl. In certain embodiments, R^{XA} is optionally substituted alkyl or optionally substituted carbocyclyl. In certain embodiments, R^{XA} is methyl, ethyl, n-propyl, iso-propyl, cyclopropyl, or cyclobutyl. In certain embodiments, R^{XA} is methyl.

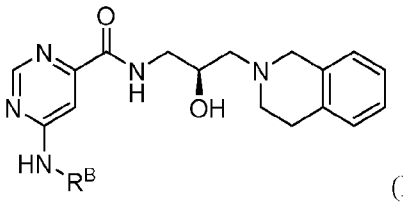
[00207] In certain embodiments of Formula (**XVII-a**), wherein R^y is $-N(R^B)_2$, provided is a compound of Formula (**XVII-a-1**):



(**XVII-a-1**)

or a pharmaceutically acceptable salt thereof, wherein R^B is as generally defined herein. In certain embodiments, at least one R^B is an optionally substituted carbocyclic ring or optionally substituted heterocyclic ring, *e.g.,* a 4- to 6-membered optionally substituted carbocyclic ring or a 4- to 6-membered optionally substituted heterocyclic ring.

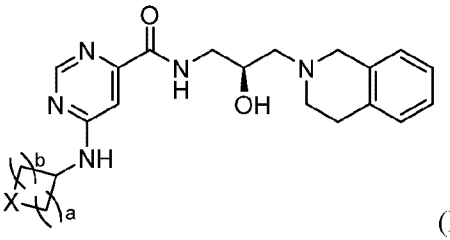
[00208] In certain embodiments of Formula (**XVII-a-1**), wherein at least one R^B is a hydrogen, provided is a compound of Formula (**XVII-a-2**):



(**XVII-a-2**)

or a pharmaceutically acceptable salt thereof, wherein R^B is an optionally substituted carbocyclic ring or optionally substituted heterocyclic ring. In certain embodiments of Formula (**XV-a-2**), R^B is an optionally substituted carbocyclic ring , *e.g.,* a 4- to 6-membered optionally substituted carbocyclic ring. In certain embodiments of Formula (**XV-a-2**), R^B is an optionally substituted heterocyclic ring , *e.g.,* or a 4- to 6-membered optionally substituted heterocyclic ring.

[00209] In certain embodiments of Formula (**XVII-a-2**), wherein R^B is an optionally substituted heterocyclic ring, provided is a compound of Formula (**XVII-a-3**):

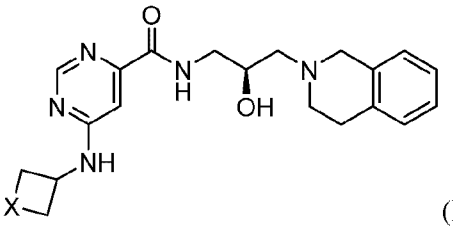


(**XVII-a-3**)

or a pharmaceutically acceptable salt thereof, wherein each instance of a and b is independently 1 or 2, and X is $–C(R^{XC})_2$-, –O-, -S-, or $-NR^{XN}$-, wherein each instance of R^{XC} is independently hydrogen, optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl; R^{XN} is independently hydrogen, optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, $-C(=O)R^{XA}$, or a nitrogen protecting group; R^{XA} is optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl. In certain embodiments, a and b are both 1. In certain embodiments, a and b are both 2. In certain embodiments, X is –O-. In certain embodiments, X is $–NR^{XN}$-, wherein R^{XN} is as generally defined above. In certain embodiments, X is $–NR^{XN}$-, wherein R^{XN} is optionally substituted alkyl, $-C(=O)R^{XA}$, or a nitrogen protecting group. In certain embodiments, X is $–NR^{XN}$-, wherein R^{XN} is $-C(=O)R^{XA}$, wherein R^{XA} is optionally substituted alkyl or optionally substituted carbocyclyl.

In certain embodiments, X is $-NR^{XN}-$, wherein R^{XN} is $-C(=O)R^{XA}$, wherein R^{XA} is methyl, ethyl, n-propyl, iso-propyl, cyclopropyl, or cyclobutyl. In certain embodiments, a and b are each independently 1 or 2; and X is–O- or $-NR^{XN}-$, wherein R^{XN} is as generally defined above. In certain embodiments, a and b are each independently 1 or 2; and X is–O- or $-NC(=O)R^{XA}$, wherein R^{XA} is as generally defined above. In certain embodiments, a and b are both 1; and X is–O- or $-NR^{XN}-$, wherein R^{XN} is as generally defined above. In certain embodiments, a and b are both 1; and X is–O- or $-NC(=O)R^{XA}$, wherein R^{XA} is as generally defined above. In certain embodiments, a and b are both 1; and X is–O- or $-NC(=O)CH_3$. In certain embodiments, a and b are both 1; and X is–O- . In certain embodiments, a and b are both 2; and X is–O- or $-NC(=O)CH_3$. In certain embodiments, a and b are both 2; and X is $-NC(=O)CH_3$.

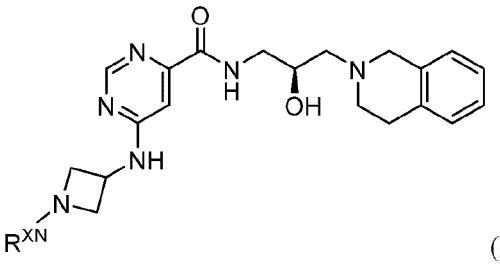
[00210] In certain embodiments of Formula (**XVII-a-3**), wherein a and b are 1, provided is a compound of Formula (**XVII-a-4**):



(**XVII-a-4**)

or a pharmaceutically acceptable salt thereof, wherein X is $-C(R^{XC})_2-$, –O-, -S-, or $-NR^{XN}-$, wherein each instance of R^{XC} is independently hydrogen, optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl; R^{XN} is independently hydrogen, optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, $-C(=O)R^{XA}$, or a nitrogen protecting group; R^{XA} is optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl. In certain embodiments, X is –O-. In certain embodiments, X is $-NR^{XN}-$, wherein R^{XN} is as generally defined above. In certain embodiments, X is $-NR^{XN}-$, wherein R^{XN} is optionally substituted alkyl, $-C(=O)R^{XA}$, or a nitrogen protecting group. In certain embodiments, X is $-NR^{XN}-$, wherein R^{XN} is $-C(=O)R^{XA}$, wherein R^{XA} is optionally substituted alkyl or optionally substituted carbocyclyl. In certain embodiments, X is $-NR^{XN}-$, wherein R^{XN} is $-C(=O)R^{XA}$, wherein R^{XA} is methyl, ethyl, n-propyl, iso-propyl, cyclopropyl, or cyclobutyl. In certain embodiments, X is $-NC(=O)CH_3$.

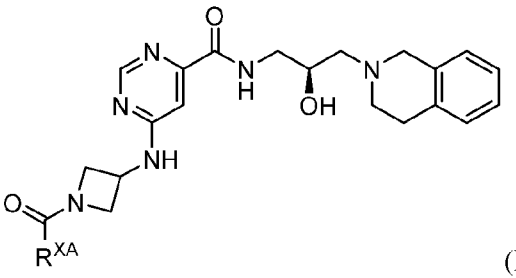
[00211] In certain embodiments of Formula (**XVII-a-4**), wherein X is $-NR^{XN}-$, provided is a compound of Formula (**XVII-a-5**):



(**XVII-a-5**)

or a pharmaceutically acceptable salt thereof, wherein R^{XN} is independently hydrogen, optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, $-C(=O)R^{XA}$, or a nitrogen protecting group; R^{XA} is optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl. In certain embodiments, R^{XN} is optionally substituted alkyl, $-C(=O)R^{XA}$, or a nitrogen protecting group. In certain embodiments, R^{XN} is $-C(=O)R^{XA}$, wherein R^{XA} is optionally substituted alkyl or optionally substituted carbocyclyl. In certain embodiments, R^{XN} is $-C(=O)R^{XA}$, wherein R^{XA} is methyl, ethyl, n-propyl, iso-propyl, cyclopropyl, or cyclobutyl. In certain embodiments, R^{XN} is $-C(=O)R^{XA}$, wherein R^{XA} is methyl.

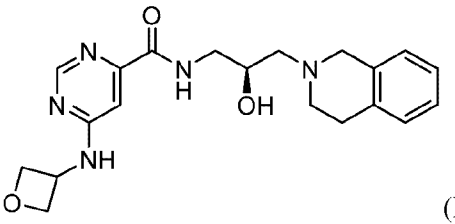
[00212] In certain embodiments of Formula (**XVII-a-5**), wherein $-NR^{XN}-$ is $-C(=O)R^{XA}$, provided is a compound of Formula (**XVII-a-6**):



(**XVII-a-6**)

or a pharmaceutically acceptable salt thereof, wherein R^{XA} is optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl. In certain embodiments, R^{XA} is optionally substituted alkyl or optionally substituted carbocyclyl. In certain embodiments, R^{XA} is methyl, ethyl, n-propyl, iso-propyl, cyclopropyl, or cyclobutyl. In certain embodiments, R^{XA} is methyl.

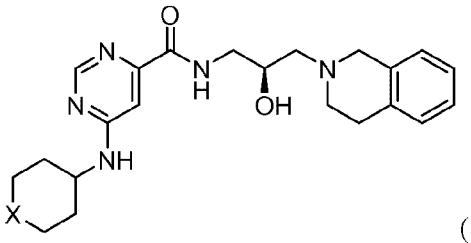
[00213] In certain embodiments of Formula (**XVII-a-4**), wherein X is -NR^{XN}-, provided is a compound of Formula (**XVII-a-7**):



(**XVII-a-7**)

or a pharmaceutically acceptable salt thereof.

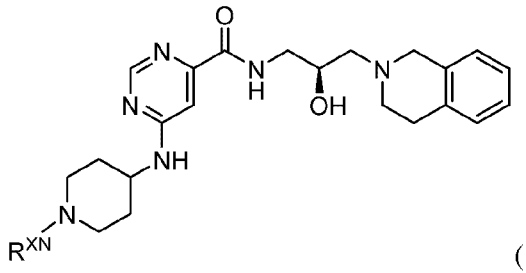
[00214] In certain embodiments of Formula (**XVII-a-3**), wherein a and b are 2, provided is a compound of Formula (**XVII-a-8**):



(**XVII-a-8**)

or a pharmaceutically acceptable salt thereof, wherein X is –$C(R^{XC})_2$-, –O-, -S-, or -NR^{XN}-, wherein each instance of R^{XC} is independently hydrogen, optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl; R^{XN} is independently hydrogen, optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, -$C(=O)R^{XA}$, or a nitrogen protecting group; R^{XA} is optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl. In certain embodiments, X is –O-. In certain embodiments, X is –NR^{XN}-, wherein R^{XN} is as generally defined above. In certain embodiments, X is –NR^{XN}-, wherein R^{XN} is optionally substituted alkyl, -$C(=O)R^{XA}$, or a nitrogen protecting group. In certain embodiments, X is –NR^{XN}-, wherein R^{XN} is -$C(=O)R^{XA}$, wherein R^{XA} is optionally substituted alkyl or optionally substituted carbocyclyl. In certain embodiments, X is –NR^{XN}-, wherein R^{XN} is -$C(=O)R^{XA}$, wherein R^{XA} is methyl, ethyl, n-propyl, iso-propyl, cyclopropyl, or cyclobutyl. In certain embodiments, X is –$NC(=O)CH_3$.

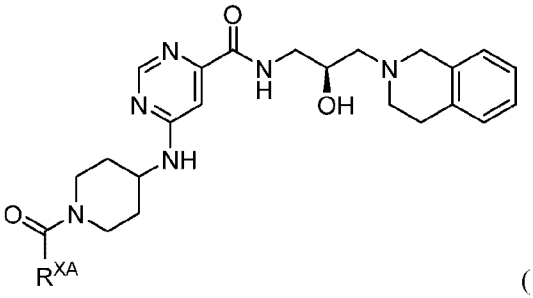
[00215] In certain embodiments of Formula (**XVII-a-8**), wherein X is $-NR^{XN}-$, provided is a compound of Formula (**XVII-a-9**):



(**XVII-a-9**)

or a pharmaceutically acceptable salt thereof, wherein R^{XN} is independently hydrogen, optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, $-C(=O)R^{XA}$, or a nitrogen protecting group; R^{XA} is optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl. In certain embodiments, R^{XN} is optionally substituted alkyl, $-C(=O)R^{XA}$, or a nitrogen protecting group. In certain embodiments, R^{XN} is $-C(=O)R^{XA}$, wherein R^{XA} is optionally substituted alkyl or optionally substituted carbocyclyl. In certain embodiments, R^{XN} is $-C(=O)R^{XA}$, wherein R^{XA} is methyl, ethyl, n-propyl, iso-propyl, cyclopropyl, or cyclobutyl. In certain embodiments, R^{XN} is $-C(=O)R^{XA}$, wherein R^{XA} is methyl.

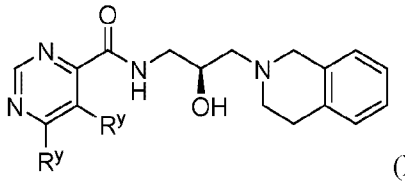
[00216] In certain embodiments of Formula (**XVII-a-9**), wherein $-NR^{XN}-$ is $-C(=O)R^{XA}$, provided is a compound of Formula (**XVII-a-10**):



(**XVII-a-10**)

or a pharmaceutically acceptable salt thereof, wherein R^{XA} is optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl. In certain embodiments, R^{XA} is optionally substituted alkyl or optionally substituted carbocyclyl. In certain embodiments, R^{XA} is methyl, ethyl, n-propyl, iso-propyl, cyclopropyl, or cyclobutyl. In certain embodiments, R^{XA} is methyl.

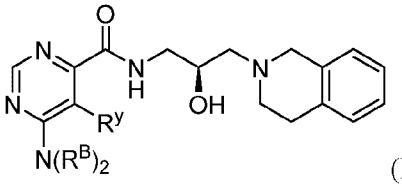
[00217] In certain embodiments, a provided compound is of Formula (**XVII-b**):



(**XVII-b**)

or a pharmaceutically acceptable salt thereof, wherein each instance of R^y is as generally defined herein.

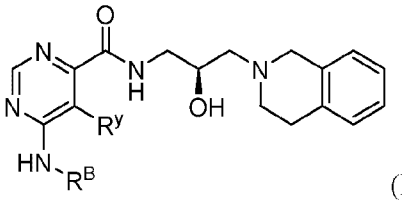
[00218] In certain embodiments of Formula (**XVII-b**), wherein at least one of R^y is $-N(R^B)_2$, provided is a compound of Formula (**XVII-b-1**):



(**XVII-b-1**)

or a pharmaceutically acceptable salt thereof, wherein R^y and each instance of R^B are as generally defined herein. In certain embodiments, at least one R^B is an optionally substituted carbocyclic ring or optionally substituted heterocyclic ring, *e.g.*, a 4- to 6-membered optionally substituted carbocyclic ring or a 4- to 6-membered optionally substituted heterocyclic ring.

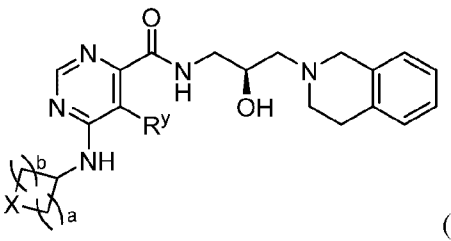
[00219] In certain embodiments of Formula (**XVII-b-1**), wherein at least one R^B is a hydrogen, provided is a compound of Formula (**XVII-b-2**):



(**XVII-b-2**)

or a pharmaceutically acceptable salt thereof, wherein R^y and R^B are as generally defined herein. In certain embodiments, R^B is an optionally substituted carbocyclic ring or optionally substituted heterocyclic ring. In certain embodiments of Formula (**XV-a-2**), R^B is an optionally substituted carbocyclic ring , *e.g.*, a 4- to 6-membered optionally substituted carbocyclic ring. In certain embodiments of Formula (**XV-a-2**), R^B is an optionally substituted heterocyclic ring , *e.g.*, or a 4- to 6-membered optionally substituted heterocyclic ring.

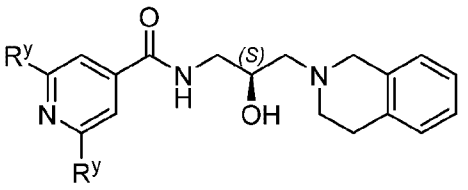
[00220] In certain embodiments of Formula (**XVII-b-2**), wherein R^B is an optionally substituted heterocyclic ring, provided is a compound of Formula (**XVII-b-3**):



(XVII-b-3)

or a pharmaceutically acceptable salt thereof, wherein each instance of a and b is independently 1 or 2, and X is $-C(R^{XC})_2-$, –O-, -S-, or $-NR^{XN}-$, wherein each instance of R^{XC} is independently hydrogen, optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl; R^{XN} is independently hydrogen, optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, $-C(=O)R^{XA}$, or a nitrogen protecting group; R^{XA} is optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl. In certain embodiments, a and b are both 1. In certain embodiments, a and b are both 2. In certain embodiments, X is –O-. In certain embodiments, X is $–NR^{XN}-$, wherein R^{XN} is as generally defined above. In certain embodiments, X is $–NR^{XN}-$, wherein R^{XN} is optionally substituted alkyl, $-C(=O)R^{XA}$, or a nitrogen protecting group. In certain embodiments, X is $–NR^{XN}-$, wherein R^{XN} is $-C(=O)R^{XA}$, wherein R^{XA} is optionally substituted alkyl or optionally substituted carbocyclyl. In certain embodiments, X is $–NR^{XN}-$, wherein R^{XN} is $-C(=O)R^{XA}$, wherein R^{XA} is methyl, ethyl, n-propyl, iso-propyl, cyclopropyl, or cyclobutyl. In certain embodiments, a and b are each independently 1 or 2; and X is–O- or $-NR^{XN}-$, wherein R^{XN} is as generally defined above. In certain embodiments, a and b are each independently 1 or 2; and X is–O- or $–NC(=O)R^{XA}$, wherein R^{XA} is as generally defined above. In certain embodiments, a and b are both 1; and X is–O- or $-NR^{XN}-$, wherein R^{XN} is as generally defined above. In certain embodiments, a and b are both 1; and X is–O- or $–NC(=O)R^{XA}$, wherein R^{XA} is as generally defined above. In certain embodiments, a and b are both 1; and X is–O- or $–NC(=O)CH_3$. In certain embodiments, a and b are both 1; and X is–O- . In certain embodiments, a and b are both 2; and X is–O- or $–NC(=O)CH_3$. In certain embodiments, a and b are both 2; and X is $–NC(=O)CH_3$.

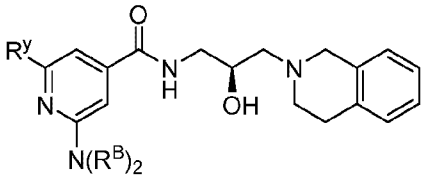
[00221] In certain embodiments, a provided compound is of Formula (**XV-b**):



(**XV-b**)

or a pharmaceutically acceptable salt thereof, wherein each R^y is as generally described herein.

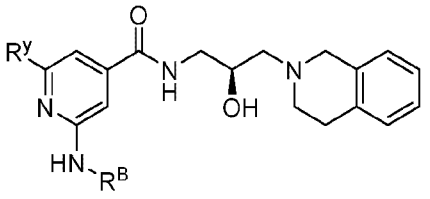
[00222] In certain embodiments of Formula (**XV-b**), wherein at least one of R^y is $-N(R^B)_2$, provided is a compound of Formula (**XV-b-1**):



(**XV-b-1**)

or a pharmaceutically acceptable salt thereof, wherein R^y and R^B are as generally described herein. In certain embodiments, at least one R^B is an optionally substituted carbocyclic ring or optionally substituted heterocyclic ring, *e.g.*, a 4- to 6-membered optionally substituted carbocyclic ring or a 4- to 6-membered optionally substituted heterocyclic ring.

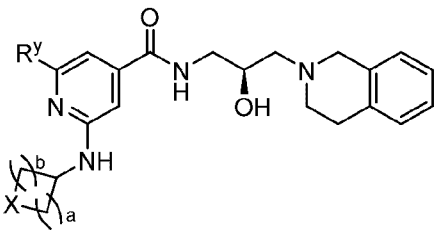
[00223] In certain embodiments of Formula (**XV-b-1**), wherein at least one R^B is a hydrogen, provided is a compound of Formula (**XV-b-2**):



(**XV-b-2**)

or a pharmaceutically acceptable salt thereof, wherein R^y and R^B are as generally described herein. In certain embodiments, R^B is an optionally substituted carbocyclic ring or optionally substituted heterocyclic ring. In certain embodiments, R^B is an optionally substituted carbocyclic ring , *e.g.*, a 4- to 6-membered optionally substituted carbocyclic ring. In certain embodiments, R^B is an optionally substituted heterocyclic ring , *e.g.*, or a 4- to 6-membered optionally substituted heterocyclic ring.

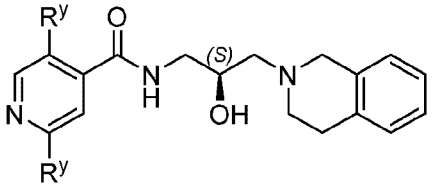
[00224] In certain embodiments of Formula (**XV-b-2**), wherein R^B is an optionally substituted heterocyclic ring, provided is a compound of Formula (**XV-b-3**):



(**XV-b-3**)

or a pharmaceutically acceptable salt thereof, wherein each instance of a and b is independently 1 or 2, and X is $-C(R^{XC})_2-$, –O-, -S-, or $-NR^{XN}-$, wherein each instance of R^{XC} is independently hydrogen, optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl; R^{XN} is independently hydrogen, optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, $-C(=O)R^{XA}$, or a nitrogen protecting group; R^{XA} is optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl. In certain embodiments, a and b are both 1. In certain embodiments, a and b are both 2. In certain embodiments, X is –O-. In certain embodiments, X is $–NR^{XN}-$, wherein R^{XN} is as generally defined above. In certain embodiments, X is $–NR^{XN}-$, wherein R^{XN} is optionally substituted alkyl, $-C(=O)R^{XA}$, or a nitrogen protecting group. In certain embodiments, X is $–NR^{XN}-$, wherein R^{XN} is $-C(=O)R^{XA}$, wherein R^{XA} is optionally substituted alkyl or optionally substituted carbocyclyl. In certain embodiments, X is $–NR^{XN}-$, wherein R^{XN} is $-C(=O)R^{XA}$, wherein R^{XA} is methyl, ethyl, n-propyl, iso-propyl, cyclopropyl, or cyclobutyl. In certain embodiments, a and b are each independently 1 or 2; and X is–O- or $-NR^{XN}-$, wherein R^{XN} is as generally defined above. In certain embodiments, a and b are each independently 1 or 2; and X is–O- or $–NC(=O)R^{XA}$, wherein R^{XA} is as generally defined above. In certain embodiments, a and b are both 1; and X is–O- or $-NR^{XN}-$, wherein R^{XN} is as generally defined above. In certain embodiments, a and b are both 1; and X is–O- or $–NC(=O)CH_3$. In certain embodiments, a and b are both 1; and X is–O- . In certain embodiments, a and b are both 2; and X is–O- or $–NC(=O)CH_3$. In certain embodiments, a and b are both 2; and X is $–NC(=O)CH_3$.

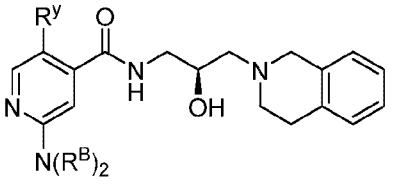
[00225] In certain embodiments, a provided compound is of Formula (**XV-c**):



(**XV-c**)

or a pharmaceutically acceptable salt thereof, wherein each R^y is as generally described herein.

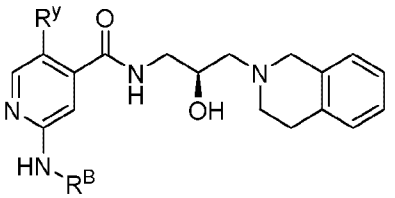
[00226] In certain embodiments of Formula (**XV-c**), wherein at least one of R^y is $-N(R^B)_2$, provided is a compound of Formula (**XV-c-1**):



(**XV-c-1**)

or a pharmaceutically acceptable salt thereof, wherein R^y and R^B are as generally described herein. In certain embodiments, at least one R^B is an optionally substituted carbocyclic ring or optionally substituted heterocyclic ring, *e.g.,* a 4- to 6-membered optionally substituted carbocyclic ring or a 4- to 6-membered optionally substituted heterocyclic ring.

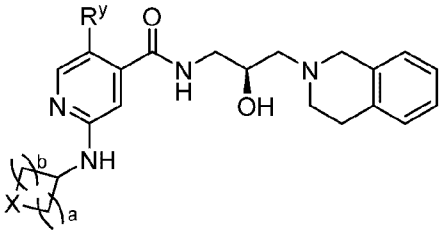
[00227] In certain embodiments of Formula (**XV-c-1**), wherein at least one R^B is a hydrogen, provided is a compound of Formula (**XV-c-2**):



(**XV-c-2**)

or a pharmaceutically acceptable salt thereof, wherein R^y and R^B are as generally described herein. In certain embodiments, R^B is an optionally substituted carbocyclic ring or optionally substituted heterocyclic ring. In certain embodiments, R^B is an optionally substituted carbocyclic ring , *e.g.,* a 4- to 6-membered optionally substituted carbocyclic ring. In certain embodiments, R^B is an optionally substituted heterocyclic ring , *e.g.,* or a 4- to 6-membered optionally substituted heterocyclic ring.

[00228] In certain embodiments of Formula (**XV-c-2**), wherein R^B is an optionally substituted heterocyclic ring, provided is a compound of Formula (**XV-c-3**):

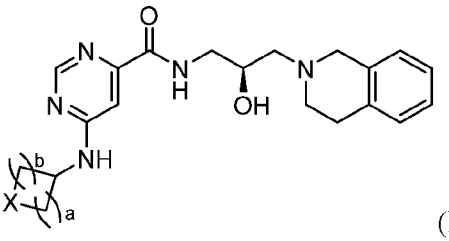


(**XV-c-3**)

or a pharmaceutically acceptable salt thereof, wherein each instance of a and b is independently 1 or 2, and X is $-C(R^{XC})_2$-, –O-, -S-, or $-NR^{XN}$-, wherein each instance of R^{XC}

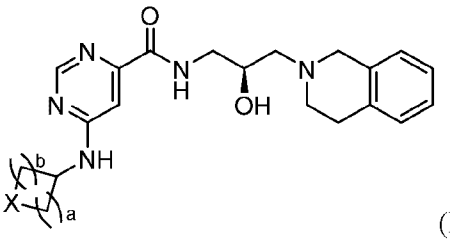
is independently hydrogen, optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl; R^{XN} is independently hydrogen, optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, $-C(=O)R^{XA}$, or a nitrogen protecting group; R^{XA} is optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl. In certain embodiments, a and b are both 1. In certain embodiments, a and b are both 2. In certain embodiments, X is –O-. In certain embodiments, X is $–NR^{XN}-$, wherein R^{XN} is as generally defined herein. In certain embodiments, X is $–NR^{XN}-$, wherein R^{XN} is optionally substituted alkyl, $-C(=O)R^{XA}$, or a nitrogen protecting group. In certain embodiments, X is $–NR^{XN}-$, wherein R^{XN} is $-C(=O)R^{XA}$, wherein R^{XA} is optionally substituted alkyl or optionally substituted carbocyclyl. In certain embodiments, X is $–NR^{XN}-$, wherein R^{XN} is $-C(=O)R^{XA}$, wherein R^{XA} is methyl, ethyl, n-propyl, iso-propyl, cyclopropyl, or cyclobutyl. In certain embodiments, a and b are each independently 1 or 2; and X is–O- or $-NR^{XN}-$, wherein R^{XN} is as generally defined herein. In certain embodiments, a and b are each independently 1 or 2; and X is–O- or $–NC(=O)R^{XA}$, wherein R^{XA} is as generally defined herein. In certain embodiments, a and b are both 1; and X is–O- or $-NR^{XN}-$, wherein R^{XN} is as generally defined herein. In certain embodiments, a and b are both 1; and X is–O- or $–NC(=O)CH_3$. In certain embodiments, a and b are both 1; and X is–O- . In certain embodiments, a and b are both 2; and X is–O- or $–NC(=O)CH_3$. In certain embodiments, a and b are both 2; and X is $–NC(=O)CH_3$.

[00229] In some embodiments, a provided compound is of Formula (**XVII-a-3):**



(**XVII-a-3**).

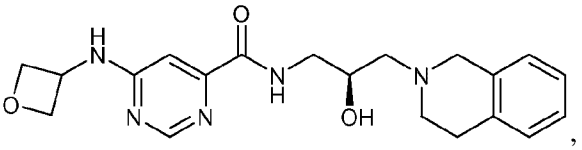
[00230] In some embodiments, a provided compound is a hydrochloride salt of Formula (**XVII-a-3):**



(**XVII-a-3**).

[00231] In some embodiments, *e.g.* for Formula (**A**) and any subgenera thereof, *e.g.* Formula (**XV**), (**XVI**), (**XVII**), (**XVIII**), (**XV-a**), (**XVI-a**), (**XVII-a**), (**XVII-b**), (**XVIII-a**), (**XV-b**), or (**XV-c**), the provided compound is of a free base form. In some embodiments, *e.g.* for Formula (**XV**), (**XVI**), (**XVII**), (**XVIII**), (**XV-a**), (**XVI-a**), (**XVII-a**), (**XVII-b**), (**XVIII-a**), (**XV-b**), or (**XV-c**), the provided compound is in the form of a pharmaceutically acceptable salt. In some embodiments, the provided pharmaceutically acceptable salt is formed with hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, perchloric acid, acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid, or malonic acid. In some embodiments, the provided pharmaceutically acceptable salt is adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2–hydroxy–ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2–naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3–phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, *p*–toluenesulfonate, undecanoate, or valerate salts. In some embodiments, the provided pharmaceutically acceptable salt is a hydrochloride salt. In some embodiments, the provided pharmaceutically acceptable salt is a tartrate salt. In some embodiments, the provided pharmaceutically acceptable salt is a monotartrate salt. In some embodiments, the provided pharmaceutically acceptable salt is a bitartrate salt.

[00232] In some embodiments, the provided compound is of one of the following formulae: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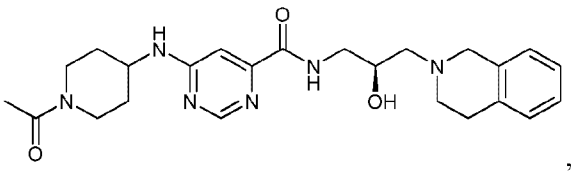
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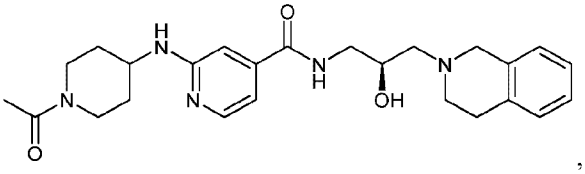
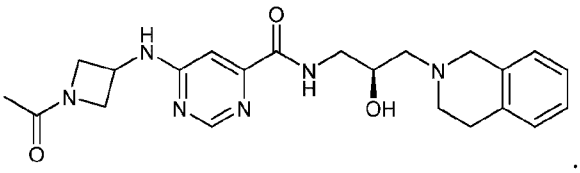
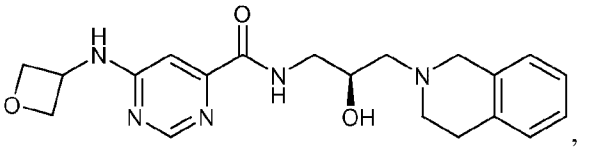

, or



.

[00233] In some embodiments, the provided compound is a hydrochloride salt of one of the following formulae:



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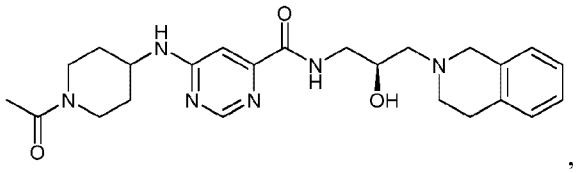
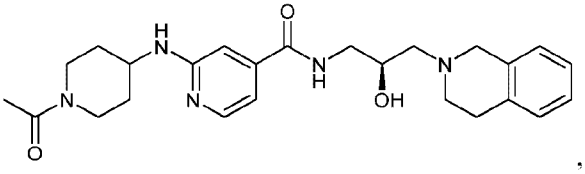
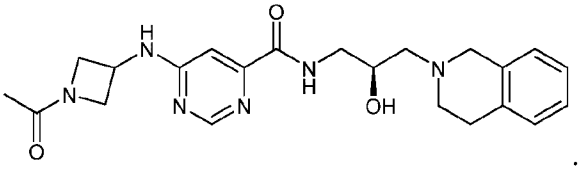


,

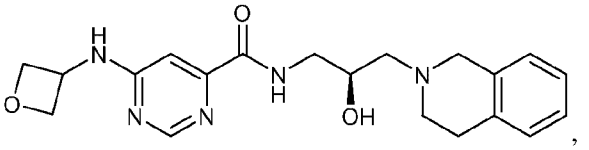


, or



.

[00234] In some embodiments, the provided compound is a tartrate salt of one of the following formulae:



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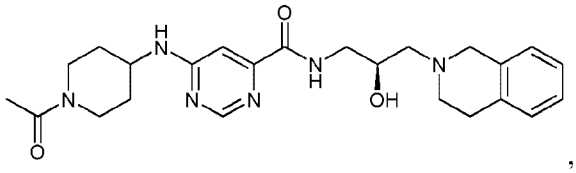

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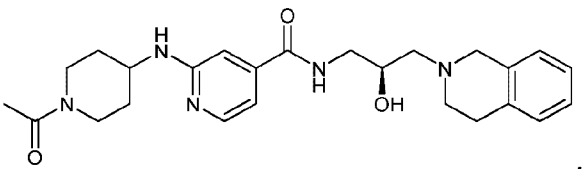
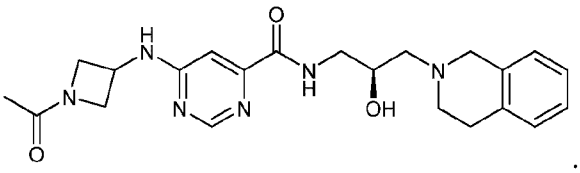


, or



[00235] In certain embodiments, the provided compound is a monotartrate salt thereof. In certain embodimetns, the provided compound is a bitartrate salt thereof.

[00236] In some embodiments, *e.g.* for Formula (**A**) and any subgenera thereof, *e.g.* for Formula (**XV**), (**XVI**), (**XVII**), (**XVIII**), (**XV-a**), (**XVI-a**), (**XVII-a**), (**XVII-b**), (**XVIII-a**), (**XV-b**), or (**XV-c**), at least one R^y is halo. In certain embodiments, at least one R^y is fluoro. In certain embodiments, at least one R^y is chloro. In some embodiments, at least one R^y is –CN.

[00237] In some embodiments, *e.g.* for Formula (**A**) and any subgenera thereof, *e.g.* for Formula (**XV**), (**XVI**), (**XVII**), (**XVIII**), (**XV-a**), (**XVI-a**), (**XVII-a**), (**XVII-b**), (**XVIII-a**), (**XV-b**), or (**XV-c**), at least one R^y is $-OR^A$, wherein R^A is optionally substituted aliphatic. In some embodiments, R^y is $-OR^A$, wherein R^A is -(optionally substituted alkyl)-(optionally substituted carbocyclyl)-, -(optionally substituted alkyl)-(optionally substituted heterocyclyl)-, or -(optionally substituted alkyl)-(optionally substituted heteroaryl)-. In some embodiments, at least one R^y is $-OR^A$, wherein R^A is unsubstituted C_{1-6} alkyl. In certain embodiments, at least one R^y is methoxy, ethoxy, or propoxy. In certain embodiments, at least one R^y is methoxy. In some embodiments, at least one R^y is $-OR^A$, wherein R^A is substituted C_{1-6} alkyl. In certain embodiments, at least one R^y is $-OCH_2CH_2N(CH_3)_2$. In some embodiments, at least one R^y is $-OR^A$, wherein R^A is optionally substituted heterocyclyl. In some embodiments, at least one R^y is $-OR^A$, wherein R^A is an optionally subsituted 4- to 7-membered heterocyclyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, at least one R^y is $-OR^A$, wherein R^A is oxetanyl, tetrahydrofuranyl, or tetrahydropyranyl. In some embodiments, at least one R^y is $-OR^A$, wherein R^A is optionally substituted piperidinyl or optionally substituted piperazinyl. In some embodiments, at least one R^y is $-OR^A$, wherein R^A is optionally substituted heterocyclyl. In some embodiments, at least one R^y is $-OR^A$, wherein R^A is optionally substituted heteroaryl. In some embodiments, at least one R^y is $-OR^A$, wherein R^A is optionally substituted cycloalkyl.

[00238] In some embodiments, *e.g.* for Formula (**A**) and any subgenera thereof, *e.g.* for Formula (**XV**), (**XVI**), (**XVII**), (**XVIII**), (**XV-a**), (**XVI-a**), (**XVII-a**), (**XVII-b**), (**XVIII-a**), (**XV-b**), or (**XV-c**), at least one R^y is $-N(R^B)_2$. In some embodiments, at least one R^y is –

$N(R^B)_2$, wherein each R^B is independently hydrogen,optionally substituted alkyl, optionally substituted heterocyclyl, optionally substituted carbocyclyl, or optionally substituted aryl. In some embodiments, at least one R^y is $-N(R^B)_2$, wherein each R^B is independently hydrogen or C_{1-6} alkyl. In some embodiments, at least one R^y is $-NHR^B$. In some embodiments, at least one R^y is $-NHR^B$, wherein each R^B is independently hydrogen,optionally substituted alkyl, optionally substituted heterocyclyl, optionally substituted carbocyclyl, or optionally substituted aryl. In some embodiments, at least one R^y is $-N(C_{1-6}$ alkyl$)_2$, $-NH(C_{1-6}$ alkyl), or $-NH_2$. In certain embodiments, at least one R^y is $-NH_2$. In certain embodiments, at least one R^y is $-NHCH_3$. In certain embodiments, at least one R^y is $-N(CH_3)_2$. In some embodiments, at least one R^y is $-N(CH_3)R^B$, wherein each R^B is independently hydrogen,optionally substituted alkyl, optionally substituted heterocyclyl, optionally substituted carbocyclyl, or optionally substituted aryl. In some embodiments, at least one R^y is $-N(R^B)_2$, wherein each R^B is independently hydrogen or C_{1-6} alkyl. In some embodiments, at least one R^y is $-NHR^B$. In some embodiments, at least one R^y is $-N(C_{1-6}$ alkyl$)_2$, $-NH(C_{1-6}$ alkyl), or $-NH_2$. In certain embodiments, at least one R^y is $-NH_2$. In some embodiments, at least one R^y is $-N(R^B)_2$, $-NHR^B$, or $-N(CH_3)R^B$, wherein at least one R^B is optionally substituted heterocyclyl. In some embodiments, at least one R^y is $-N(R^B)_2$, $-NHR^B$, or $-N(CH_3)R^B$, wherein at least one R^B is an optionally subsituted 4- to 7-membered heterocyclyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, at least one R^y is $-N(R^B)_2$, $-NHR^B$, or $-N(CH_3)R^B$, wherein at least one R^B is oxetanyl, tetrahydropyranyl, or tetrahydrofuranyl. In some embodiments, at least one R^y is $—N(R^B)_2$, $-NHR^B$, or $-N(CH_3)R^B$, wherein at least one R^B is optionally substituted piperidinyl or optionally substituted piperazinyl. In some embodiments, at least one R^y is $-N(R^B)_2$, $-NHR^B$, or $-N(CH_3)R^B$, wherein at least one R^B is –(optionally substituted C_{1-6} alkyl)-(C_{1-6} alkyl heterocyclyl). In some embodiments, at least one R^y is $-N(R^B)_2$, wherein one R^B is optionally substituted heterocyclyl, and the other R^B is C_{1-4} alkyl. In some embodiments, at least one R^y is $-N(R^B)_2$, wherein one R^B is optionally substituted heteroaryl, and the other R^B is C_{1-4} alkyl. In some embodiments, at least one R^y is $-N(R^B)_2$, wherein one R^B is optionally substituted cycloalkyl, and the other R^B is C_{1-4} alkyl.

[00239] In some embodiments, *e.g.* for Formula (**A**) and any subgenera thereof, *e.g.* for Formula (**XV**), (**XVI**), (**XVII**), (**XVIII**), (**XV-a**), (**XVI-a**), (**XVII-a**), (**XVII-b**), (**XVIII-a**), (**XV-b**), or (**XV-c**), at least one R^y is optionally substituted aliphatic. In certain embodiments, at least one R^y is substituted aliphatic. In certain embodiments, at least one R^y is unsubstituted aliphatic. In some embodiments, at least one R^y is optionally substituted C_{1-6}

alkyl. In certain embodiments, at least one R^y is unsubstituted C_{1-6} alkyl. In certain embodiments, at least one R^y is substituted C_{1-6} alkyl. In certain embodiments, at least one R^y is methyl, ethyl, or propyl. In certain embodiments, at least one R^y is methyl. In certain embodiments, at least one R^y is $-CF_3$, CHF_2, or CH_2F. In certain embodiments, at least one R^y is optionally substituted C_{1-6} alkyl further substituted with optionally substituted aryl, heteroaryl, or heterocyclyl. In certain embodiments, at least one R^y is benzyl. In certain embodiments, at least one R^y is $-(C_{1-6}$ alkyl)-(optionally substitutedaryl). In certain embodiments, at least one R^y is $-(C_{1-6}$ alkyl)-(optionally substituted heteroaryl). In certain embodiments, at least one R^y is $-(C_{1-6}$ alkyl)-(optionally substituted heterocyclyl). In certain embodiments, at least one R^y is $-(C_{1-6}$ alkyl)-aryl. In certain embodiments, at least one R^y is $-(C_{1-6}$ alkyl)-heteroaryl. In certain embodiments, at least one R^y is $-(C_{1-6}$ alkyl)-heterocyclyl. In certain embodiments, at least one R^y is $-CH_2$-aryl. In certain embodiments, at least one R^y is $-CH_2$-heteroaryl. In certain embodiments, at least one R^y is $-CH_2$-heterocyclyl.

[00240] In some embodiments, *e.g.* for Formula (**A**) and any subgenera thereof, *e.g.* for Formula (**XV**), (**XVI**), (**XVII**), (**XVIII**), (**XV-a**), (**XVI-a**), (**XVII-a**), (**XVII-b**), (**XVIII-a**), (**XV-b**), or (**XV-c**), at least one R^y is $-C(O)N(R^B)_2$. In certain embodiments, at least one R^y is $-C(O)NHR^B$. In certain embodiments, at least one R^y is $-C(O)NH_2$. In certain embodiments, at least one R^y is $-C(O)N(R^B)_2$, wherein the R^B groups are taken together with their intervening atoms to form an optionally substituted 5- to 6-membered heterocyclyl. In certain embodiments, at least one R^y is $-C(O)N(R^B)_2$, wherein the R^B groups are taken together with their intervening atoms to form an optionally substituted morpholinyl.

[00241] In some embodiments, *e.g.* for Formula (**A**) and any subgenera thereof, *e.g.* for Formula (**XV**), (**XVI**), (**XVII**), (**XVIII**), (**XV-a**), (**XVI-a**), (**XVII-a**), (**XVII-b**), (**XVIII-a**), (**XV-b**), or (**XV-c**), at least one R^y is $-SO_2N(R^B)_2$. In certain embodiments, at least one R^y is $-SO_2NHR^B$. In certain embodiments, at least one R^y is $-SO_2NH_2$. In certain embodiments, at least one R^y is $-SO_2N(R^B)_2$, wherein neither R^B is hydrogen. In certain embodiments, at least one R^y is $-SO_2NH(C_{1-6}$ alkyl) or $-SO_2N(C_{1-6}$ alkyl)$_2$. In certain embodiments, at least one R^y is $-SO_2N(CH_3)_2$. In certain embodiments, at least one R^y is $-SO_2N(R^B)_2$, wherein the R^B groups are taken together with their intervening atoms to form an optionally substituted 5- to 6-membered heterocyclyl. In certain embodiments, at least one R^y is $-SO_2$-morpholinyl. In certain embodiments, at least one R^y is $-SO_2$-piperidinyl, $-SO_2$-piperazinyl, or $-SO_2$-piperidinyl.

[00242] In some embodiments, *e.g.* for Formula (**A**) and any subgenera thereof, *e.g.* for Formula (**XV**), (**XVI**), (**XVII**), (**XVIII**), (**XV-a**), (**XVI-a**), (**XVII-a**), (**XVII-b**), (**XVIII-a**), (**XV-b**), or (**XV-c**), at least one R^y is $-SO_2R^A$. In some embodiments, at least one R^y is $-SO_2R^A$, wherein R^A is optionally substituted aliphatic. In some embodiments, at least one R^y is $-SO_2(C_{1-6}$ alkyl). In some embodiments, at least one R^y is $-SO_2CH_3$. In some embodiments, at least one R^y is $-C(O)R^A$. In some embodiments, at least one R^y is $-C(O)R^A$, wherein R^A is optionally substituted aliphatic. In some embodiments, at least one R^y is $-C(O)(C_{1-6}$ alkyl). In some embodiments, at least one R^y is $-C(O)CH_3$.

[00243] In some embodiments, *e.g.* for Formula (**A**) and any subgenera thereof, *e.g.* for Formula (**XV**), (**XVI**), (**XVII**), (**XVIII**), (**XV-a**), (**XVI-a**), (**XVII-a**), (**XVII-b**), (**XVIII-a**), (**XV-b**), or (**XV-c**), at least one R^y is $-N(R^B)C(O)R^A$. In certain embodiments, at least one R^y is $-NHC(O)R^A$. In certain embodiments, at least one R^y is $-NHC(O)(C_{1-6}$ alkyl). In certain embodiments, at least one R^y is $-NHC(O)CH_3$.

[00244] In some embodiments, *e.g.* for Formula (**A**) and any subgenera thereof, *e.g.* for Formula (**XV**), (**XVI**), (**XVII**), (**XVIII**), (**XV-a**), (**XVI-a**), (**XVII-a**), (**XVII-b**), (**XVIII-a**), (**XV-b**), or (**XV-c**), at least one R^y is $-N(R^B)SO_2R^A$. In some embodiments, at least one R^y is $-NHSO_2R^A$. In some embodiments, at least one R^y is $-N(C_{1-6}$ alkyl)SO_2R^A. In certain embodiments, at least one R^y is $-NHSO_2(C_{1-6}$ alkyl) or $-N(C_{1-6}$ alkyl)$SO_2(C_{1-6}$ alkyl). In certain embodiments, at least one R^y is $-NHSO_2CH_3$. In certain embodiments, at least one R^y is $-N(CH_3)SO_2CH_3$.

[00245] In some embodiments, *e.g.* for Formula (**A**) and any subgenera thereof, *e.g.* for Formula (**XV**), (**XVI**), (**XVII**), (**XVIII**), (**XV-a**), (**XVI-a**), (**XVII-a**), (**XVII-b**), (**XVIII-a**), (**XV-b**), or (**XV-c**), at least one R^y is optionally substituted heterocyclyl, optionally substituted carbocyclyl, optionally substituted aryl, or optionally substituted heteroaryl. In certain embodiments, at least one R^y is an optionally substituted 5- to 6-membered heterocyclyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, at least one R^y is an optionally substituted 5-membered heterocyclyl having one heteroatom selected from nitrogen, oxygen, and sulfur. In certain embodiments, at least one R^y is optionally substituted pyrrolidinyl. In certain embodiments, at least one R^y is pyrroldinyl, hydroxypyrrolidinyl, or methylpyrrolidinyl. In certain embodiments, at least one R^y is an optionally substituted 6-membered heterocyclyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, at least one R^y is an optionally substituted 6-membered heterocyclyl having one heteroatom selected from nitrogen, oxygen, and sulfur. In certain embodiments, at least

one R^y is optionally substituted piperidinyl. In certain embodiments, at least one R^y is an optionally substituted 6-membered heterocyclyl having two heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, at least one R^y is optionally substituted piperdinyl, optionally substituted piperazinyl, or optionally substituted morpholinyl. In certain embodiments, at least one R^y is morpholinyl, tetrahydropyranyl, piperidinyl, methylpiperidinyl, piperazinyl, methylpiperazinyl, acetylpiperazinyl, methylsulfonylpiperazinyl, aziridinyl, or methylaziridinyl. In some embodiments, at least one R^y is an optionally substituted 5- to 6-membered heteroaryl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, at least one R^y is an optionally substituted 5-membered heteroaryl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, at least one R^y is an optionally substituted 5-membered heteroaryl having one heteroatom selected from nitrogen, oxygen, and sulfur. In certain embodiments, at least one R^y is an optionally substituted 5-membered heteroaryl having two heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, at least one R^y is an optionally substituted 6-membered heteroaryl having 1-3 nitrogens. In certain embodiments, at least one R^y is an optionally substituted pyrazolyl. In certain embodiments, at least one R^y is an optionally substituted imidazolyl. In certain embodiments, at least one R^y is an optionally substituted pyridyl. In certain embodiments, at least one R^y is an optionally substituted pyrimidyl. In certain embodiments, at least one R^y is pyrazolyl, methylpyrazolyl, imidazolyl, or methylimidazolyl.

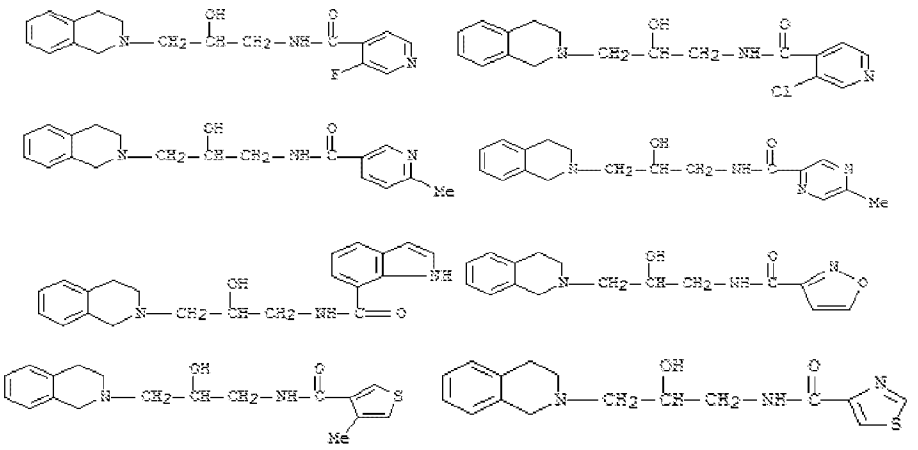
[00246] As generally defined above, R^{A1} and R^{A2} are independently hydrogen, substituted or unsubstituted C_{1-3} alkyl, substituted or unsubstituted acyl, or a nitrogen protecting group. In some embodiments, R^{A1} is hydrogen. In some embodiments, R^{A1} is substituted or unsubstituted C_{1-3} alkyl. In some embodiments, R^{A1} is unsubstituted C_{1-3} alkyl. In some embodiments, R^{A1} is methyl, ethyl, n-propyl, or isopropyl. In some embodiments, R^{A1} is substituted C_{1-3} alkyl. In some embodiments, R^{A1} is $-CF_3$, $-CHF_2$, $-CH_2F$, or $-CH(CF_3)CH_3$. In some embodiments, R^{A1} is substituted or unsubstituted acyl. In some embodiments, R^{A1} is acetyl. In some embodiments, R^{A1} is a nitrogen protecting group. In some embodiments, R^{A1} is CH_3SO_2-. In some embodiments, R^{A2} is hydrogen. In some embodiments, R^{A2} is substituted or unsubstituted C_{1-3} alkyl. In some embodiments, R^{A2} is unsubstituted C_{1-3} alkyl. In some embodiments, R^{A2} is methyl, ethyl, n-propyl, or isopropyl. In some embodiments, R^{A2} is substituted C_{1-3} alkyl. In some embodiments, R^{A2} is $-CF_3$, $-CHF_2$, $-CH_2F$, or $-CH(CF_3)CH_3$. In some embodiments, R^{A2} is substituted or unsubstituted acyl. In some

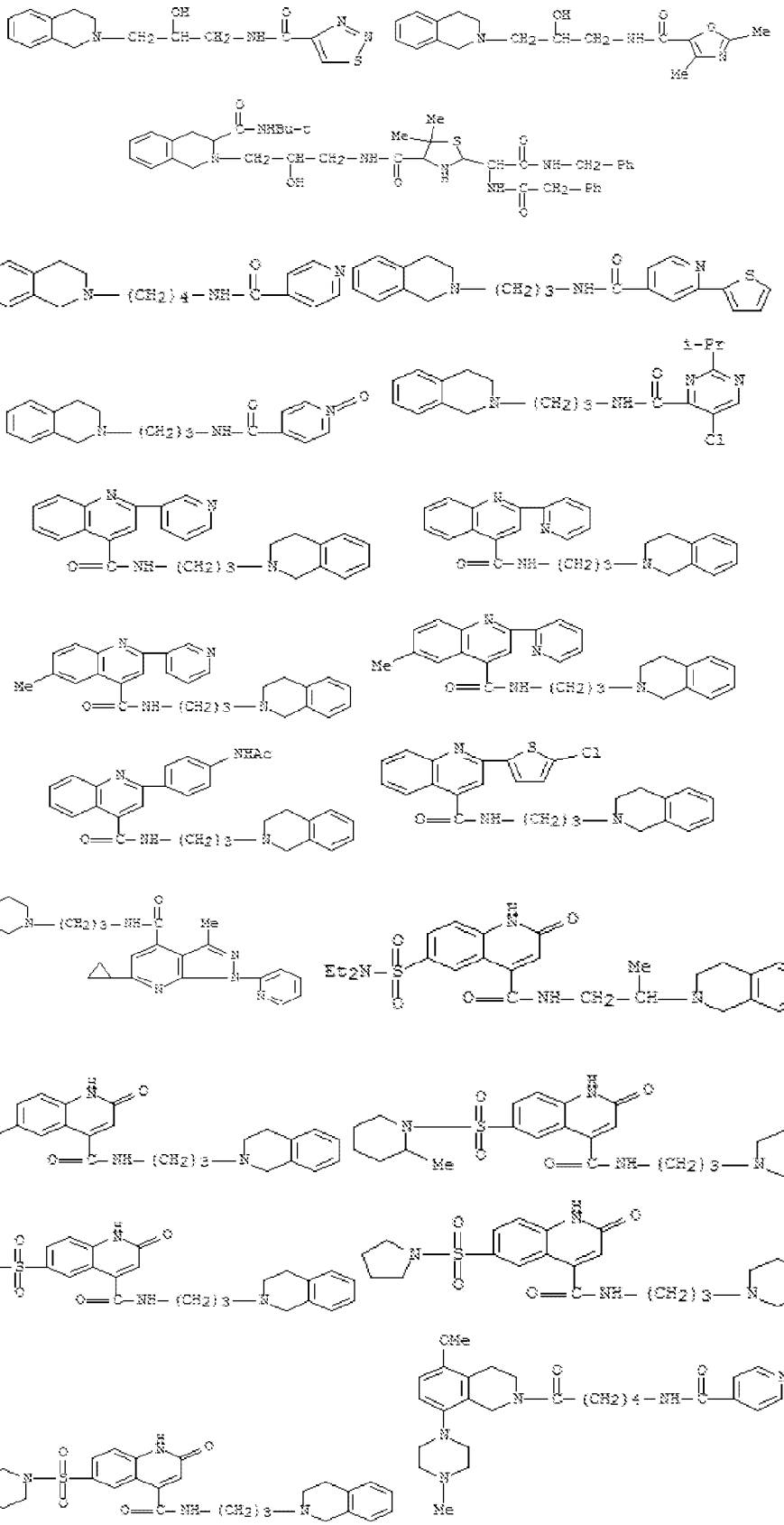
embodiments, R^{A2} is acetyl. In some embodiments, R^{A2} is a nitrogen protecting group. In some embodiments, R^{A2} is CH_3SO_2–. In some embodiments, R^{A1} is hydrogen, and R^{A2} is hydrogen. In some embodiments, R^{A1} is hydrogen, and R^{A2} is substituted or unsubstituted C_{1-3} alkyl. In some embodiments, R^{A1} is hydrogen, and R^{A2} is methyl, ethyl, n-propyl, or isopropyl. In some embodiments, R^{A1} is hydrogen, and R^{A2} is –CF_3, -CHF_2, -CH_2F, or –$CH(CF_3)CH_3$. In some embodiments, R^{A1} is hydrogen, and R^{A2} is substituted or unsubstituted acyl. In some embodiments, R^{A1} is hydrogen, and R^{A2} is acetyl. In some embodiments, R^{A1} is hydrogen, and R^{A2} is a nitrogen protecting group. In some embodiments, R^{A1} is hydrogen and R^{A2} is CH_3SO_2–. In some embodiments, R^{A1} is substituted or unsubstituted C_{1-3} alkyl, and R^{A2} is substituted or unsubstituted C_{1-3} alkyl. In some embodiments, R^{A1} is substituted or unsubstituted C_{1-3} alkyl, and R^{A2} is methyl. In some embodiments, R^{A1} is substituted or unsubstituted C_{1-3} alkyl, and R^{A2} is ethyl. In some embodiments, R^{A1} is substituted or unsubstituted C_{1-3} alkyl, and R^{A2} is n-propyl. In some embodiments, R^{A1} is substituted or unsubstituted C_{1-3} alkyl, and R^{A2} is isopropyl. In some embodiments, R^{A1} is substituted or unsubstituted C_{1-3} alkyl, and R^{A2} is substituted or unsubstituted acyl. In some embodiments, R^{A1} is substituted or unsubstituted C_{1-3} alkyl, and R^{A2} is a nitrogen protecting group. In some embodiments, R^{A1} is methyl, and R^{A2} is substituted or unsubstituted C_{1-3} alkyl. In some embodiments, R^{A1} is methyl, and R^{A2} is methyl. In some embodiments, R^{A1} is methyl, and R^{A2} is ethyl. In some embodiments, R^{A1} is methyl, and R^{A2} is n-propyl. In some embodiments, R^{A1} is methyl, and R^{A2} is isopropyl. In some embodiments, R^{A1} is methyl, and R^{A2} is substituted or unsubstituted acyl. In some embodiments, R^{A1} is methyl, and R^{A2} is a nitrogen protecting group. In some embodiments, R^{A1} is ethyl, and R^{A2} is substituted or unsubstituted C_{1-3} alkyl. In some embodiments, R^{A1} is ethyl, and R^{A2} is methyl. In some embodiments, R^{A1} is ethyl, and R^{A2} is ethyl. In some embodiments, R^{A1} is ethyl, and R^{A2} is n-propyl. In some embodiments, R^{A1} is ethyl, and R^{A2} is isopropyl. In some embodiments, R^{A1} is ethyl, and R^{A2} is substituted or unsubstituted acyl. In some embodiments, R^{A1} is ethyl, and R^{A2} is a nitrogen protecting group. In some embodiments, R^{A1} is n-propyl, and R^{A2} is substituted or unsubstituted C_{1-3} alkyl. In some embodiments, R^{A1} is n-propyl, and R^{A2} is methyl. In some embodiments, R^{A1} is n-propyl, and R^{A2} is ethyl. In some embodiments, R^{A1} is n-propyl, and R^{A2} is n-propyl. In some embodiments, R^{A1} is n-propyl and R^{A2} is isopropyl. In some embodiments, R^{A1} is n-propyl, and R^{A2} is substituted or unsubstituted acyl. In some embodiments, R^{A1} is n-propyl and R^{A2} is a nitrogen protecting group. In some embodiments, R^{A1} is isopropyl and R^{A2} is substituted or unsubstituted C_{1-3} alkyl. In some embodiments, R^{A1} is isopropyl and R^{A2} is methyl. In

some embodiments, R^{A1} is isopropyl and R^{A2} is ethyl. In some embodiments, R^{A1} is isopropyl, and R^{A2} is n-propyl. In some embodiments, R^{A1} is isopropyl, and R^{A2} is isopropyl. In some embodiments, R^{A1} is isopropyl, and R^{A2} is substituted or unsubstituted acyl. In some embodiments, R^{A1} is isopropyl, and R^{A2} is a nitrogen protecting group. In some embodiments, R^{A1} is substituted or unsubstituted acyl, and R^{A2} is substituted or unsubstituted C_{1-3} alkyl. In some embodiments, R^{A1} is a nitrogen protecting group, and R^{A2} is substituted or unsubstituted C_{1-3} alkyl. In some embodiments, R^{A1} is a nitrogen protecting group and R^{A2} is methyl. In some embodiments, R^{A1} is a nitrogen protecting group, and R^{A2} is ethyl. In some embodiments, R^{A1} is a nitrogen protecting group, and R^{A2} is n-propyl. In some embodiments, R^{A1} is a nitrogen protecting group, and R^{A2} is isopropyl. In some embodiments, R^{A1} is a nitrogen protecting group, and R^{A2} is a nitrogen protecting group.

[00247] As generally defined above, R^{A1} and R^{A2} can be taken together with the intervening nitrogen atom to form a substituted or unsubstituted 3-6 membered heterocyclic ring. In certain embodiments, R^{A1} and R^{A2} can be taken together with the intervening nitrogen atom to form a substituted or unsubstituted azetidine. In certain embodiments, R^{A1} and R^{A2} can be taken together with the intervening nitrogen atom to form a substituted or unsubstituted pyrrolidine. In certain embodiments, R^{A1} and R^{A2} can be taken together with the intervening nitrogen atom to form a substituted or unsubstituted piperidine. In certain embodiments, R^{A1} and R^{A2} can be taken together with the intervening nitrogen atom to form a substituted or unsubstituted piperazine. In certain embodiments, R^{A1} and R^{A2} can be taken together with the intervening nitrogen atom to form a substituted or unsubstituted morpholine.

[00248] In certain embodiments, a provided compound is not of any one of the following formulae:





[00249] In certain embodiments, a provided compound is a compound listed in Table 1A, or a pharmaceutically acceptable salt thereof.

Table 1A. Exemplary Compounds

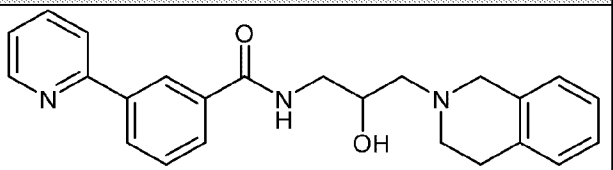
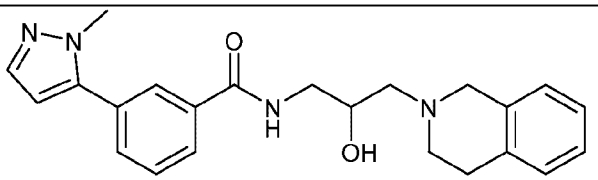
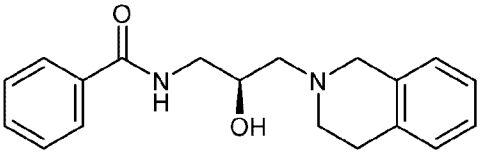
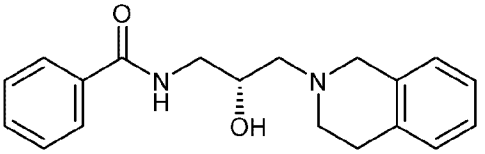
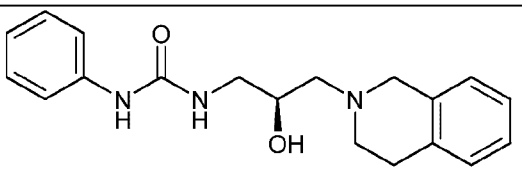
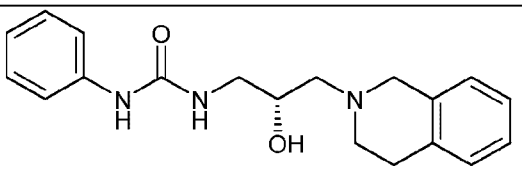
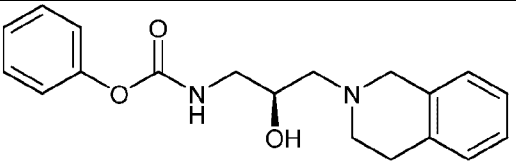
Cmpd No	Structure	Exact Mass	LCMS m/z (M+H)
1		387.1947	388.2
2		390.2056	391.2
3		310.1681	311.1
4		310.1681	311.1
5		325.179	326.2
6		325.179	326.2
7		326.163	327.2

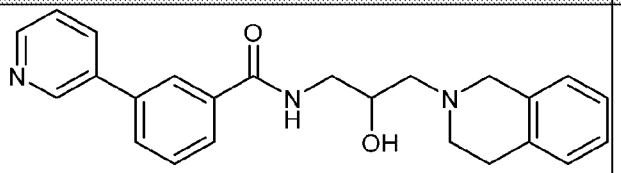
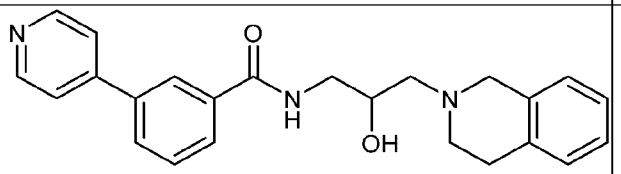
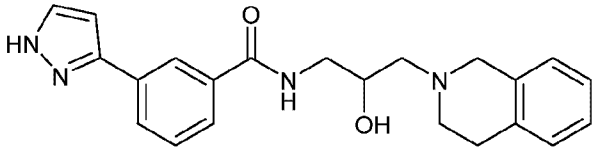
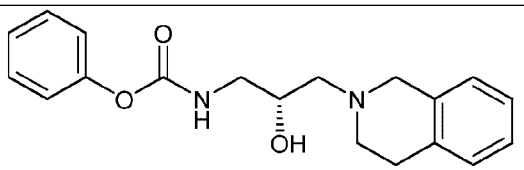
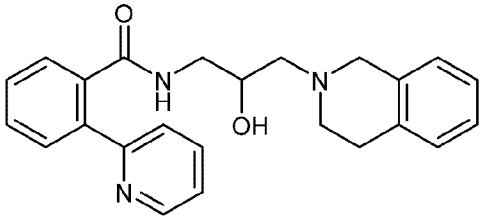
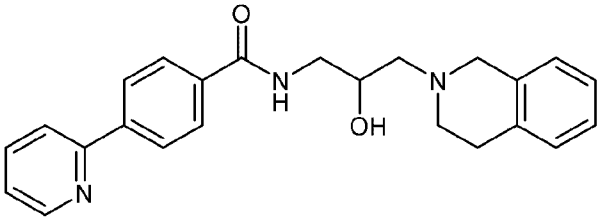
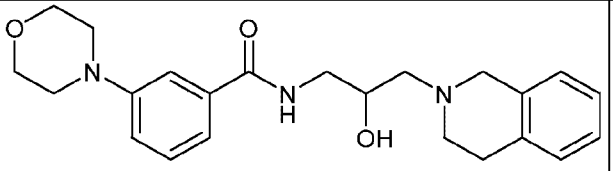
Table 1A. Exemplary Compounds			
Cmpd No	Structure	Exact Mass	LCMS m/z (M+H)
8		387.1947	388.2
9		387.1947	388.2
10		376.1899	377.2
11		326.163	327.2
12		387.1947	388.2
13		387.1947	388.2
14		395.2209	396.2

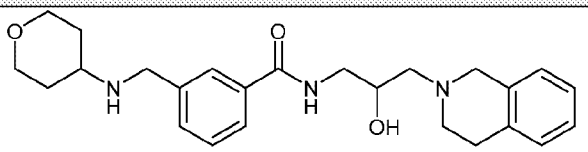
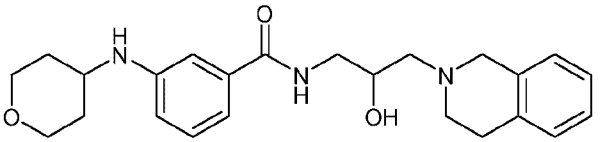
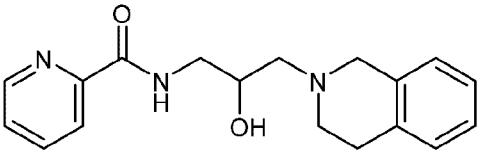
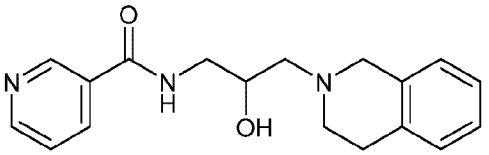
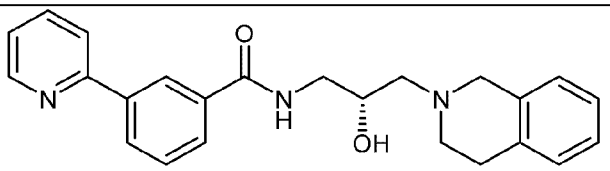
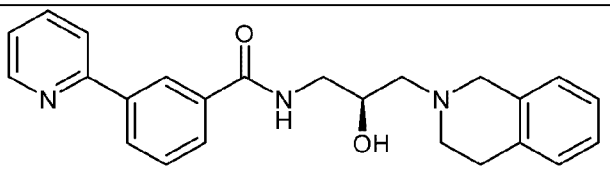
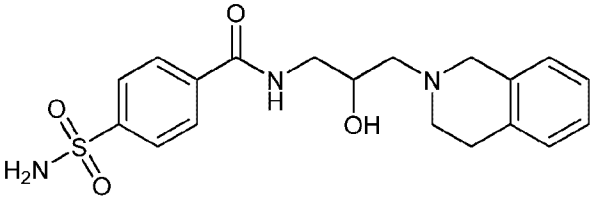
Table 1A. Exemplary Compounds			
Cmpd No	Structure	Exact Mass	LCMS m/z (M+H)
15		423.2522	424.2
16		409.2365	410.2
17		311.1634	312.1
18		311.1634	312.2
19		387.1947	388.2
20		387.1947	388.2
21		389.1409	390.1

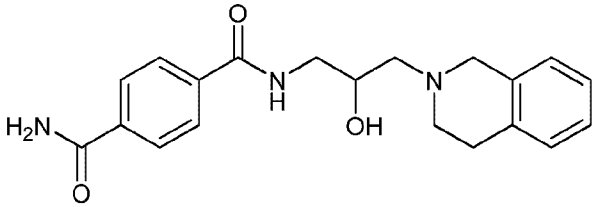
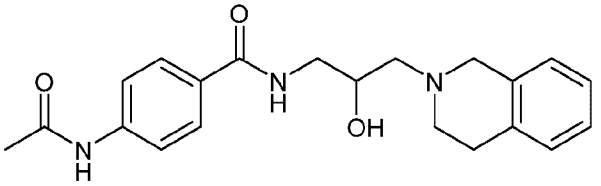
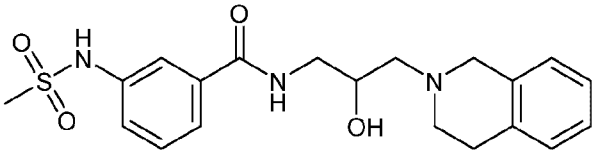
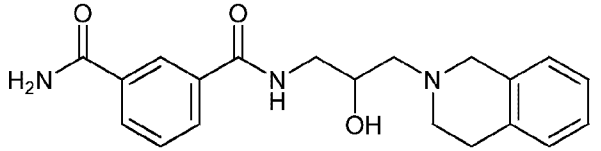
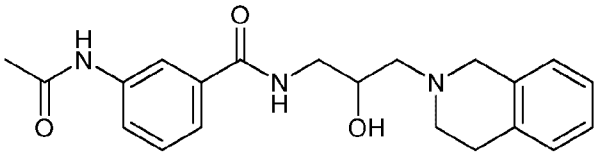
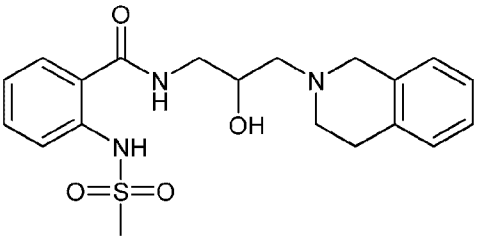
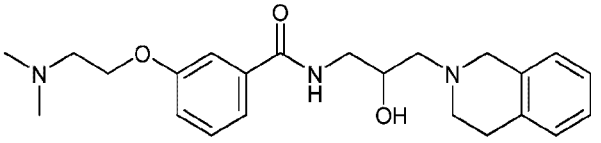
Table 1A. Exemplary Compounds			
Cmpd No	**Structure**	**Exact Mass**	**LCMS m/z (M+H)**
22		353.1739	354.1
23		367.1896	368.1
24		403.1566	404.1
25		353.1739	354.2
26		367.1896	368.2
27		403.1566	404.2
28		397.2365	398.1

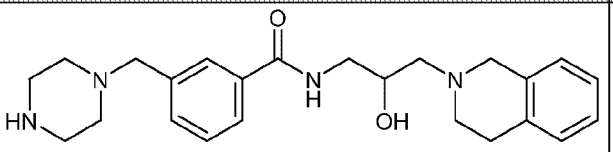
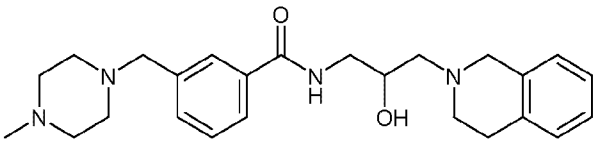
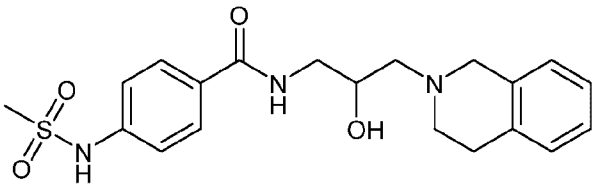
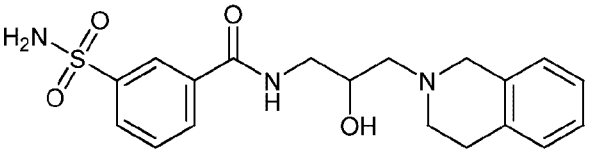
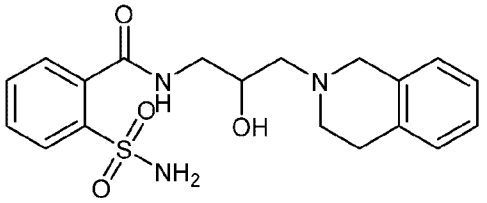
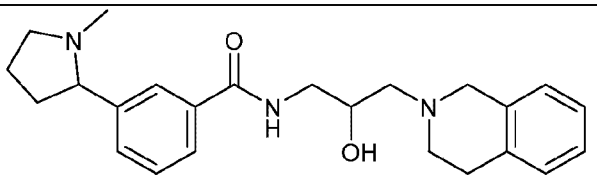
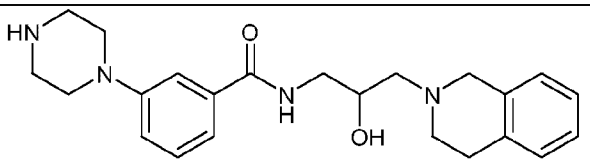
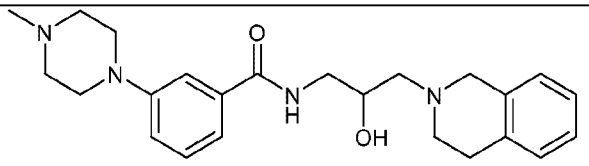
Table 1A. Exemplary Compounds			
Cmpd No	Structure	Exact Mass	LCMS m/z (M+H)
29		408.2525	409.2
30		422.2682	423.2
31		403.1566	404.2
32		389.1409	390.1
33		389.1409	390
34		393.2416	394.1
35		394.2369	395.2
36		408.2525	409.2

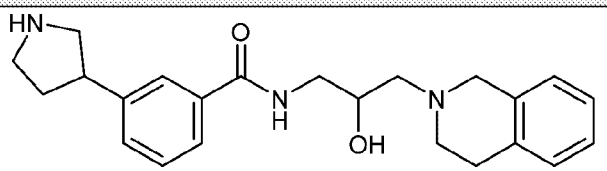
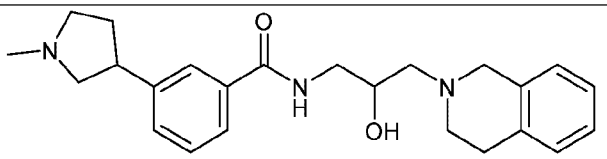
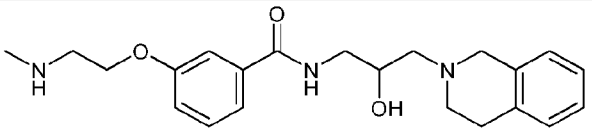
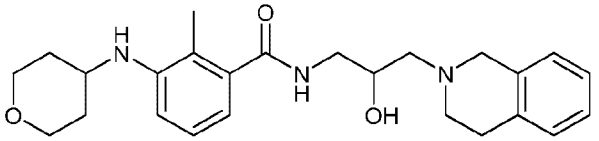
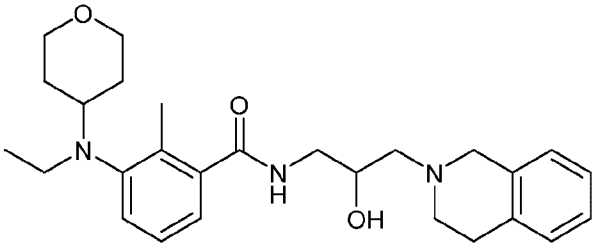
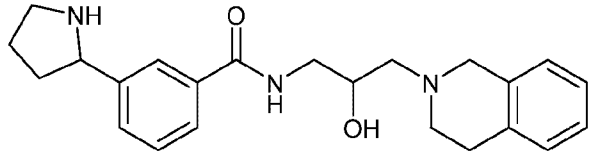
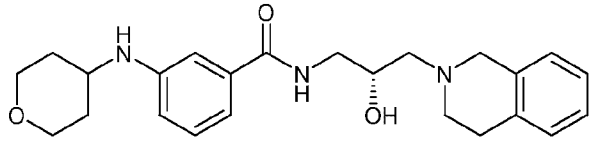
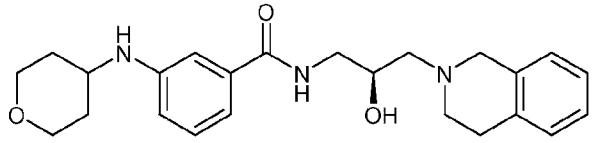
Table 1A. Exemplary Compounds			
Cmpd No	**Structure**	**Exact Mass**	**LCMS m/z (M+H)**
37		379.226	380.2
38		393.2416	394.2
39		383.2209	384.2
40		423.2522	424.2
41		451.2835	452.3
42		379.226	380.2
43		409.2365	410.2
44		409.2365	410.2

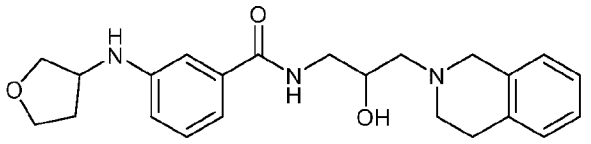
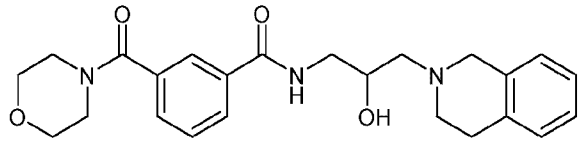
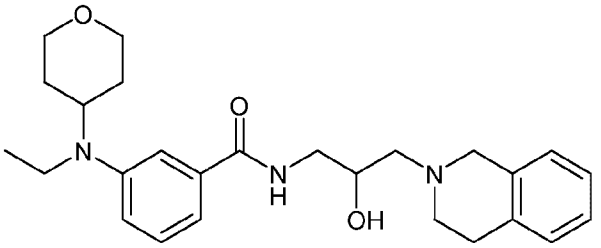
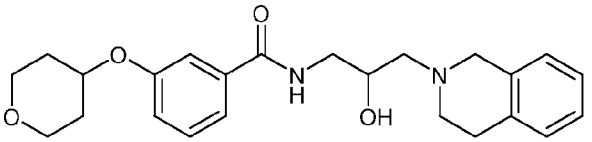
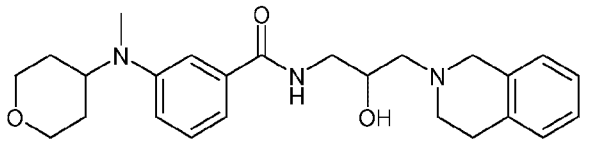
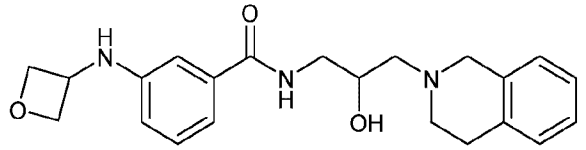
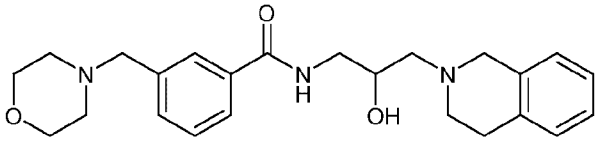
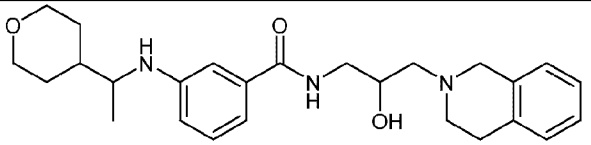
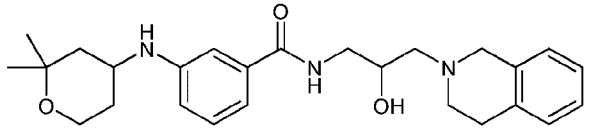
Table 1A. Exemplary Compounds			
Cmpd No	**Structure**	**Exact Mass**	**LCMS m/z (M+H)**
45		395.2209	396.2
46		423.2158	424.2
47		437.2678	438.3
48		410.2206	411.2
49		423.2522	424.1
50		381.2052	382.2
51		409.2365	410.1
52		437.2678	438.3
53		437.2678	438.3

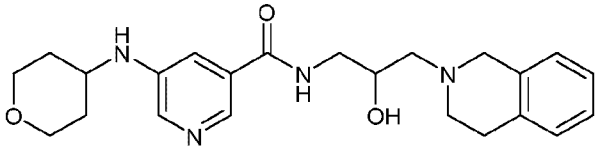
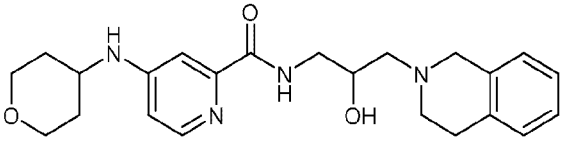
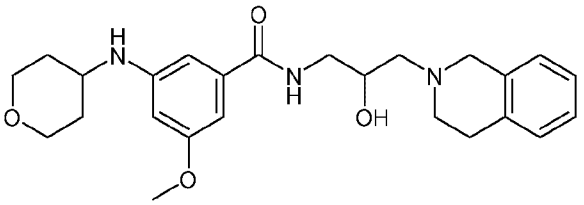
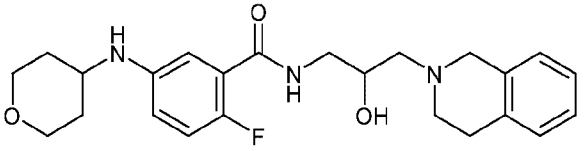
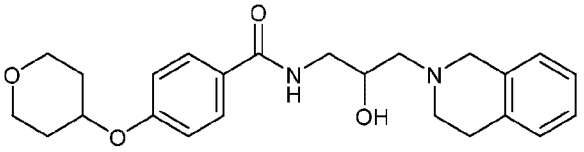
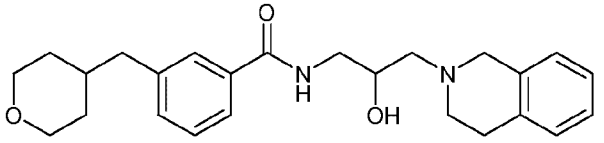
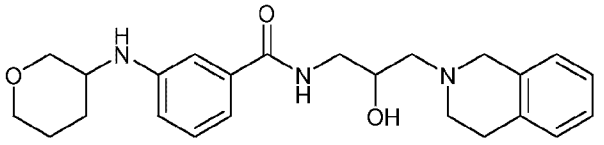
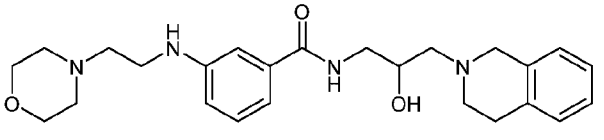
Table 1A. Exemplary Compounds			
Cmpd No	**Structure**	**Exact Mass**	**LCMS m/z (M+H)**
54		410.2318	411.1
55		410.2318	411.1
56		439.2471	440.1
57		427.2271	428.2
58		410.2206	411.2
59		408.2413	409.1
60		409.2365	410.2
61		438.2631	439.2

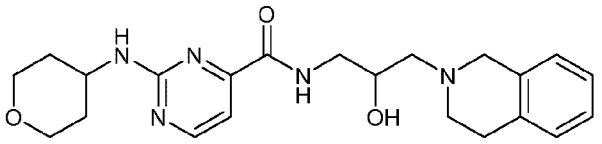
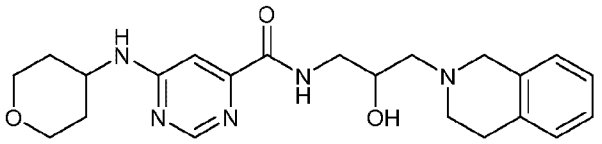
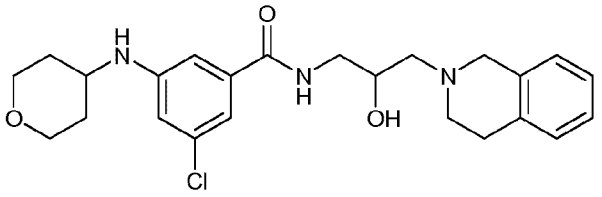
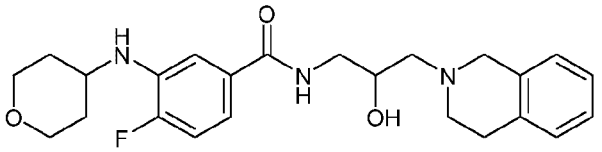
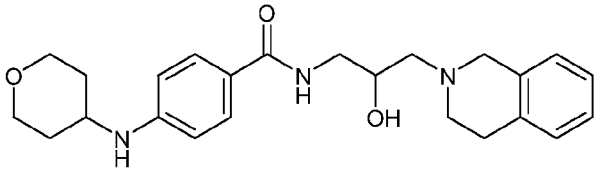
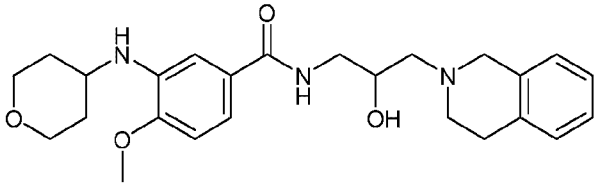
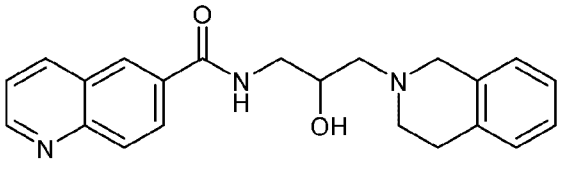
Table 1A. Exemplary Compounds			
Cmpd No	Structure	Exact Mass	LCMS m/z (M+H)
62		411.227	412.2
63		411.227	412.2
64		443.1976	444.1
65		427.2271	428
66		409.2365	410.1
67		439.2471	440.2
68		361.179	362.1

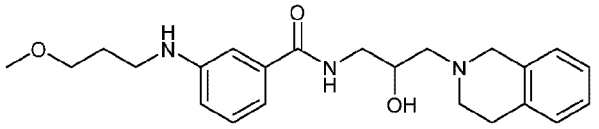
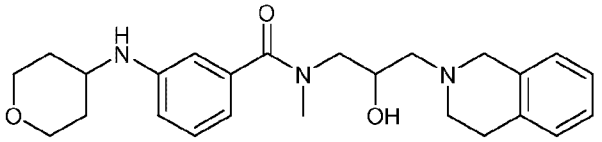
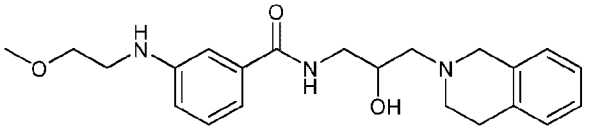
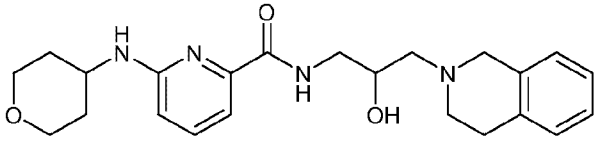
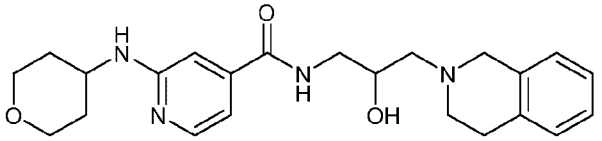
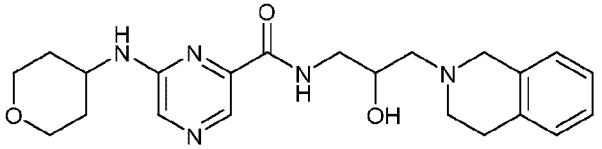
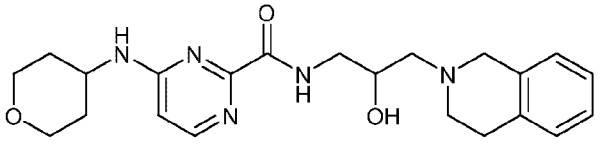
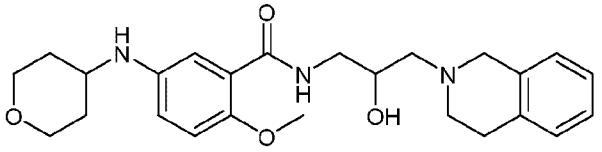
Table 1A. Exemplary Compounds			
Cmpd No	**Structure**	**Exact Mass**	**LCMS m/z (M+H)**
69		397.2365	398.2
71		423.2522	424.2
72		383.2209	384.2
73		410.2318	411.1
74		410.2318	411.2
75		411.227	412.1
76		411.227	412.2
77		439.2471	440.2

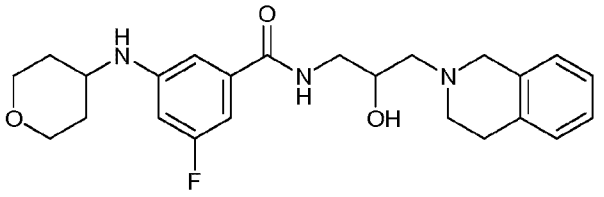
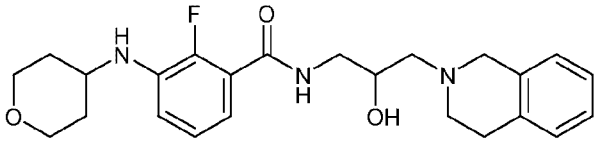
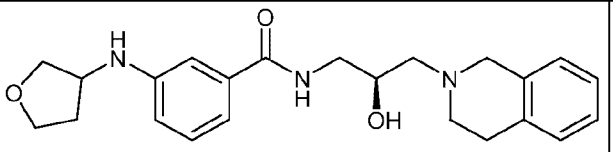
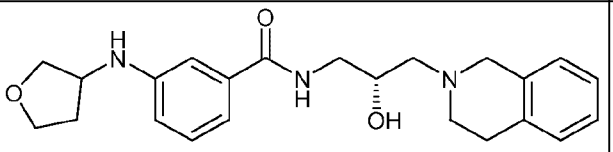
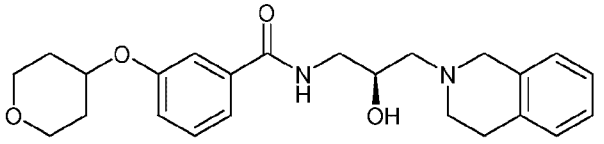
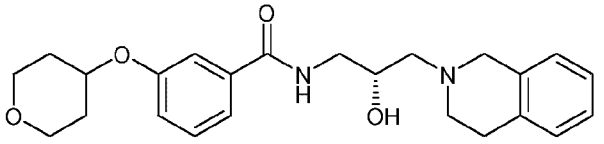
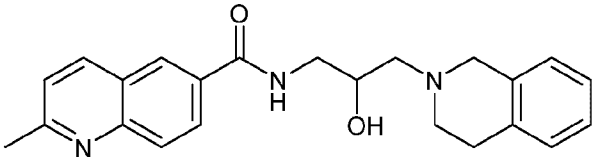
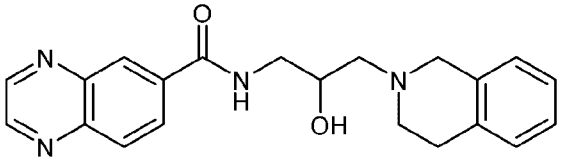
Table 1A. Exemplary Compounds			
Cmpd No	Structure	Exact Mass	LCMS m/z (M+H)
78		427.2271	428.2
79		427.2271	428.2
80		395.2209	396.2
81		395.2209	396.2
82		410.2206	411.1
83		410.2206	411.1
84		375.1947	376
85		362.1743	363.1

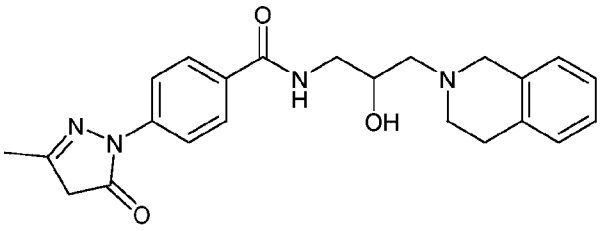
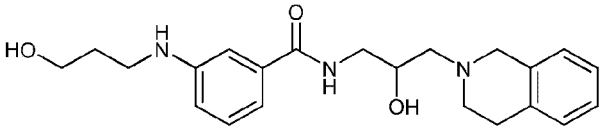
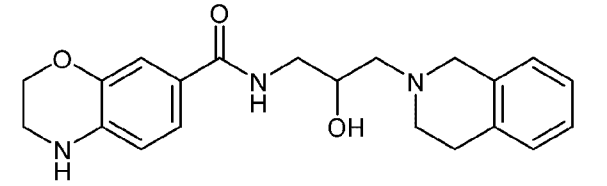
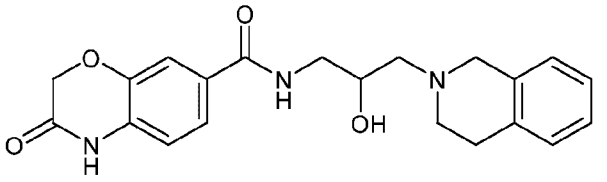
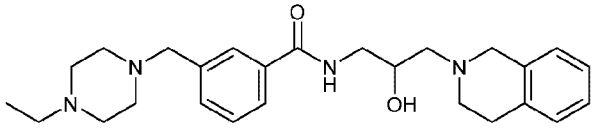
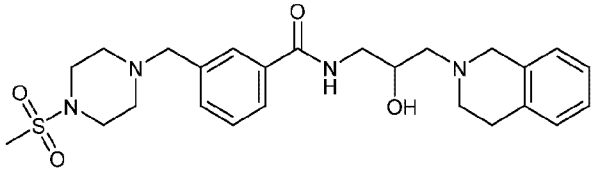
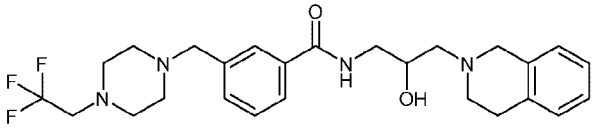
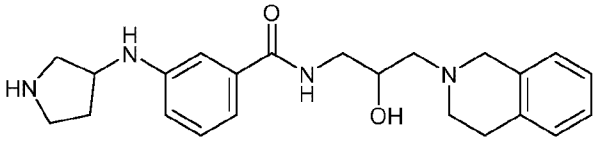
Table 1A. Exemplary Compounds			
Cmpd No	Structure	Exact Mass	LCMS m/z (M+H)
86		406.2005	407.2
87		383.2209	384.2
88		367.1896	368.1
89		381.1689	382.1
90		436.2838	437.2
91		486.2301	487.2
92		490.2556	491.3
93		394.2369	395.2

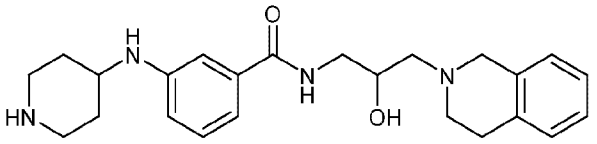
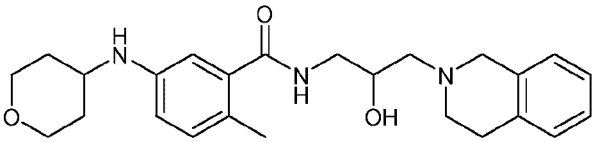
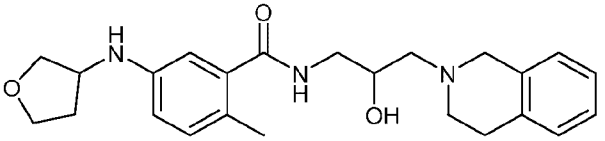
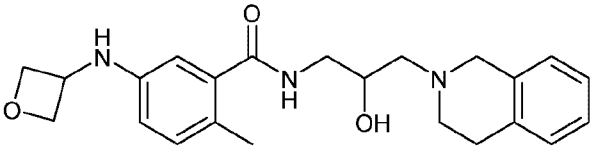
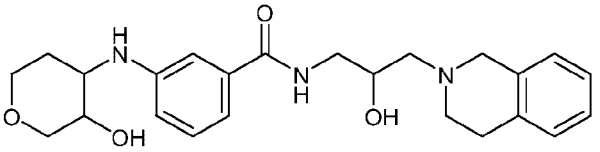
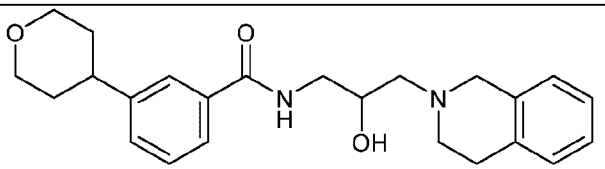
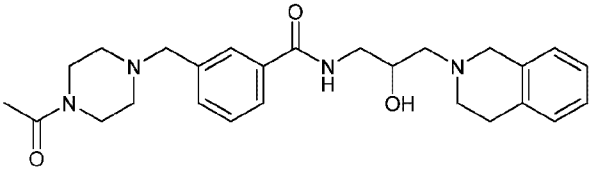
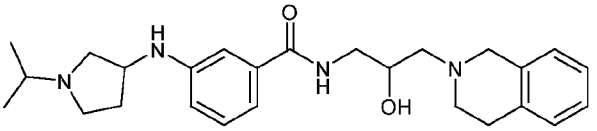
Table 1A. Exemplary Compounds			
Cmpd No	**Structure**	**Exact Mass**	**LCMS m/z (M+H)**
94		408.2525	409.3
95		423.2522	424.3
96		409.2365	410.3
97		395.2209	396.2
98		425.2315	426.2
99		394.2256	395.2
100		450.2631	451.2
101		436.2838	437.2

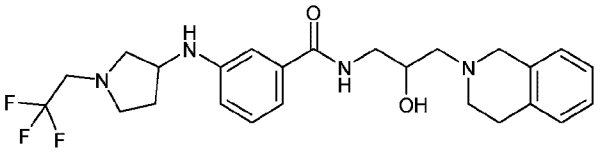
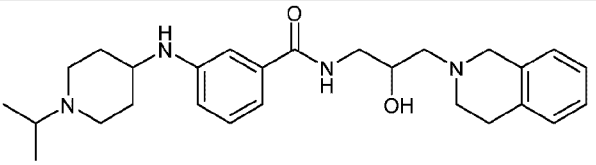
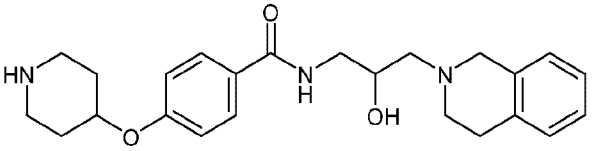
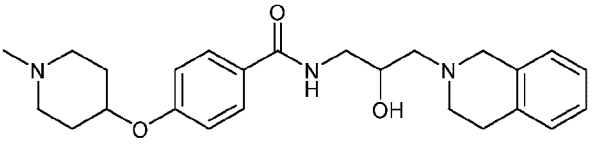
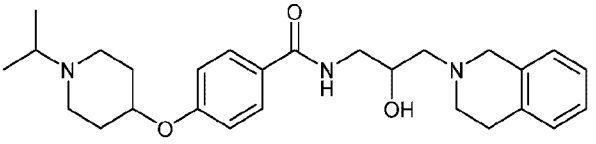
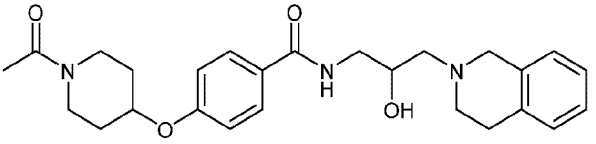
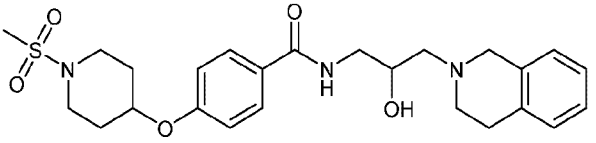
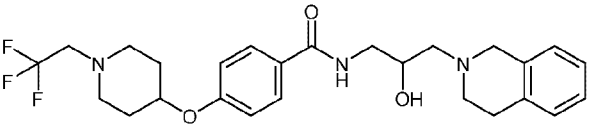
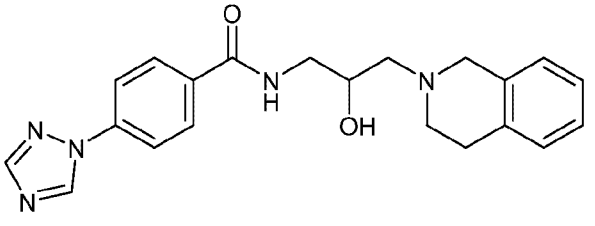
Table 1A. Exemplary Compounds			
Cmpd No	Structure	Exact Mass	LCMS m/z (M+H)
102		476.2399	477.2
103		450.2995	451.3
104		409.2365	410.2
105		423.2522	424.2
106		451.2835	452.2
107		451.2471	452.2
108		487.2141	488.2
109		491.2396	492.2
110		377.1852	378.2

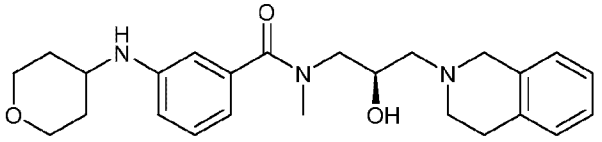
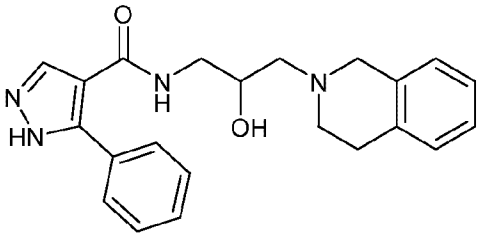
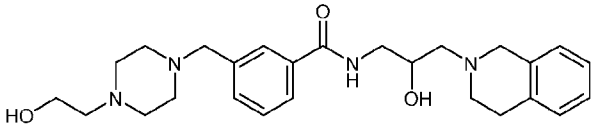
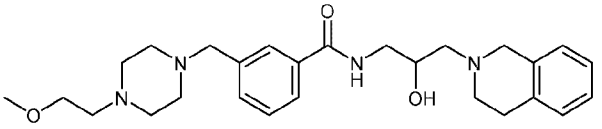
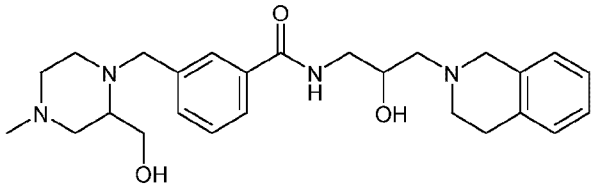
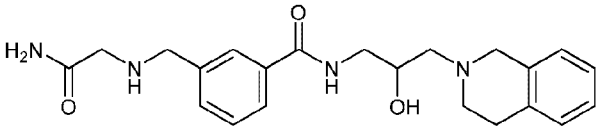
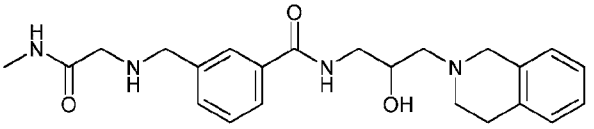
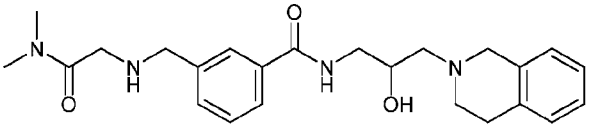
Table 1A. Exemplary Compounds			
Cmpd No	**Structure**	**Exact Mass**	**LCMS m/z (M+H)**
111		423.2522	424.2
112		376.1899	377.1
113		452.2787	453.2
114		466.2944	467.2
115		452.2787	453.2
116		396.2161	397.1
117		410.2318	411.1
118		424.2474	425.1

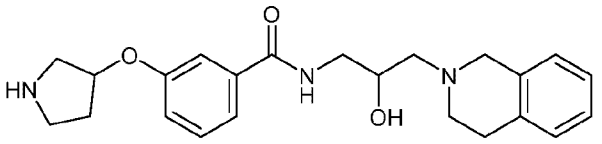
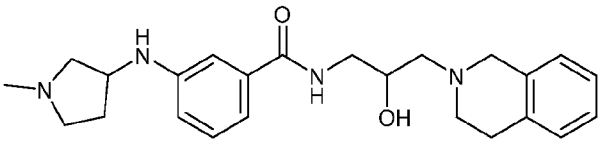
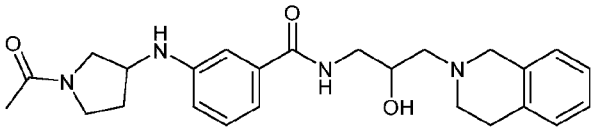
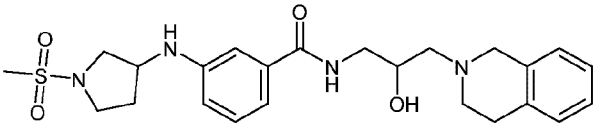
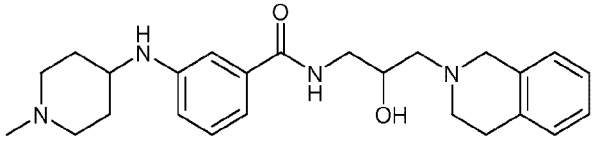
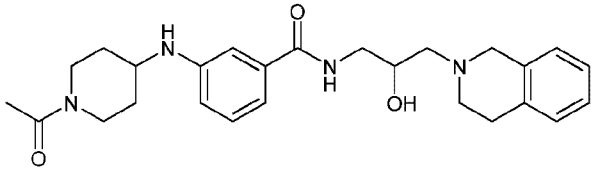
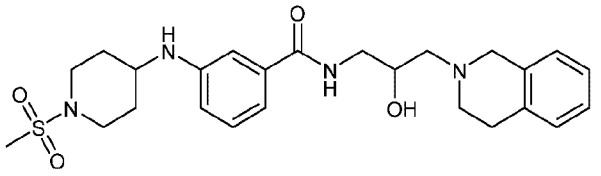
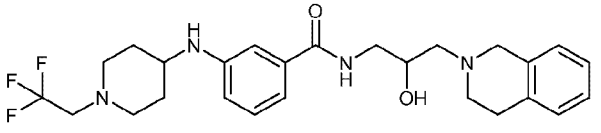
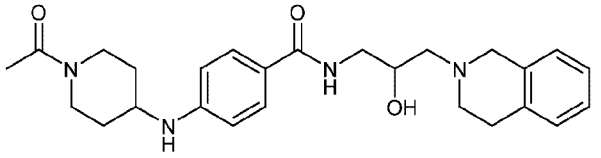
Table 1A. Exemplary Compounds			
Cmpd No	Structure	Exact Mass	LCMS m/z (M+H)
119		395.2209	396.2
120		408.2525	409.2
121		436.2474	437.2
122		472.2144	473
123		422.2682	423.2
124		450.2631	451.3
125		486.2301	487.2
126		490.2556	491.2
127		450.2631	451.3

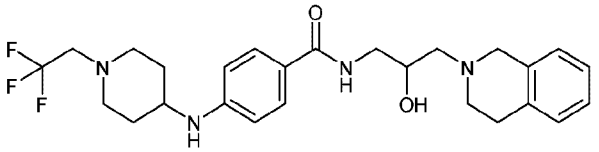
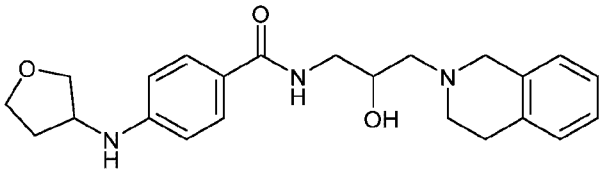
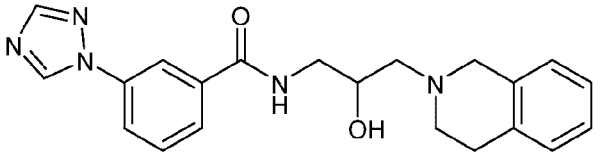
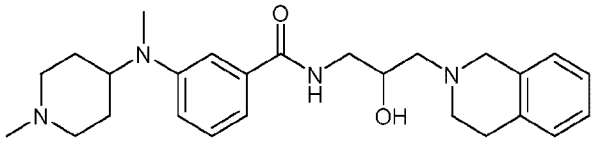
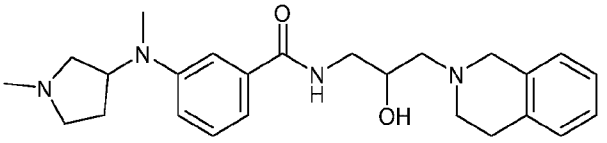
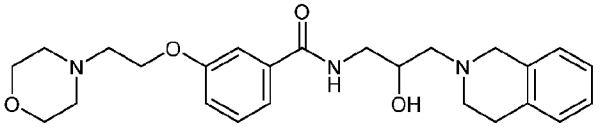
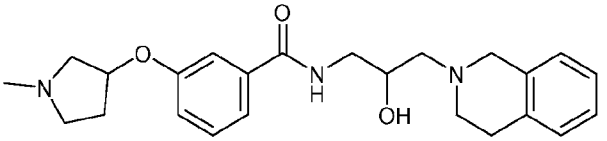
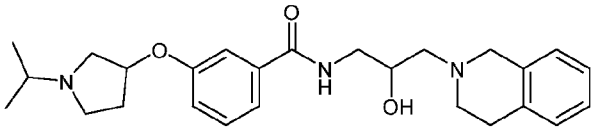
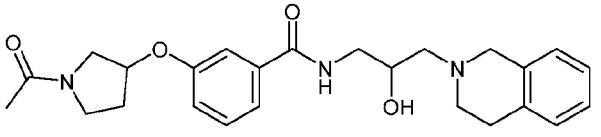
Table 1A. Exemplary Compounds			
Cmpd No	Structure	Exact Mass	LCMS m/z (M+H)
128		490.2556	491.2
129		395.2209	396.2
130		377.1852	378.2
131		436.2838	437.2
132		422.2682	423.2
133		439.2471	440.2
134		409.2365	410.3
135		437.2678	438.3
136		437.2315	438.2

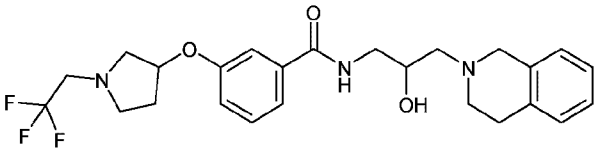
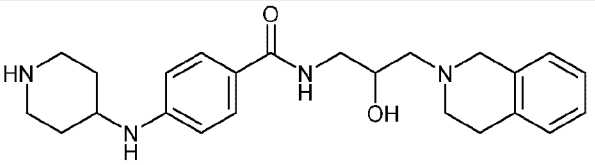
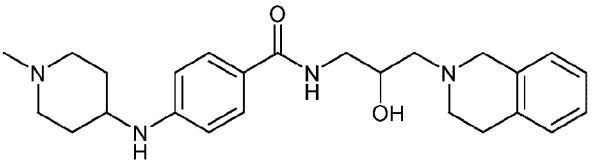
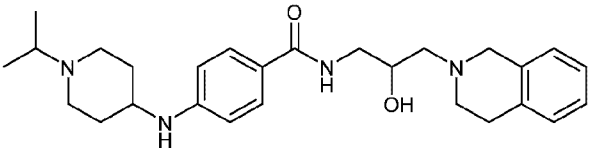
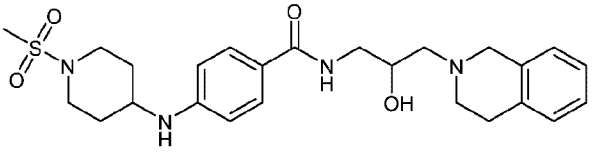
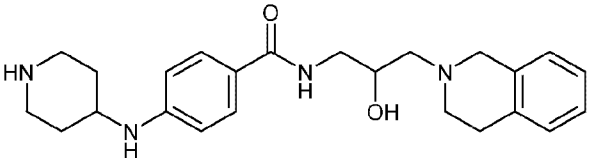
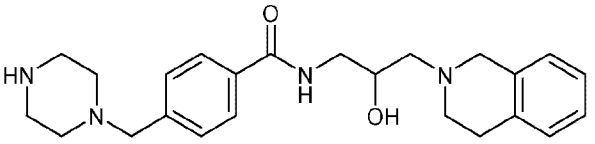
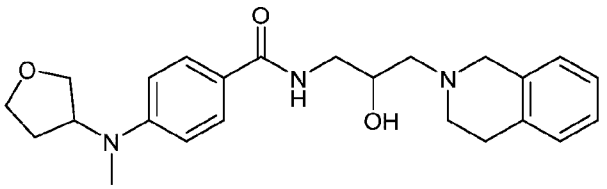
Table 1A. Exemplary Compounds			
Cmpd No	Structure	Exact Mass	LCMS m/z (M+H)
137		477.2239	478.3
138		408.2525	409.3
139		422.2682	423.2
140		450.2995	451.2
141		486.2301	487.2
142		396.2049	397.2
143		408.2525	409.3
144		409.2365	410.2

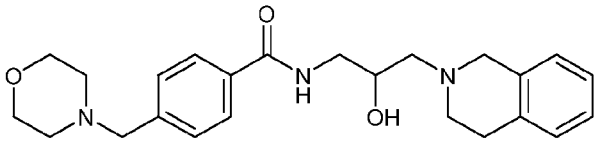
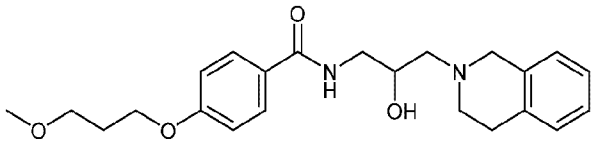
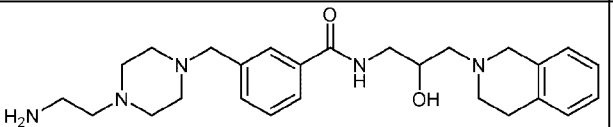
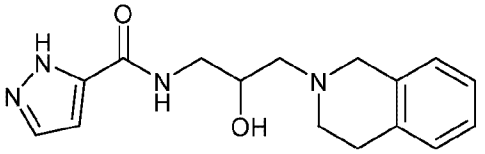
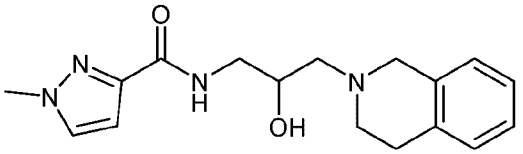
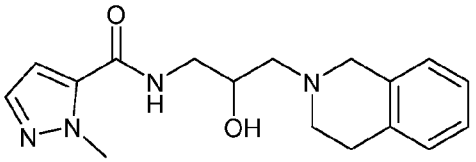
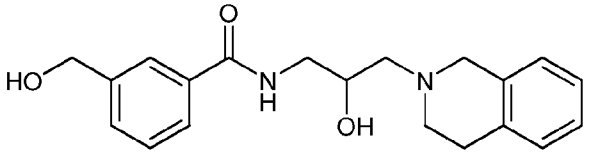
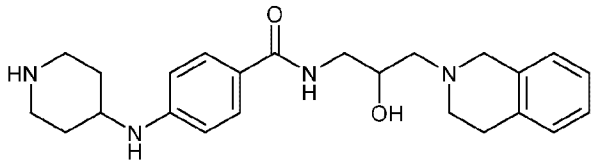
Table 1A. Exemplary Compounds			
Cmpd No	Structure	Exact Mass	LCMS m/z (M+H)
145		409.2365	410.2
146		398.2206	399.2
147		451.2947	452.2
148		300.1586	315.2
149		314.1743	315.1
150		314.1743	315.1
151		340.1787	341.1
152		437.2678	438.3

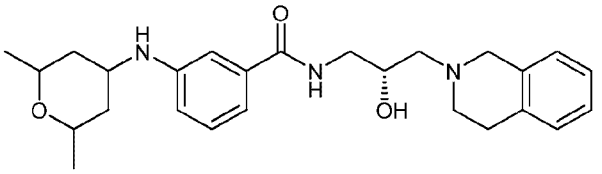
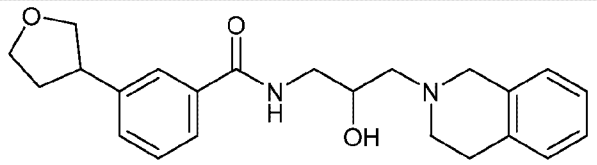
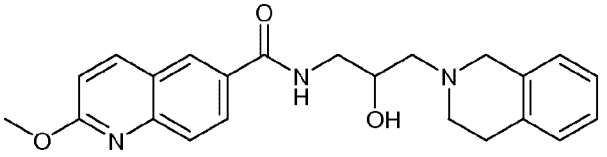
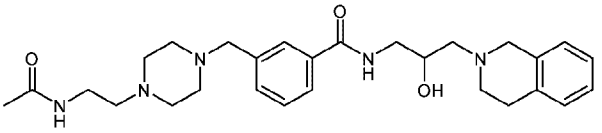
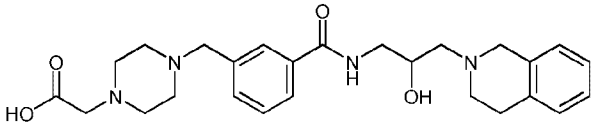
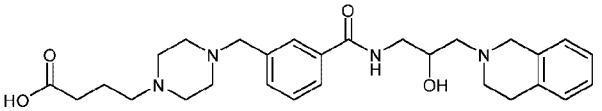
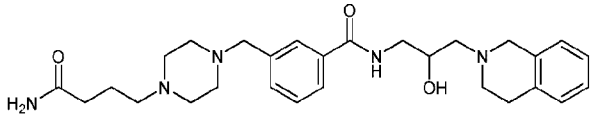
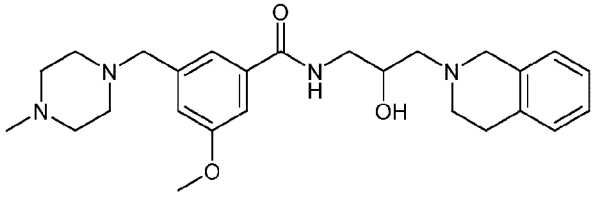
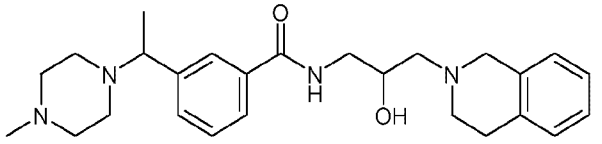
Table 1A. Exemplary Compounds			
Cmpd No	Structure	Exact Mass	LCMS m/z (M+H)
153		437.2678	438.3
154		380.21	381.2
155		391.1896	392.2
156		493.3053	494.2
157		466.258	467.2
158		494.2893	495.3
159		493.3053	494.2
160		452.2787	453.3
161		436.2838	437.2

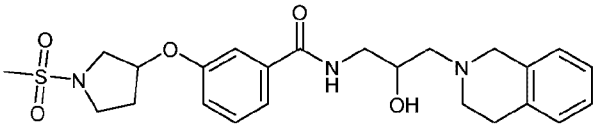
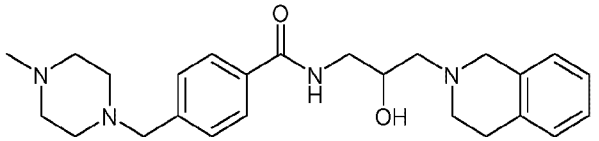
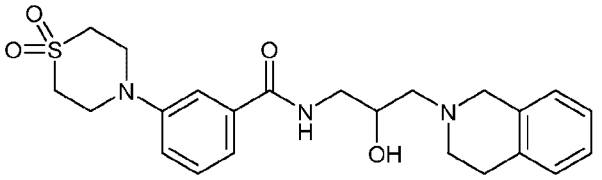
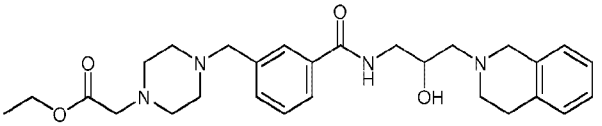
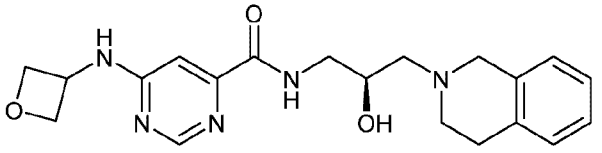
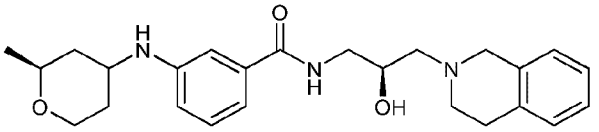
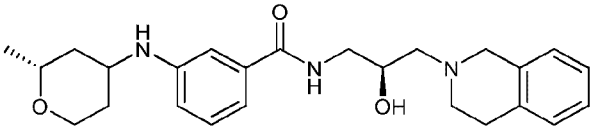
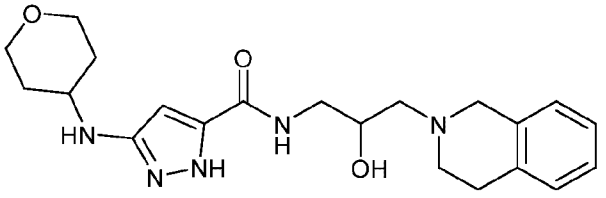
Table 1A. Exemplary Compounds			
Cmpd No	Structure	Exact Mass	LCMS m/z (M+H)
162		473.1984	474.2
163		422.2682	423.3
164		443.1879	444.2
165		494.2893	495.2
166		383.1957	384.1
167		423.2522	424.2
168		423.2522	424.2
169		399.227	400.2

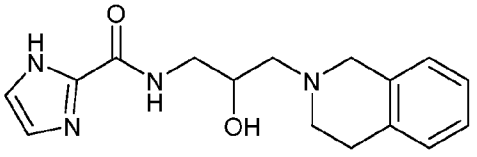
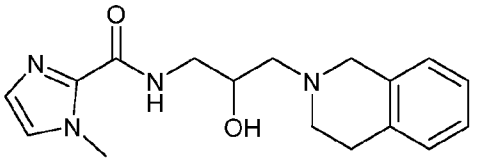
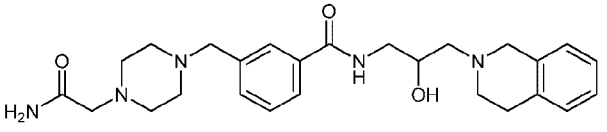
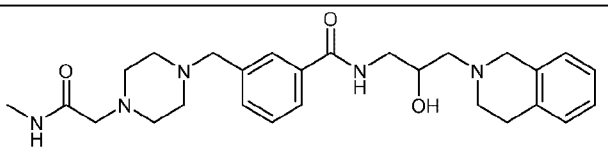
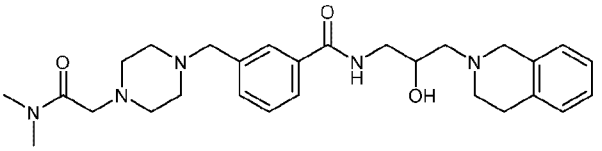
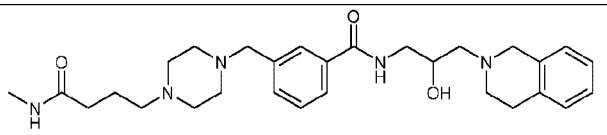
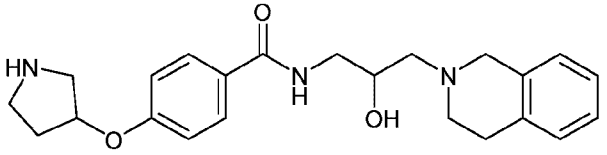
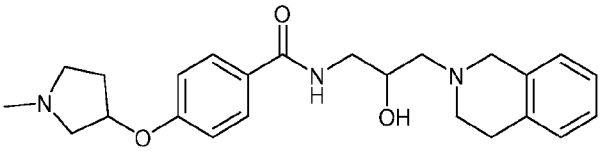
Table 1A. Exemplary Compounds			
Cmpd No	**Structure**	**Exact Mass**	**LCMS m/z (M+H)**
170		300.1586	301.1
171		314.1743	315.1
172		465.274	466.2
173		479.2896	480.3
174		493.3053	494.4
175		507.3209	508.3
176		395.2209	396.2
177		409.2365	410.2

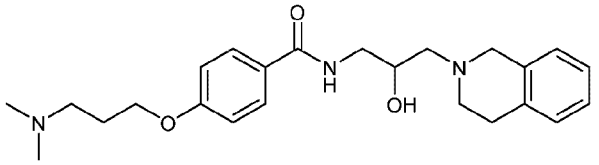
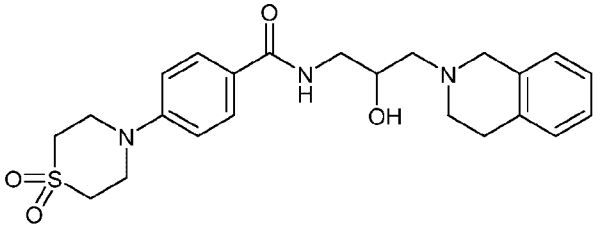
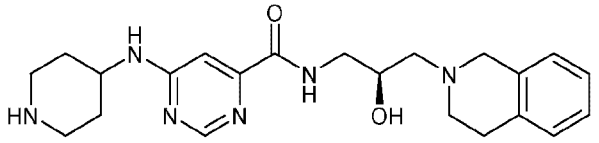
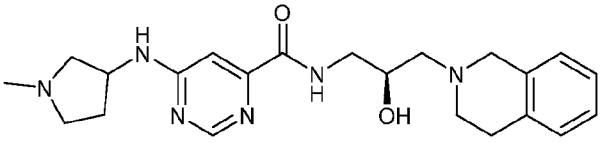
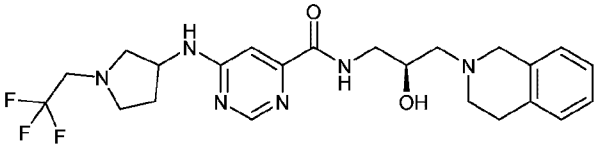
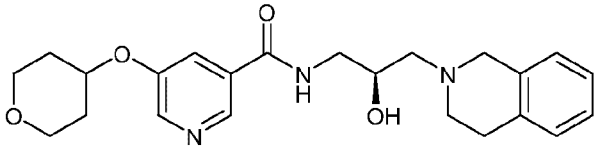
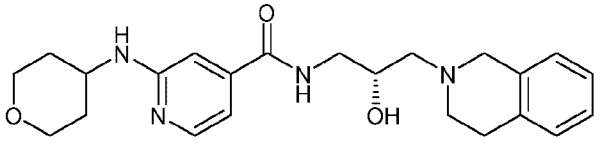
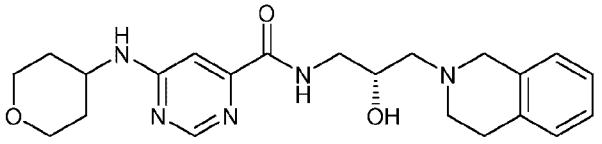
Table 1A. Exemplary Compounds			
Cmpd No	Structure	Exact Mass	LCMS m/z (M+H)
178		411.2522	412.2
179		443.1879	444.2
180		410.243	411.2
181		410.243	411.3
182		478.2304	479.3
183		411.2158	412.3
184		410.2318	411.3
185		411.227	412.1

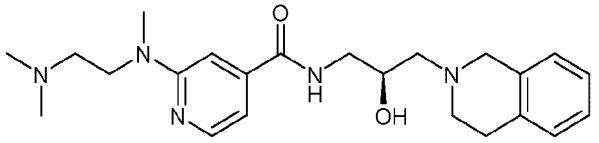
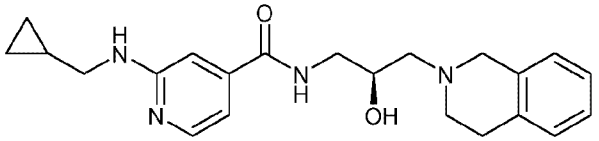
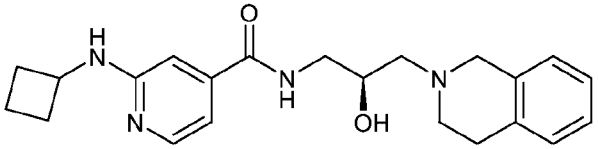
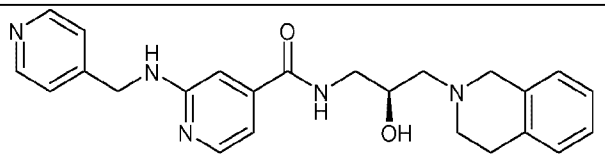
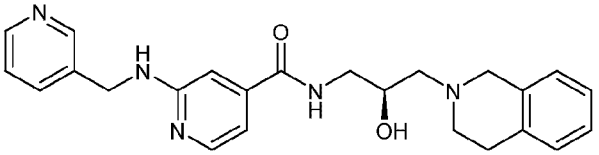
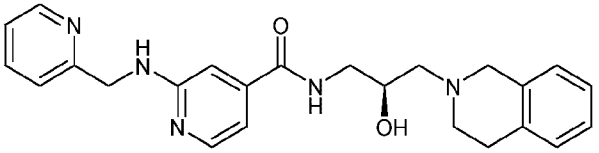
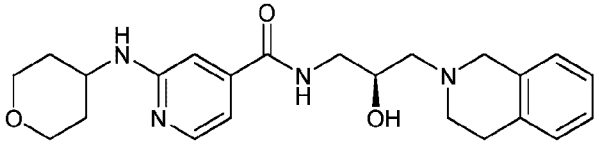
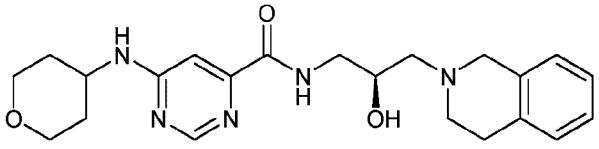
Table 1A. Exemplary Compounds			
Cmpd No	Structure	Exact Mass	LCMS m/z (M+H)
186		411.2634	412.3
187		380.2212	381.3
188		380.2212	381.2
189		417.2165	418.2
190		417.2165	418.3
191		417.2165	418.2
192		410.2318	411.3
193		411.227	412.2

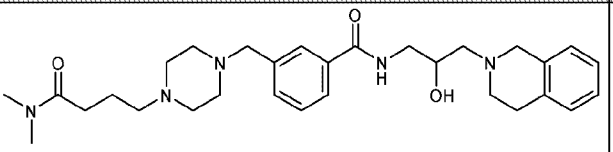
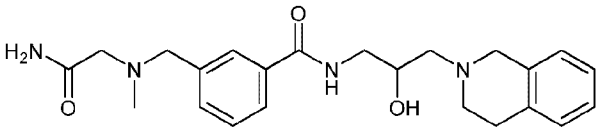
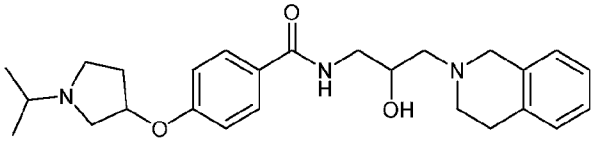
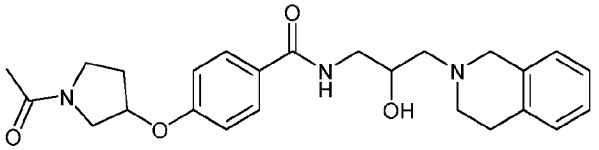
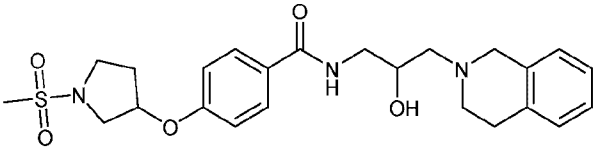
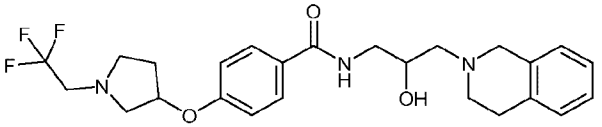
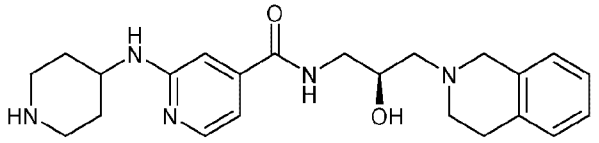
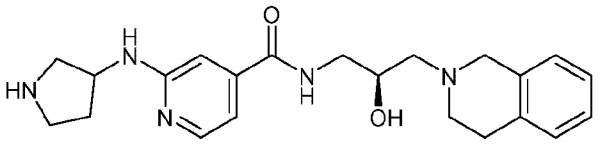
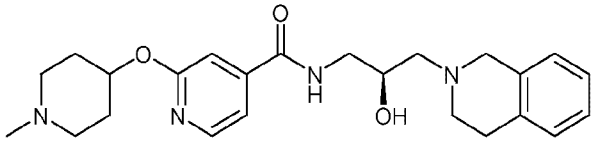
Table 1A. Exemplary Compounds			
Cmpd No	Structure	Exact Mass	LCMS m/z (M+H)
194		521.3366	522.3
195		410.2318	411.2
196		437.2678	438.3
197		437.2315	438.2
198		473.1984	474.2
199		477.2239	478.3
200		409.2478	410.3
201		395.2321	396.2
202		424.2474	425.3

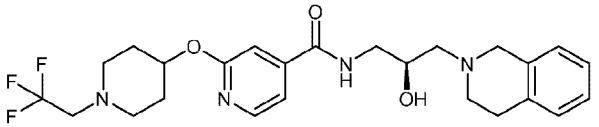
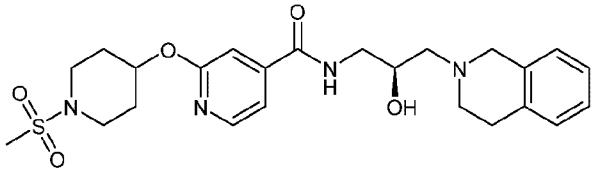
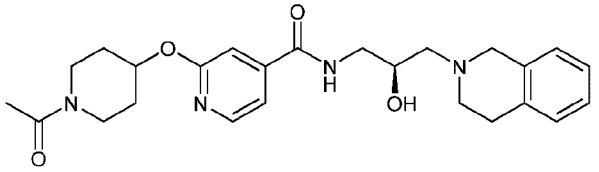
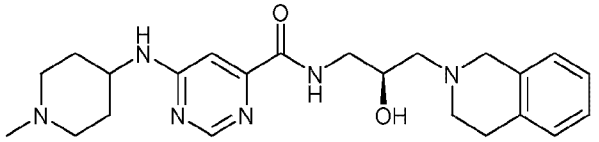
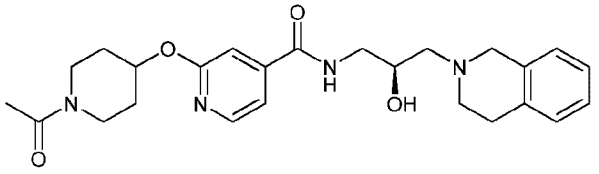
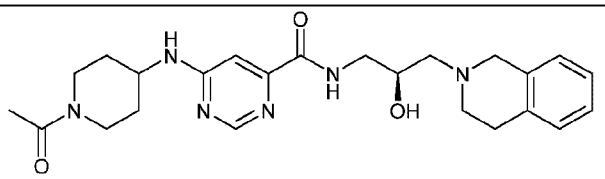
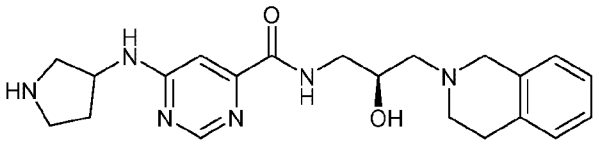
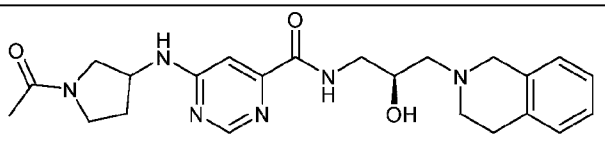
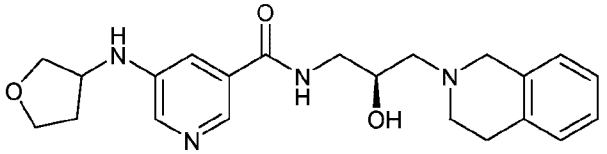
Table 1A. Exemplary Compounds			
Cmpd No	Structure	Exact Mass	LCMS m/z (M+H)
203		492.2348	493.3
204		488.2093	489.3
205		452.2424	453.3
206		424.2587	425.2
207		492.2461	493.3
208		452.2536	453.3
209		396.2274	397.3
210		438.2379	439.3
211		396.2161	397.1

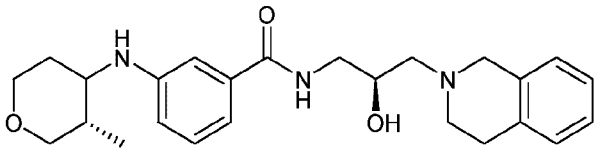
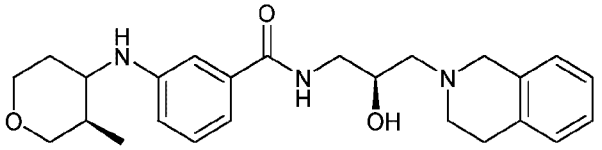
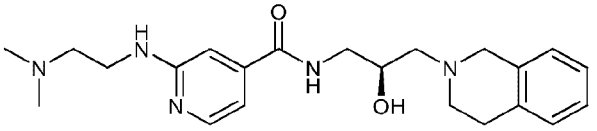
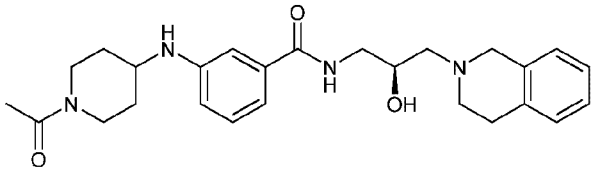
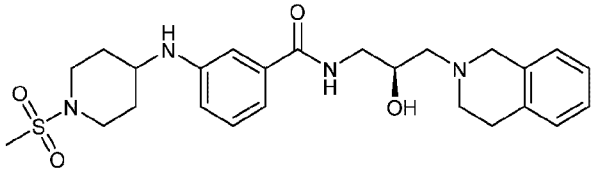
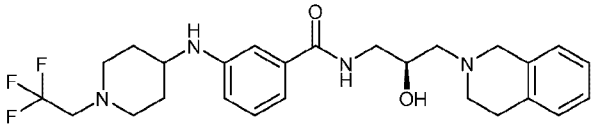
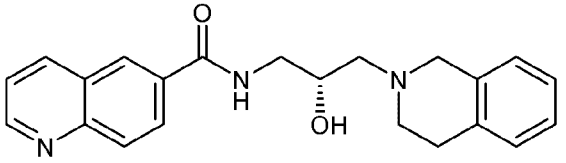
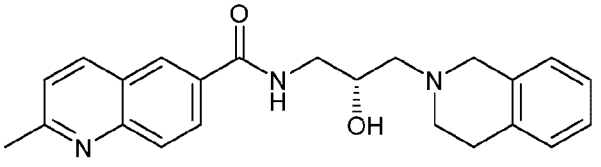
Table 1A. Exemplary Compounds			
Cmpd No	Structure	Exact Mass	LCMS m/z (M+H)
212		423.2522	424.3
213		423.2522	424.3
214		397.2478	398.2
215		450.2631	451.3
216		486.2301	487.3
217		490.2556	491.3
218		361.179	362.1
219		375.1947	376.1

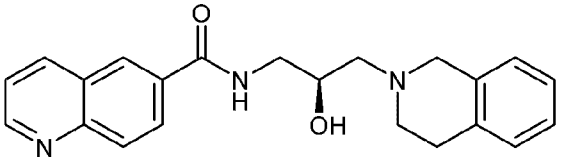
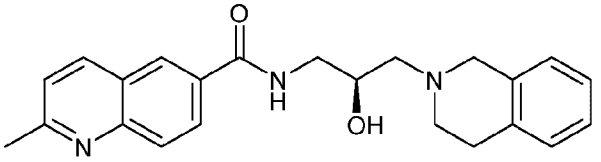
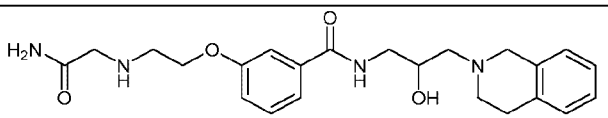
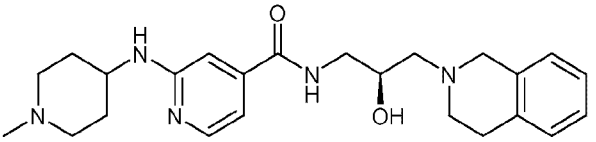
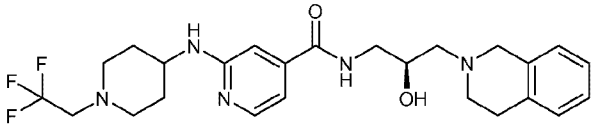
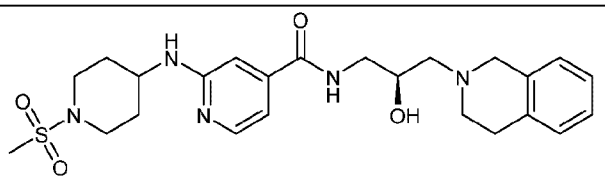
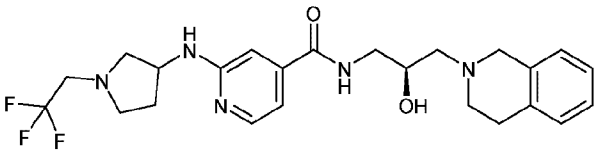
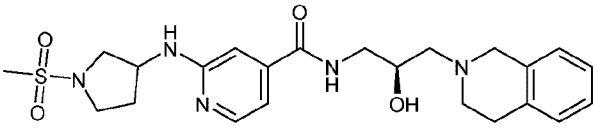
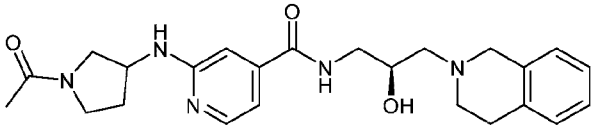
Table 1A. Exemplary Compounds			
Cmpd No	Structure	Exact Mass	LCMS m/z (M+H)
220		361.179	362.1
221		375.1947	376.1
222		426.2267	427.1
223		423.2634	424.1
224		491.2508	492.2
225		487.2253	488.3
226		477.2352	478.3
227		473.2097	474.2
228		437.2427	438.3

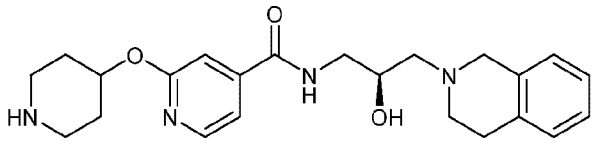
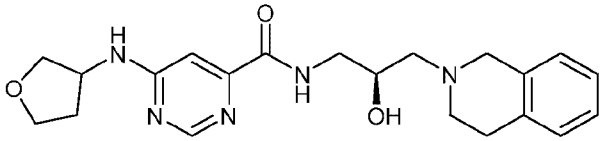
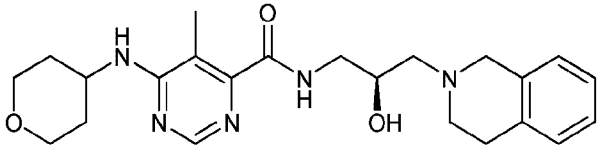
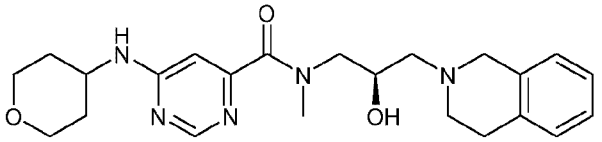
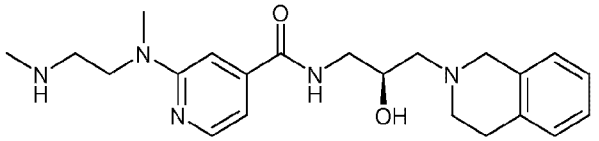
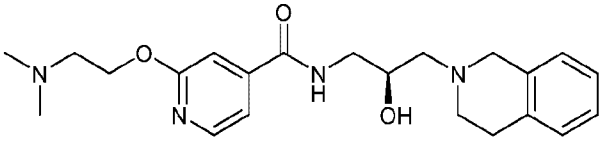
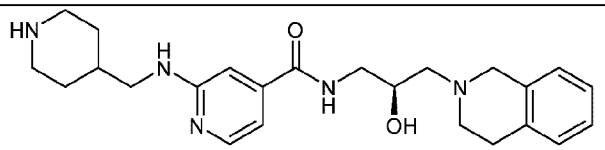
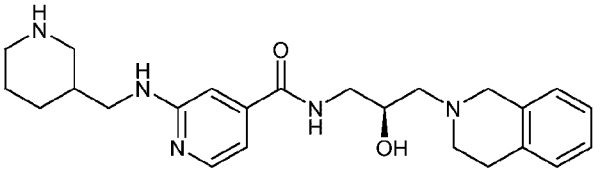
Table 1A. Exemplary Compounds			
Cmpd No	Structure	Exact Mass	LCMS m/z (M+H)
229		410.2318	411.3
230		397.2114	398.1
231		425.2427	426.1
232		425.2427	426.3
233		397.2478	398.3
234		398.2318	399.3
235		423.2634	424.3
236		423.2634	424.3

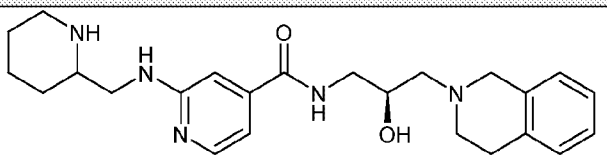
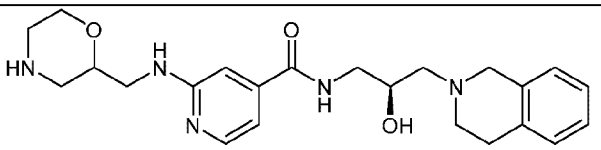
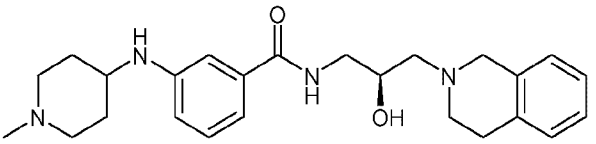
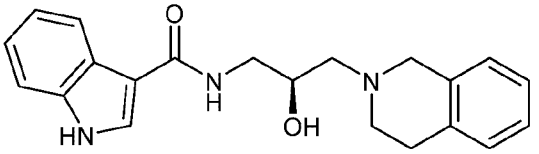
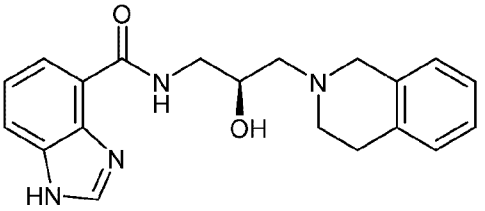
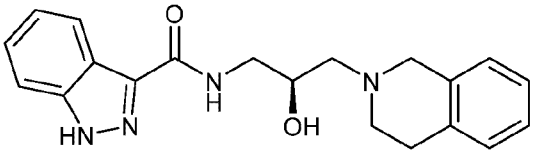
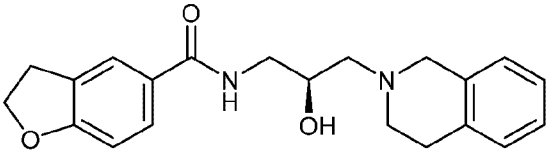
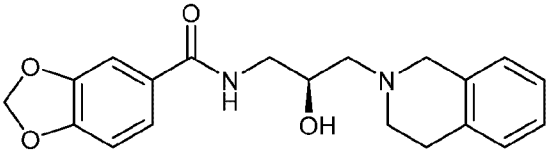
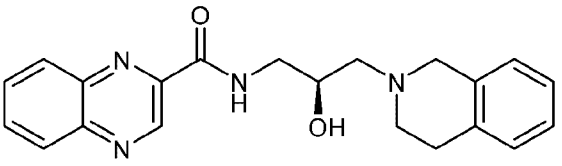
Table 1A. Exemplary Compounds			
Cmpd No	Structure	Exact Mass	LCMS m/z (M+H)
237		423.2634	424.3
238		425.2427	426.3
239		422.2682	423.1
240		349.179	350.1
241		350.1743	351.1
242		350.1743	351.1
243		352.1787	353.2
244		354.158	355
245		362.1743	363.1

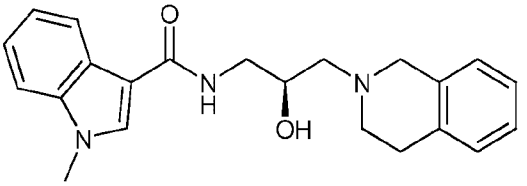
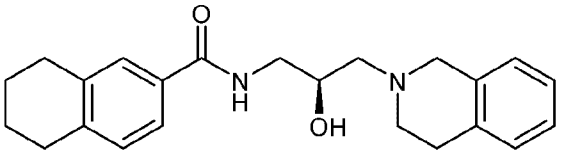
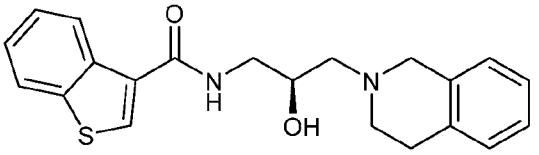
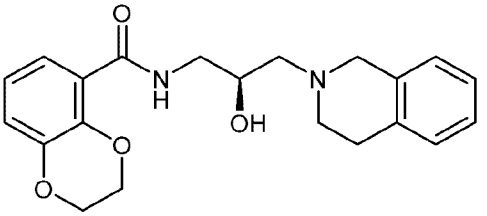
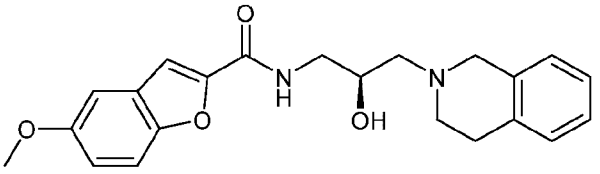
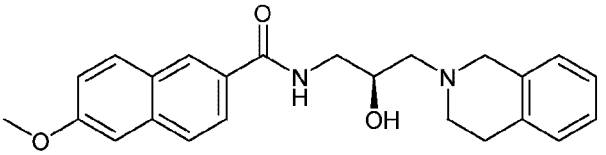
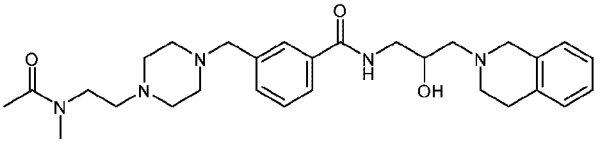
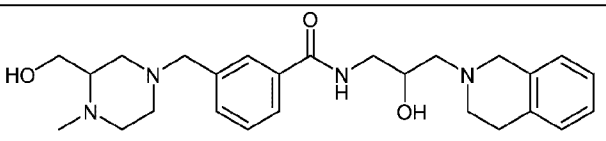
Table 1A. Exemplary Compounds			
Cmpd No	Structure	Exact Mass	LCMS m/z (M+H)
246		363.1947	364.1
247		364.2151	365.1
248		366.1402	367
249		368.1736	369.1
250		380.1736	381.1
251		390.1943	391.1
252		507.3209	508.2
253		452.2787	453.2

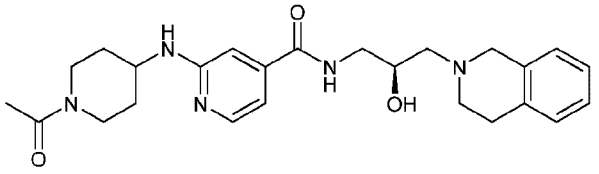
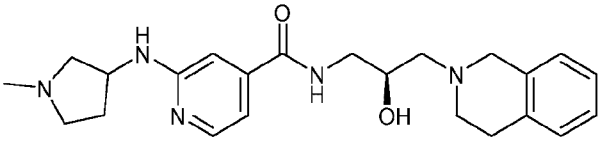
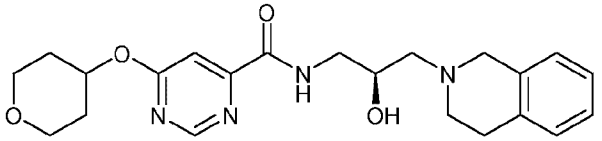
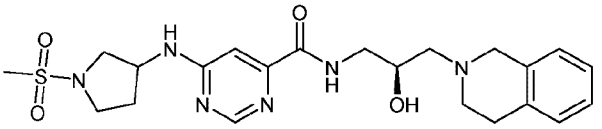
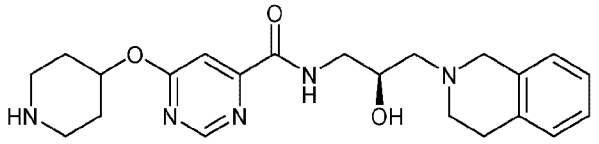
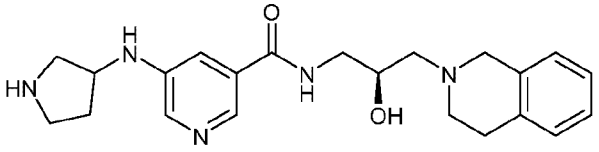
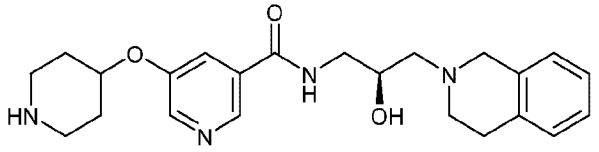
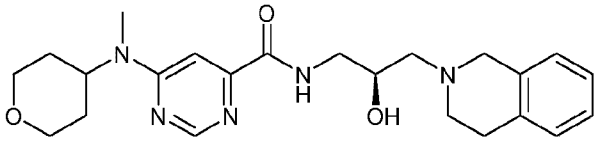
Table 1A. Exemplary Compounds			
Cmpd No	Structure	Exact Mass	LCMS m/z (M+H)
254		451.2583	452.3
255		409.2478	410.3
256		412.2111	413.1
257		474.2049	475.3
258		411.227	412.2
259		395.2321	396.1
260		410.2318	411.1
261		425.2427	426.3

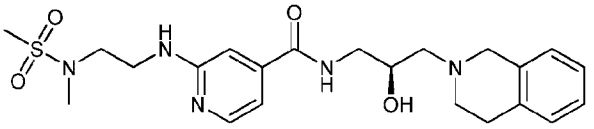
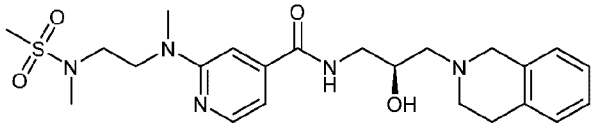
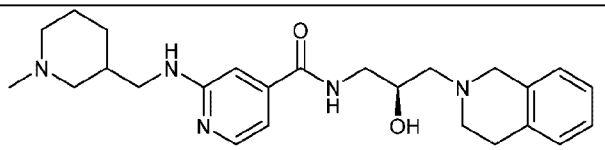
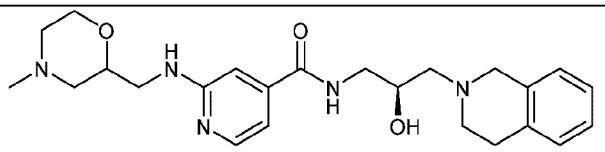
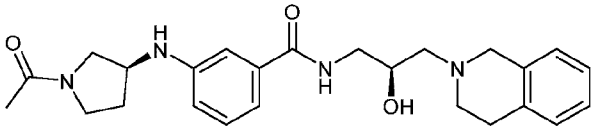
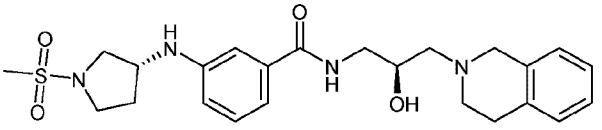
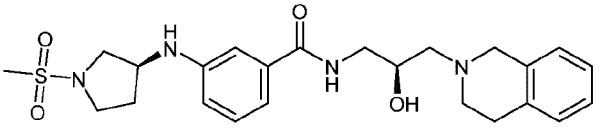
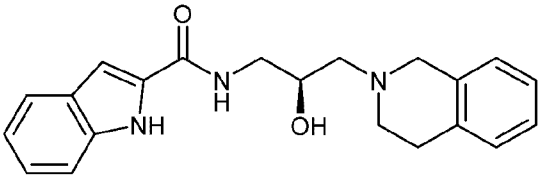
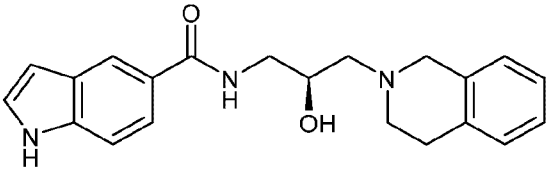
Table 1A. Exemplary Compounds			
Cmpd No	Structure	Exact Mass	LCMS m/z (M+H)
262		461.2097	462.3
263		475.2253	476.3
264		437.2791	438.3
265		439.2583	440.3
266		436.2474	437.3
267		472.2144	473.3
268		472.2144	473.3
269		349.179	350.2
270		349.179	350

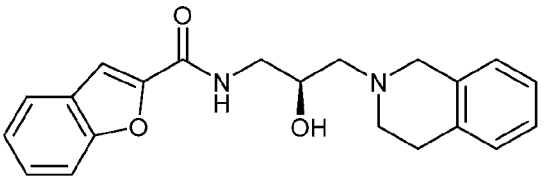
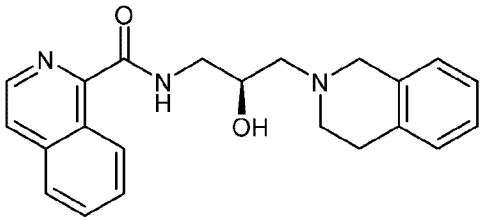
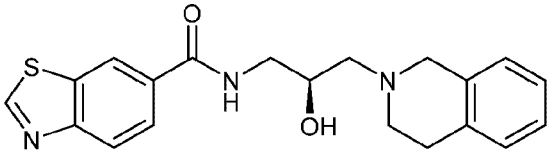
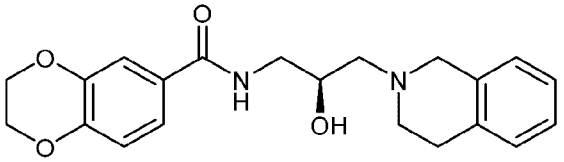
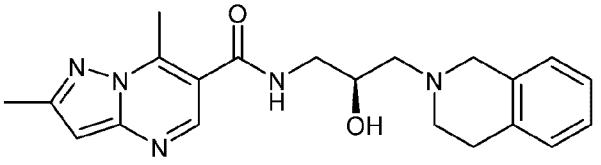
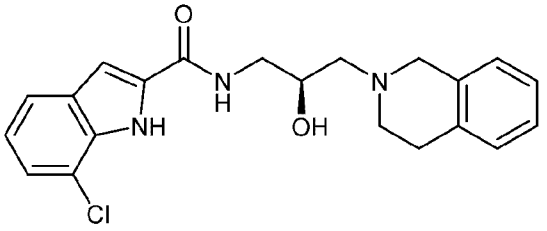
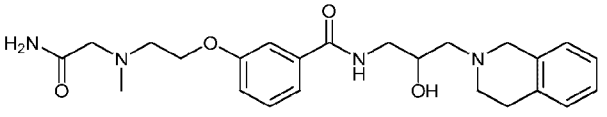
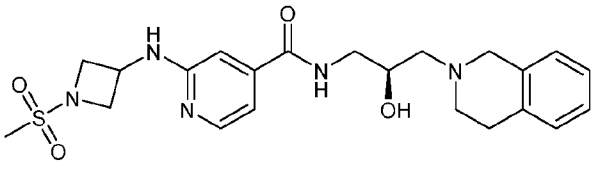
Table 1A. Exemplary Compounds			
Cmpd No	Structure	Exact Mass	LCMS m/z (M+H)
271		350.163	351
272		361.179	362.1
273		367.1354	368
274		368.1736	369.1
275		379.2008	380.1
276		383.1401	384.2
277		440.2424	441.1
278		459.194	460.2

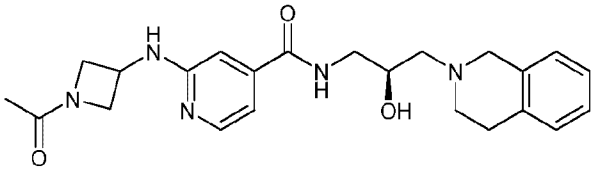
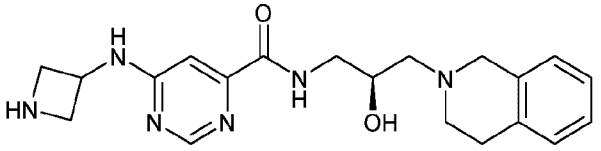
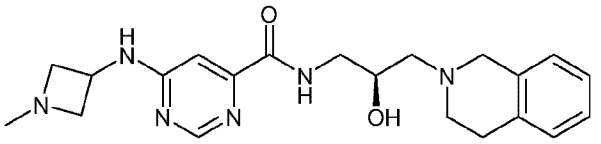
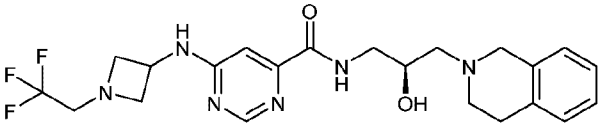
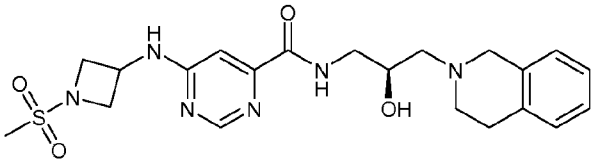
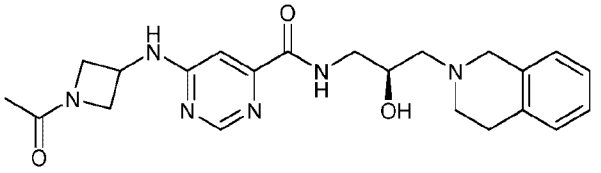
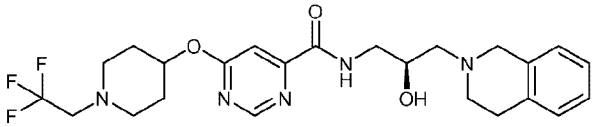
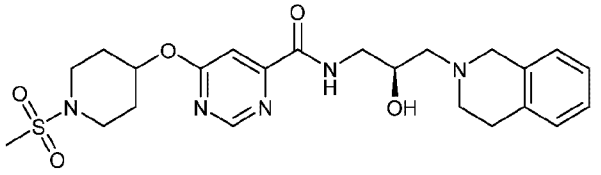
Table 1A. Exemplary Compounds			
Cmpd No	Structure	Exact Mass	LCMS m/z (M+H)
279		423.227	424.3
280		382.2117	383.1
281		396.2274	397.2
282		464.2148	465.1
283		460.1893	461.2
284		424.2223	425.3
285		493.2301	494.1
286		489.2046	490.3

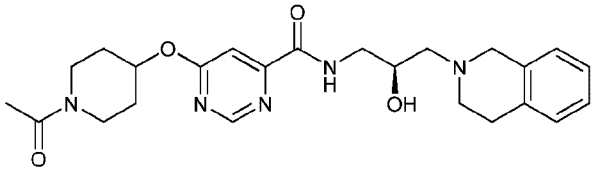
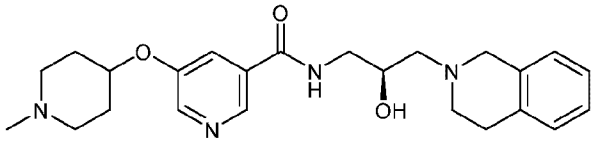
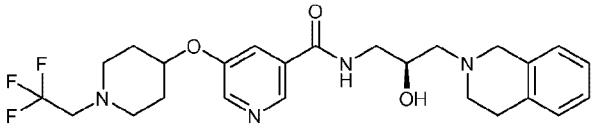
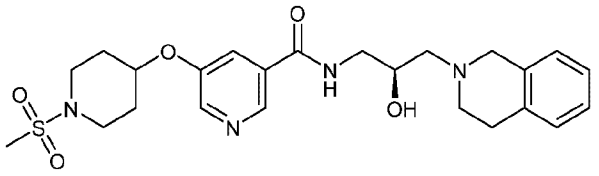
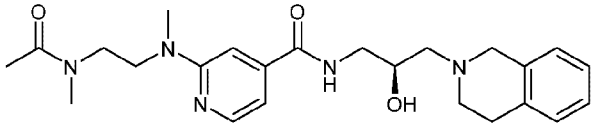
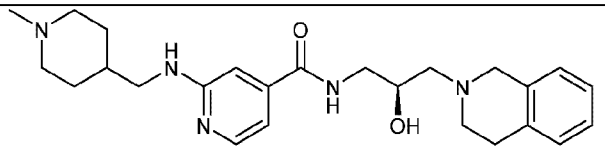
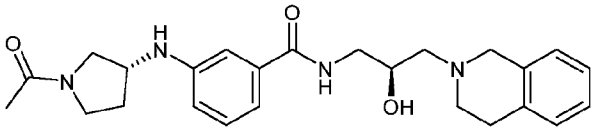
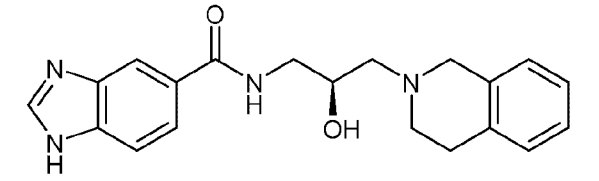
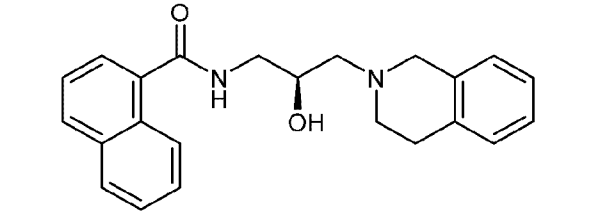
Table 1A. Exemplary Compounds			
Cmpd No	Structure	Exact Mass	LCMS m/z (M+H)
287		453.2376	454.3
288		424.2474	425.3
289		492.2348	493.3
290		488.2093	489.2
291		439.2583	440.3
292		437.2791	438.3
293		436.2474	437.3
294		350.1743	351.1
295		360.1838	361.1

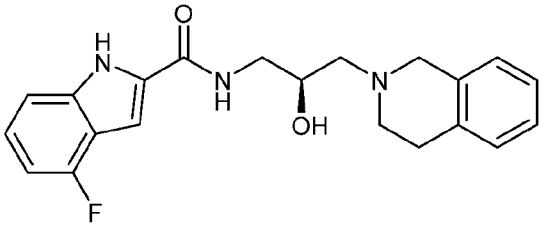
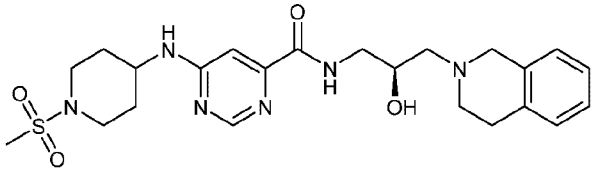
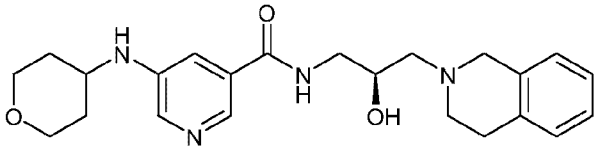
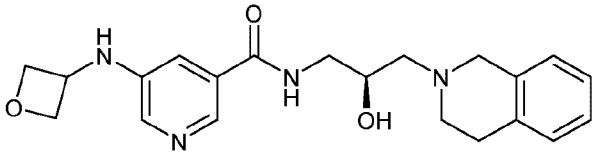
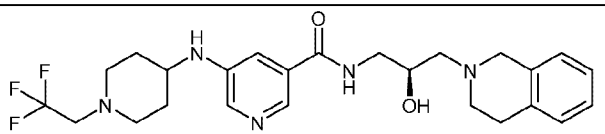
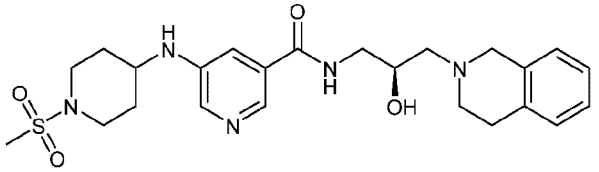
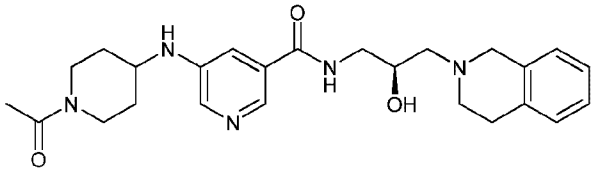
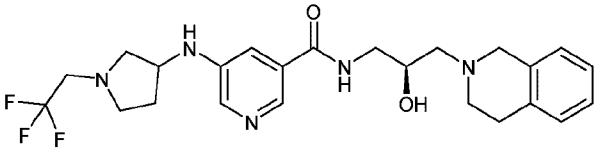
Table 1A. Exemplary Compounds			
Cmpd No	Structure	Exact Mass	LCMS m/z (M+H)
296		367.1696	368.2
297		488.2206	489.3
298		410.2318	411.1
299		382.2005	383.1
300		491.2508	492.1
301		487.2253	488.1
302		451.2583	452.3
303		477.2352	478.1

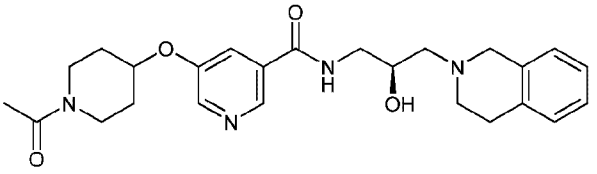
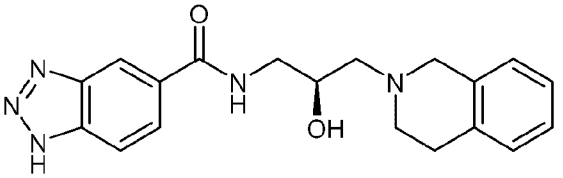
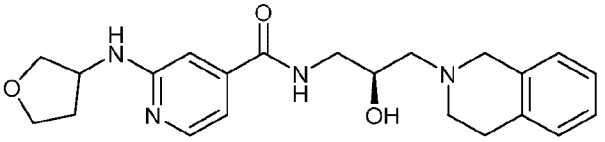
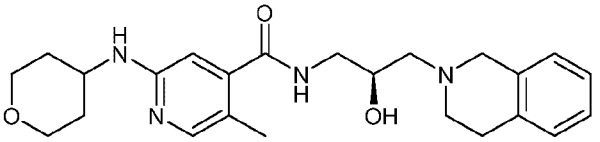
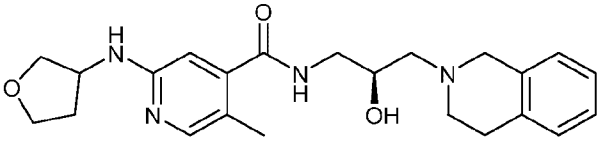
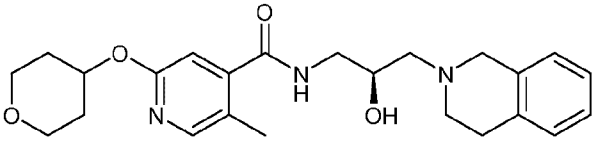
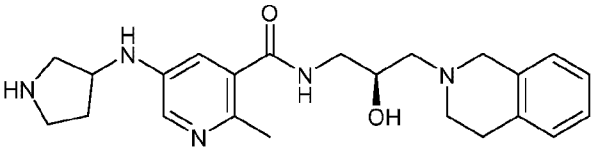
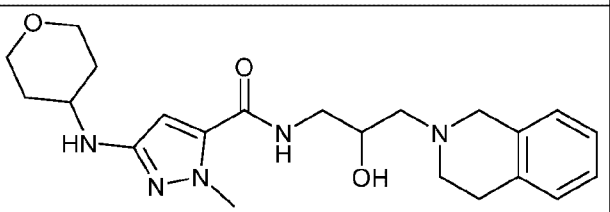
Table 1A. Exemplary Compounds			
Cmpd No	Structure	Exact Mass	LCMS m/z (M+H)
304		452.2424	453.3
305		351.1695	352.1
306		396.2161	397.2
307		424.2474	425.1
308		410.2318	411.1
309		425.2315	426.1
310		409.2478	410.3
311		413.2427	414.3

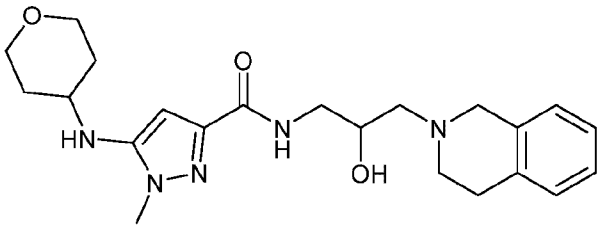
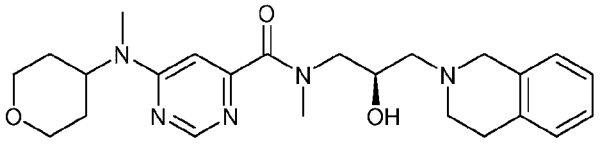
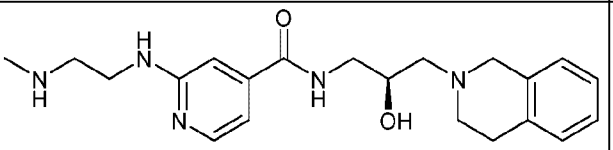
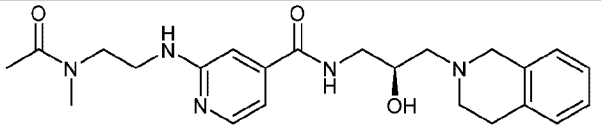
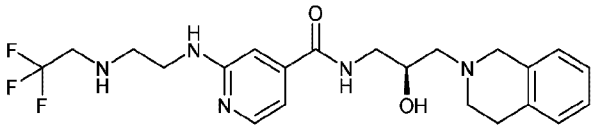
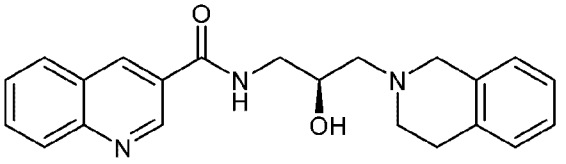
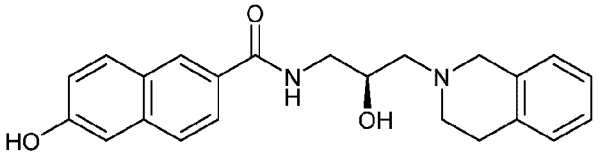
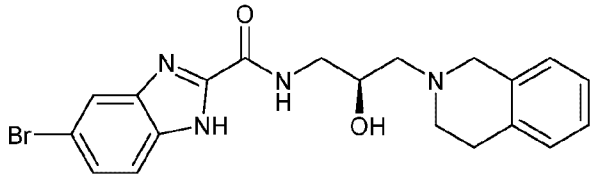
Table 1A. Exemplary Compounds			
Cmpd No	Structure	Exact Mass	LCMS m/z (M+H)
312		413.2427	301.1
313		439.2583	440.1
314		383.2321	384.1
315		425.2427	426.1
316		451.2195	452.3
317		361.179	362.1
318		376.1787	377.1
319		428.0848	429

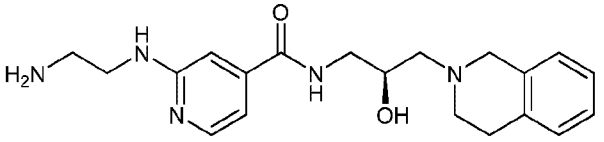
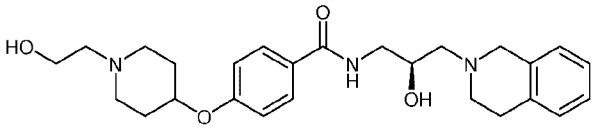
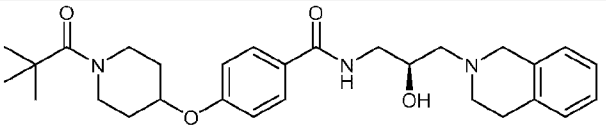
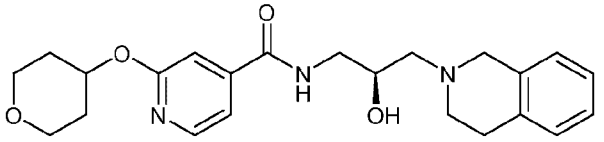
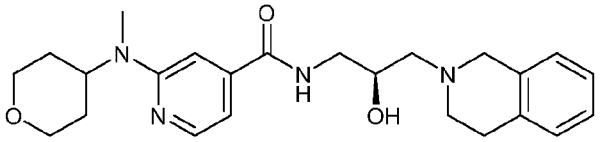
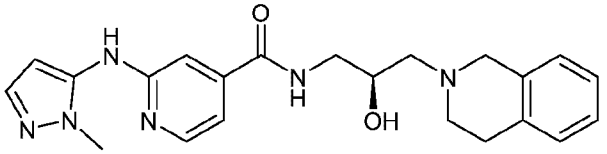
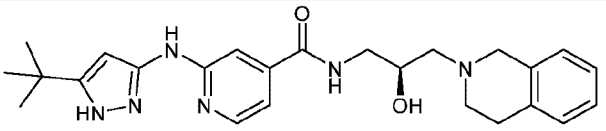
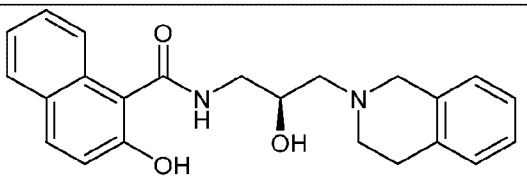
Table 1A. Exemplary Compounds			
Cmpd No	Structure	Exact Mass	LCMS m/z (M+H)
320		369.2165	370.1
321		453.2628	454.2
322		493.2941	494.2
323		411.2158	412.3
324		424.2474	425.1
325		406.2117	407.3
326		448.2587	449.3
327		376.1787	377.2

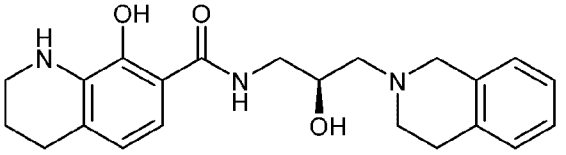
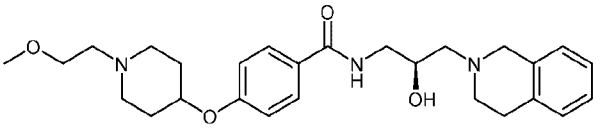
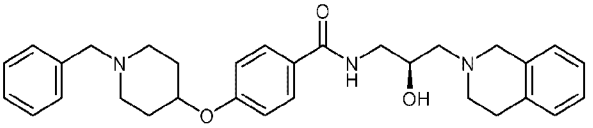
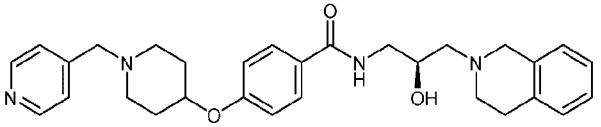
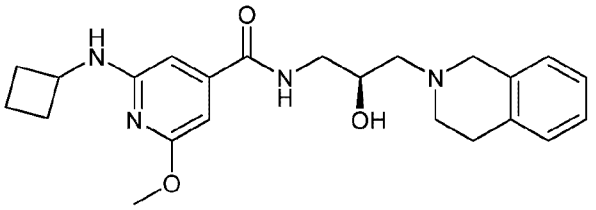
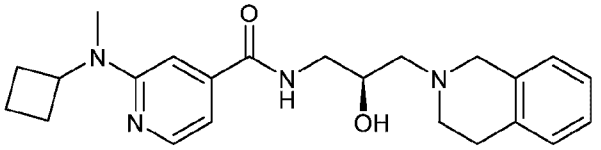
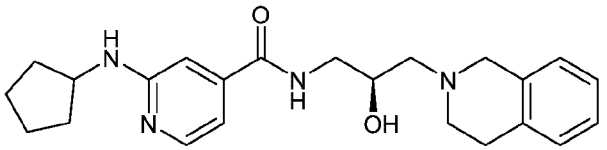
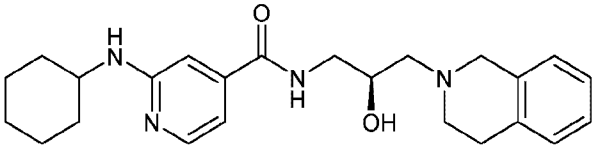
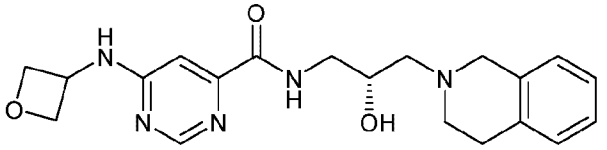
Table 1A. Exemplary Compounds			
Cmpd No	Structure	Exact Mass	LCMS m/z (M+H)
328		381.2052	382.2
329		467.2784	468.2
330		499.2835	500.2
331		500.2787	501.2
332		410.2318	411.1
333		394.2369	395.3
334		394.2369	395.3
335		408.2525	409.1

Table 1A. Exemplary Compounds			
Cmpd No	Structure	Exact Mass	LCMS m/z (M+H)
336		383.1957	384.2

[00250] In certain embodiments, a provided compound is a compound listed in Table 1B, or a pharmaceutically acceptable salt thereof.

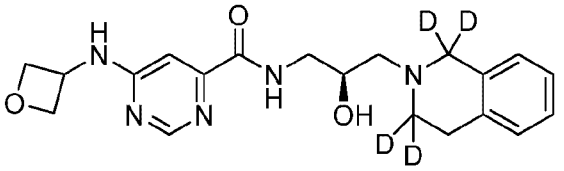
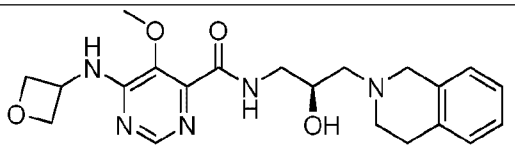
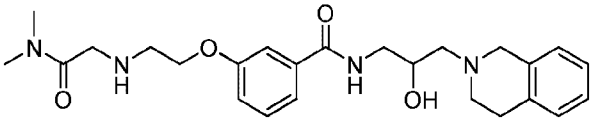
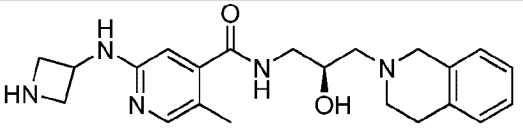
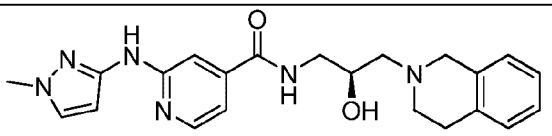
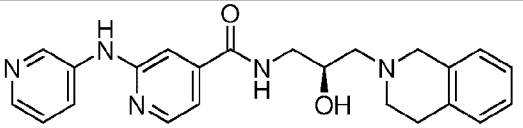
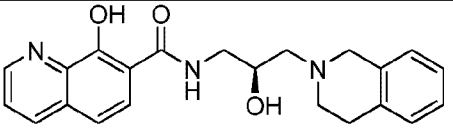
Table 1B. Exemplary compounds			
Cmpd No	Structure	Exact Mass	LCMS m/z (M+H)
337		387.2208	388.0
338		413.2063	414.1
340		454.258	455.3
341		395.2321	396.3
342		406.2117	407.3
343		403.2008	404.2
344		377.1739	378.2

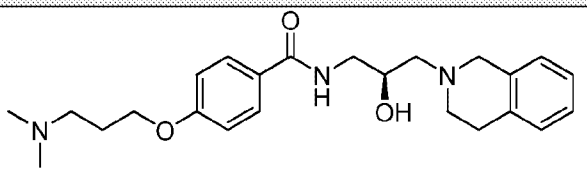
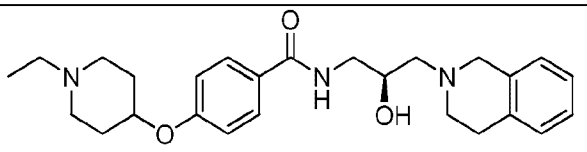
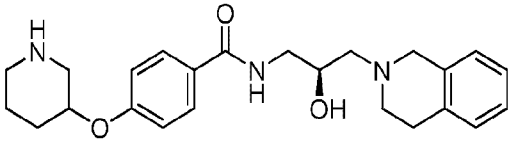
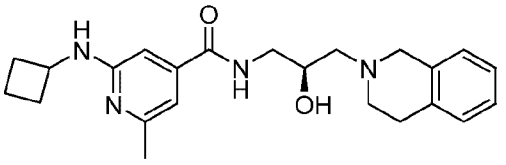
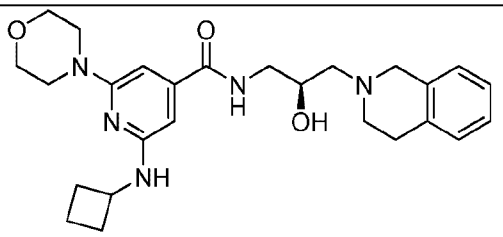
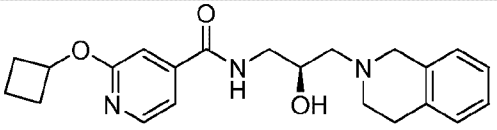
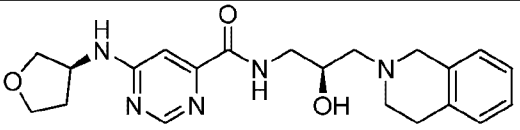
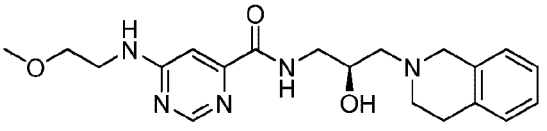
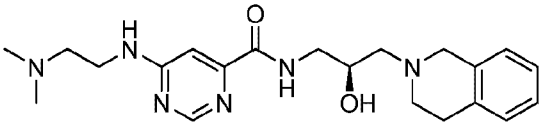
Table 1B. Exemplary compounds			
Cmpd No	Structure	Exact Mass	LCMS m/z (M+H)
345		411.2522	412.2
346		437.2678	438.3
347		409.2365	410.1
348		394.2369	395.1
349		465.274	466.3
350		381.2052	382.2
351		397.2114	398.1
352		385.2114	386.1
353		398.243	399.1

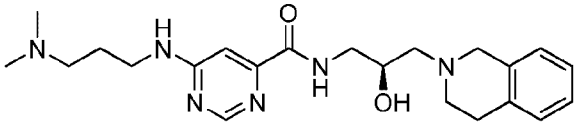
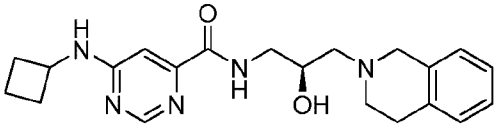
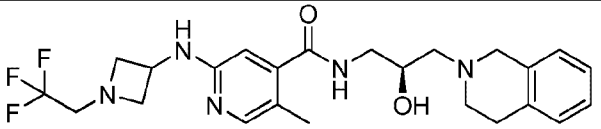
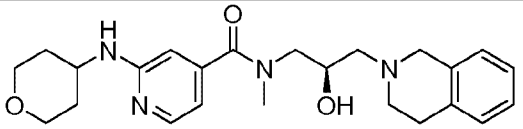
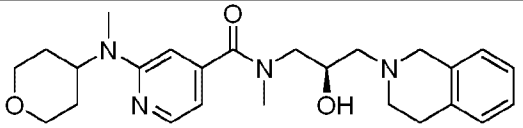
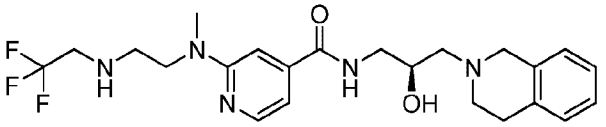
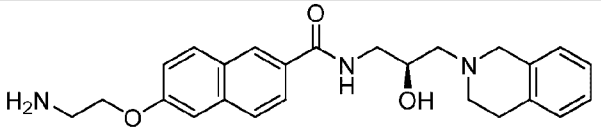
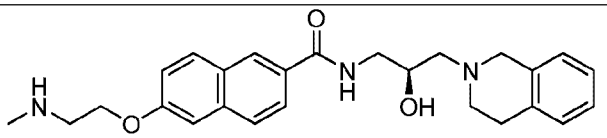
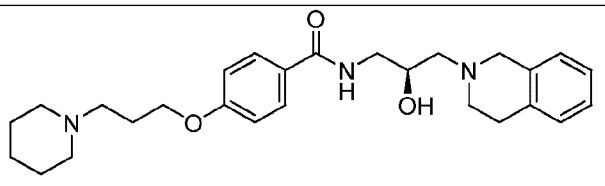
Table 1B. Exemplary compounds			
Cmpd No	**Structure**	**Exact Mass**	**LCMS m/z (M+H)**
354		412.2587	413.1
355		381.2165	382.2
356		477.2352	478.2
357		424.2474	425.1
358		438.2631	439.2
359		465.2352	466.3
360		419.2209	420.3
361		433.2365	434.3
362		451.2835	452.1

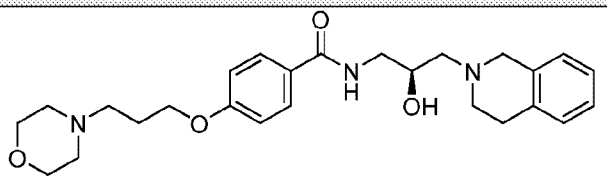
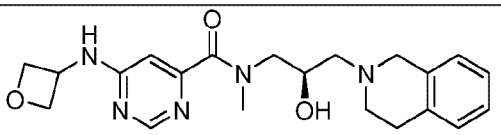
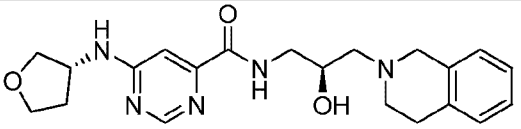
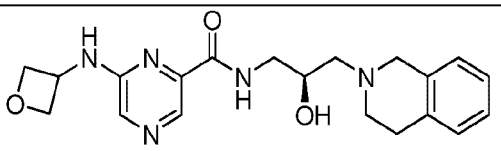
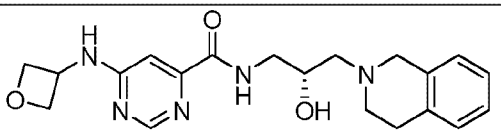
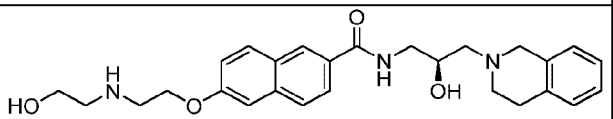
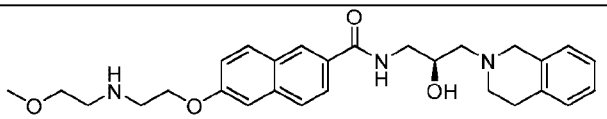
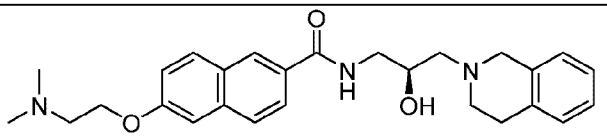
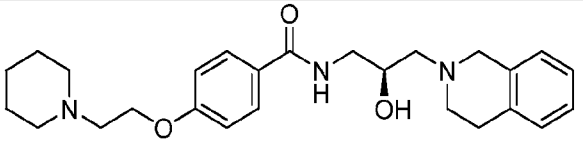
Table 1B. Exemplary compounds			
Cmpd No	Structure	Exact Mass	LCMS m/z (M+H)
363		453.2628	454.1
364		397.2114	398.2
365		397.2114	398.1
366		383.1957	384.2
367		383.1957	384.2
368		463.2471	464.3
369		477.2628	478.3
370		447.2522	448.3
371		437.2678	438.3

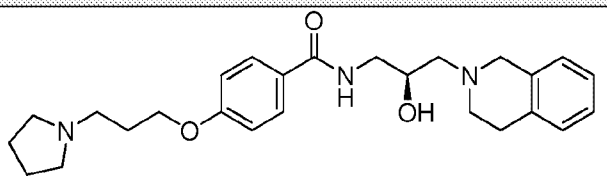
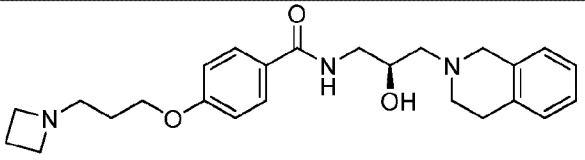
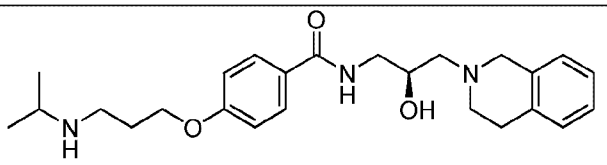
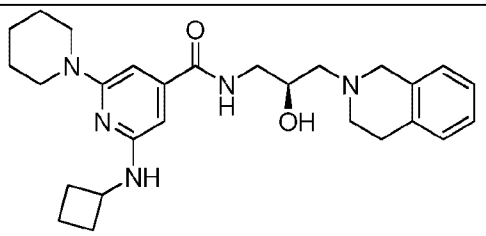
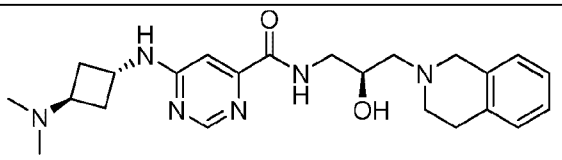
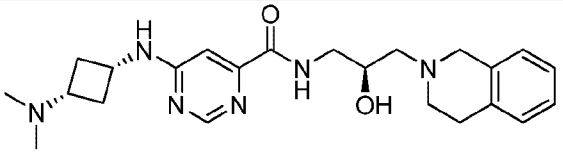
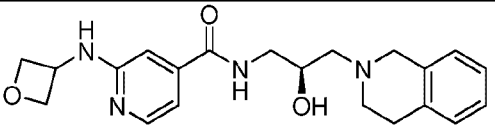
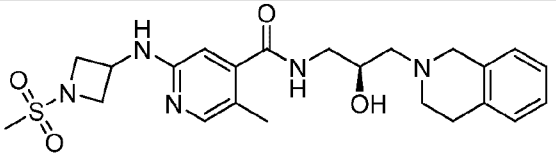
Table 1B. Exemplary compounds			
Cmpd No	Structure	Exact Mass	LCMS m/z (M+H)
372		437.2678	438.3
373		423.2522	424.3
374		425.2678	426.3
375		463.2947	464.3
376		424.2587	425.1
377		424.2587	425.1
378		382.2005	383.1
379		473.2097	474.1

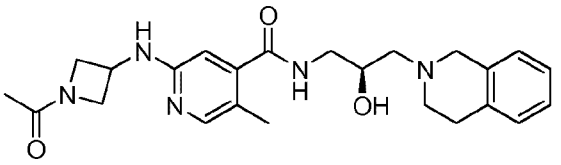
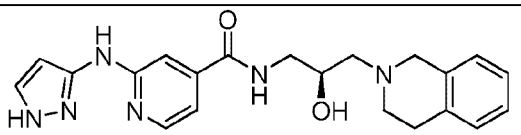
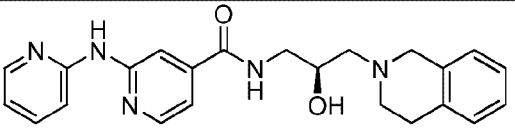
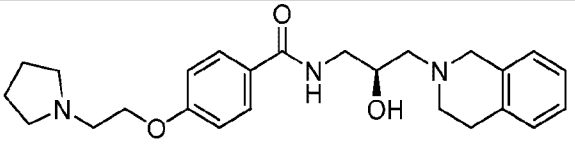
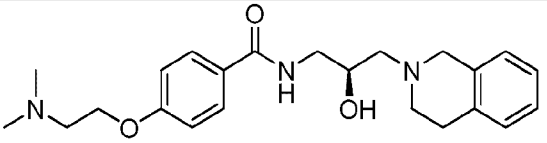
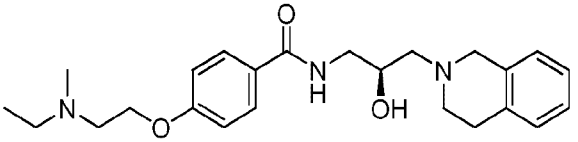
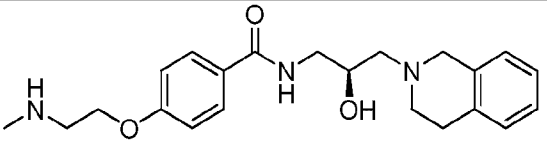
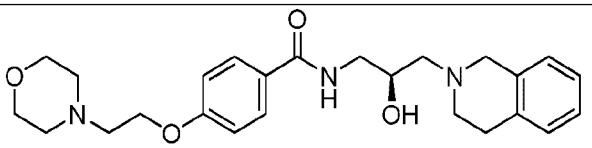
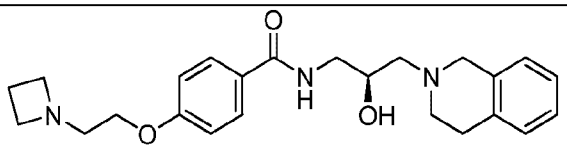
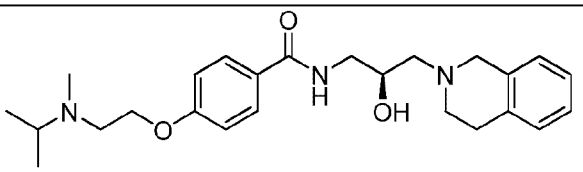
Table 1B. Exemplary compounds			
Cmpd No	**Structure**	**Exact Mass**	**LCMS m/z (M+H)**
380		437.2427	438.2
381		392.1961	393.1
382		403.2008	404.2
383		423.2522	424.1
384		397.2365	398.2
385		411.2522	412.3
386		383.2209	384.3
387		439.2471	440.1
388		409.2365	410.2
389		425.2678	426.1

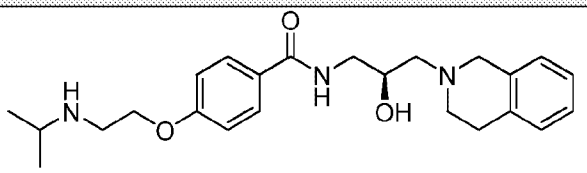
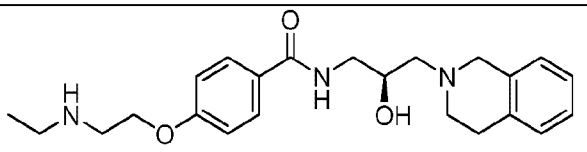
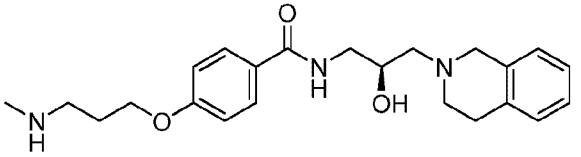
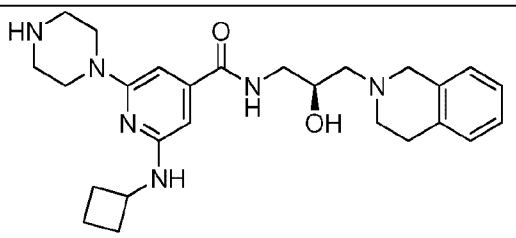
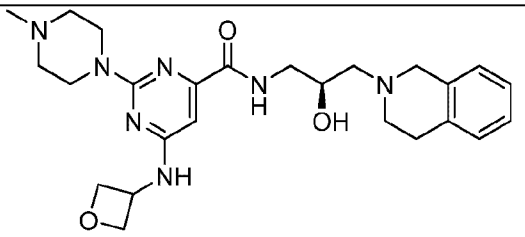
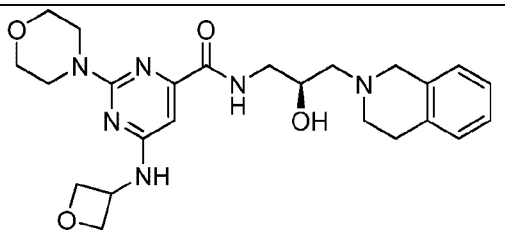
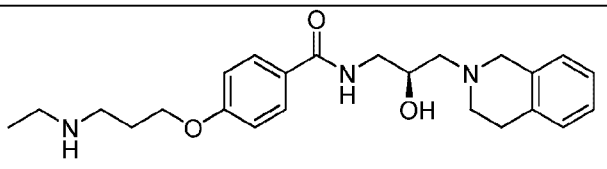
Table 1B. Exemplary compounds			
Cmpd No	**Structure**	**Exact Mass**	**LCMS m/z (M+H)**
390		411.2522	412.2
391		397.2365	398.2
392		397.2365	398.2
393		464.29	465.3
394		481.2801	482.3
395		468.2485	469.1
396		411.2522	412.2

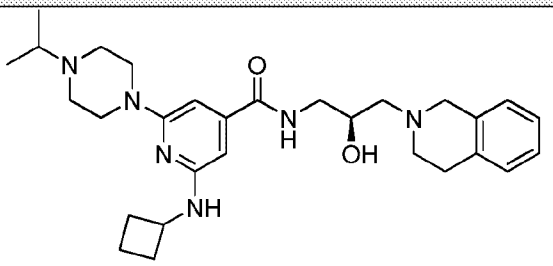
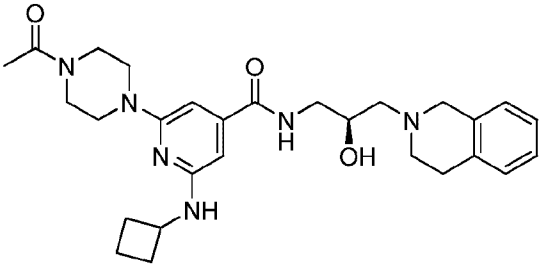
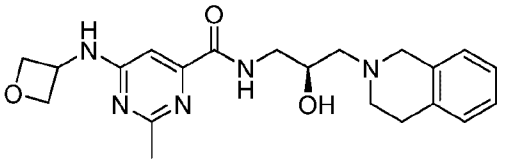
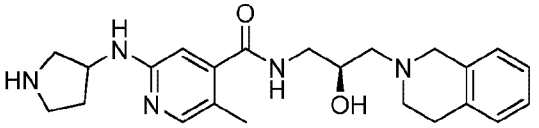
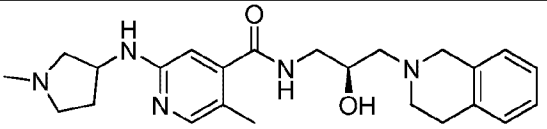
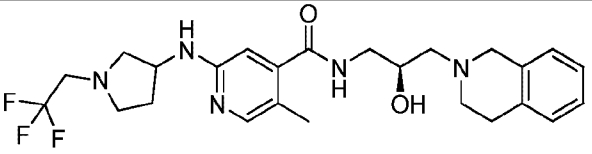
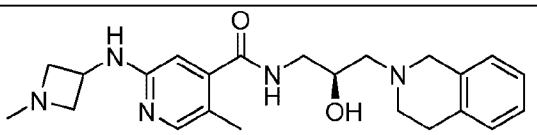
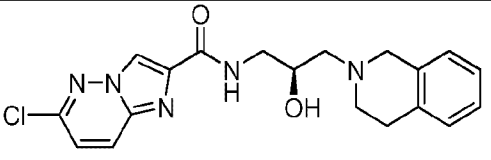
Table 1B. Exemplary compounds			
Cmpd No	Structure	Exact Mass	LCMS m/z (M+H)
397		506.3369	507.2
398		506.3005	507.3
399		397.2114	398.1
400		409.2478	410.2
401		423.2634	424.1
402		491.2508	492.2
403		409.2478	410.3
404		385.1306	386.0

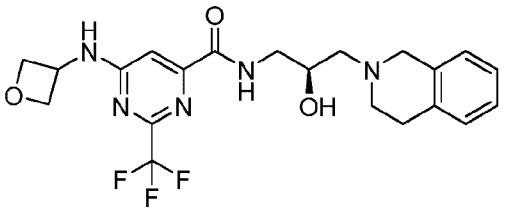
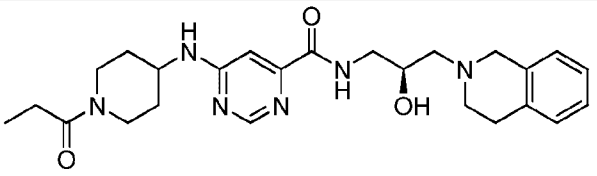
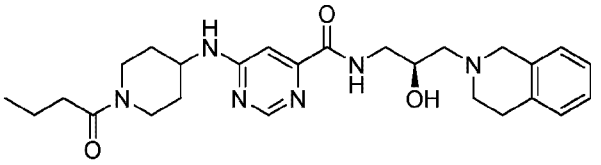
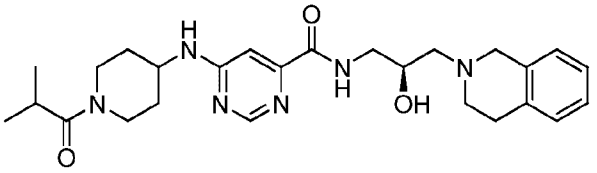
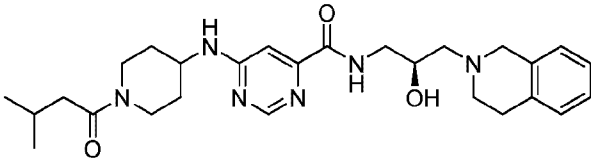
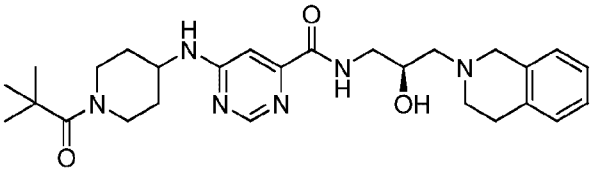
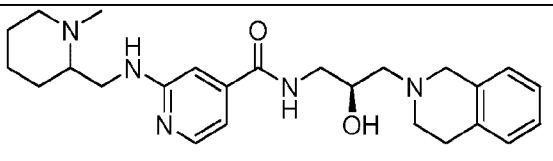
Table 1B. Exemplary compounds			
Cmpd No	**Structure**	**Exact Mass**	**LCMS m/z (M+H)**
405		451.1831	452.1
406		466.2692	467.2
407		480.2849	481.1
408		480.2849	481.2
409		494.3005	495.2
410		494.3005	495.2
411		437.2791	438.2

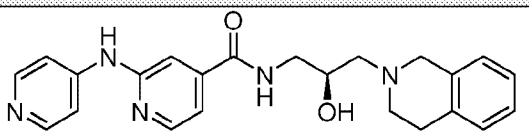
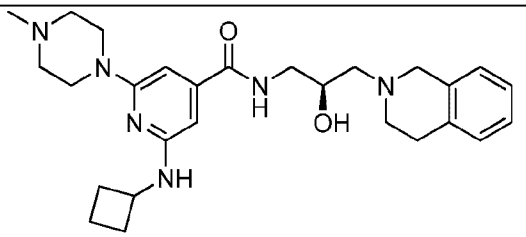
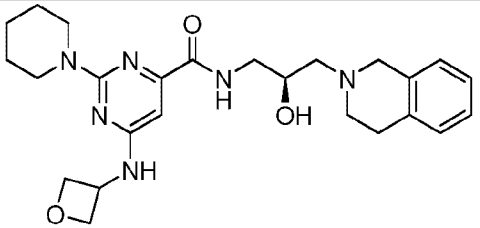
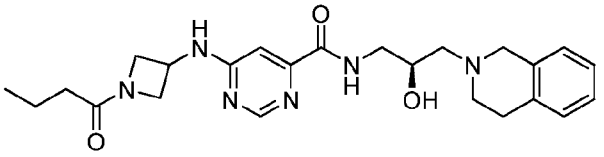
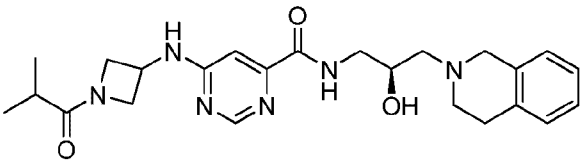
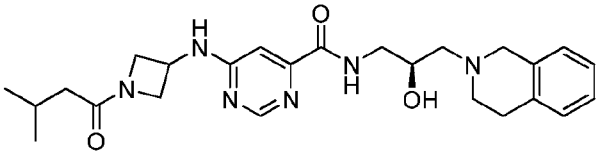
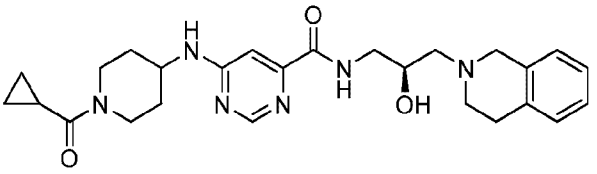
Table 1B. Exemplary compounds			
Cmpd No	Structure	Exact Mass	LCMS m/z (M+H)
412		403.2008	404.1
413		478.3056	479.3
414		466.2692	467.2
415		452.2536	453.2
416		452.2536	453.2
417		466.2692	467.2
418		478.2692	479.2

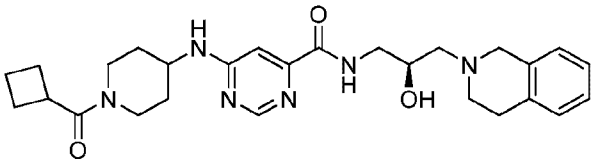
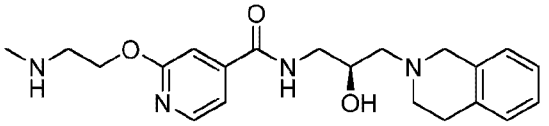
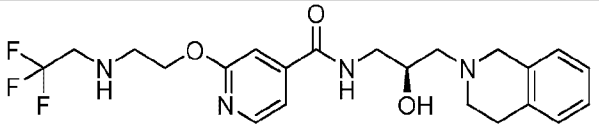
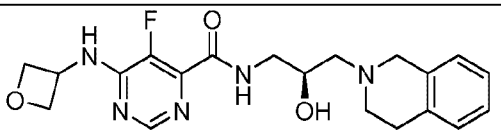
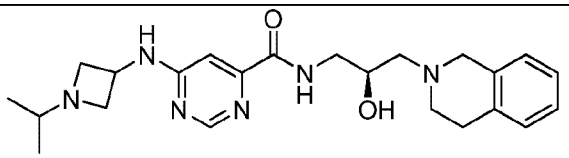
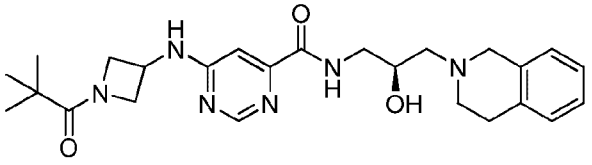
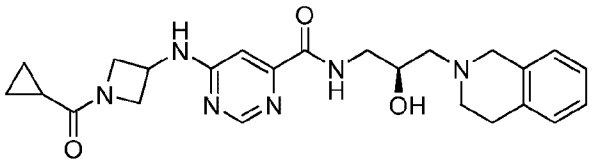
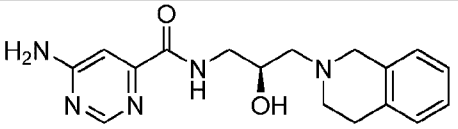
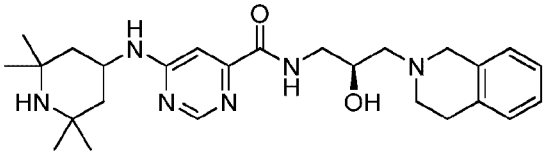
Table 1B. Exemplary compounds			
Cmpd No	Structure	Exact Mass	LCMS m/z (M+H)
419		492.2849	493.2
420		384.2161	385.1
421		452.2035	453.2
422		401.1863	402.1
423		424.2587	425.2
424		466.2692	467.2
425		450.2379	451.2
429		327.1695	328.0
430		466.3056	467.3

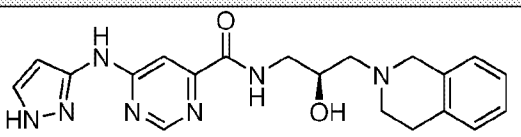
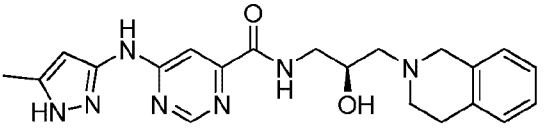
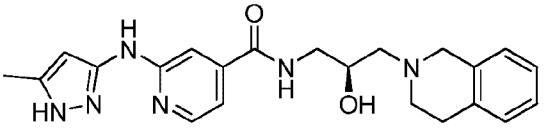
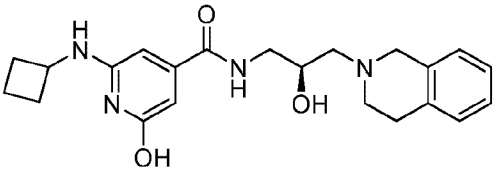
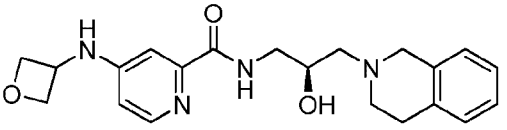
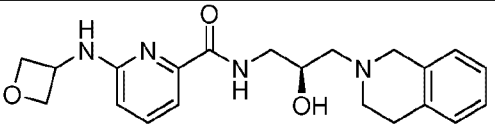
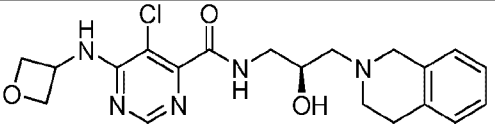
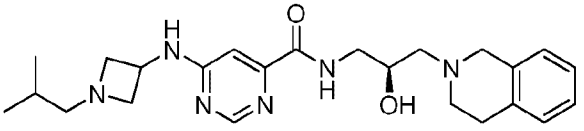
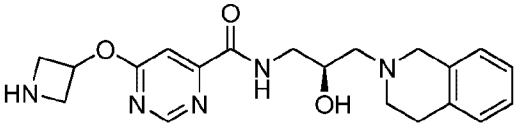
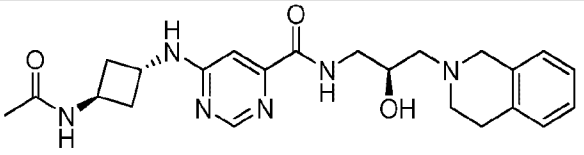
Table 1B. Exemplary compounds			
Cmpd No	Structure	Exact Mass	LCMS m/z (M+H)
431		393.1913	394.1
432		407.207	408.1
433		406.2117	407.2
434		396.2161	397.1
435		382.2005	383.1
436		382.2005	383.1
437		417.1568	418.0
438		438.2743	439.2
439		383.1957	384.2
440		438.2379	439.1

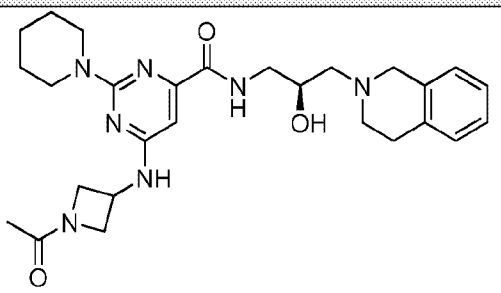
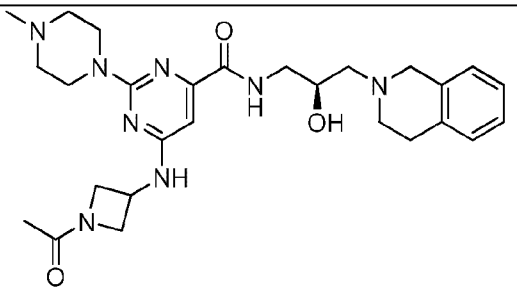
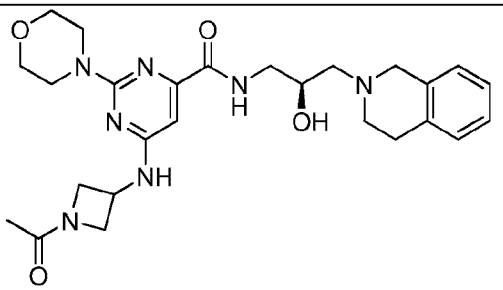
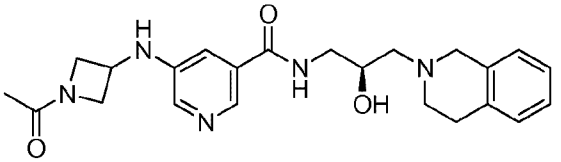
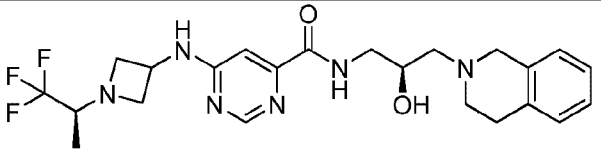
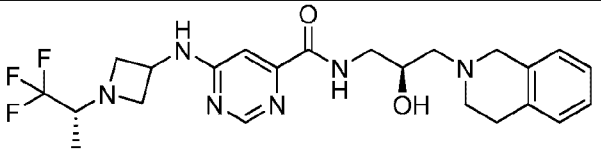
Table 1B. Exemplary compounds			
Cmpd No	**Structure**	**Exact Mass**	**LCMS m/z (M+H)**
441		507.2958	508.3
442		522.3067	523.2
443		509.2751	510.2
444		423.227	424.2
445		478.2304	479.2
446		478.2304	479.2

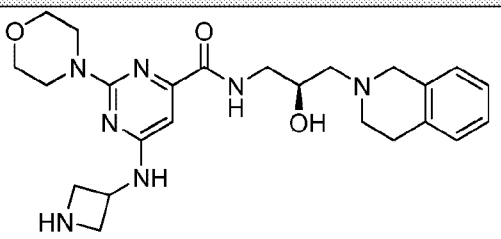
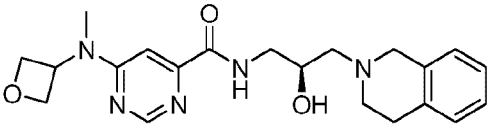
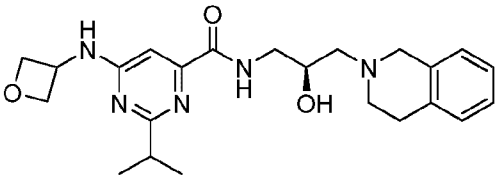
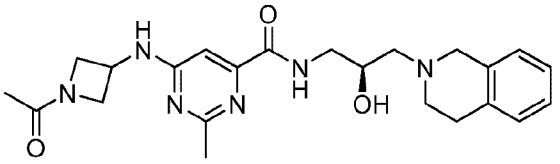
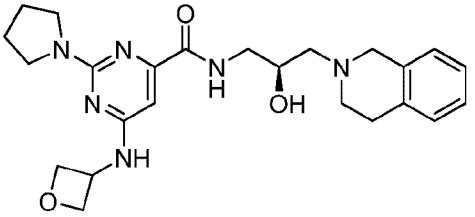
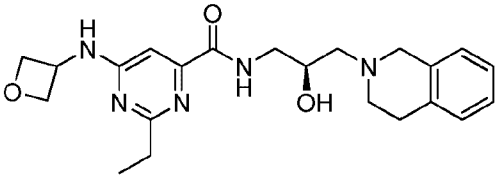
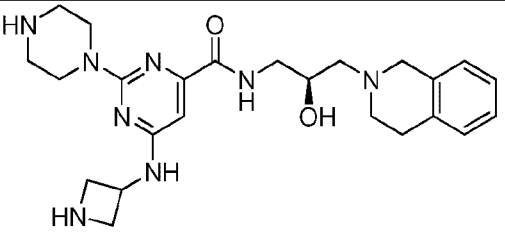
Table 1B. Exemplary compounds			
Cmpd No	**Structure**	**Exact Mass**	**LCMS m/z (M+H)**
447		467.2645	468.3
448		397.2114	398.1
449		425.2427	426.2
450		438.2379	439.1
451		452.2536	453.2
452		411.227	412.2
453		466.2805	467.2

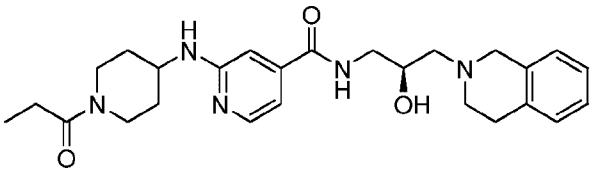
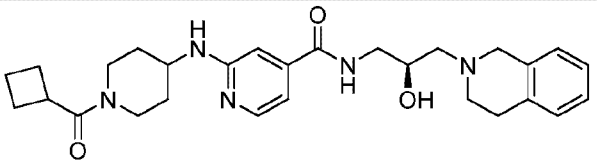
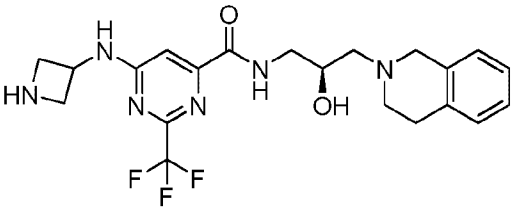
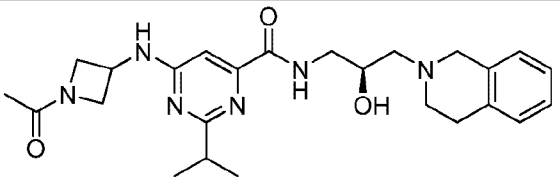
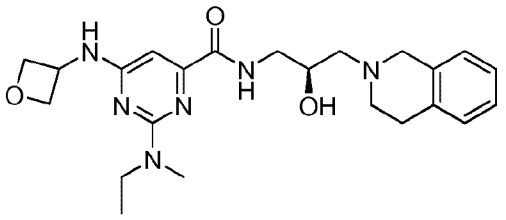
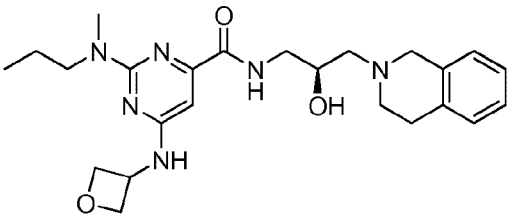
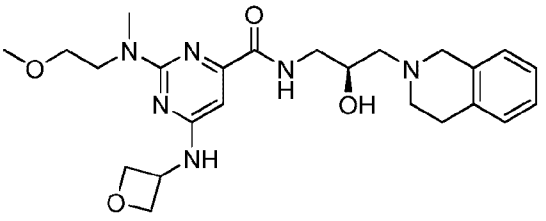
Table 1B. Exemplary compounds			
Cmpd No	Structure	Exact Mass	LCMS m/z (M+H)
454		465.274	466.2
455		491.2896	492.3
456		450.1991	451.1
457		466.2692	467.2
458		440.2536	441.2
459		454.2692	455.2
460		470.2642	471.2

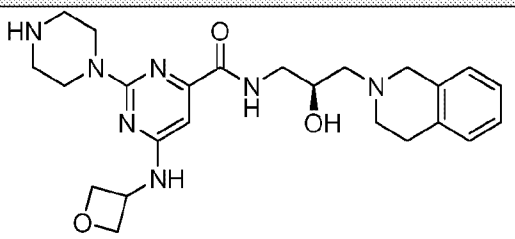
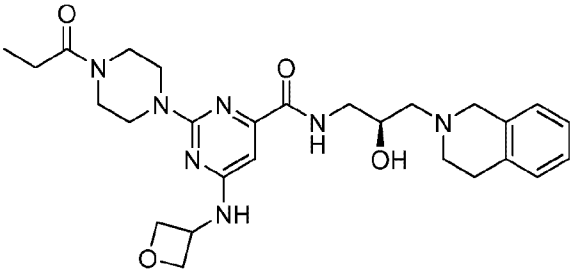
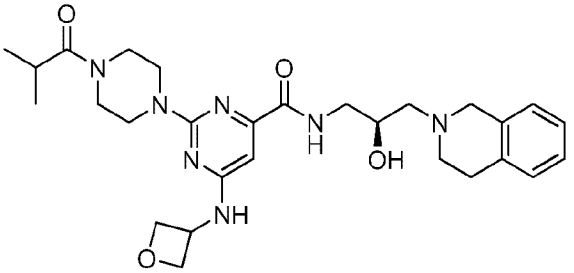
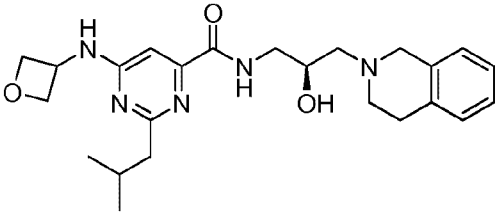
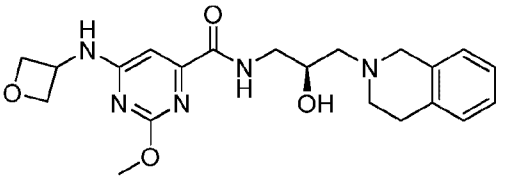
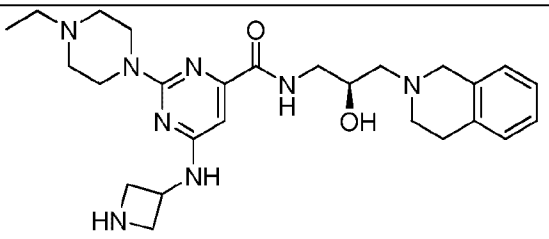
Table 1B. Exemplary compounds			
Cmpd No	Structure	Exact Mass	LCMS m/z (M+H)
461		467.2645	468.2
462		523.2907	524.3
463		537.3064	538.3
464		439.2583	440.2
465		413.2063	414.1
466		494.3118	495.2

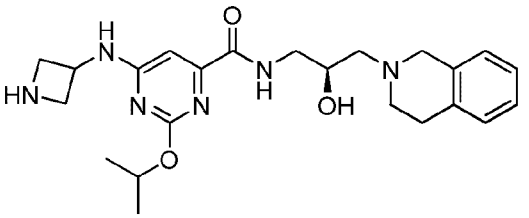
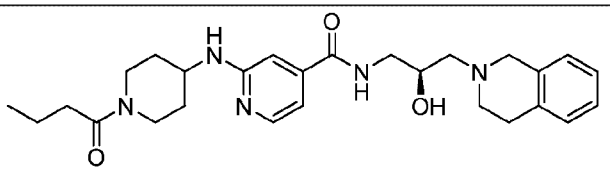
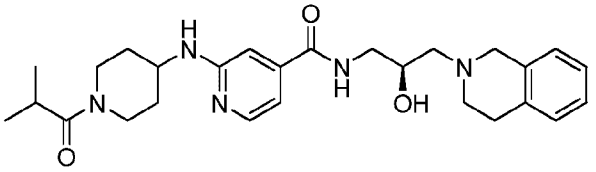
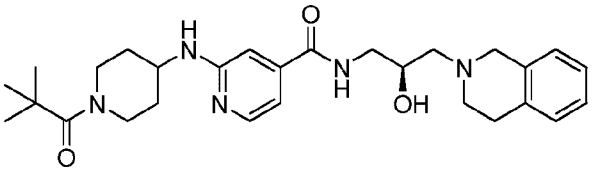
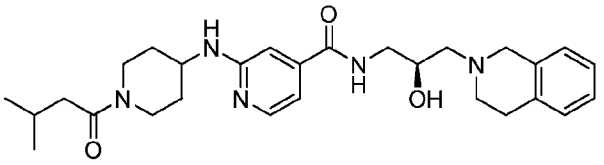
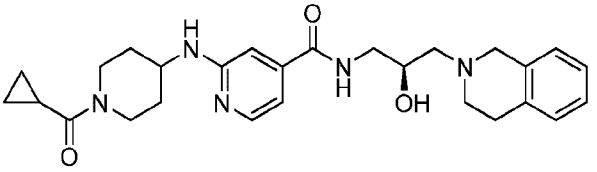
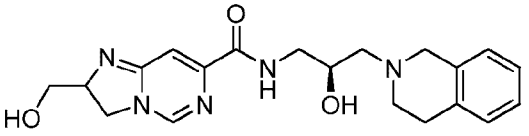
Table 1B. Exemplary compounds			
Cmpd No	**Structure**	**Exact Mass**	**LCMS m/z (M+H)**
467		440.2536	441.2
468		479.2896	480.2
469		479.2896	480.2
470		493.3053	494.2
471		493.3053	494.2
472		477.274	478.2
473		383.1957	384.1

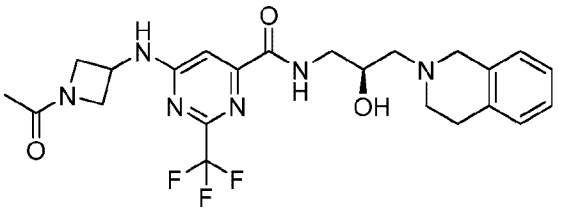
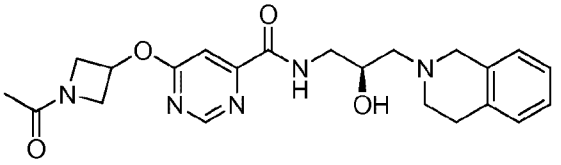
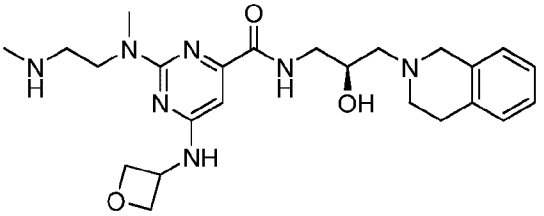
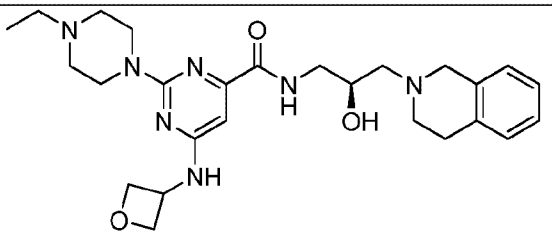
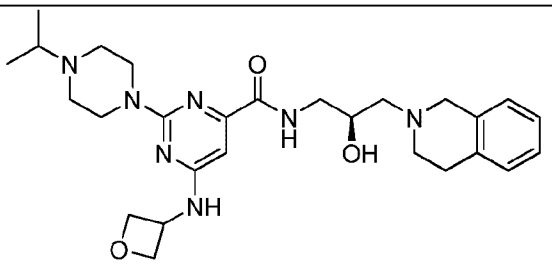
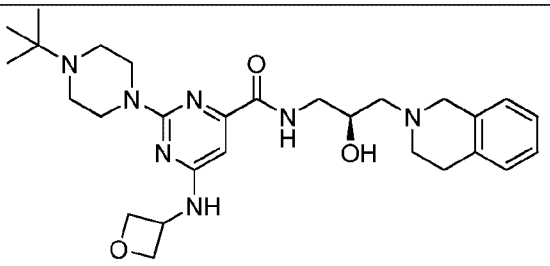
Table 1B. Exemplary compounds			
Cmpd No	**Structure**	**Exact Mass**	**LCMS m/z (M+H)**
474		492.2097	493.2
475		425.2063	426.2
476		469.2801	470.2
477		495.2958	496.3
478		509.3114	510.3
479		551.322	552.3

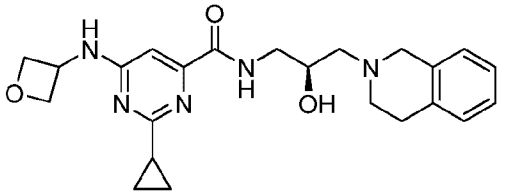
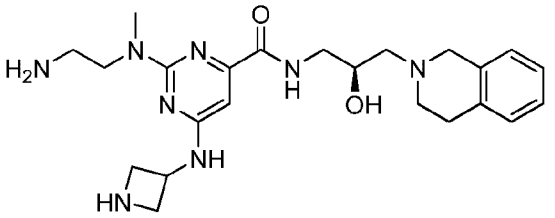
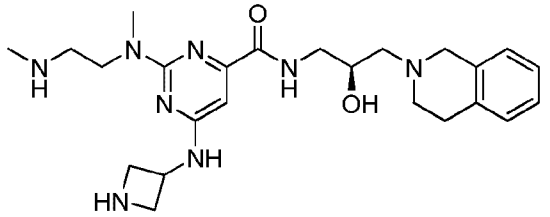
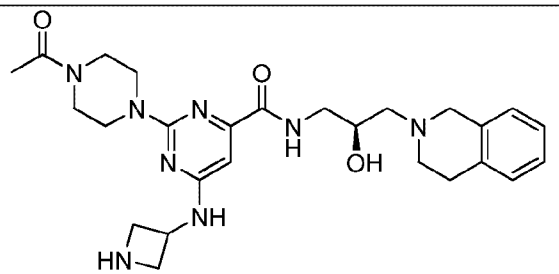
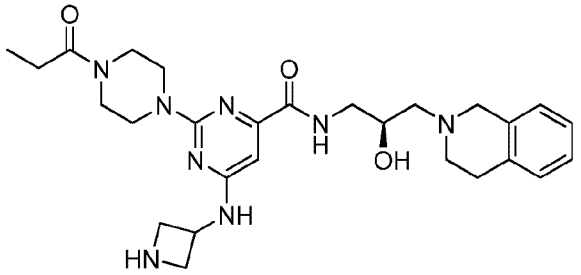
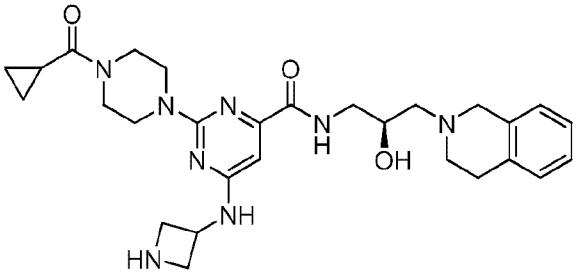
Table 1B. Exemplary compounds			
Cmpd No	Structure	Exact Mass	LCMS m/z (M+H)
480		423.227	424.2
481		454.2805	455.2
482		468.2961	469.3
483		508.291	509.2
484		522.3067	523.3
485		534.3067	535.3

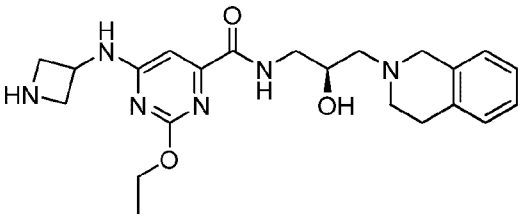
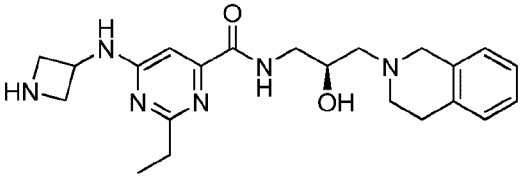
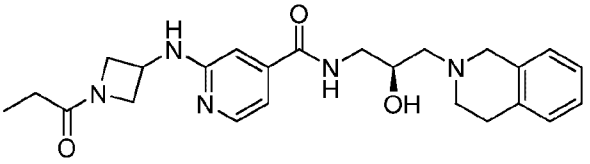
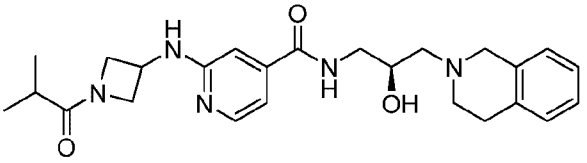
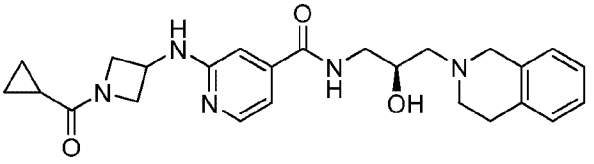
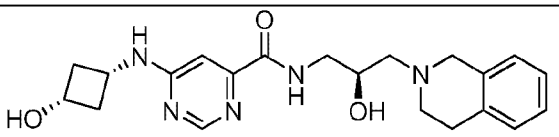
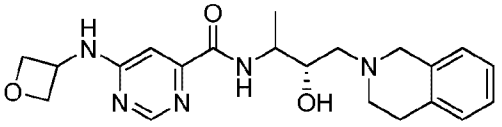
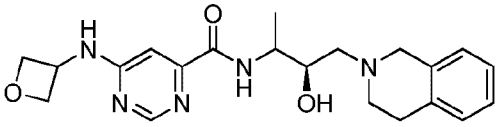
Table 1B. Exemplary compounds			
Cmpd No	Structure	Exact Mass	LCMS m/z (M+H)
486		426.2379	427.1
487		410.243	411.2
488		437.2427	438.1
489		451.2583	452.1
490		449.2427	450.1
491		397.2114	398.2
492		397.2114	398.2
493		397.2114	398.2

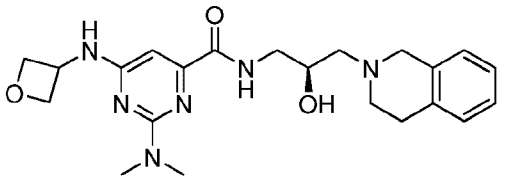
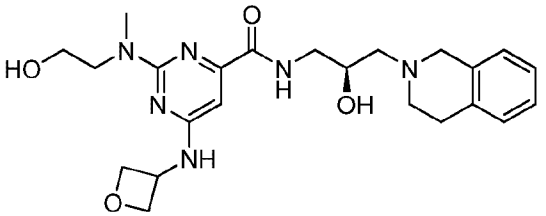
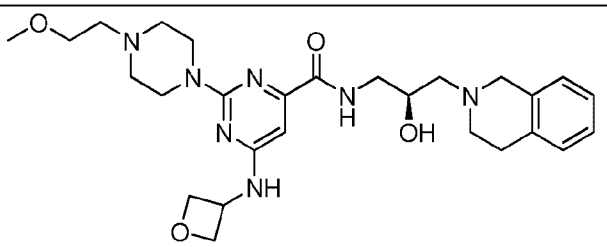
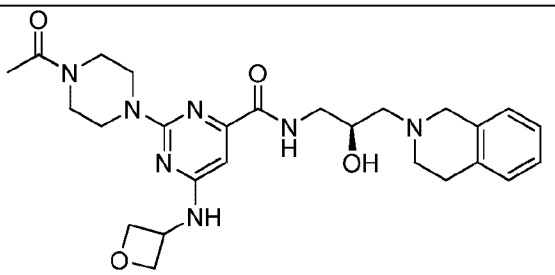
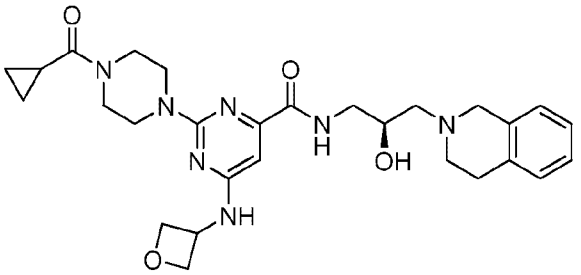
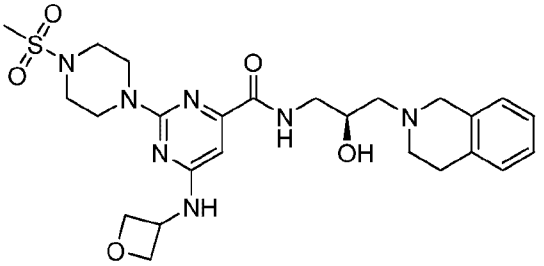
Table 1B. Exemplary compounds			
Cmpd No	Structure	Exact Mass	LCMS m/z (M+H)
494		426.2379	427.3
495		456.2485	457.1
496		525.3064	526.3
497		509.2751	510.2
498		535.2907	536.3
499		545.242	546.3

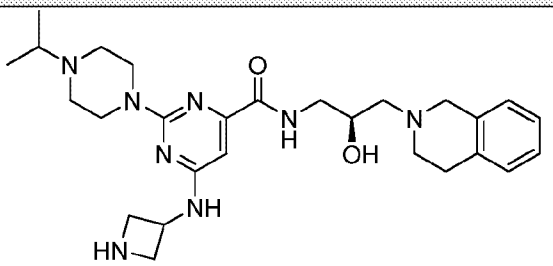
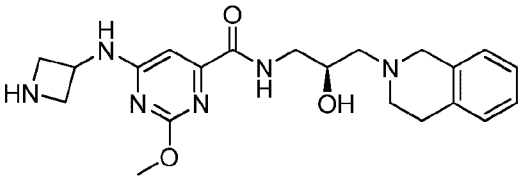
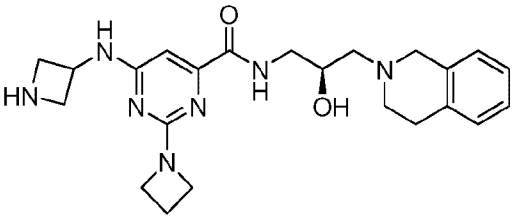
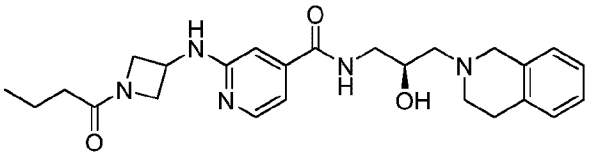
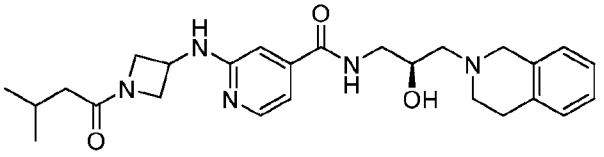
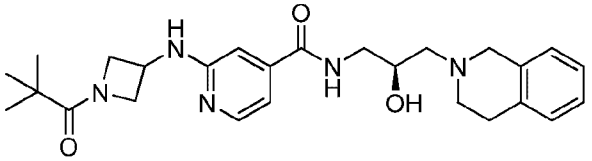
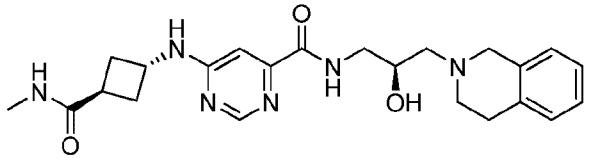
Table 1B. Exemplary compounds			
Cmpd No	**Structure**	**Exact Mass**	**LCMS m/z (M+H)**
500		508.3274	509.3
501		412.2223	413.1
502		437.2539	438.1
503		451.2583	452.3
504		465.274	466.3
505		465.274	466.3
506		438.2379	439.2

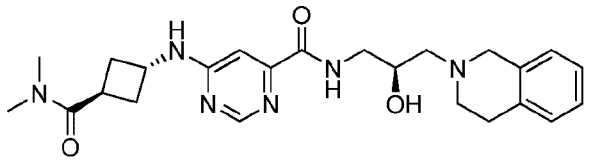
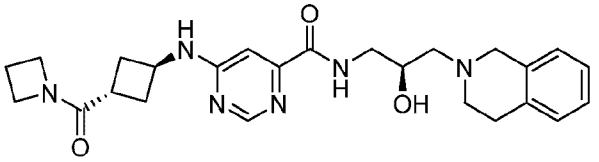
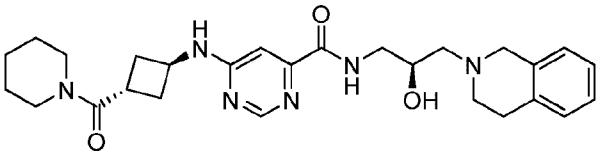
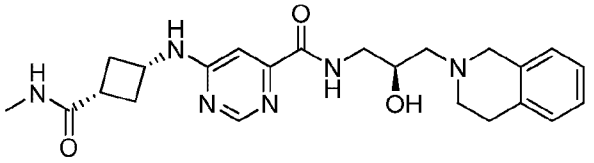
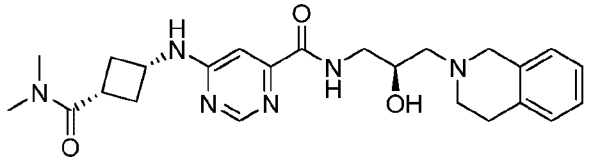
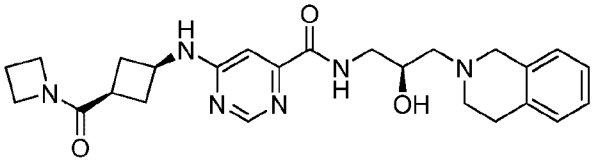
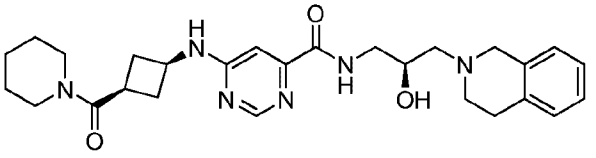
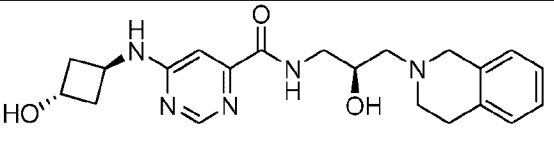
Table 1B. Exemplary compounds			
Cmpd No	**Structure**	**Exact Mass**	**LCMS m/z (M+H)**
507		452.2536	453.2
509		464.2536	465.2
511		492.2849	493.2
513		438.2379	439.2
515		452.2536	453.2
517		464.2536	465.2
519		492.2849	493.3
521		397.2114	398.2

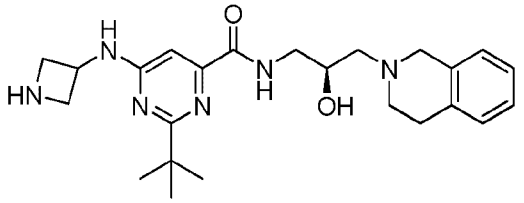
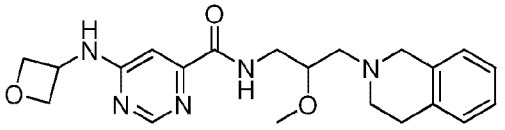
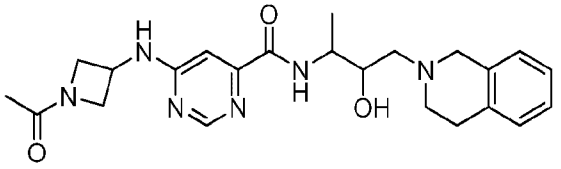
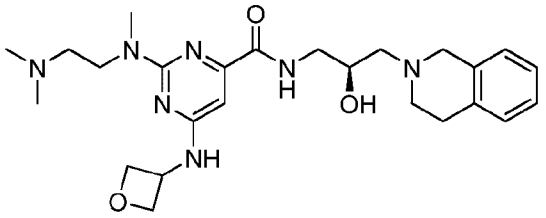
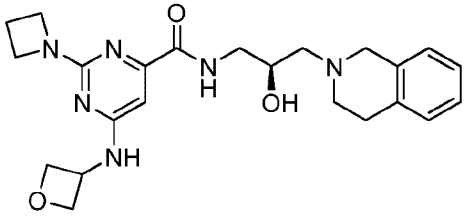
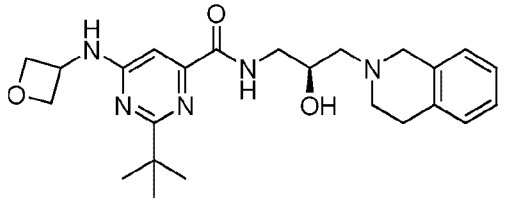
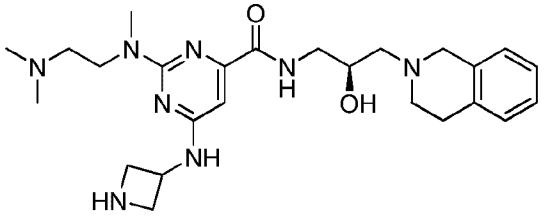
Table 1B. Exemplary compounds			
Cmpd No	Structure	Exact Mass	LCMS m/z (M+H)
522		438.2743	439.2
523		397.2114	398.2
524		438.2379	439.1
525		483.2958	484.3
526		438.2379	439.2
527		439.2583	440.3
528		482.3118	483.2

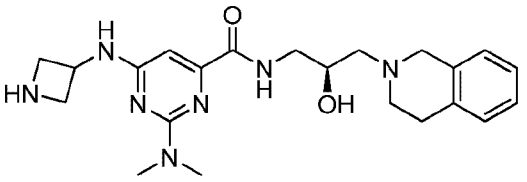
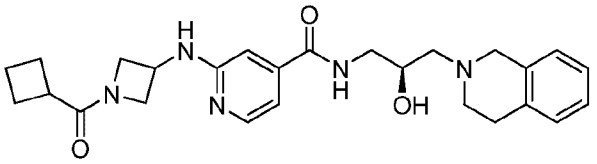
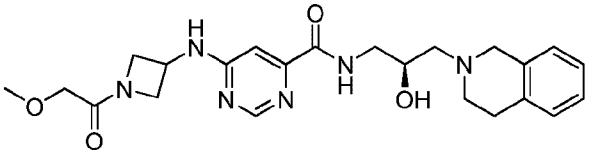
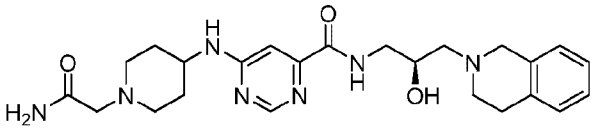
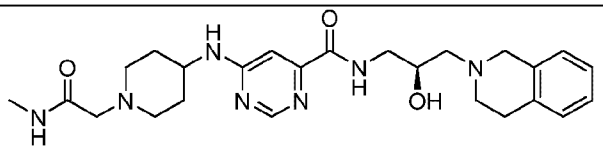
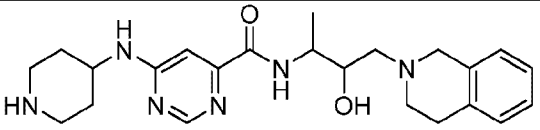
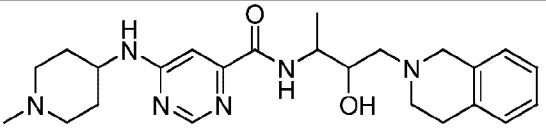
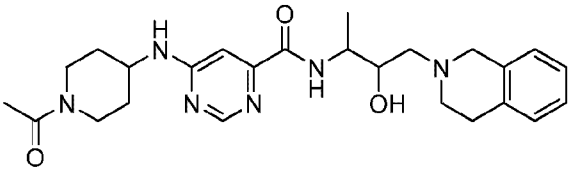
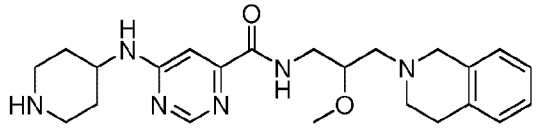
Table 1B. Exemplary compounds			
Cmpd No	Structure	Exact Mass	LCMS m/z (M+H)
529		425.2539	426.2
530		463.2583	464.3
531		454.2329	455.2
532		467.2645	468.3
533		481.2801	482.3
534		424.2587	425.2
535		438.2743	439.2
536		466.2692	467.2
538		424.2587	425.2

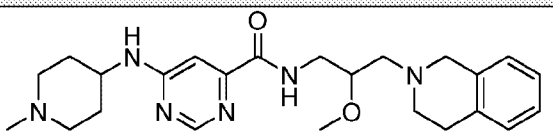
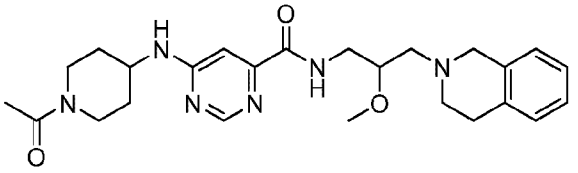
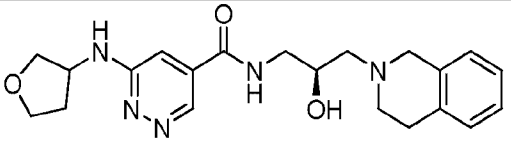
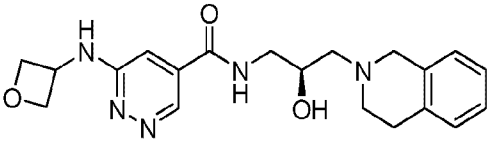
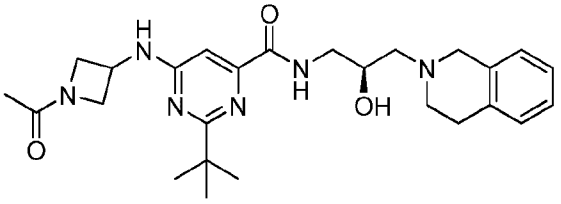
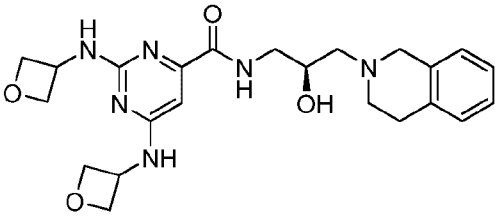
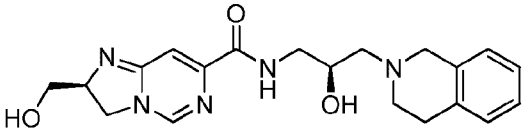
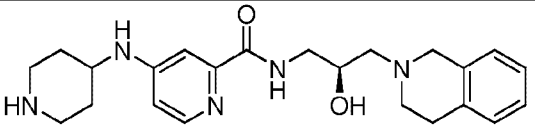
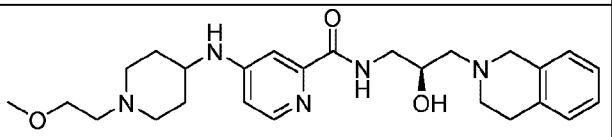
Table 1B. Exemplary compounds			
Cmpd No	Structure	Exact Mass	LCMS m/z (M+H)
540		438.2743	439.3
542		466.2692	467.3
544		397.2114	398.2
545		383.1957	384.1
546		480.2849	481.3
547		454.2329	455.3
548		383.1957	384.2
549		409.2478	410.2
550		467.2896	468.2

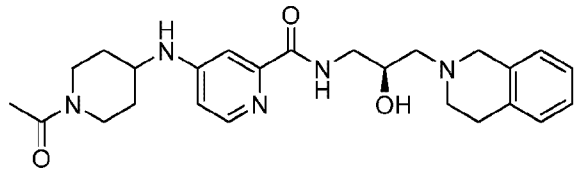
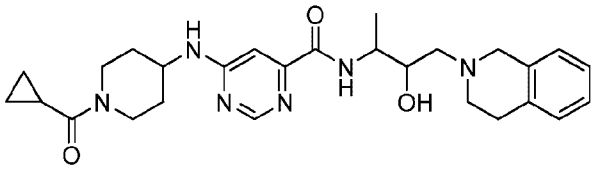
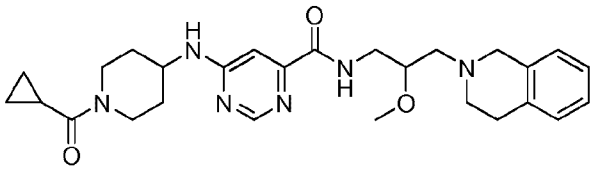
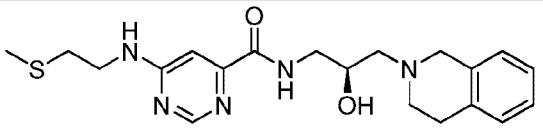
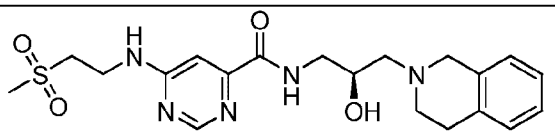
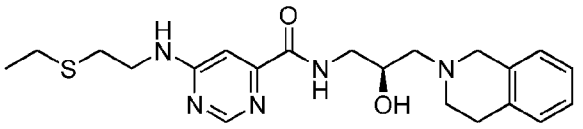
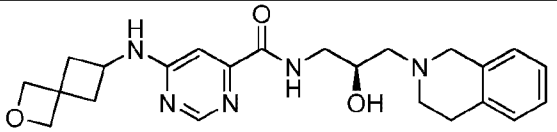
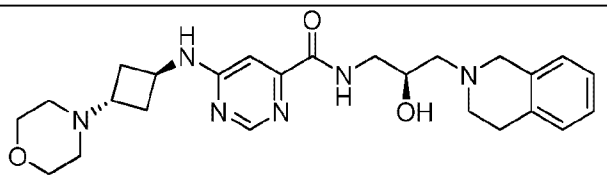
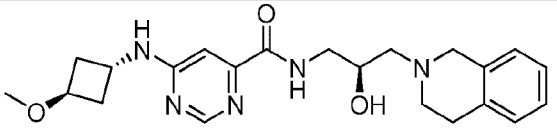
Table 1B. Exemplary compounds			
Cmpd No	Structure	Exact Mass	LCMS m/z (M+H)
551		451.2583	452.2
552		492.2849	493.2
553		492.2849	493.3
554		401.1885	402.2
555		433.1784	434.1
556		415.2042	416.2
557		423.227	424.0
558		466.2692	467.3
559		411.227	412.3

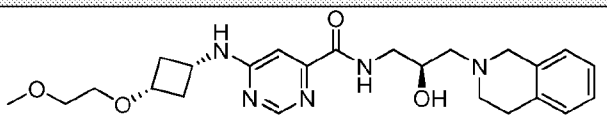
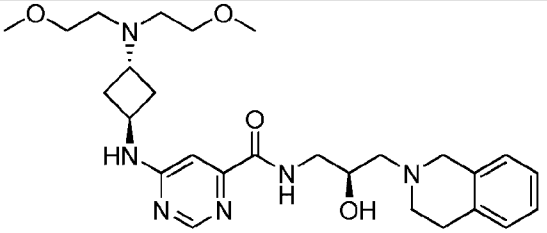
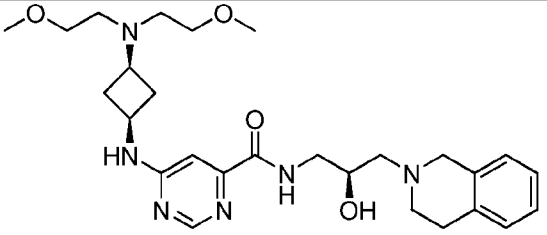
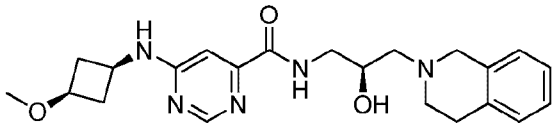
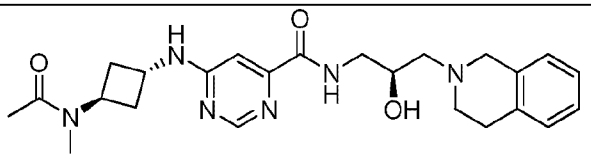
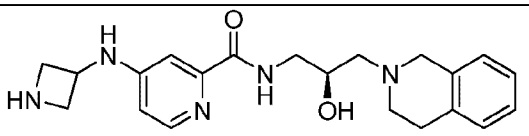
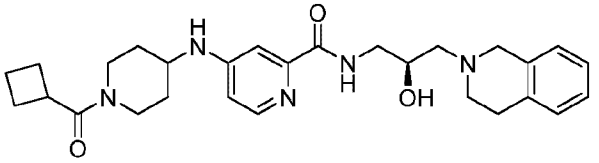
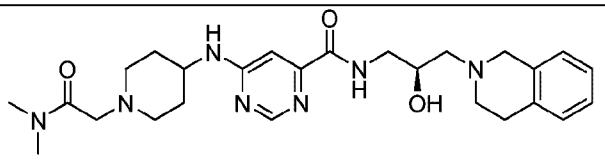
Table 1B. Exemplary compounds			
Cmpd No	Structure	Exact Mass	LCMS m/z (M+H)
560		455.2533	456.0
561		512.3111	512.2
562		512.3111	513.2
563		411.227	412.2
564		452.2536	453.2
565		381.2165	382.2
566		491.2896	492.2
567		495.2958	496.3

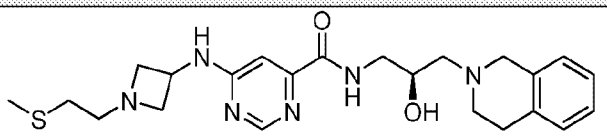
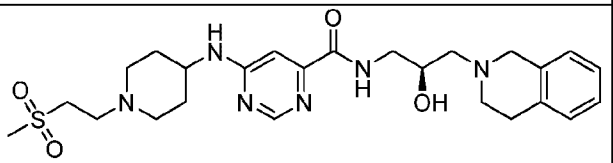
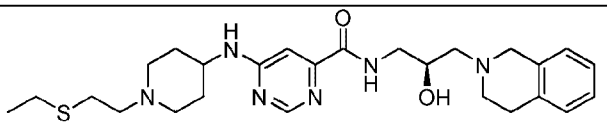
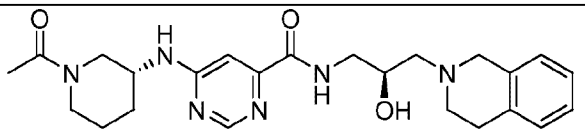
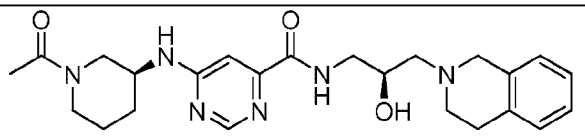
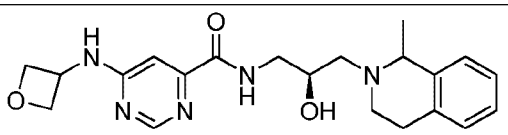
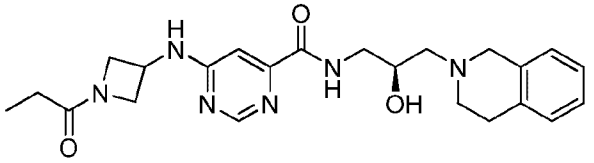
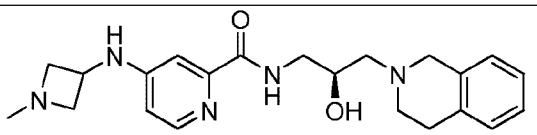
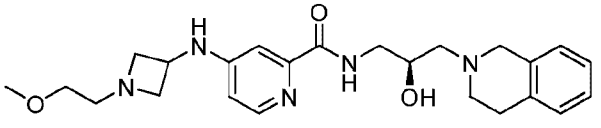
Table 1B. Exemplary compounds			
Cmpd No	Structure	Exact Mass	LCMS m/z (M+H)
568		456.2307	457.3
569		516.2519	517.3
570		498.2777	499.3
571		452.2536	453.2
572		452.2536	453.2
573		397.2114	398.2
574		438.2379	439.2
575		395.2321	396.2
576		439.2583	440.3

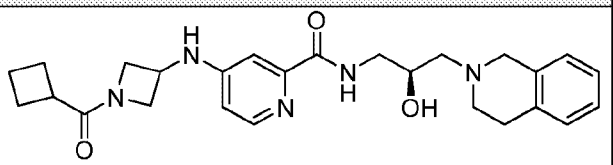
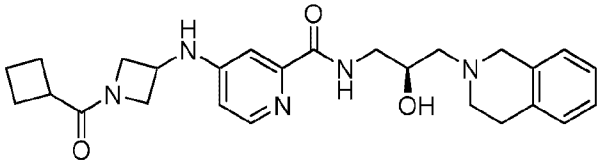
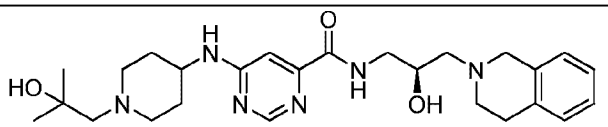
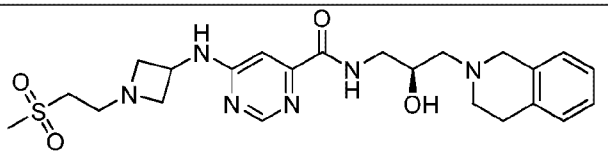
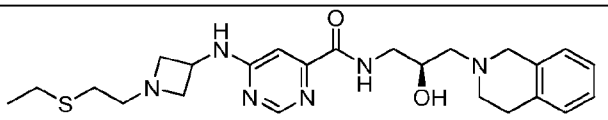
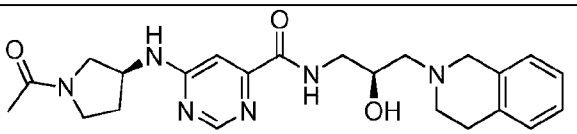
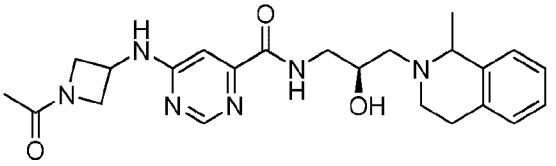
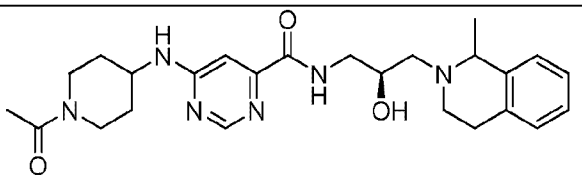
Table 1B. Exemplary compounds			
Cmpd No	Structure	Exact Mass	LCMS m/z (M+H)
577		463.2583	464.3
578		463.2583	464.3
579		482.3005	483.3
580		488.2206	489.2
581		470.2464	471.3
582		438.2379	439.1
583		438.2379	439.2
584		466.2692	467.3

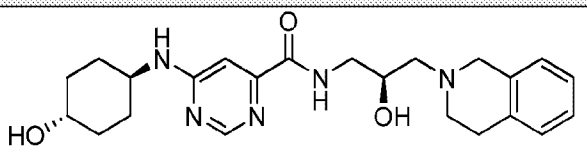
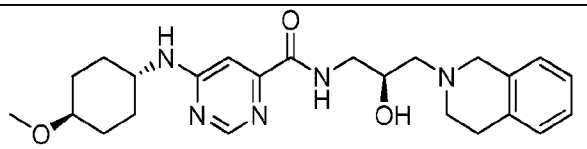
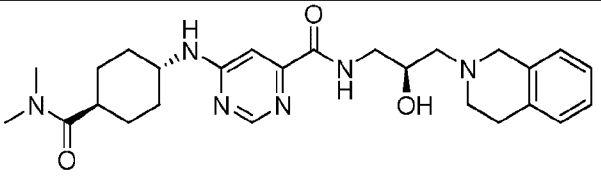
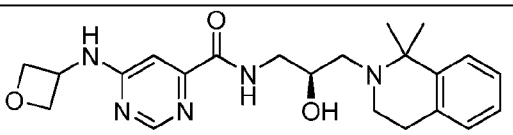
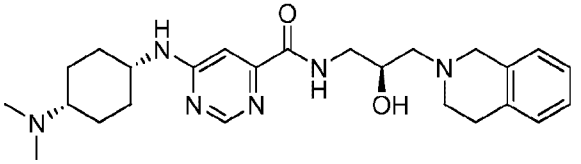
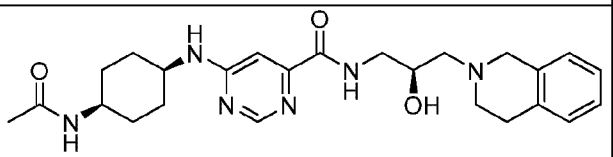
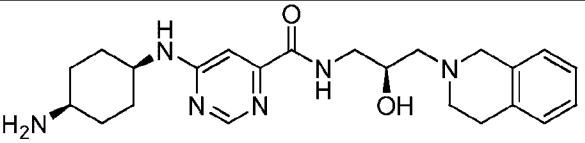
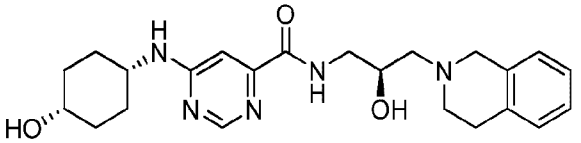
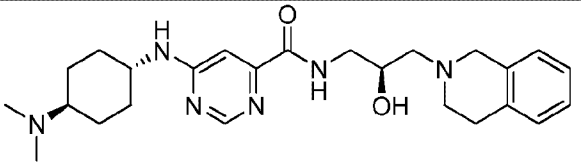
Table 1B. Exemplary compounds			
Cmpd No	Structure	Exact Mass	LCMS m/z (M+H)
585		425.2427	426.2
586		439.2583	440.3
587		480.2849	481.3
588		411.227	412.2
589		452.29	453.3
590		466.2692	467.3
591		424.2587	425.2
592		425.2427	426.2
593		452.29	453.2

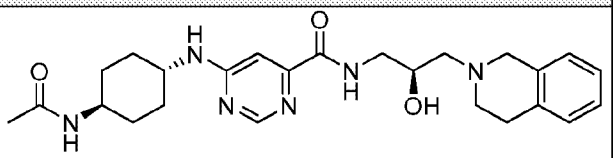
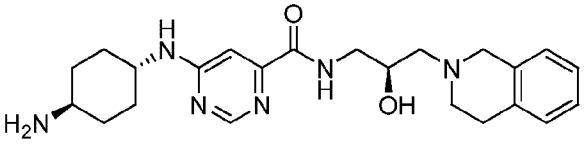
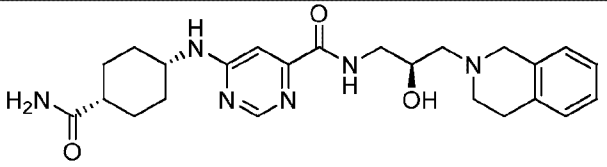
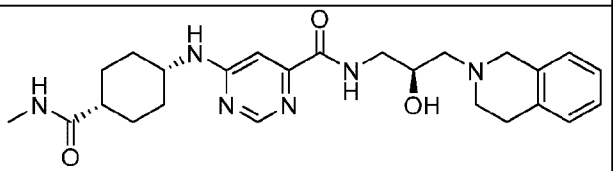
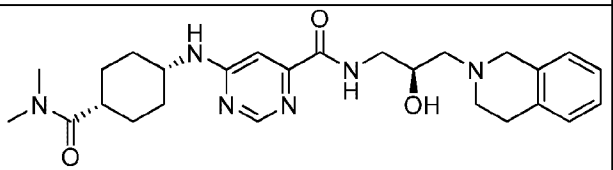
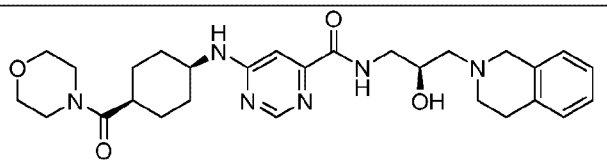
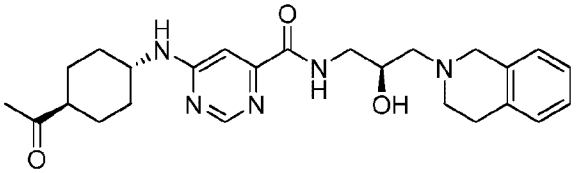
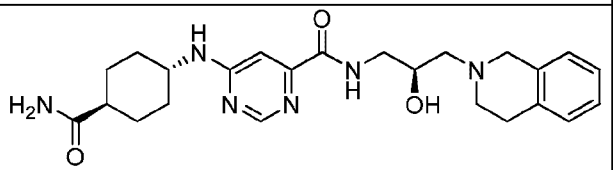
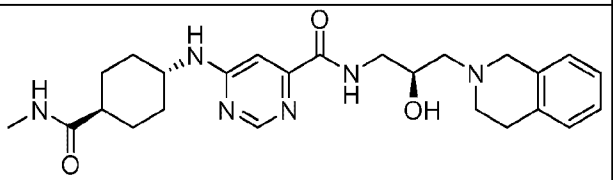
Table 1B. Exemplary compounds			
Cmpd No	Structure	Exact Mass	LCMS m/z (M+H)
594		466.2692	467.2
595		424.2587	425.2
596		452.2536	453.2
597		466.2692	467.2
598		480.2849	481.2
599		522.2955	523.2
600		451.2583	452.2
601		452.2536	453.3
602		466.2692	467.3

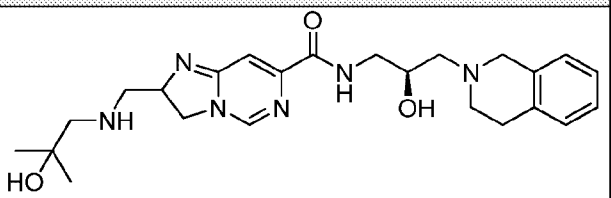
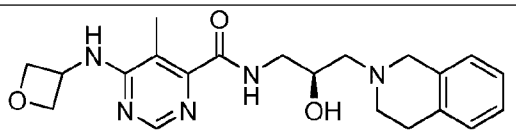
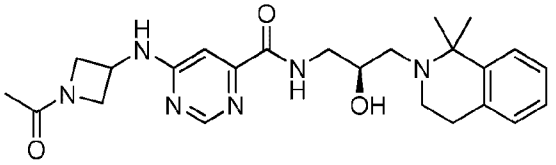
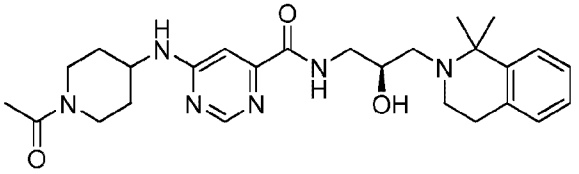
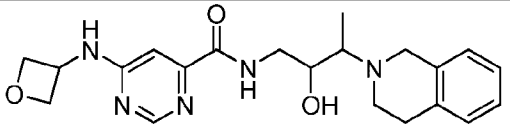
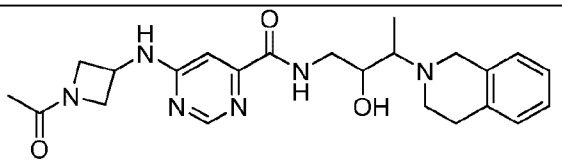
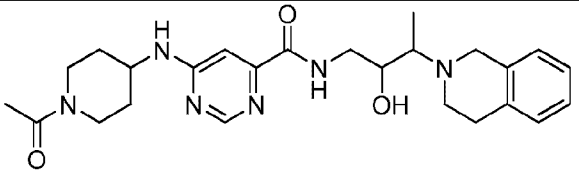
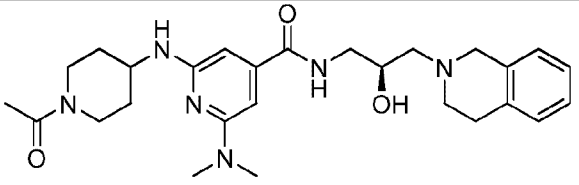
Table 1B. Exemplary compounds			
Cmpd No	**Structure**	**Exact Mass**	**LCMS m/z (M+H)**
603		454.2692	455.3
604		397.2114	398.2
605		452.2536	453.3
606		480.2849	481.3
607		397.2114	398.2
608		438.2379	439.3
609		466.2692	467.3
610		494.3005	495.3

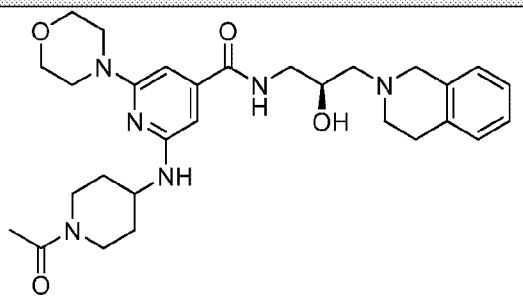
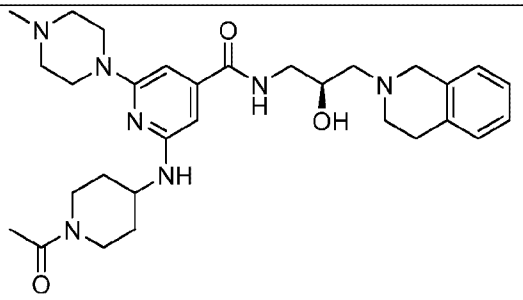
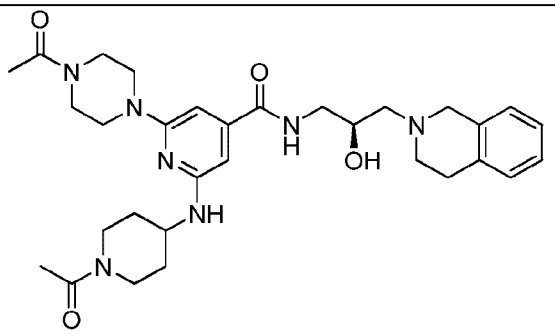
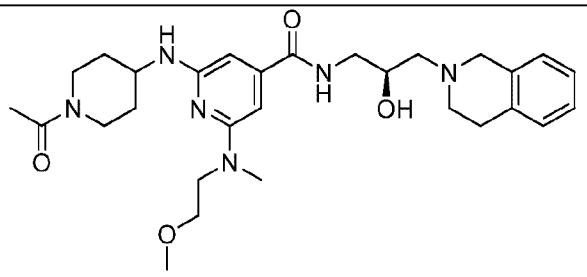
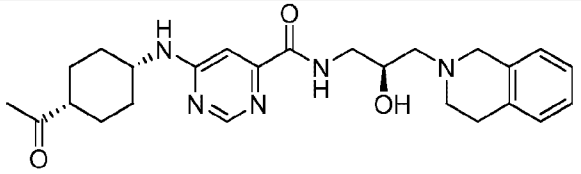
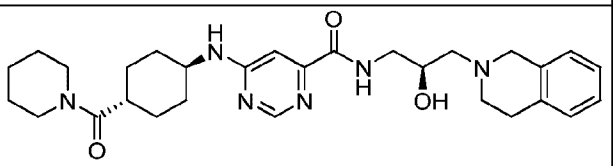
Table 1B. Exemplary compounds			
Cmpd No	**Structure**	**Exact Mass**	**LCMS m/z (M+H)**
611		536.3111	537.3
612		549.3427	550.3
613		577.3377	578.4
614		538.3268	539.3
615		451.2583	452.2
616		522.2955	523.3

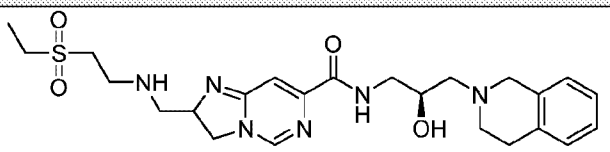
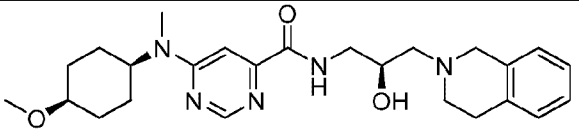
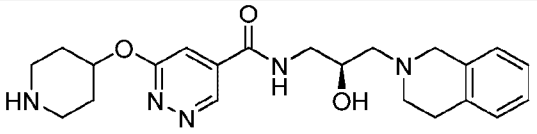
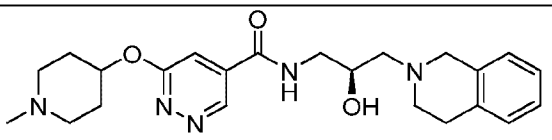
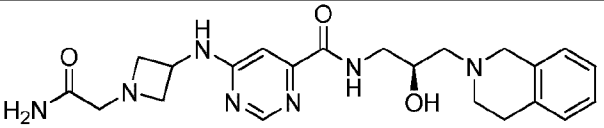
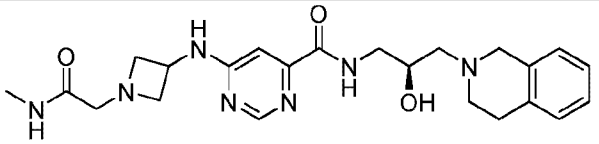
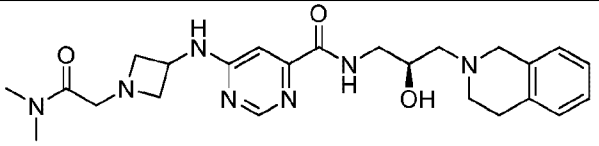
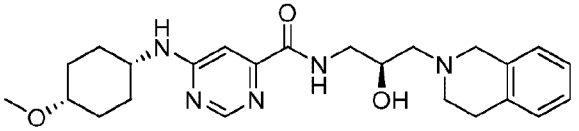
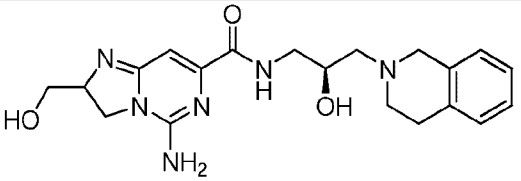
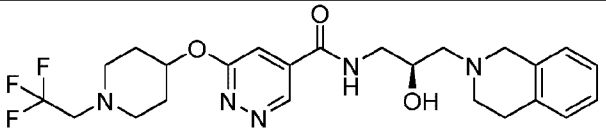
Table 1B. Exemplary compounds			
Cmpd No	Structure	Exact Mass	LCMS m/z (M+H)
617		502.2362	503.2
618		453.274	454.2
619		411.227	412.2
620		425.2427	426.3
621		439.2332	440.3
622		453.2488	454.2
623		467.2645	468.2
624		439.2583	440.1
625		398.2066	399.2
626		493.2301	494.2

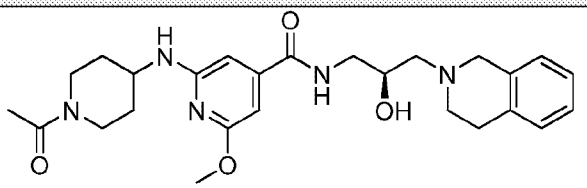
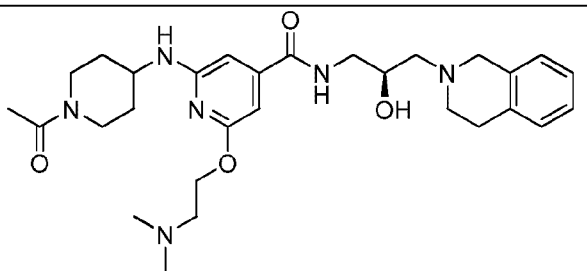
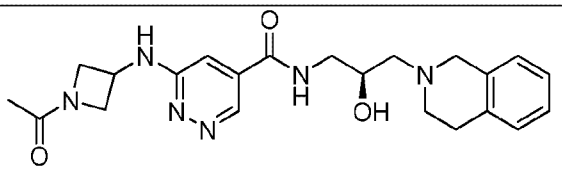
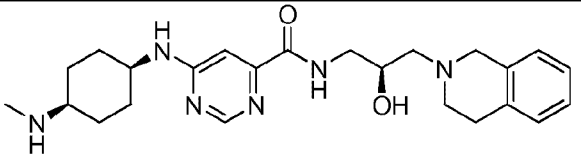
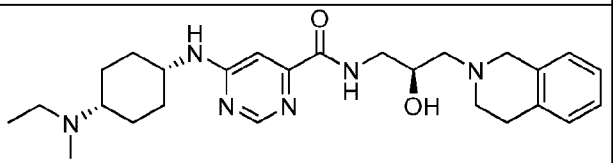
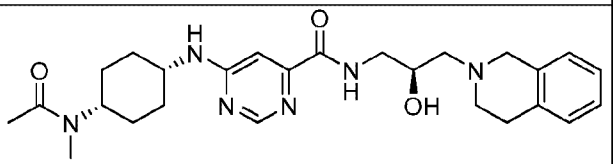
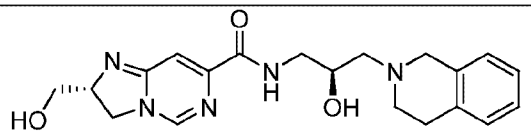
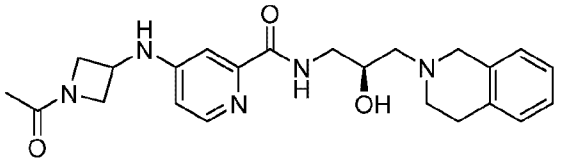
Table 1B. Exemplary compounds			
Cmpd No	**Structure**	**Exact Mass**	**LCMS m/z (M+H)**
627		481.2689	482.1
628		538.3268	539.2
629		424.2223	425.2
630		438.2743	439.2
631		466.3056	467.2
632		480.2849	481.2
634		383.1957	384.2
635		423.227	424.2

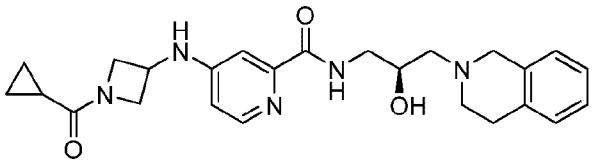
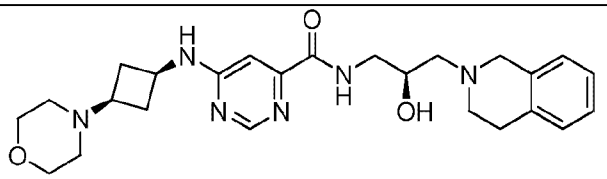
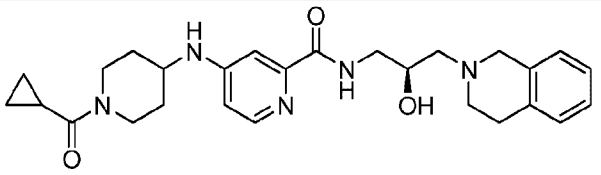
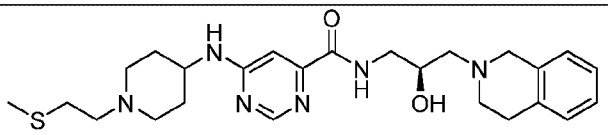
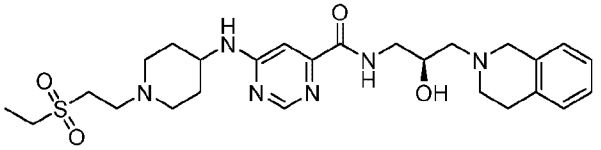
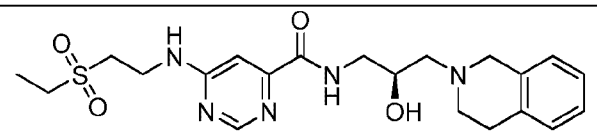
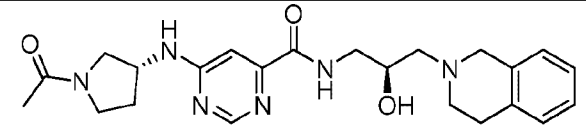
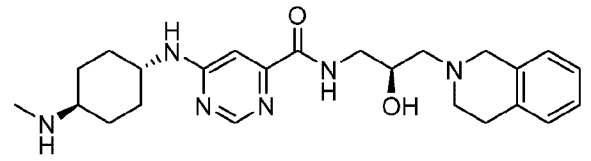
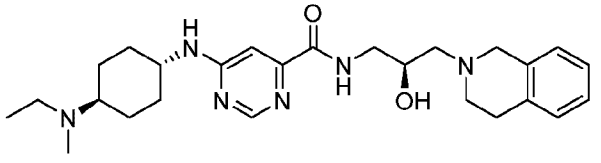
Table 1B. Exemplary compounds			
Cmpd No	Structure	Exact Mass	LCMS m/z (M+H)
636		449.2427	450.3
637		466.2692	467.3
638		477.274	478.2
639		484.262	485.3
640		530.2675	531.3
641		447.194	448.2
642		438.2379	439.1
661		438.2743	439.2
662		466.3056	467.3

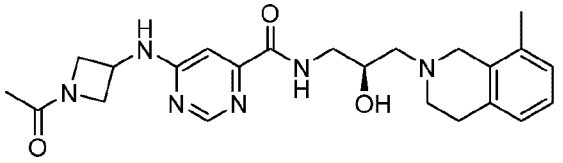
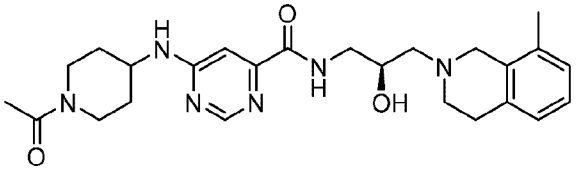
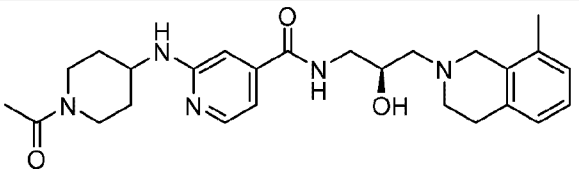
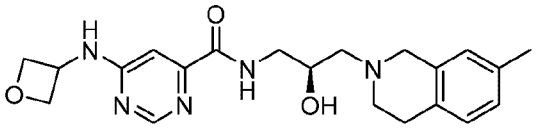
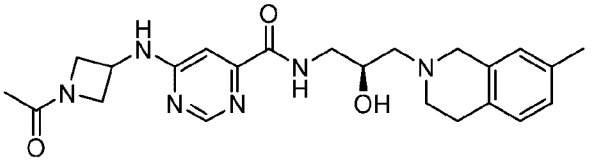
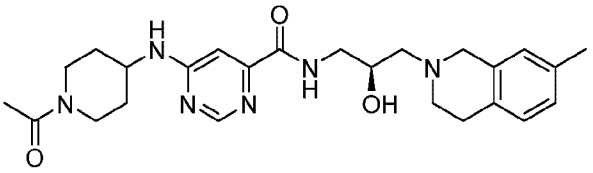
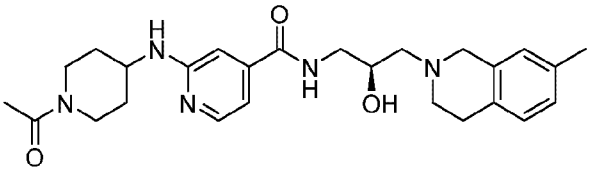
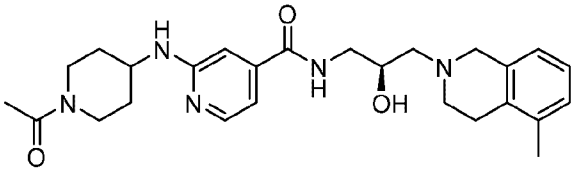
Table 1B. Exemplary compounds			
Cmpd No	Structure	Exact Mass	LCMS m/z (M+H)
663		438.2379	439.2
664		466.2692	467.3
665		465.274	466.3
666		397.2114	398.2
667		438.2379	439.3
668		466.2692	467.3
669		465.274	466.2
670		465.274	466.3

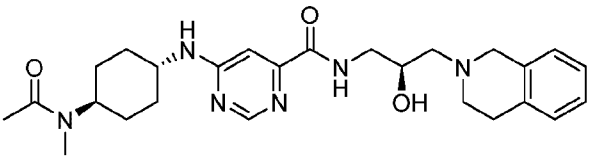
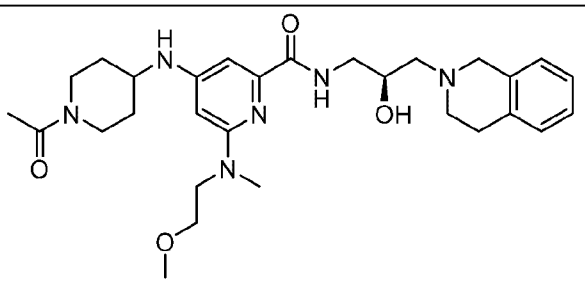
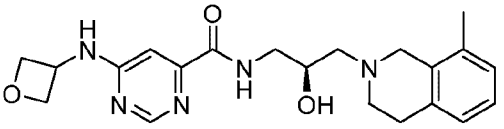
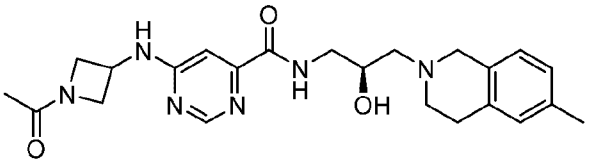
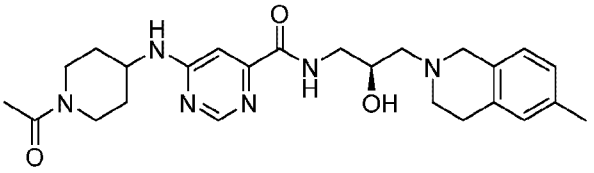
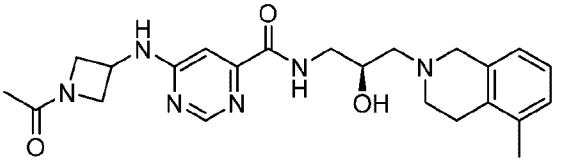
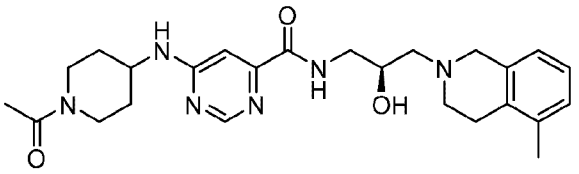
Table 1B. Exemplary compounds			
Cmpd No	**Structure**	**Exact Mass**	**LCMS m/z (M+H)**
671		480.2849	481.0
672		538.3268	539.2
673		397.2114	398.2
674		438.2379	439.3
675		466.2692	467.3
676		438.2379	439.3
677		466.2692	467.0

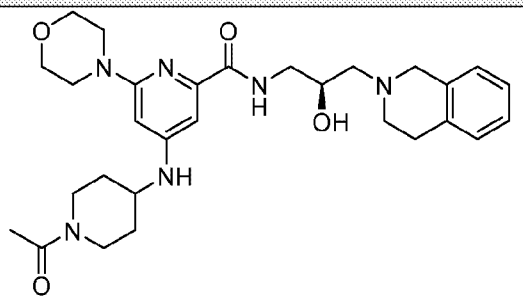
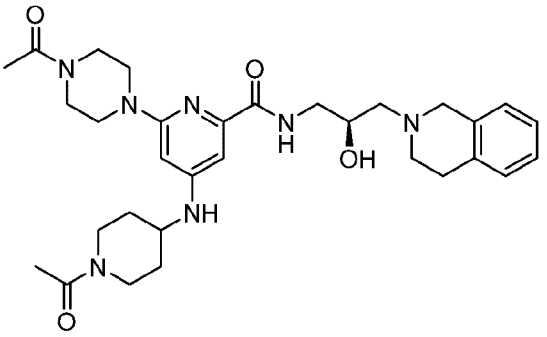
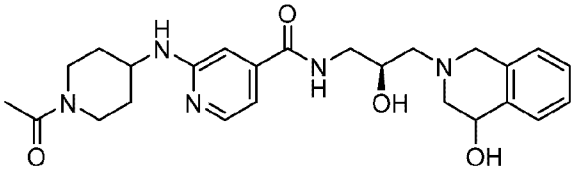
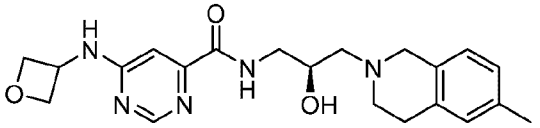
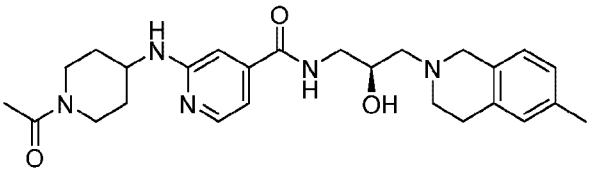
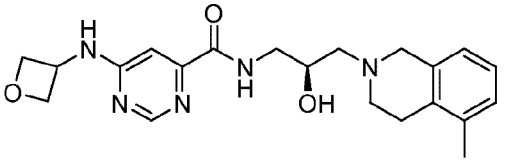
Table 1B. Exemplary compounds			
Cmpd No	Structure	Exact Mass	LCMS m/z (M+H)
678		536.3111	537.2
679		577.3377	578.3
680		467.2533	468.3
681		397.2114	398.2
682		465.274	466.3
683		397.2114	398.2

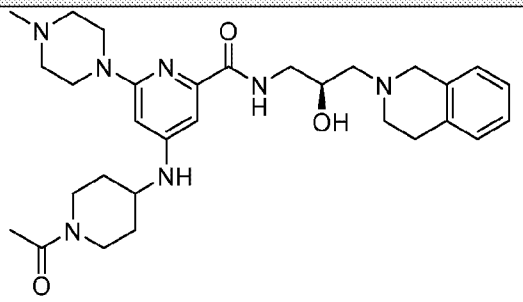
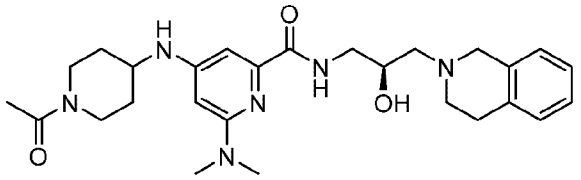
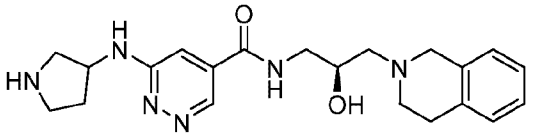
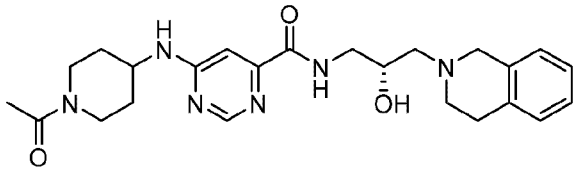
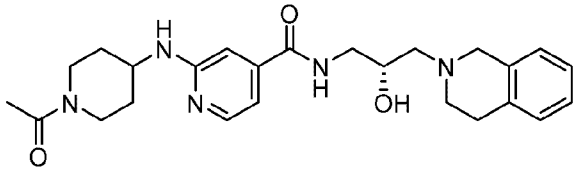
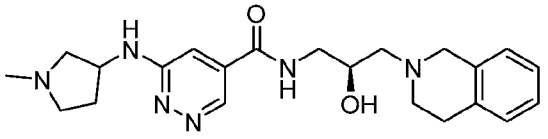
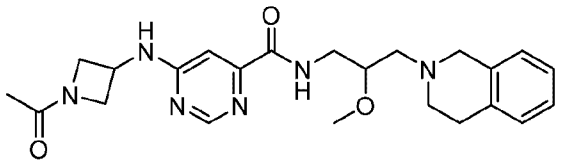
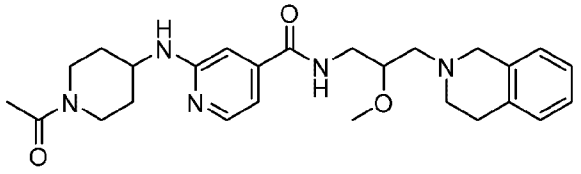
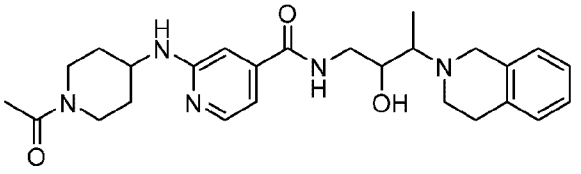
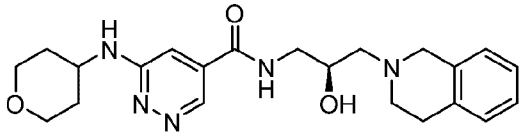
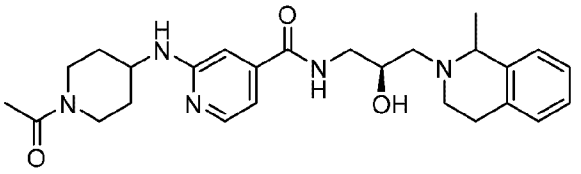
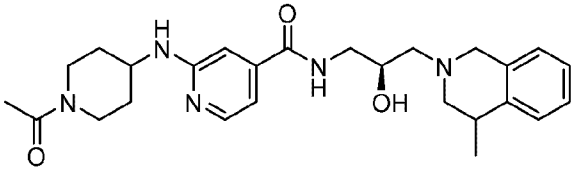
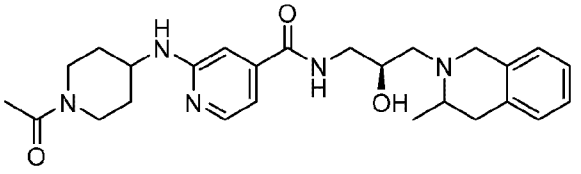
Table 1B. Exemplary compounds			
Cmpd No	**Structure**	**Exact Mass**	**LCMS m/z (M+H)**
684		549.3427	550.3
685		494.3005	495.2
686		396.2274	397.2
687		452.2536	453.1
688		451.2583	452.1
689		410.243	411.1
690		438.2379	439.3
691		465.274	466.3

Table 1B. Exemplary compounds			
Cmpd No	Structure	Exact Mass	LCMS m/z (M+H)
692		465.274	466.3
693		411.227	412.2
694		465.274	466.1
695		465.274	466.3
696		465.274	466.3

[00251] In certain embodiments, a provided compound is a compound listed in Table 1C, or a pharmaceutically acceptable salt thereof.

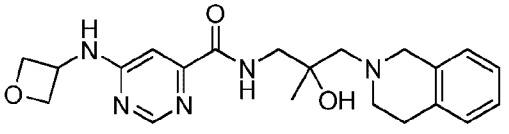
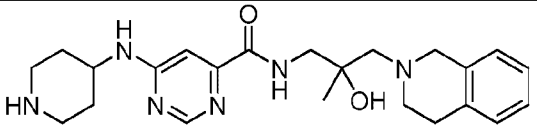
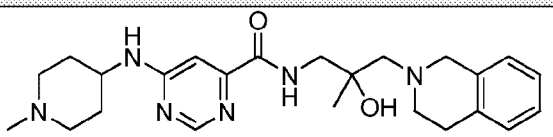
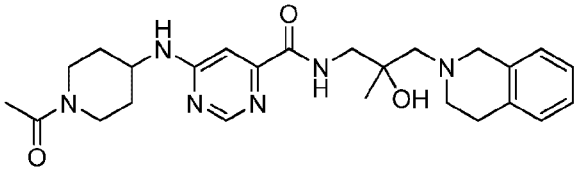
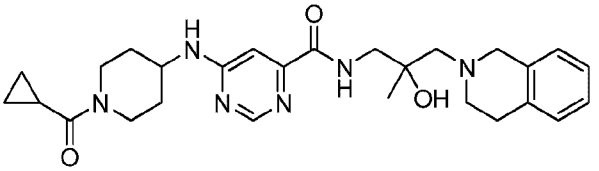
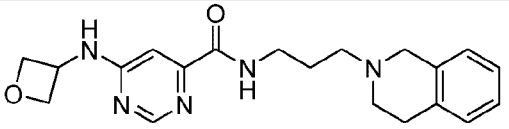
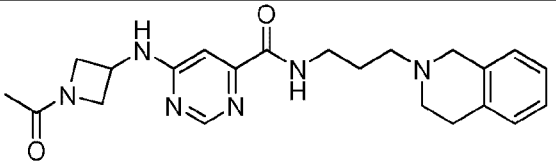
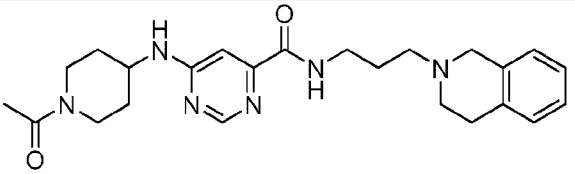
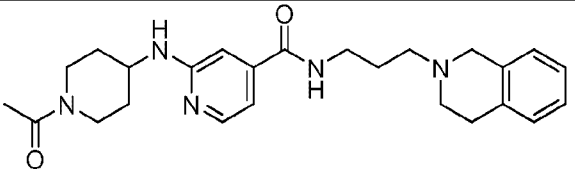
Table 1C. Exemplary compounds			
Cmpd No	Structure	Exact Mass	LCMS m/z (M+H)
646		397.2114	398.1
647		424.2587	425.2

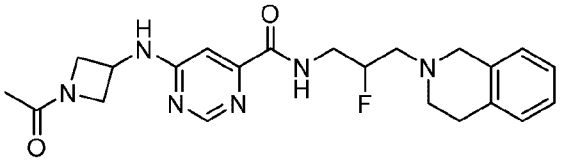
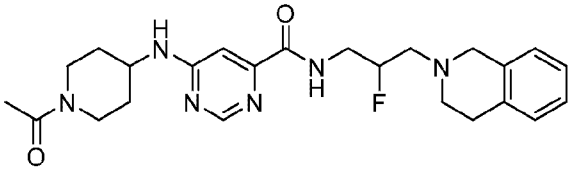
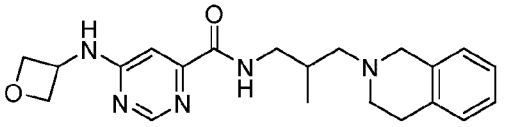
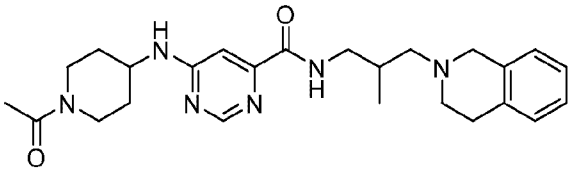
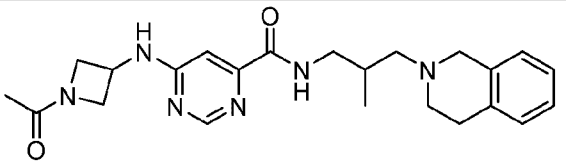
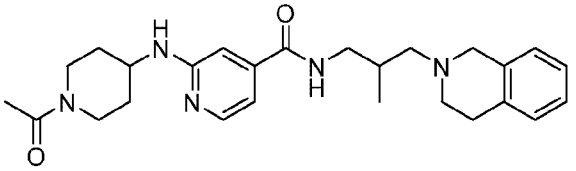
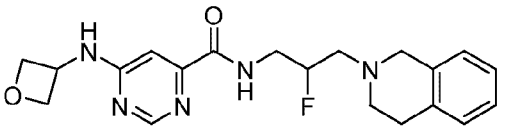
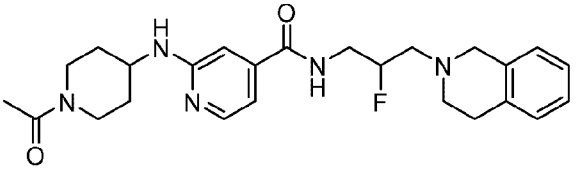
Table 1C. Exemplary compounds			
Cmpd No	Structure	Exact Mass	LCMS m/z (M+H)
648		438.2743	439.2
649		466.2692	467.2
650		492.2849	493.2

[00252] In certain embodiments, a provided compound is a compound listed in Table 1D, or a pharmaceutically acceptable salt thereof.

Table 1D. Exemplary compounds			
Cmpd No	Structure	Exact Mass	LCMS m/z (M+H)
651		367.2008	368.2
652		408.2274	409.2
653		436.2587	437.3
654		435.2634	436.3

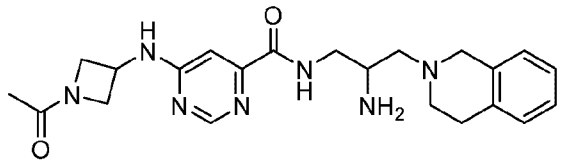
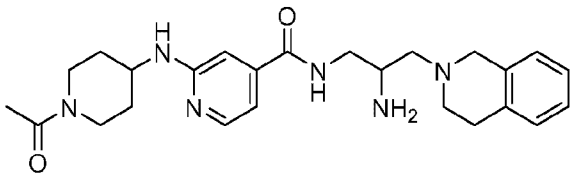
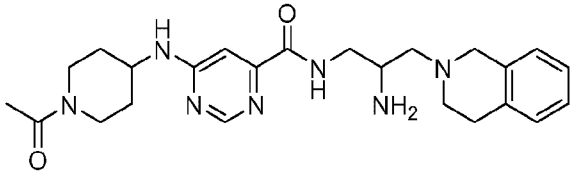
[00253] In certain embodiments, a provided compound is a compound listed in Table 1E, or a pharmaceutically acceptable salt thereof.

Table 1E. Exemplary compounds

Cmpd No	Structure	Exact Mass	LCMS m/z (M+H)
655		426.218	427.2
656		454.2493	455.3
657		381.2165	382.2
658		450.2743	451.3
659		422.243	423.2
660		449.2791	450.3
697		385.1914	386.0
698		453.254	454.3

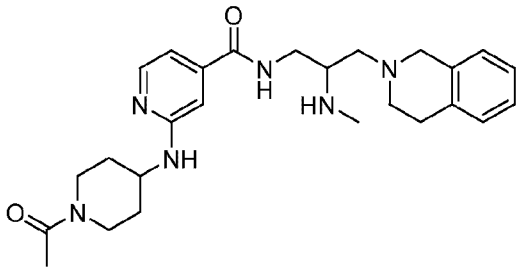
[00254] In certain embodiments, a provided compound is a compound listed in Table 1F, or a pharmaceutically acceptable salt thereof.

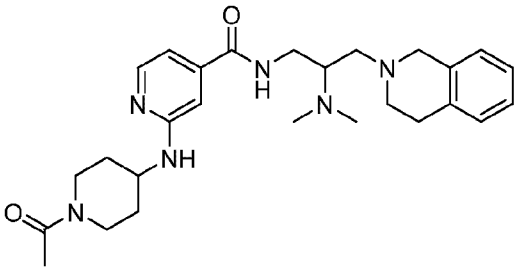
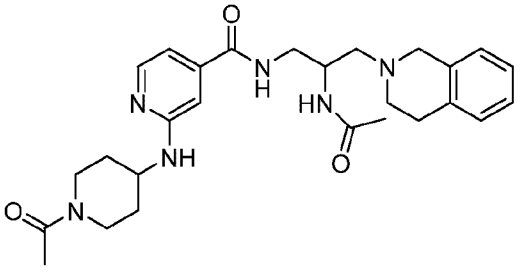
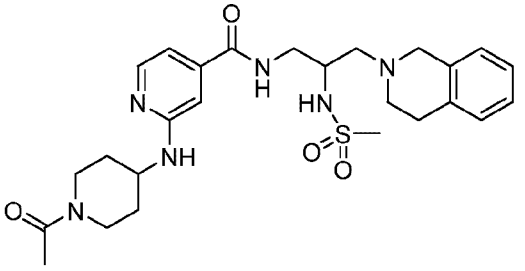
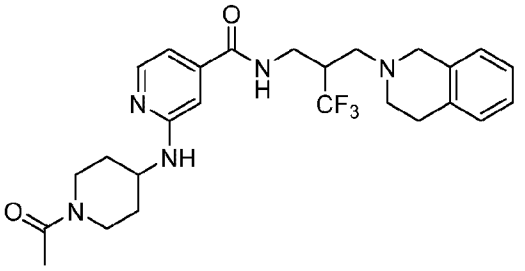
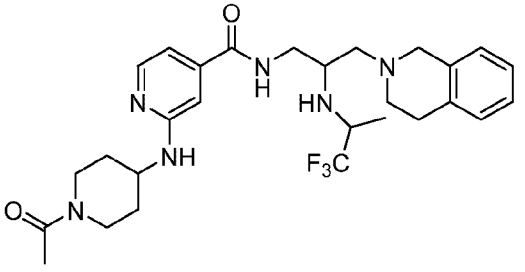
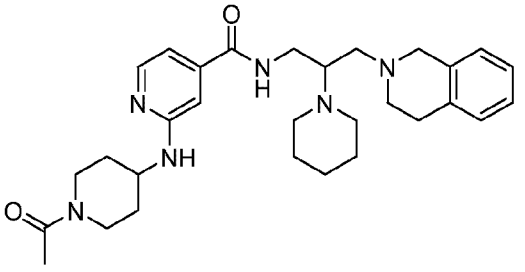
Table 1F. Exemplary Compounds

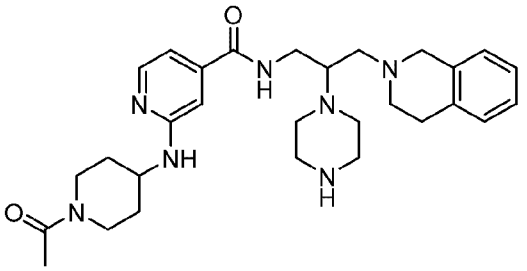
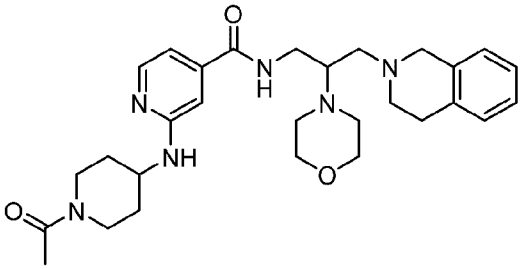
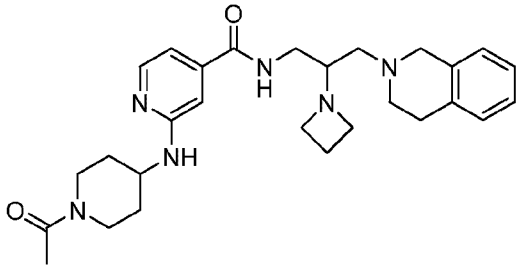
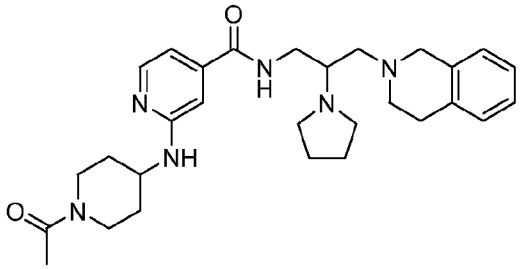
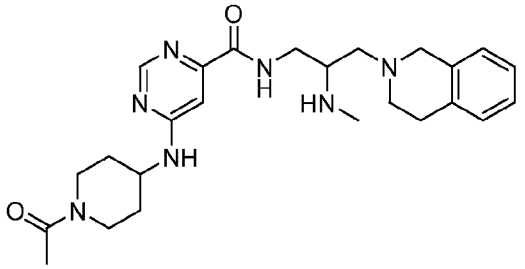
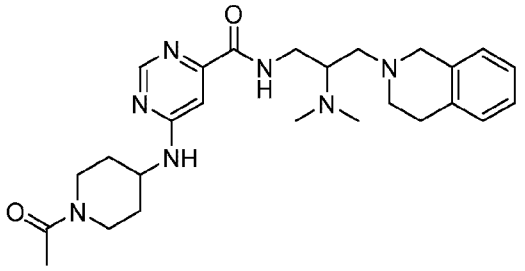
Cmpd No	Structure	Exact Mass	LCMS m/z (M+H)
699		423.2383	424.2
700		450.2743	451.3
701		451.2696	452.3

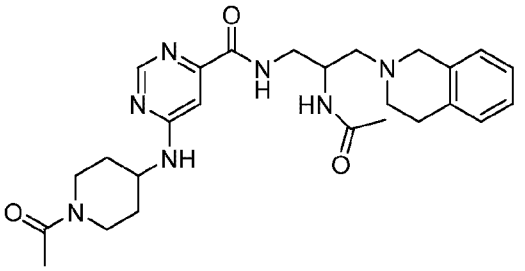
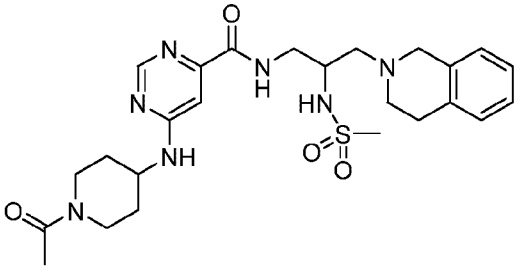
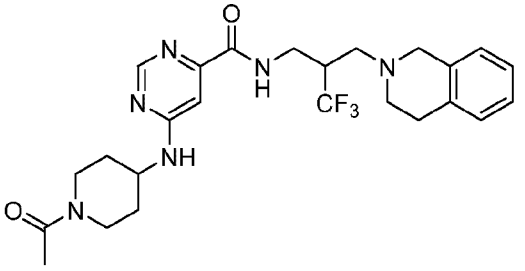
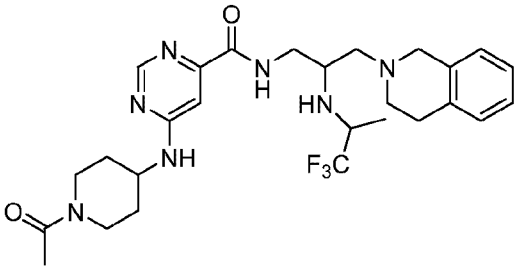
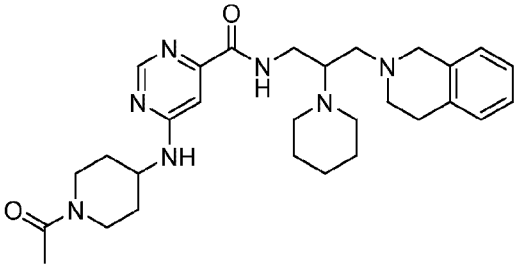
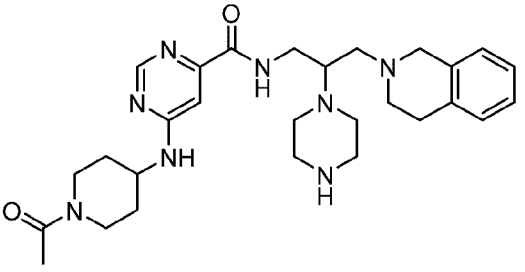
[00255] In certain embodiments, a provided compound is a compound listed in Table 1G, or a pharmaceutically acceptable salt thereof.

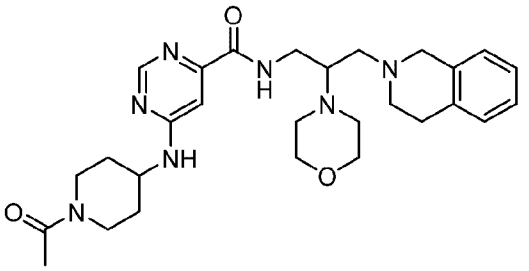
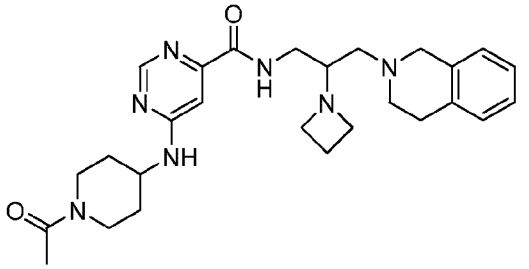
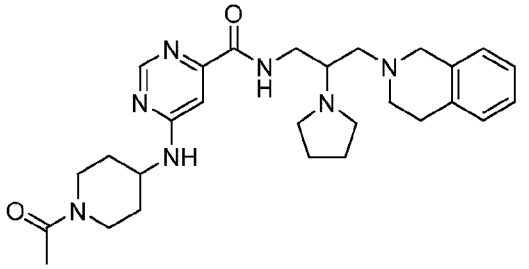
Table 1G. Exemplary Compounds

Cmpd No	Structure	Exact Mass
702		464.2900

703		478.3056
704		492.2849
705		528.2519
706		503.2508
707		546.2930
708		518.3369

709		519.3322
710		520.3162
711		490.3056
712		504.3213
713		465.2852
714		479.3009

715		493.2801
716		529.2471
717		504.2461
718		547.2883
719		519.3322
720		520.3274

721		521.3114
722		491.3009
723		505.3165

[00256] In certain embodiments, a provided compound inhibits PRMT5. In certain embodiments, a provided compound inhibits wild-type PRMT5. In certain embodiments, a provided compound inhibits a mutant PRMT5. In certain embodiments, a provided compound inhibits PRMT5, *e.g.*, as measured in an assay described herein. In certain embodiments, the PRMT5 is from a human. In certain embodiments, a provided compound inhibits PRMT5 at an IC_{50} less than or equal to 10 μM. In certain embodiments, a provided compound inhibits PRMT5 at an IC_{50} less than or equal to 1 μM. In certain embodiments, a provided compound inhibits PRMT5 at an IC_{50} less than or equal to 0.1 μM. In certain embodiments, a provided compound inhibits PRMT5 in a cell at an EC_{50} less than or equal to 10 μM. In certain embodiments, a provided compound inhibits PRMT5 in a cell at an EC_{50} less than or equal to 1 μM. In certain embodiments, a provided compound inhibits PRMT5 in a cell at an EC_{50} less than or equal to 0.1 μM. In certain embodiments, a provided compound inhibits cell proliferation at an EC_{50} less than or equal to 10 μM. In certain embodiments, a provided compound inhibits cell proliferation at an EC_{50} less than or equal to 1 μM. In certain embodiments, a provided compound inhibits cell proliferation at an EC_{50} less than or equal to 0.1 μM. In some embodiments, a provided compound is selective for PRMT5 over

other methyltransferases. In certain embodiments, a provided compound is at least about 10-fold selective, at least about 20-fold selective, at least about 30-fold selective, at least about 40-fold selective, at least about 50-fold selective, at least about 60-fold selective, at least about 70-fold selective, at least about 80-fold selective, at least about 90-fold selective, or at least about 100-fold selective for PRMT5 relative to one or more other methyltransferases.

[00257] It will be understood by one of ordinary skill in the art that the PRMT5 can be wild-type PRMT5, or any mutant or variant of PRMT5.

[00258] In some embodiments embodiment, the mutant or variant of PRMT5 contains one or more mutations (e.g., conservative substitutions). In some embodiments, provided herein is a PRMT5 point mutant. In some embodiments, the PRMT point mutant has an amino acid sequence that a degree of homology to the amino acid sequence of SEQ ID NO: 1 of at least about 80%, e.g., at least about 85%, at least about 90%, at least about 95% , or at least about 97%. Further provided is a protein that has a degree of homology to the amino acid sequence of SEQ ID NO: 2 of at least about 80%, e.g., at least about 85%, at least about 90%, at least about 95% , or at least about 97%.

[00259] In certain embodiments, the PRMT5 is isoform A (GenBank accession no. NP006100) (SEQ ID NO.:1):

MAAMAVGGAG GSRVSSGRDL NCVPEIADTL GAVAKQGFDF LCMPVFHPRF
KREFIQEPAK NRPGPQTRSD LLLSGRDWNT LIVGKLSPWI RPDSKVEKIR
RNSEAAMLQE LNFGAYLGLP AFLLPLNQED NTNLARVLTN HIHTGHHSSM
FWMRVPLVAP EDLRDDIIEN APTTHTEEYS GEEKTWMWWH NFRTLCDYSK
RIAVALEIGA DLPSNHVIDR WLGEPIKAAI LPTSIFLTNK KGFPVLSKMH
QRLIFRLLKL EVQFIITGTN HHSEKEFCSY LQYLEYLSQN RPPPNAYELF
AKGYEDYLQS PLQPLMDNLE SQTYEVFEKD PIKYSQYQQA IYKCLLDRVP
EEEKDTNVQV LMVLGAGRGP LVNASLRAAK QADRRIKLYA VEKNPNAVVT
LENWQFEEWG SQVTVVSSDM REWVAPEKAD IIVSELLGSF ADNELSPECL
DGAQHFLKDD GVSIPGEYTS FLAPISSSKL YNEVRACREK DRDPEAQFEM
PYVVRLHNFH QLSAPQPCFT FSHPNRDPMI DNNRYCTLEF PVEVNTVLHG
FAGYFETVLY QDITLSIRPE THSPGMFSWF PILFPIKQPI TVREGQTICV
RFWRCSNSKK VWYEWAVTAP VCSAIHNPTG RSYTIGL

[00260] In certain embodiments, the PRMT5 is isoform B (GenBank accession no. NP001034708) (SEQ ID NO.:2)

MRGPNSGTEK GRLVIPEKQG FDFLCMPVFH PRFKREFIQE PAKNRPGPQT
RSDLLLSGRD WNTLIVGKLS PWIRPDSKVE KIRRNSEAAM LQELNFGAYL

GLPAFLLPLN QEDNTNLARV LTNHIHTGHH SSMFWMRVPL VAPEDLRDDI
IENAPTTHTE EYSGEEKTWM WWHNFRTLCD YSKRIAVALE IGADLPSNHV
IDRWLGEPIK AAILPTSIFL TNKKGFPVLS KMHQRLIFRL LKLEVQFIIT
GTNHHSEKEF CSYLQYLEYL SQNRPPPNAY ELFAKGYEDY LQSPLQPLMD
NLESQTYEVF EKDPIKYSQY QQAIYKCLLD RVPEEEKDTN VQVLMVLGAG
RGPLVNASLR AAKQADRRIK LYAVEKNPNA VVTLENWQFE EWGSQVTVVS
SDMREWVAPE KADIIVSELL GSFADNELSP ECLDGAQHFL KDDGVSIPGE
YTSFLAPISS SKLYNEVRAC REKDRDPEAQ FEMPYVVRLH NFHQLSAPQP
CFTFSHPNRD PMIDNNRYCT LEFPVEVNTV LHGFAGYFET VLYQDITLSI
RPETHSPGMF SWFPILFPIK QPITVREGQT ICVRFWRCSN SKKVWYEWAV
TAPVCSAIHN PTGRSYTIGL

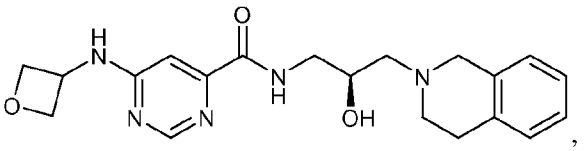
[00261] In certain embodiments, the PRMT5 is transcript variant 1 (GenBank accession no. NM_006109).

[00262] The present disclosure provides pharmaceutical compositions comprising a compound described herein, *e.g.*, a compound of Formula (**A**), *e.g.*, Formula (**I**), or a pharmaceutically acceptable salt thereof, as described herein, and optionally a pharmaceutically acceptable excipient. It will be understood by one of ordinary skill in the art that the compounds described herein, or salts thereof, may be present in various forms, such as amorphous, hydrates, solvates, or polymorphs. In certain embodiments, a provided composition comprises two or more compounds described herein. In certain embodiments, a compound described herein, or a pharmaceutically acceptable salt thereof, is provided in an effective amount in the pharmaceutical composition. In certain embodiments, the effective amount is a therapeutically effective amount. In certain embodiments, the effective amount is an amount effective for inhibiting PRMT5. In certain embodiments, the effective amount is an amount effective for treating a PRMT5-mediated disorder. In certain embodiments, the effective amount is a prophylactically effective amount. In certain embodiments, the effective amount is an amount effective to prevent a PRMT5-mediated disorder.

[00263] In certain embodiments, the provided pharmaceutical compositions comprise a compound described herein, *e.g.*, a compound of Formula (**A**), *e.g.*, Formula (**I**), or any subgenera thereof, *e.g* Formula (**XV**), (**XVI**), (**XVII**), (**XVIII**), (**XV-a**), (**XVI-a**), (**XVII-a**), (**XVII-b**), (**XVIII-a**), (**XV-b**), or (**XV-c**), and optionally a pharmaceutically acceptable excipient, wherein the compound is of a free base form. In certain embodiments, the provided pharmaceutical compositions comprise a compound described herein, *e.g.*, a compound of Formula (**A**), *e.g.*, Formula (**I**), or any subgenera thereof, *e.g* Formula (**XV**), (**XVI**), (**XVII**),

(**XVIII**), (**XV-a**), (**XVI-a**), (**XVII-a**), (**XVII-b**), (**XVIII-a**), (**XV-b**), or (**XV-c**), and optionally a pharmaceutically acceptable excipient, wherein the compound is in the form of a pharmaceutically acceptablesalt as generally defined herein. In certain embodiments, the provided pharmaceutical compositions comprise a hydrochloride salt of a compound described herein and optionally a pharmaceutically acceptable excipient. In certain embodiments, the provided pharmaceutical compositions comprise a tartrate salt of a compound described herein and optionally a pharmaceutically acceptable excipient. In certain embodiments, the provided pharmaceutical compositions comprise a monotartrate salt of a compound described herein and optionally a pharmaceutically acceptable excipient. In certain embodiments, the provided pharmaceutical compositions comprise a bitartrate salt of a compound described herein and optionally a pharmaceutically acceptable excipient. In certain embodiments, the provided pharmaceutical compositions comprise a monotartrate salt and a bitartrate salt of a compound described herein and optionally a pharmaceutically acceptable excipient. In certain embodiments, the provided pharmaceutical compositions comprise a compound described herein in a form of free base, and a pharmaceutically acceptable salt thereof, and optionally a pharmaceutically acceptable excipient.

[00264] In certain embodiments, the provided pharmaceutical compositions comprise a compound of one of the following formulae in a free base form and optionally a pharmaceutically acceptable excipient: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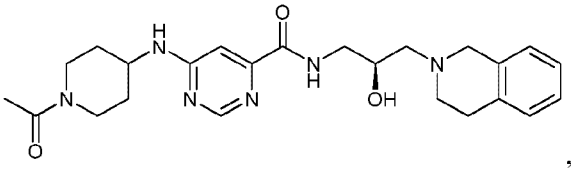
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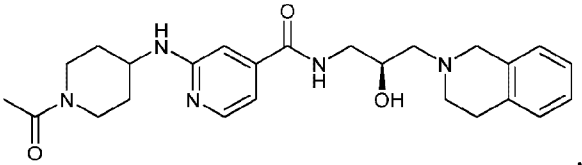
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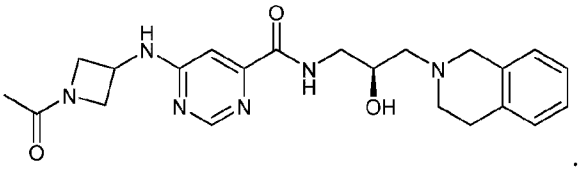
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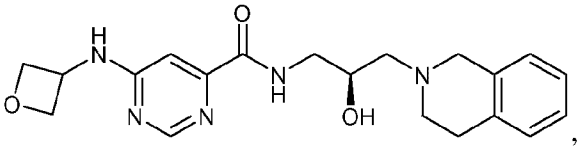
[00265] In certain embodiments, the provided pharmaceutical compositions comprise a compound of one of the following formulae in the form of a pharmaceutically acceptable salt as generally defined herein and optionally a pharmaceutically acceptable excipient:



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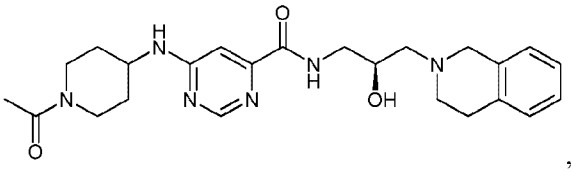

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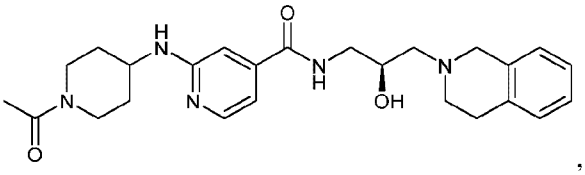

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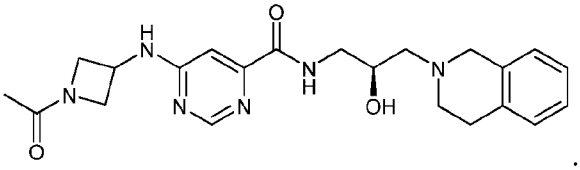

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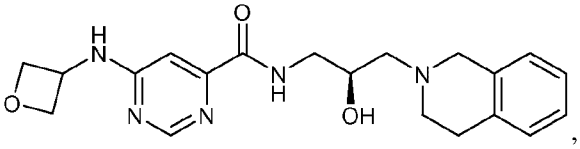
[00266] In certain embodiments, the provided pharmaceutical compositions comprise a hydrochloride salt of a compound of one of the following formulae and optionally a pharmaceutically acceptable excipient:



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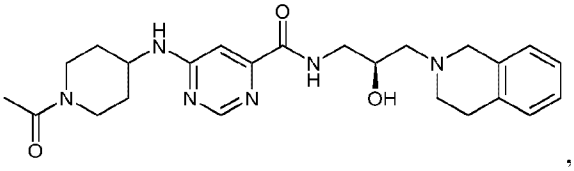

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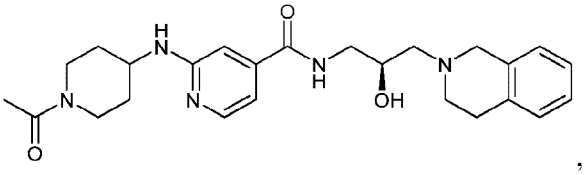

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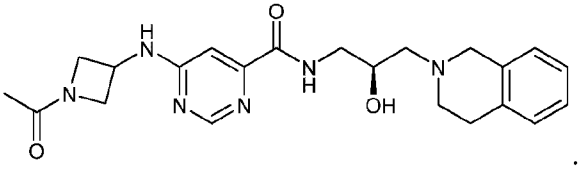

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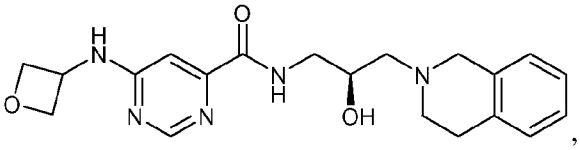
[00267] In certain embodiments, the provided pharmaceutical compositions comprising a tartrate salt of a compound of one of the following formulae and optionally a pharmaceutically acceptable excipient: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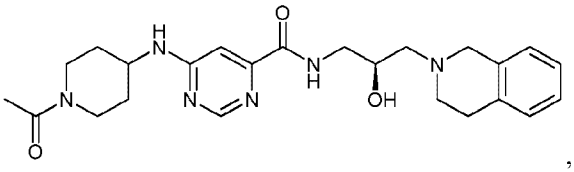
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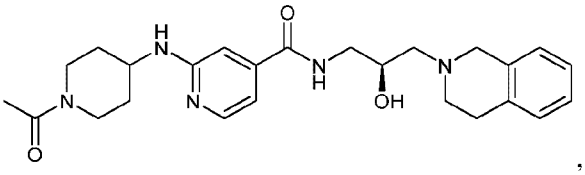
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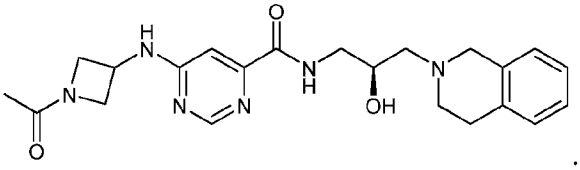
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[00268] In certain embodiments, the tartrate salt is a monotartrate salt. In certain embodiments, the tartrate salt is a bitartrate salt. In certain embodiments, the provided pharmaceutical compositions comprises a monotartrate salt thereof, and a bitartrate salt thereof, and optionally a pharmaceutically acceptable excipient.

[00269] Pharmaceutically acceptable excipients include any and all solvents, diluents, or other liquid vehicles, dispersions, suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, solid binders, lubricants, and the like, as suited to the particular dosage form desired. General considerations in formulation and/or manufacture of pharmaceutical compositions agents can be found, for example, in *Remington's Pharmaceutical Sciences*, Sixteenth Edition, E. W. Martin (Mack Publishing Co., Easton, Pa., 1980), and *Remington: The Science and Practice of Pharmacy*, 21st Edition (Lippincott Williams & Wilkins, 2005).

[00270] Pharmaceutical compositions described herein can be prepared by any method known in the art of pharmacology. In general, such preparatory methods include the steps of bringing a compound described herein (the "active ingredient") into association with a carrier and/or one or more other accessory ingredients, and then, if necessary and/or desirable, shaping and/or packaging the product into a desired single– or multi–dose unit.

[00271] Pharmaceutical compositions can be prepared, packaged, and/or sold in bulk, as a single unit dose, and/or as a plurality of single unit doses. As used herein, a "unit dose" is discrete amount of the pharmaceutical composition comprising a predetermined amount of the active ingredient. The amount of the active ingredient is generally equal to the dosage of the active ingredient which would be administered to a subject and/or a convenient fraction of such a dosage such as, for example, one–half or one–third of such a dosage.

[00272] Relative amounts of the active ingredient, the pharmaceutically acceptable excipient, and/or any additional ingredients in a pharmaceutical composition of the present disclosure will vary, depending upon the identity, size, and/or condition of the subject treated and further depending upon the route by which the composition is to be administered. By way of example, the composition may comprise between 0.1% and 100% (w/w) active ingredient.

[00273] Pharmaceutically acceptable excipients used in the manufacture of provided pharmaceutical compositions include inert diluents, dispersing and/or granulating agents, surface active agents and/or emulsifiers, disintegrating agents, binding agents, preservatives, buffering agents, lubricating agents, and/or oils. Excipients such as cocoa butter and suppository waxes, coloring agents, coating agents, sweetening, flavoring, and perfuming agents may also be present in the composition.

[00274] Exemplary diluents include calcium carbonate, sodium carbonate, calcium phosphate, dicalcium phosphate, calcium sulfate, calcium hydrogen phosphate, sodium phosphate lactose, sucrose, cellulose, microcrystalline cellulose, kaolin, mannitol, sorbitol, inositol, sodium chloride, dry starch, cornstarch, powdered sugar, and mixtures thereof.

[00275] Exemplary granulating and/or dispersing agents include potato starch, corn starch, tapioca starch, sodium starch glycolate, clays, alginic acid, guar gum, citrus pulp, agar, bentonite, cellulose and wood products, natural sponge, cation–exchange resins, calcium carbonate, silicates, sodium carbonate, cross–linked poly(vinyl–pyrrolidone) (crospovidone), sodium carboxymethyl starch (sodium starch glycolate), carboxymethyl cellulose, cross–linked sodium carboxymethyl cellulose (croscarmellose), methylcellulose, pregelatinized starch (starch 1500), microcrystalline starch, water insoluble starch, calcium carboxymethyl cellulose, magnesium aluminum silicate (Veegum), sodium lauryl sulfate, quaternary ammonium compounds, and mixtures thereof.

[00276] Exemplary surface active agents and/or emulsifiers include natural emulsifiers (*e.g.,* acacia, agar, alginic acid, sodium alginate, tragacanth, chondrux, cholesterol, xanthan, pectin, gelatin, egg yolk, casein, wool fat, cholesterol, wax, and lecithin), colloidal clays (*e.g.,*

bentonite (aluminum silicate) and Veegum™ (magnesium aluminum silicate)), long chain amino acid derivatives, high molecular weight alcohols (*e.g.,* stearyl alcohol, cetyl alcohol, oleyl alcohol, triacetin monostearate, ethylene glycol distearate, glyceryl monostearate, and propylene glycol monostearate, polyvinyl alcohol), carbomers (*e.g.,* carboxy polymethylene, polyacrylic acid, acrylic acid polymer, and carboxyvinyl polymer), carrageenan, cellulosic derivatives (*e.g.,* carboxymethylcellulose sodium, powdered cellulose, hydroxymethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose), sorbitan fatty acid esters (*e.g.,* polyoxyethylene sorbitan monolaurate (Tween™ 20), polyoxyethylene sorbitan (Tween 60), polyoxyethylene sorbitan monooleate (Tween 80), sorbitan monopalmitate (Span™ 40), sorbitan monostearate (Span 60], sorbitan tristearate (Span 65), glyceryl monooleate, sorbitan monooleate (Span 80)), polyoxyethylene esters (*e.g.,* polyoxyethylene monostearate (Myrj™ 45), polyoxyethylene hydrogenated castor oil, polyethoxylated castor oil, polyoxymethylene stearate, and Solutol), sucrose fatty acid esters, polyethylene glycol fatty acid esters (*e.g.,* Cremophor™), polyoxyethylene ethers, (*e.g.,* polyoxyethylene lauryl ether (Brij™ 30)), poly(vinyl–pyrrolidone), diethylene glycol monolaurate, triethanolamine oleate, sodium oleate, potassium oleate, ethyl oleate, oleic acid, ethyl laurate, sodium lauryl sulfate, Pluronic™ F68, Poloxamer™ 188, cetrimonium bromide, cetylpyridinium chloride, benzalkonium chloride, docusate sodium, and/or mixtures thereof.

[00277] Exemplary binding agents include starch (*e.g.,* cornstarch and starch paste), gelatin, sugars (*e.g.,* sucrose, glucose, dextrose, dextrin, molasses, lactose, lactitol, mannitol, *etc.*), natural and synthetic gums (*e.g.,* acacia, sodium alginate, extract of Irish moss, panwar gum, ghatti gum, mucilage of isapol husks, carboxymethylcellulose, methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, microcrystalline cellulose, cellulose acetate, poly(vinyl–pyrrolidone), magnesium aluminum silicate (Veegum), and larch arabogalactan), alginates, polyethylene oxide, polyethylene glycol, inorganic calcium salts, silicic acid, polymethacrylates, waxes, water, alcohol, and/or mixtures thereof.

[00278] Exemplary preservatives include antioxidants, chelating agents, antimicrobial preservatives, antifungal preservatives, alcohol preservatives, acidic preservatives, and other preservatives.

[00279] Exemplary antioxidants include alpha tocopherol, ascorbic acid, acorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, monothioglycerol, potassium metabisulfite, propionic acid, propyl gallate, sodium ascorbate, sodium bisulfite, sodium metabisulfite, and sodium sulfite.

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[00280] Exemplary chelating agents include ethylenediaminetetraacetic acid (EDTA) and salts and hydrates thereof (*e.g.*, sodium edetate, disodium edetate, trisodium edetate, calcium disodium edetate, dipotassium edetate, and the like), citric acid and salts and hydrates thereof (*e.g.*, citric acid monohydrate), fumaric acid and salts and hydrates thereof, malic acid and salts and hydrates thereof, phosphoric acid and salts and hydrates thereof, and tartaric acid and salts and hydrates thereof. Exemplary antimicrobial preservatives include benzalkonium chloride, benzethonium chloride, benzyl alcohol, bronopol, cetrimide, cetylpyridinium chloride, chlorhexidine, chlorobutanol, chlorocresol, chloroxylenol, cresol, ethyl alcohol, glycerin, hexetidine, imidurea, phenol, phenoxyethanol, phenylethyl alcohol, phenylmercuric nitrate, propylene glycol, and thimerosal.

[00281] Exemplary antifungal preservatives include butyl paraben, methyl paraben, ethyl paraben, propyl paraben, benzoic acid, hydroxybenzoic acid, potassium benzoate, potassium sorbate, sodium benzoate, sodium propionate, and sorbic acid.

[00282] Exemplary alcohol preservatives include ethanol, polyethylene glycol, phenol, phenolic compounds, bisphenol, chlorobutanol, hydroxybenzoate, and phenylethyl alcohol. Exemplary acidic preservatives include vitamin A, vitamin C, vitamin E, beta–carotene, citric acid, acetic acid, dehydroacetic acid, ascorbic acid, sorbic acid, and phytic acid.

[00283] Other preservatives include tocopherol, tocopherol acetate, deteroxime mesylate, cetrimide, butylated hydroxyanisol (BHA), butylated hydroxytoluened (BHT), ethylenediamine, sodium lauryl sulfate (SLS), sodium lauryl ether sulfate (SLES), sodium bisulfite, sodium metabisulfite, potassium sulfite, potassium metabisulfite, Glydant Plus,™ Phenonip,™ methylparaben, Germall™ 115, Germaben™ II, Neolone,™ Kathon,™ and Euxyl.™ In certain embodiments, the preservative is an anti–oxidant. In other embodiments, the preservative is a chelating agent.

[00284] Exemplary buffering agents include citrate buffer solutions, acetate buffer solutions, phosphate buffer solutions, ammonium chloride, calcium carbonate, calcium chloride, calcium citrate, calcium glubionate, calcium gluceptate, calcium gluconate, D–gluconic acid, calcium glycerophosphate, calcium lactate, propanoic acid, calcium levulinate, pentanoic acid, dibasic calcium phosphate, phosphoric acid, tribasic calcium phosphate, calcium hydroxide phosphate, potassium acetate, potassium chloride, potassium gluconate, potassium mixtures, dibasic potassium phosphate, monobasic potassium phosphate, potassium phosphate mixtures, sodium acetate, sodium bicarbonate, sodium chloride, sodium citrate, sodium lactate, dibasic sodium phosphate, monobasic sodium phosphate, sodium

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phosphate mixtures, tromethamine, magnesium hydroxide, aluminum hydroxide, alginic acid, pyrogen–free water, isotonic saline, Ringer's solution, ethyl alcohol, and mixtures thereof.

[00285] Exemplary lubricating agents include magnesium stearate, calcium stearate, stearic acid, silica, talc, malt, glyceryl behanate, hydrogenated vegetable oils, polyethylene glycol, sodium benzoate, sodium acetate, sodium chloride, leucine, magnesium lauryl sulfate, sodium lauryl sulfate, and mixtures thereof.

[00286] Exemplary natural oils include almond, apricot kernel, avocado, babassu, bergamot, black current seed, borage, cade, camomile, canola, caraway, carnauba, castor, cinnamon, cocoa butter, coconut, cod liver, coffee, corn, cotton seed, emu, eucalyptus, evening primrose, fish, flaxseed, geraniol, gourd, grape seed, hazel nut, hyssop, isopropyl myristate, jojoba, kukui nut, lavandin, lavender, lemon, litsea cubeba, macademia nut, mallow, mango seed, meadowfoam seed, mink, nutmeg, olive, orange, orange roughy, palm, palm kernel, peach kernel, peanut, poppy seed, pumpkin seed, rapeseed, rice bran, rosemary, safflower, sandalwood, sasquana, savoury, sea buckthorn, sesame, shea butter, silicone, soybean, sunflower, tea tree, thistle, tsubaki, vetiver, walnut, and wheat germ oils. Exemplary synthetic oils include, but are not limited to, butyl stearate, caprylic triglyceride, capric triglyceride, cyclomethicone, diethyl sebacate, dimethicone 360, isopropyl myristate, mineral oil, octyldodecanol, oleyl alcohol, silicone oil, and mixtures thereof.

[00287] Liquid dosage forms for oral and parenteral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active ingredients, the liquid dosage forms may comprise inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3–butylene glycol, dimethylformamide, oils (*e.g.*, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents. In certain embodiments for parenteral administration, the compounds described herein are mixed with solubilizing agents such as Cremophor™, alcohols, oils, modified oils, glycols, polysorbates, cyclodextrins, polymers, and mixtures thereof.

[00288] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions can be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation can be a sterile

injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3–butanediol. Among the acceptable vehicles and solvents that can be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono– or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

[00289] The injectable formulations can be sterilized, for example, by filtration through a bacterial–retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[00290] In order to prolong the effect of a drug, it is often desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This can be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

[00291] Compositions for rectal or vaginal administration are typically suppositories which can be prepared by mixing the compounds described herein with suitable non–irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active ingredient.

[00292] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active ingredient is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols,

sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may comprise buffering agents.

[00293] Solid compositions of a similar type can be employed as fillers in soft and hard–filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally comprise opacifying agents and can be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes. Solid compositions of a similar type can be employed as fillers in soft and hard–filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

[00294] The active ingredient can be in micro–encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active ingredient can be admixed with at least one inert diluent such as sucrose, lactose, or starch. Such dosage forms may comprise, as is normal practice, additional substances other than inert diluents, *e.g.*, tableting lubricants and other tableting aids such a magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets, and pills, the dosage forms may comprise buffering agents. They may optionally comprise opacifying agents and can be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes.

[00295] Dosage forms for topical and/or transdermal administration of a provided compound may include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants and/or patches. Generally, the active ingredient is admixed under sterile conditions with a pharmaceutically acceptable carrier and/or any desired preservatives and/or buffers as can be required. Additionally, the present disclosure encompasses the use of transdermal patches, which often have the added advantage of providing controlled delivery of an active ingredient to the body. Such dosage forms can be prepared, for example, by dissolving and/or dispensing the active ingredient in the proper medium. Alternatively or additionally,

the rate can be controlled by either providing a rate controlling membrane and/or by dispersing the active ingredient in a polymer matrix and/or gel.

[00296] Suitable devices for use in delivering intradermal pharmaceutical compositions described herein include short needle devices such as those described in U.S. Patents 4,886,499; 5,190,521; 5,328,483; 5,527,288; 4,270,537; 5,015,235; 5,141,496; and 5,417,662. Intradermal compositions can be administered by devices which limit the effective penetration length of a needle into the skin, such as those described in PCT publication WO 99/34850 and functional equivalents thereof. Jet injection devices which deliver liquid vaccines to the dermis via a liquid jet injector and/or via a needle which pierces the stratum corneum and produces a jet which reaches the dermis are suitable. Jet injection devices are described, for example, in U.S. Patents 5,480,381; 5,599,302; 5,334,144; 5,993,412; 5,649,912; 5,569,189; 5,704,911; 5,383,851; 5,893,397; 5,466,220; 5,339,163; 5,312,335; 5,503,627; 5,064,413; 5,520,639; 4,596,556; 4,790,824; 4,941,880; 4,940,460; and PCT publications WO 97/37705 and WO 97/13537. Ballistic powder/particle delivery devices which use compressed gas to accelerate vaccine in powder form through the outer layers of the skin to the dermis are suitable. Alternatively or additionally, conventional syringes can be used in the classical mantoux method of intradermal administration.

[00297] Formulations suitable for topical administration include, but are not limited to, liquid and/or semi liquid preparations such as liniments, lotions, oil in water and/or water in oil emulsions such as creams, ointments and/or pastes, and/or solutions and/or suspensions. Topically–administrable formulations may, for example, comprise from about 1% to about 10% (w/w) active ingredient, although the concentration of the active ingredient can be as high as the solubility limit of the active ingredient in the solvent. Formulations for topical administration may further comprise one or more of the additional ingredients described herein.

[00298] A provided pharmaceutical composition can be prepared, packaged, and/or sold in a formulation suitable for pulmonary administration via the buccal cavity. Such a formulation may comprise dry particles which comprise the active ingredient and which have a diameter in the range from about 0.5 to about 7 nanometers or from about 1 to about 6 nanometers. Such compositions are conveniently in the form of dry powders for administration using a device comprising a dry powder reservoir to which a stream of propellant can be directed to disperse the powder and/or using a self propelling solvent/powder dispensing container such as a device comprising the active ingredient dissolved and/or suspended in a low–boiling propellant in a sealed container. Such powders

comprise particles wherein at least 98% of the particles by weight have a diameter greater than 0.5 nanometers and at least 95% of the particles by number have a diameter less than 7 nanometers. Alternatively, at least 95% of the particles by weight have a diameter greater than 1 nanometer and at least 90% of the particles by number have a diameter less than 6 nanometers. Dry powder compositions may include a solid fine powder diluent such as sugar and are conveniently provided in a unit dose form.

[00299] Low boiling propellants generally include liquid propellants having a boiling point of below 65 °F at atmospheric pressure. Generally the propellant may constitute 50 to 99.9% (w/w) of the composition, and the active ingredient may constitute 0.1 to 20% (w/w) of the composition. The propellant may further comprise additional ingredients such as a liquid non–ionic and/or solid anionic surfactant and/or a solid diluent (which may have a particle size of the same order as particles comprising the active ingredient).

[00300] Pharmaceutical compositions formulated for pulmonary delivery may provide the active ingredient in the form of droplets of a solution and/or suspension. Such formulations can be prepared, packaged, and/or sold as aqueous and/or dilute alcoholic solutions and/or suspensions, optionally sterile, comprising the active ingredient, and may conveniently be administered using any nebulization and/or atomization device. Such formulations may further comprise one or more additional ingredients including, but not limited to, a flavoring agent such as saccharin sodium, a volatile oil, a buffering agent, a surface active agent, and/or a preservative such as methylhydroxybenzoate. The droplets provided by this route of administration may have an average diameter in the range from about 0.1 to about 200 nanometers.

[00301] Formulations described herein as being useful for pulmonary delivery are useful for intranasal delivery of a pharmaceutical composition. Another formulation suitable for intranasal administration is a coarse powder comprising the active ingredient and having an average particle from about 0.2 to 500 micrometers. Such a formulation is administered by rapid inhalation through the nasal passage from a container of the powder held close to the nares.

[00302] Formulations for nasal administration may, for example, comprise from about as little as 0.1% (w/w) and as much as 100% (w/w) of the active ingredient, and may comprise one or more of the additional ingredients described herein. A provided pharmaceutical composition can be prepared, packaged, and/or sold in a formulation for buccal administration. Such formulations may, for example, be in the form of tablets and/or lozenges made using conventional methods, and may contain, for example, 0.1 to 20% (w/w)

active ingredient, the balance comprising an orally dissolvable and/or degradable composition and, optionally, one or more of the additional ingredients described herein. Alternately, formulations for buccal administration may comprise a powder and/or an aerosolized and/or atomized solution and/or suspension comprising the active ingredient. Such powdered, aerosolized, and/or aerosolized formulations, when dispersed, may have an average particle and/or droplet size in the range from about 0.1 to about 200 nanometers, and may further comprise one or more of the additional ingredients described herein.

[00303] A provided pharmaceutical composition can be prepared, packaged, and/or sold in a formulation for ophthalmic administration. Such formulations may, for example, be in the form of eye drops including, for example, a 0.1/1.0% (w/w) solution and/or suspension of the active ingredient in an aqueous or oily liquid carrier. Such drops may further comprise buffering agents, salts, and/or one or more other of the additional ingredients described herein. Other opthalmically–administrable formulations which are useful include those which comprise the active ingredient in microcrystalline form and/or in a liposomal preparation. Ear drops and/or eye drops are contemplated as being within the scope of this disclosure.

[00304] Although the descriptions of pharmaceutical compositions provided herein are principally directed to pharmaceutical compositions which are suitable for administration to humans, it will be understood by the skilled artisan that such compositions are generally suitable for administration to animals of all sorts. Modification of pharmaceutical compositions suitable for administration to humans in order to render the compositions suitable for administration to various animals is well understood, and the ordinarily skilled veterinary pharmacologist can design and/or perform such modification with ordinary experimentation.

[00305] Compounds provided herein are typically formulated in dosage unit form for ease of administration and uniformity of dosage. It will be understood, however, that the total daily usage of provided compositions will be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically effective dose level for any particular subject or organism will depend upon a variety of factors including the disease, disorder, or condition being treated and the severity of the disorder; the activity of the specific active ingredient employed; the specific composition employed; the age, body weight, general health, sex and diet of the subject; the time of administration, route of administration, and rate of excretion of the specific active ingredient employed; the duration

of the treatment; drugs used in combination or coincidental with the specific active ingredient employed; and like factors well known in the medical arts.

[00306] The compounds and compositions provided herein can be administered by any route, including enteral (*e.g.*, oral), parenteral, intravenous, intramuscular, intra–arterial, intramedullary, intrathecal, subcutaneous, intraventricular, transdermal, interdermal, rectal, intravaginal, intraperitoneal, topical (as by powders, ointments, creams, and/or drops), mucosal, nasal, bucal, sublingual; by intratracheal instillation, bronchial instillation, and/or inhalation; and/or as an oral spray, nasal spray, and/or aerosol. Specifically contemplated routes are oral administration, intravenous administration (*e.g.*, systemic intravenous injection), regional administration via blood and/or lymph supply, and/or direct administration to an affected site. In general the most appropriate route of administration will depend upon a variety of factors including the nature of the agent (*e.g.*, its stability in the environment of the gastrointestinal tract), and/or the condition of the subject (*e.g.*, whether the subject is able to tolerate oral administration).

[00307] The exact amount of a compound required to achieve an effective amount will vary from subject to subject, depending, for example, on species, age, and general condition of a subject, severity of the side effects or disorder, identity of the particular compound(s), mode of administration, and the like. The desired dosage can be delivered three times a day, two times a day, once a day, every other day, every third day, every week, every two weeks, every three weeks, or every four weeks. In certain embodiments, the desired dosage can be delivered using multiple administrations (*e.g.*, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or more administrations).

[00308] In certain embodiments, an effective amount of a compound for administration one or more times a day to a 70 kg adult human may comprise about 0.0001 mg to about 3000 mg, about 0.0001 mg to about 2000 mg, about 0.0001 mg to about 1000 mg, about 0.001 mg to about 1000 mg, about 0.01 mg to about 1000 mg, about 0.1 mg to about 1000 mg, about 1 mg to about 1000 mg, about 1 mg to about 100 mg, about 10 mg to about 1000 mg, or about 100 mg to about 1000 mg, of a compound per unit dosage form.

[00309] In certain embodiments, a compound described herein may be administered at dosage levels sufficient to deliver from about 0.001 mg/kg to about 1000 mg/kg, from about 0.01 mg/kg to about mg/kg, from about 0.1 mg/kg to about 40 mg/kg, from about 0.5 mg/kg to about 30 mg/kg, from about 0.01 mg/kg to about 10 mg/kg, from about 0.1 mg/kg to about 10 mg/kg, or from about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect.

[00310] In some embodiments, a compound described herein is administered one or more times per day, for multiple days. In some embodiments, the dosing regimen is continued for days, weeks, months, or years.

[00311] It will be appreciated that dose ranges as described herein provide guidance for the administration of provided pharmaceutical compositions to an adult. The amount to be administered to, for example, a child or an adolescent can be determined by a medical practitioner or person skilled in the art and can be lower or the same as that administered to an adult.

[00312] It will be also appreciated that a compound or composition, as described herein, can be administered in combination with one or more additional therapeutically active agents. In certain embodiments, a compound or composition provided herein is administered in combination with one or more additional therapeutically active agents that improve its bioavailability, reduce and/or modify its metabolism, inhibit its excretion, and/or modify its distribution within the body. It will also be appreciated that the therapy employed may achieve a desired effect for the same disorder, and/or it may achieve different effects.

[00313] The compound or composition can be administered concurrently with, prior to, or subsequent to, one or more additional therapeutically active agents. In certain embodiments, the additional therapeutically active agent is a compound of Formula (**A**), *e.g.*, Formula (**I**). In certain embodiments, the additional therapeutically active agent is not a compound of Formula (**A**), *e.g.*, Formula (**I**). In general, each agent will be administered at a dose and/or on a time schedule determined for that agent. In will further be appreciated that the additional therapeutically active agent utilized in this combination can be administered together in a single composition or administered separately in different compositions. The particular combination to employ in a regimen will take into account compatibility of a provided compound with the additional therapeutically active agent and/or the desired therapeutic effect to be achieved. In general, it is expected that additional therapeutically active agents utilized in combination be utilized at levels that do not exceed the levels at which they are utilized individually. In some embodiments, the levels utilized in combination will be lower than those utilized individually.

[00314] Exemplary additional therapeutically active agents include, but are not limited to, small organic molecules such as drug compounds (*e.g.*, compounds approved by the U.S. Food and Drug Administration as provided in the Code of Federal Regulations (CFR)), peptides, proteins, carbohydrates, monosaccharides, oligosaccharides, polysaccharides, nucleoproteins, mucoproteins, lipoproteins, synthetic polypeptides or proteins, small

molecules linked to proteins, glycoproteins, steroids, nucleic acids, DNAs, RNAs, nucleotides, nucleosides, oligonucleotides, antisense oligonucleotides, lipids, hormones, vitamins, and cells.

[00315] Also encompassed by the present discosure are kits (*e.g.*, pharmaceutical packs). The kits provided may comprise a provided pharmaceutical composition or compound and a container (*e.g.*, a vial, ampule, bottle, syringe, and/or dispenser package, or other suitable container). In some embodiments, provided kits may optionally further include a second container comprising a pharmaceutical excipient for dilution or suspension of a provided pharmaceutical composition or compound. In some embodiments, a provided pharmaceutical composition or compound provided in the container and the second container are combined to form one unit dosage form. In some embodiments, a provided kits further includes instructions for use.

[00316] Compounds and compositions described herein are generally useful for the inhibition of PRMT5. In some embodiments, methods of treating PRMT5-mediated disorder in a subject are provided which comprise administering an effective amount of a compound described herein (*e.g.*, a compound of Formula (**A**), *e.g.*, Formula (**I**)), or a pharmaceutically acceptable salt thereof), to a subject in need of treatment. In certain embodiments, the effective amount is a therapeutically effective amount. In certain embodiments, the effective amount is a prophylactically effective amount. In certain embodiments, the subject is suffering from a PRMT5-mediated disorder. In certain embodiments, the subject is susceptible to a PRMT5-mediated disorder.

[00317] As used herein, the term "PRMT5-mediated disorder" means any disease, disorder, or other pathological condition in which PRMT5 is known to play a role. Accordingly, in some embodiments, the present disclosure relates to treating or lessening the severity of one or more diseases in which PRMT5 is known to play a role.

[00318] In some embodiments, the present disclosure provides a method of inhibiting PRMT5 comprising contacting PRMT5with an effective amount of a compound described herein (*e.g.*, a compound of Formula (**A**), *e.g.*, Formula (**I**)), or a pharmaceutically acceptable salt thereof. The PRMT5 may be purified or crude, and may be present in a cell, tissue, or subject. Thus, such methods encompass both inhibition of *in vitro* and *in vivo* PRMT5 activity. In certain embodiments, the method is an *in vitro* method, *e.g.,* such as an assay method. It will be understood by one of ordinary skill in the art that inhibition of PRMT5 does not necessarily require that all of the PRMT5 be occupied by an inhibitor at once. Exemplary levels of inhibition of PRMT5 include at least 10% inhibition, about 10% to about

25% inhibition, about 25% to about 50% inhibition, about 50% to about 75% inhibition, at least 50% inhibition, at least 75% inhibition, about 80% inhibition, about 90% inhibition, and greater than 90% inhibition.

[00319] In some embodiments, provided is a method of inhibiting PRMT5 activity in a subject in need thereof comprising administering to the subject an effective amount of a compound described herein (*e.g.*, a compound of Formula (**A**), *e.g.*, Formula (**I**)), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof.

[00320] In certain embodiments, provided is a method of altering gene expression in a cell which comprises contacting a cell with an effective amount of a compound of Formula (**A**), *e.g.*, Formula (**I**), or a pharmaceutically acceptable salt thereof. In certain embodiments, the cell in culture *in vitro*. In certain embodiments, the cell is in an animal, *e.g.*, a human. In certain embodiments, the cell is in a subject in need of treatment.

[00321] In certain embodiments, provided is a method of altering transcription in a cell which comprises contacting a cell with an effective amount of a compound of Formula (**A**), *e.g.*, Formula (**I**), or a pharmaceutically acceptable salt thereof. In certain embodiments, the cell in culture *in vitro*. In certain embodiments, the cell is in an animal, *e.g.*, a human. In certain embodiments, the cell is in a subject in need of treatment.

[00322] In certain embodiments, a method is provided of selecting a therapy for a subject having a disease associated with PRMT5-mediated disorder or mutation comprising the steps of determining the presence of PRMT5-mediated disorder or gene mutation in the PRMT5 gene or and selecting, based on the presence of PRMT5-mediated disorder a gene mutation in the PRMT5 gene a therapy that includes the administration of a provided compound. In certain embodiments, the disease is cancer.

[00323] In certain embodiments, a method of treatment is provided for a subject in need thereof comprising the steps of determining the presence of PRMT5-mediated disorder or a gene mutation in the PRMT5 gene and treating the subject in need thereof, based on the presence of a PRMT5-mediated disorder or gene mutation in the PRMT5 gene with a therapy that includes the administration of a provided compound. In certain embodiments, the subject is a cancer patient.

[00324] In some embodiments, a provided compound is useful in treating a proliferative disorder, such as cancer, a benign neoplasm, an autoimmune disease, or an inflammatory disease. For example, while not being bound to any particular mechanism, PRMT5 has been shown to be involved in cyclin D1 dysregulated cancers. Increased PRMT5 activity mediates key events associated with cyclin D1-dependent neoplastic growth including CUL4

repression, CDT1 overexpression, and DNA re-replication. Further, human cancers harboring mutations in Fbx4, the cyclin D1 E3 ligase, exhibit nuclear cyclin D1 accumulation and increased PRMT5 activity. See, *e.g.*, Aggarwal *et al., Cancer Cell.* (2010) 18(4):329-40. Additionally, PRMT5 has also been implicated in accelerating cell cycle progression through G1 phase and modulating regulators of G1; for example, PRMT5 may upregulate cyclin-dependent kinase (CDK) 4, CDK6, and cyclins D1, D2 and E1. Moreover, PRMT5 may activate phosphoinositide 3-kinase (PI3K)/AKT signaling. See, *e.g.*, Wei *et al.*, *Cancer Sci.* (2012) 103(9):1640-50. PRMT5 has been reported to play a role in apoptosis through methylation of E2F-1. See, *e.g.*, Cho *et al.*, *EMBO J.* (2012) 31:1785-1797; Zheng *et al.*, *Mol. Cell.* (2013) 52:37-51. PRMT5 has been reported to be an essential regulator of splicing and affect the alternative splicing of 'sensor' mRNAs that can then lead to defects in downstream events such as apoptosis. See, *e.g.*, Bezzi *et al.*, *Genes Dev.* (2013) 27:1903-1916. PRMT5 has been reported to play a role in the RAS-ERK pathway. See, *e.g.*, Andrew-Perez *et al.*, *Sci Signal.* (2011) Sep 13;4(190)ra58 doi: 10.1126/scisignal.2001936. PRMT5 has been reported to affect C/EBPb target genes through interaction with the Mediator complex and hence affect cellular differentiation and inflammatory response. See, *e.g.*,Tsutsui *et al.*, *J. Biol. Chem.* (2013) 288:20955-20965. PRMT5 has been shown to methylate HOXA9 essential for ELAM expression during the EC inflammatory response. See, *e.g.*, Bandyopadhyay *et al.*, *Mol. Cell. Biol.* (2012) 32:1202-1203. Thus in some embodiments, the inhibition of PRMT5 by a provided compound is useful in treating the following non-limiting list of cancers: breast cancer, esophageal cancer, bladder cancer, lung cancer, hematopoietic cancer, lymphoma, medulloblastoma, rectum adenocarcinoma, colon adenocarcinoma, gastric cancer, pancreatic cancer, liver cancer, adenoid cystic carcinoma, lung adenocarcinoma, head and neck squamous cell carcinoma, brain tumors, hepatocellular carcinoma, renal cell carcinoma, melanoma, oligodendroglioma, ovarian clear cell carcinoma, and ovarian serous cystadenocarcinoma. See, *e.g.*, Pal *et al.*, *EMBO J.* (2007) 26:3558-3569 (mantle cell lymphoma); Wang *et al.*, *Mol. Cell Biol.* (2008) 28:6262-77 (chronic lymphocytic leukemia (CLL)); and Tae *et al.*, *Nucleic Acids Res.* (2011) 39:5424-5438.

[00325] In some embodiments, the inhibition of PRMT5 by a provided compound is useful in treating prostate cancer and lung cancer, in which PRMT5 has been shown to play a role. See, *e.g.,* Gu *et al.*, *PLoS One* 2012;7(8):e44033; Gu *et al.*, *Biochem. J.* (2012) 446:235–241. In some embodiments, a provided compound is useful to delay the onset of, slow the progression of, or ameliorate the symptoms of cancer. In some embodiments, a provided

compound is administered in combination with other compounds, drugs, or therapeutics to treat cancer.

[00326] In some embodiments, compounds described herein are useful for treating a cancer including, but not limited to, acoustic neuroma, adenocarcinoma, adrenal gland cancer, anal cancer, angiosarcoma (*e.g.,* lymphangiosarcoma, lymphangioendotheliosarcoma, hemangiosarcoma), appendix cancer, benign monoclonal gammopathy, biliary cancer (*e.g.,* cholangiocarcinoma), bladder cancer, breast cancer (*e.g.,* adenocarcinoma of the breast, papillary carcinoma of the breast, mammary cancer, medullary carcinoma of the breast), brain cancer (*e.g.,* meningioma; glioma, *e.g.,* astrocytoma, oligodendroglioma; medulloblastoma), bronchus cancer, carcinoid tumor, cervical cancer (*e.g.,* cervical adenocarcinoma), choriocarcinoma, chordoma, craniopharyngioma, colorectal cancer (*e.g.,* colon cancer, rectal cancer, colorectal adenocarcinoma), epithelial carcinoma, ependymoma, endotheliosarcoma (*e.g.,* Kaposi's sarcoma, multiple idiopathic hemorrhagic sarcoma), endometrial cancer (*e.g.*, uterine cancer, uterine sarcoma), esophageal cancer (*e.g.,* adenocarcinoma of the esophagus, Barrett's adenocarinoma), Ewing sarcoma, eye cancer (*e.g.,* intraocular melanoma, retinoblastoma), familiar hypereosinophilia, gall bladder cancer, gastric cancer (*e.g.,* stomach adenocarcinoma), gastrointestinal stromal tumor (GIST), head and neck cancer (*e.g.,* head and neck squamous cell carcinoma, oral cancer (*e.g.,* oral squamous cell carcinoma (OSCC), throat cancer (*e.g.,* laryngeal cancer, pharyngeal cancer, nasopharyngeal cancer, oropharyngeal cancer)), hematopoietic cancers (*e.g.,* leukemia such as acute lymphocytic leukemia (ALL) (*e.g.,* B-cell ALL, T-cell ALL), acute myelocytic leukemia (AML) (*e.g.,* B-cell AML, T-cell AML), chronic myelocytic leukemia (CML) (*e.g.,* B-cell CML, T-cell CML), and chronic lymphocytic leukemia (CLL) (*e.g.,* B-cell CLL, T-cell CLL); lymphoma such as Hodgkin lymphoma (HL) (*e.g.,* B-cell HL, T-cell HL) and non–Hodgkin lymphoma (NHL) (*e.g.*, B-cell NHL such as diffuse large cell lymphoma (DLCL) (*e.g.,* diffuse large B–cell lymphoma (DLBCL)), follicular lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), mantle cell lymphoma (MCL), marginal zone B-cell lymphomas (*e.g.,* mucosa-associated lymphoid tissue (MALT) lymphomas, nodal marginal zone B-cell lymphoma, splenic marginal zone B-cell lymphoma), primary mediastinal B-cell lymphoma, Burkitt lymphoma, lymphoplasmacytic lymphoma (*i.e.,* "Waldenström's macroglobulinemia"), hairy cell leukemia (HCL), immunoblastic large cell lymphoma, precursor B-lymphoblastic lymphoma and primary central nervous system (CNS) lymphoma; and T-cell NHL such as precursor T-lymphoblastic lymphoma/leukemia, peripheral T-cell lymphoma (PTCL) (*e.g.,* cutaneous T-cell lymphoma

(CTCL) (*e.g.*, mycosis fungiodes, Sezary syndrome), angioimmunoblastic T-cell lymphoma, extranodal natural killer T-cell lymphoma, enteropathy type T-cell lymphoma, subcutaneous panniculitis-like T-cell lymphoma, anaplastic large cell lymphoma); a mixture of one or more leukemia/lymphoma as described above; and multiple myeloma (MM)), heavy chain disease (*e.g.*, alpha chain disease, gamma chain disease, mu chain disease), hemangioblastoma, inflammatory myofibroblastic tumors, immunocytic amyloidosis, kidney cancer (*e.g.*, nephroblastoma *a.k.a.* Wilms' tumor, renal cell carcinoma), liver cancer (*e.g.*, hepatocellular cancer (HCC), malignant hepatoma), lung cancer (*e.g.*, bronchogenic carcinoma, small cell lung cancer (SCLC), non–small cell lung cancer (NSCLC), adenocarcinoma of the lung), leiomyosarcoma (LMS), mastocytosis (*e.g.*, systemic mastocytosis), myelodysplastic syndrome (MDS), mesothelioma, myeloproliferative disorder (MPD) (*e.g.*, polycythemia Vera (PV), essential thrombocytosis (ET), agnogenic myeloid metaplasia (AMM) *a.k.a.* myelofibrosis (MF), chronic idiopathic myelofibrosis, chronic myelocytic leukemia (CML), chronic neutrophilic leukemia (CNL), hypereosinophilic syndrome (HES)), neuroblastoma, neurofibroma (*e.g.*, neurofibromatosis (NF) type 1 or type 2, schwannomatosis), neuroendocrine cancer (*e.g.*, gastroenteropancreatic neuroendoctrine tumor (GEP-NET), carcinoid tumor), osteosarcoma, ovarian cancer (*e.g.*, cystadenocarcinoma, ovarian embryonal carcinoma, ovarian adenocarcinoma), papillary adenocarcinoma, pancreatic cancer (*e.g.*, pancreatic andenocarcinoma, intraductal papillary mucinous neoplasm (IPMN), Islet cell tumors), penile cancer (*e.g.*, Paget's disease of the penis and scrotum), pinealoma, primitive neuroectodermal tumor (PNT), prostate cancer (*e.g.*, prostate adenocarcinoma), rectal cancer, rhabdomyosarcoma, salivary gland cancer, skin cancer (*e.g.*, squamous cell carcinoma (SCC), keratoacanthoma (KA), melanoma, basal cell carcinoma (BCC)), small bowel cancer (*e.g.*, appendix cancer), soft tissue sarcoma (*e.g.*, malignant fibrous histiocytoma (MFH), liposarcoma, malignant peripheral nerve sheath tumor (MPNST), chondrosarcoma, fibrosarcoma, myxosarcoma), sebaceous gland carcinoma, sweat gland carcinoma, synovioma, testicular cancer (*e.g.*, seminoma, testicular embryonal carcinoma), thyroid cancer (*e.g.*, papillary carcinoma of the thyroid, papillary thyroid carcinoma (PTC), medullary thyroid cancer), urethral cancer, vaginal cancer, and vulvar cancer (*e.g.*, Paget's disease of the vulva).

[00327] In some embodiments, a provided compound is useful in treating a metabolic disorder, such as diabetes or obesity. For example, while not being bound to any particular mechanism, a role for PRMT5 has been recognized in adipogenesis. Inhibition of PRMT5 expression in multiple cell culture models for adipogenesis prevented the activation of

adipogenic genes, while overexpression of PRMT5 enhanced adipogenic gene expression and differentiation. See, *e.g.*, LeBlanc *et al.*, *Mol Endocrinol.* (2012) 26:583-597. Additionally, it has been shown that adipogenesis plays a pivotal role in the etiology and progression of diabetes and obesity. See, *e.g.*, Camp *et al.*, *Trends Mol Med.* (2002) 8:442-447. Thus in some embodiments, the inhibition of PRMT5 by a provided compound is useful in treating diabetes and/or obesity.

[00328] In some embodiments, a provided compound is useful to delay the onset of, slow the progression of, or ameliorate the symptoms of, diabetes. In some embodiments, the diabetes is Type 1 diabetes. In some embodiments, the diabetes is Type 2 diabetes. In some embodiments, a provided compound is useful to delay the onset of, slow the progression of, or ameliorate the symptoms of, obesity. In some embodiments, a provided compound is useful to help a subject lose weight. In some embodiments, a provided compound could be used in combination with other compounds, drugs, or therapeutics, such as metformin and insulin, to treat diabetes and/or obesity.

[00329] In some embodiments, a provided compound is useful in treating a blood disorder, *e.g.*, a hemoglobinopathy, such as sickle cell disease or β-thalassemia. For example, while not being bound to any particular mechanism, PRMT5 is a known repressor of γ-globin gene expression, and increased fetal γ-globin (HbF) levels in adulthood are associated with symptomatic amelioration in sickle cell disease and β-thalassemia. See, *e.g.,* Xu *et al., Haematologica.* (2012) 97:1632-1640; Rank *et al. Blood.* (2010) 116:1585-1592. Thus in some embodiments, the inhibition of PRMT5 by a provided compound is useful in treating a blood disorder, such as a hemoglobinopathy such as sickle cell disease or β-thalassemia.

[00330] In some embodiments, a provided compound is useful to delay the onset of, slow the progression of, or ameliorate the symptoms of, sickle cell disease. In some embodiments, a provided compound is useful to delay the onset of, slow the progression of, or ameliorate the symptoms of, β-thalassemia. In some embodiments, a provided compound could be used in combination with other compounds, drugs, or therapeutics, to treat a hemoglobinopathy such as sickle cell disease or β-thalassemia.

[00331] In some embodiments, a provided compound is useful in treating inflammatory and autoimmune disease. PRMT5 is reported to activate NFkB signaling pathway through the methylation of p65. PRMT5 is reported to interact with Death receptor 4 and Death receptor 5 contributing to TRAIL-induced activation of inhibitor or kB kinase (IKK) and nuclear factor-kB (NF-kB). See, *e.g.,* Tanaka *et al., Mol. Cancer. Res.* (2009) 7:557-569.; Wei *et al., Proc. Nat'l. Acad. Sci. USA* (2013) 110:13516-21.

[00332] The term "inflammatory disease" refers to those diseases, disorders or conditions that are characterized by signs of pain (dolor, from the generation of noxious substances and the stimulation of nerves), heat (calor, from vasodilatation), redness (rubor, from vasodilatation and increased blood flow), swelling (tumor, from excessive inflow or restricted outflow of fluid), and/or loss of function (functio laesa, which can be partial or complete, temporary or permanent. Inflammation takes on many forms and includes, but is not limited to, acute, adhesive, atrophic, catarrhal, chronic, cirrhotic, diffuse, disseminated, exudative, fibrinous, fibrosing, focal, granulomatous, hyperplastic, hypertrophic, interstitial, metastatic, necrotic, obliterative, parenchymatous, plastic, productive, proliferous, pseudomembranous, purulent, sclerosing,
seroplastic, serous, simple, specific, subacute, suppurative, toxic, traumatic, and/or ulcerative inflammation.

[00333] Exemplary inflammatory diseases include, but are not limited to, inflammation associated with acne, anemia (*e.g.*, aplastic anemia, haemolytic autoimmune anaemia), asthma, arteritis (*e.g.*, polyarteritis, temporal arteritis, periarteritis nodosa, Takayasu's arteritis), arthritis (*e.g.*, crystalline arthritis, osteoarthritis, psoriatic arthritis, gouty arthritis, reactive arthritis, rheumatoid arthritis and Reiter's arthritis), ankylosing spondylitis, amylosis, amyotrophic lateral sclerosis, autoimmune diseases, allergies or allergic reactions, atherosclerosis, bronchitis, bursitis, chronic prostatitis, conjunctivitis, Chagas disease, chronic obstructive pulmonary disease, cermatomyositis, diverticulitis, diabetes (*e.g.*, type I diabetes mellitus, type 2 diabetes mellitus), a skin condition (*e.g.*, psoriasis, eczema, burns, dermatitis, pruritus (itch)), endometriosis, Guillain-Barre syndrome, infection, ischaemic heart disease, Kawasaki disease, glomerulonephritis, gingivitis, hypersensitivity, headaches (*e.g.*, migraine headaches, tension headaches), ileus (*e.g.*, postoperative ileus and ileus during sepsis), idiopathic thrombocytopenic purpura, interstitial cystitis (painful bladder syndrome), gastrointestinal disorder (*e.g.*, selected from peptic ulcers, regional enteritis, diverticulitis, gastrointestinal bleeding, eosinophilic gastrointestinal disorders (*e.g.*, eosinophilic esophagitis, eosinophilic gastritis, eosinophilic gastroenteritis, eosinophilic colitis), gastritis, diarrhea, gastroesophageal reflux disease (GORD, or its synonym GERD), inflammatory bowel disease (IBD) (*e.g.*, Crohn's disease, ulcerative colitis, collagenous colitis, lymphocytic colitis, ischaemic colitis, diversion colitis, Behcet's syndrome, indeterminate colitis) and inflammatory bowel syndrome (IBS)), lupus, multiple sclerosis, morphea, myeasthenia gravis, myocardial ischemia, nephrotic syndrome, pemphigus vulgaris, pernicious aneaemia, peptic ulcers, polymyositis, primary biliary cirrhosis, neuroinflammation associated with

brain disorders (*e.g.*, Parkinson's disease, Huntington's disease, and Alzheimer's disease), prostatitis, chronic inflammation associated with cranial radiation injury, pelvic inflammatory disease, reperfusion injury, regional enteritis, rheumatic fever, systemic lupus erythematosus, schleroderma, scierodoma, sarcoidosis, spondyloarthopathies, Sjogren's syndrome, thyroiditis, transplantation rejection, tendonitis, trauma or injury (*e.g.*, frostbite, chemical irritants, toxins, scarring, burns, physical injury), vasculitis, vitiligo and Wegener's granulomatosis.

[00334] In certain embodiments, the inflammatory disease is an acute inflammatory disease (*e.g.*, for example, inflammation resulting from infection). In certain embodiments, the inflammatory disease is a chronic inflammatory disease (*e.g.*, conditions resulting from asthma, arthritis and inflammatory bowel disease). The compounds may also be useful in treating inflammation associated with trauma and non-inflammatory myalgia. The compounds may also be useful in treating inflammation associated with cancer.

[00335] Exemplary autoimmune diseases, include, but are not limited to, arthritis (including rheumatoid arthritis, spondyloarthopathies, gouty arthritis, degenerative joint diseases such as osteoarthritis, systemic lupus erythematosus, Sjogren's syndrome, ankylosing spondylitis, undifferentiated spondylitis, Behcet's disease, haemolytic autoimmune anaemias, multiple sclerosis, amyotrophic lateral sclerosis, amylosis, acute painful shoulder, psoriatic, and juvenile arthritis), asthma, atherosclerosis, osteoporosis, bronchitis, tendonitis, bursitis, skin condition (*e.g.*, psoriasis, eczema, burns, dermatitis, pruritus (itch)), enuresis, eosinophilic disease, gastrointestinal disorder (*e.g.*, selected from peptic ulcers, regional enteritis, diverticulitis, gastrointestinal bleeding, eosinophilic gastrointestinal disorders (*e.g.*, eosinophilic esophagitis, eosinophilic gastritis, eosinophilic gastroenteritis, eosinophilic colitis), gastritis, diarrhea, gastroesophageal reflux disease (GORD, or its synonym GERD), inflammatory bowel disease (IBD) (*e.g.*, Crohn's disease, ulcerative colitis, collagenous colitis, lymphocytic colitis, ischaemic colitis, diversion colitis, Behcet's syndrome, indeterminate colitis) and inflammatory bowel syndrome (IBS)), and disorders ameliorated by a gastroprokinetic agent (*e.g.*, ileus, postoperative ileus and ileus during sepsis; gastroesophageal reflux disease (GORD, or its synonym GERD); eosinophilic esophagitis, gastroparesis such as diabetic gastroparesis; food intolerances and food allergies and other functional bowel disorders, such as non-ulcerative dyspepsia (NUD) and non-cardiac chest pain (NCCP, including costo-chondritis)).

[00336] In some embodiments, a provided compound is useful in somatic cell reprogramming, such as reprogramming somatic cells into stem cells. See, *e.g.*, Nagamatsu *et*

al., J Biol Chem. (2011) 286:10641-10648. In some embodiments, a provided compound is useful in germ cell development, and are thus envisioned useful in the areas of reproductive technology and regenerative medicine. See, *e.g.,* Ancelin *et al., Nat. Cell. Biol.* (2006) 8:623-630.

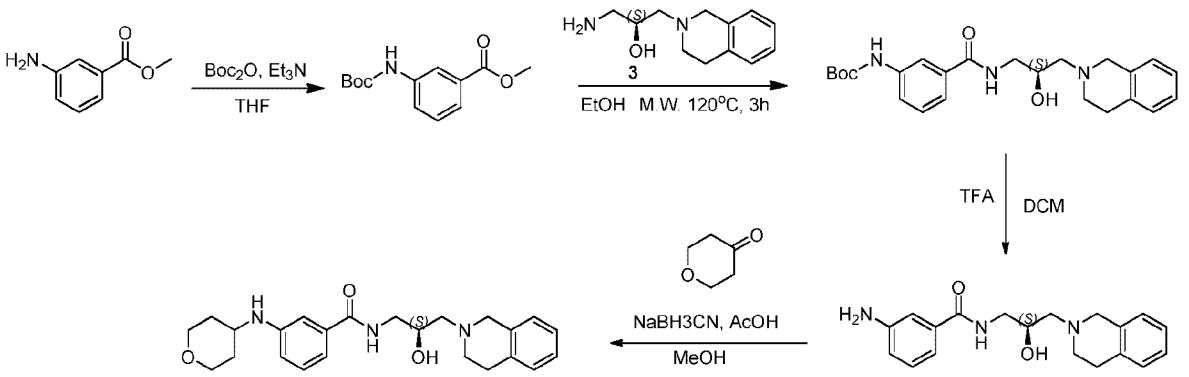
[00337] In some embodiments, compounds described herein can prepared using methods shown in Scheme 1. Compound B can be prepared via ring opening of a chiral or racemic epoxide group. This amino alcohol intermediate can be coupled to form an amide via normal amide coupling methodology using a carboxylic acid A wherein Z is hydrogen or via amination of an ester of intermediate A when Z is an optionally substituted aliphatic group. Further substitution of the tetrahydroisoquinoline ring and/or the Ar ring can be carried out before or after the coupling reaction.

A B

Scheme 1

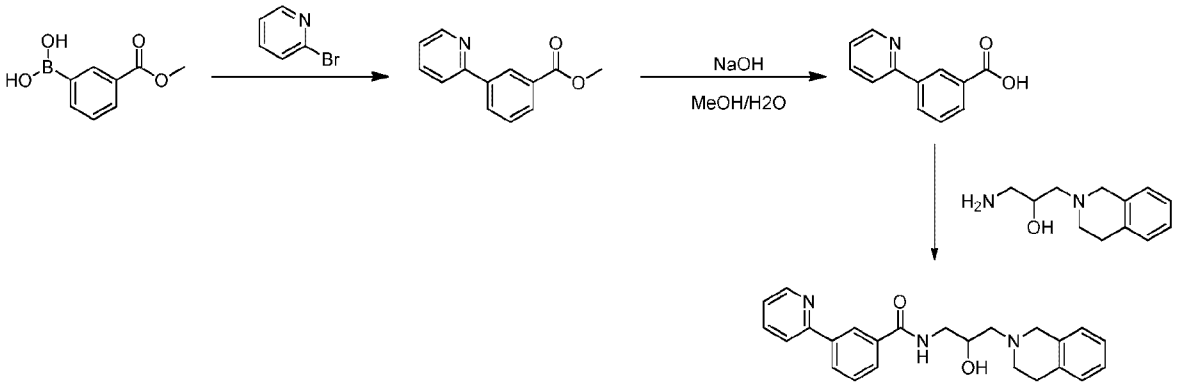
[00338] Analogous reactions may be performed to form a carbamate or urea bond using methods known to one of ordinary skill in the art.

[00339] In some embodiments, such couplings can be used to provide a key intermediate for further synthesis, as shown, for example, in Scheme 2.



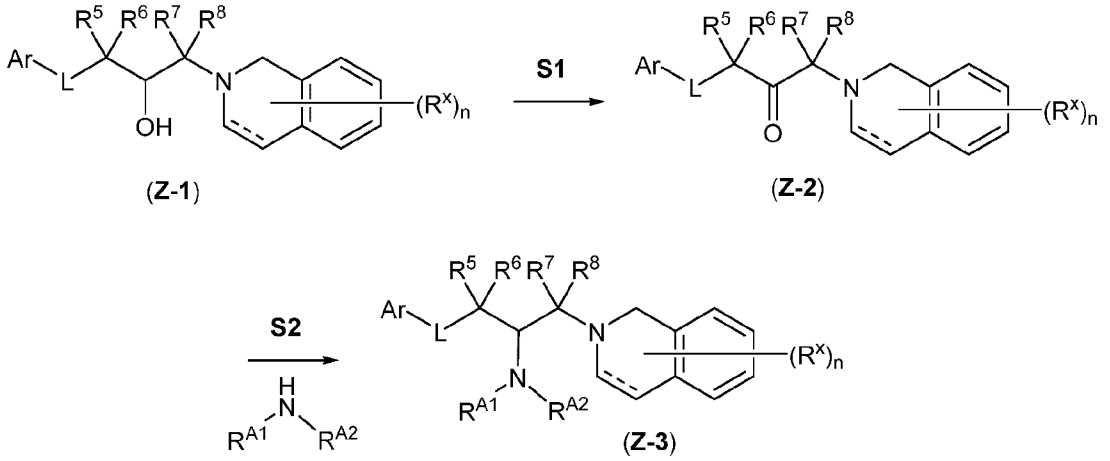
Scheme 2

[00340] In other embodiments, an amide coupling step is the final synthetic step as shown in Scheme 3.



Scheme 3

[00341] In some embodiments of the compounds described herein, R^{12} or R^{13} is an amine. A non-limiting example of the synthetic sequence used to prepare such analogs is provided herein (see, e.g., Scheme 4). In this example, an alcohol of Formula (**Z-1**) is oxidized under suitable conditions **S1** to affect transformation into an intermediate ketone of Formula (**Z-2**). A ketone of Formula (**Z-2**) can be contacted with a primary or secondary amine under suitable conditions **S2** to affect a reductive amination which would afford an amino compound of Formula (**Z-3**).



Scheme 4

[00342] In some embodiments, the oxidation reaction **S1** is carried out using a stoichiometeric oxidant. In some embodiments, the stoichiometric oxidant is pyridinium chlorochromate. In some embodiments, the stoichiometric oxidant is pyridinium dichromate. In some embodiments, the stoichiometric oxidant is Dess-Martin periodinane. In some

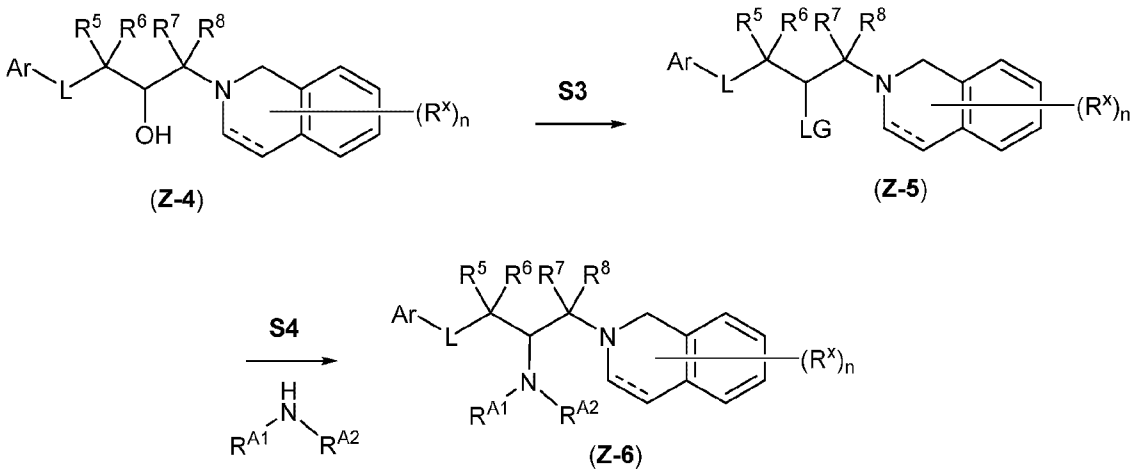
embodiments, the stoichiometric oxidant is prepared *in situ*. In some embodiments, the stoichiometric oxidant is prepared *in situ* using sulfur trioxide pyridine complex and dimethylsulfoxide. In some embodiments, the stoichiometric oxidant is prepared *in situ* using oxallyl chloride and dimethylsulfoxide. In some embodiments, the stoichiometric oxidant is prepared *in situ* using a carbodiimide and dimethylsulfoxide. In some embodiments, the stoichiometric oxidant is prepared *in situ* using *N*-chlorosuccinimide and dimethylsulfide. In some embodiments, the oxidation reaction **S1** is catalyzed. In some embodiments, the catalyst is (2,2,6,6-tetramethyl-piperidin-1-yl)oxyl. In some embodiments, the catalyst is a ruthenium complex. In some embodiments, the catalyst is a palladium complex. In some embodiments, the catalyst is a copper complex. For examples of standard methods and conditions for alcohol oxidation, see Epstein *et al.*, *Chem. Rev.* (1967) 67(3):247-260 and B.M. Trost ed. "Comprehensive Organic Synthesis", (1991), Vol. 7, p 281-305.

[00343] In some embodiments, both the oxidation step **S1** and reductive amination step **S2** occur in one pot. In some embodiments, both the oxidation step **S1** and the reductive amination step **S2** are carried out using the same catalyst. In some embodiments, the catalyst is a rhodium complex. In some embodiments, the catalyst is a ruthenium complex. In some embodiments, the catalyst is an iridium complex.

[00344] In some embodiments, the reductive amination reaction **S2** is carried out using a borohydride. In some embodiments, the reductive amination reaction **S2** is carried out using sodium borohydride. In some embodiments, the reductive amination reaction **S2** is carried out using sodium cyanoborohydride. In some embodiments, the reductive amination reaction **S2** is carried out using sodium triacetoxyborohydride. In some embodiments, the reductive amination reaction **S2** is carried out using a borane. In some embodiments, the reductive amination reaction **S2** is carried out using a silyl hydride. In some embodiments, the reductive amination reaction **S2** is carried out using hydrogen. In some embodiments, the reductive amination reaction **S2** is carried out in two steps, by first contacting a ketone of (**Z-2**) with an amine to form an intermediate imine, and then reducing the intermediate imine under sufficient conditions to afford a compound of Formula (**Z-3**). In some embodiments, the reaction conditions **S2** comprise addition of a protic acid. In some embodiments, the reaction conditions **S2** comprise addition of an aprotic acid. In some embodiments, the reaction conditions **S2** comprise *in situ* formation of the reducing agent. In some embodiments, the reaction conditions **S2** comprise a catalyst. In some embodiments, the reaction conditions **S2** comprise a transition metal catalyst. In some embodiments, the reaction conditions **S2** comprise a palladium or nickel catalyst. In some embodiments, the

reductive amination reaction **S2** is stereoselective. In some embodiments, the stereoselective reductive amination reaction **S2** is carried out in the presence of a chiral catalyst. For examples of standard methods and conditions for reductive aminations, see Gomez *et al.*, *Adv. Synth. Catal.* (2002) 344(10):1037-1057 and Abdel-Magid *et al.*, *J. Org. Chem.* (1996), 61:3849.

[00345] An alterantive non-limiting synthetic sequence leading to the aforementioned amine analogs is described herein (see Scheme 5). The hydroxyl moiety of a compound of Formula (**Z-4**) can be transformed into a leaving group under sufficient conditions **S3** to afford a compound of Formula (**Z-5**). The leaving group of a compound of Formula (**Z-5**) can be displaced with an amine under suitable conditions **S4** to produce an amino compound of Formula (**Z-6**).



Scheme 5

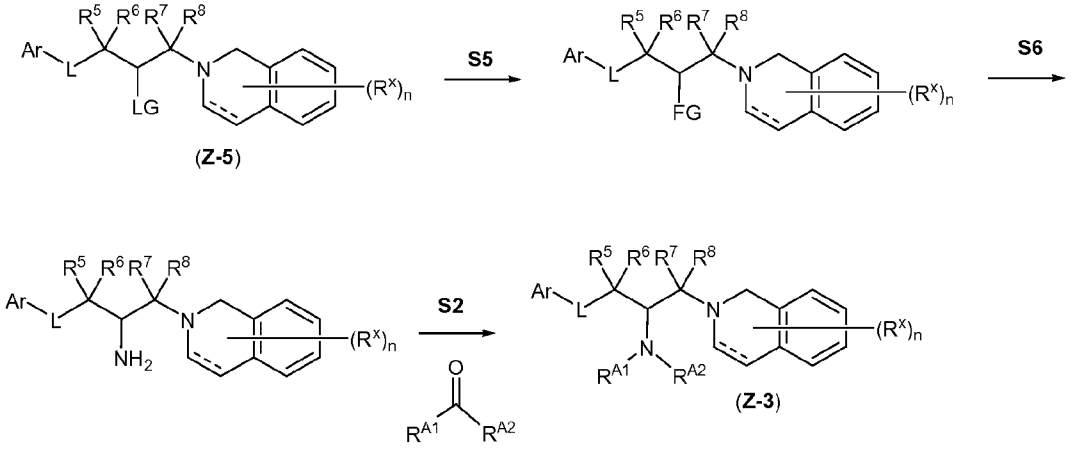
[00346] In some embodiments, LG of Formula (**Z-5**) is a halide. In some embodiments, LG of Formula (**Z-5**) is bromine. In some embodiments, LG of Formula (**Z-5**) is iodine. In some embodiments, LG of Formula (**Z-5**) is a substituted or unsubstituted alkyl sulfonate. In some embodiments, LG of Formula (**Z-5**) is a substituted or unsubstituted aryl sulfonate. In some embodiments, LG of Formula (**Z-5**) is methyl sulfonate. In some embodiments, LG of Formula (**A-5**) is trifluoromethane sulfonate. In some embodiments, LG of Formula (**Z-5**) is a toluene sulfonate. In some embodiments, LG of Formula (**Z-5**) is a nitrobenzene sulfonate. In some embodiments, when LG of Formula (**Z-5**) is halide, conditions **S3** comprise a phosphoryl halide. In some embodiments, when LG of Formula (**Z-5**) is halide, conditions **S3** comprise a sulfuryl halide. In some embodiments, when LG of Formula (**Z-5**) is

sulfonate, conditions **S3** comprise a sulfonyl halide. In some embodiments, when LG of Formula (**Z-5**) is sulfonate, conditions **S3** comprise a sulfonyl anhydride. For examples of standard methods and conditions for organohalide or sulfonate ester synthesis, see Lautens *et al.*, *Synthesis* (2011) 2:342-346 or Marcotullio *et al.*, *Synthesis* (2006) 16:2760-2766.

[00347] In some embodiments, conditions **S4** are neutral. In some embodiments, conditions **S4** comprise addition of a base. In certain embodiments of conditions **S4**, the base is either inorganic or organic. In certain embodiments of conditions **S4**, the base is inorganic. In certain embodiments of conditions **S4**, the base is organic. In certain embodiments of conditions **S4**, the base is a metal acetate, alkoxide, amide, amidine, carbonate, hydroxide, phenoxide, or phosphate. In certain embodiments of conditions **S4**, the base is sodium, potassium, or caesium carbonate. In certain embodiments of conditions **S4**, the base is sodium, potassium, or caesium bicarbonate. In certain embodiments of conditions **S4**, the base is 1,1,3,3-tetramethylguanidine, 1,4-diazabicyclo[2.2.2]octane, 1,8-bis(dimethylamino)naphthalene, 1,8-diazabicycloundec-7-ene, ammonia, diisopropylamine, imidazole, N,N-diisopropylethylamine, piperidine, pyridine, pyrrolidine, or triethylamine. In some embodiments of conditions **S4**, the solvent is a polar protic solvent. In some embodiments of conditions **S4**, the solvent is a polar aprotic solvent. In some embodiments of conditions **S4**, the reaction is performed in the absence of solvent. In some embodiments, conditions **S4** comprise a catalyst. In some embodiments of conditions **S4**, the catalyst is an iodide salt. In some embodiments, both step **S3** and the displacement step **S4** occur in one pot. In some embodiments, the hydroxyl moiety of a compound of Formula (**Z-4**) is converted into a leaving group *in situ*. In some embodiments, the hydroxyl moiety of a compound of Formula (**Z-4**) is converted into a leaving group *in situ* using an azodicarboxylate and an aryl or alkyl phosphine. For examples of standard methods and conditions for amine syntheses through alkylation reactions, see Salvatore *et. al*, *Tetrahedron* (2001) 57:7785-7811.

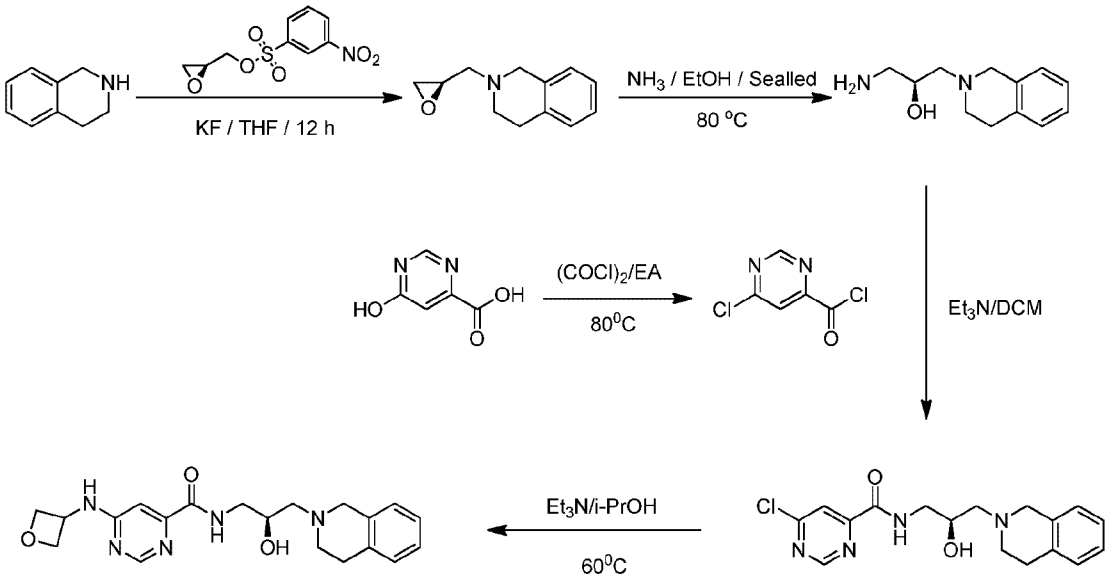
[00348] An exemplary synthetic route leading to the aforementioned amine analogs is described herein (see Scheme 6). Under conditions **S5**, Z-5 reacts with a functional group (FG) derivative which can be subsequently converted into a primary amine. Examples of such reactions include, but are not limited to, formation of an azide (e.g. via sodium azide, TMS azide etc) or phthalimide or similarly protected amine derivatives. Under conditions **S6**, the product from S5 can be further reduced to amine (e.g. by catalytic hydrogenation or under Staudinger condition in the presence of PPh_3 (azide) or hydrazine (Phthalimide)). The target amine analog can be obtained via reductive amination using **S2** conditions similar to those

described in Scheme 4. Additional modification of the Ar moiety can be carried out by, for example, aromatic substitutions.



Scheme 6

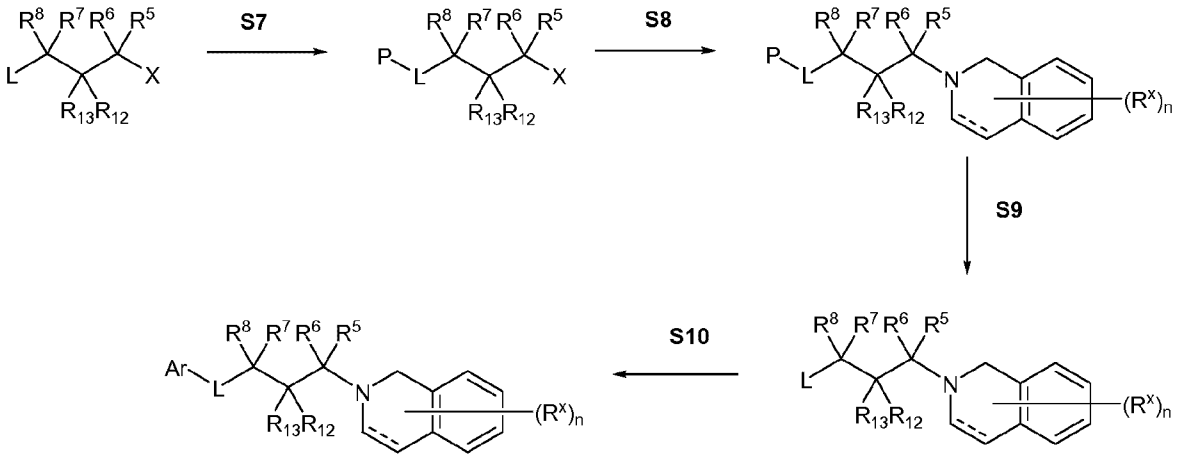
[00349] A further exemplary synthetic route leading to the aforementioned amine analogs is shown in Scheme 7.



Scheme 7

[00350] A further exemplary synthetic route leading to the aforementioned amine analogs is described in Scheme 9. The tetrahydroisoquinoline or dihydroisoquinoline moiety is coupled with a protected alkylene chain by amination or reductive amination under **S8**

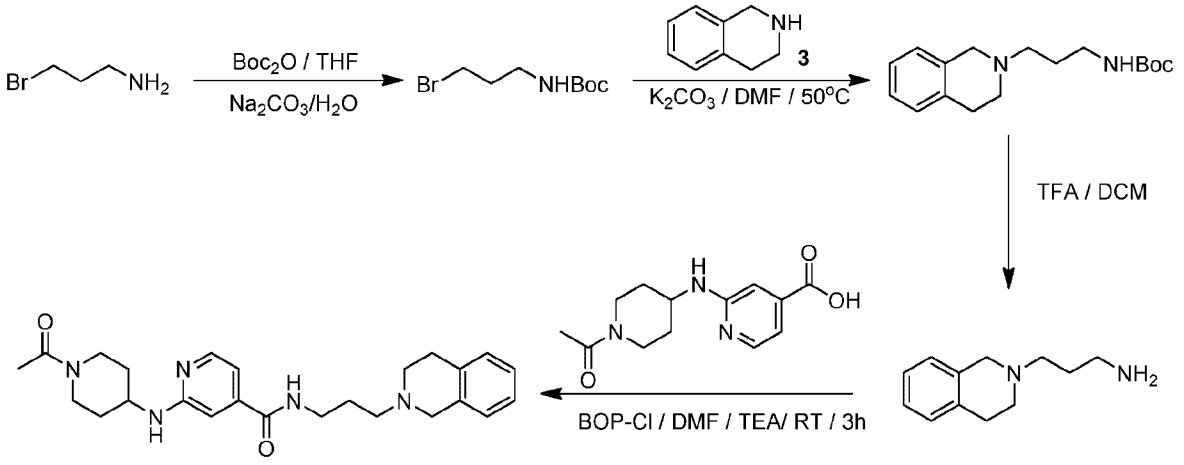
conditions. Deproection of the resulting product followed by the standard amide coupling reaction (*e.g.* as shown in Scheme 1) provides the target amine analog. Additional modifications can be carried out on the Ar moiety by reactions such as aromatic substitutions.



Scheme 8

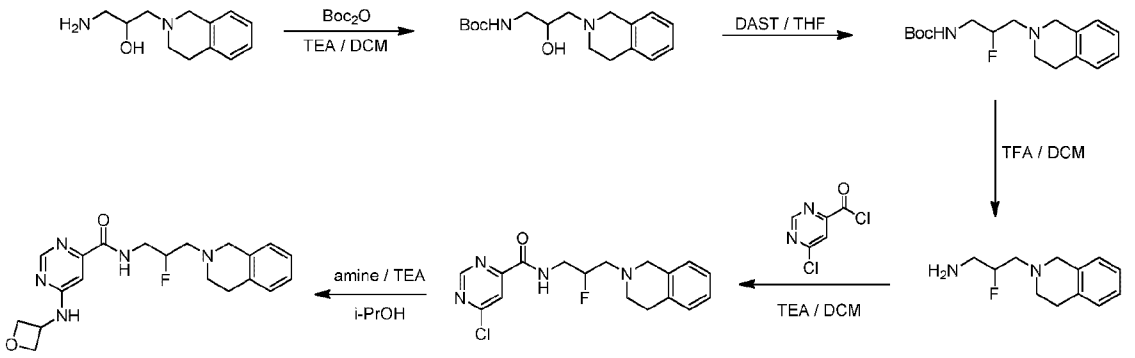
[00351] A further exemplary synthetic route leading to the aforementioned amine analogs is described in Scheme 9.

[00352]



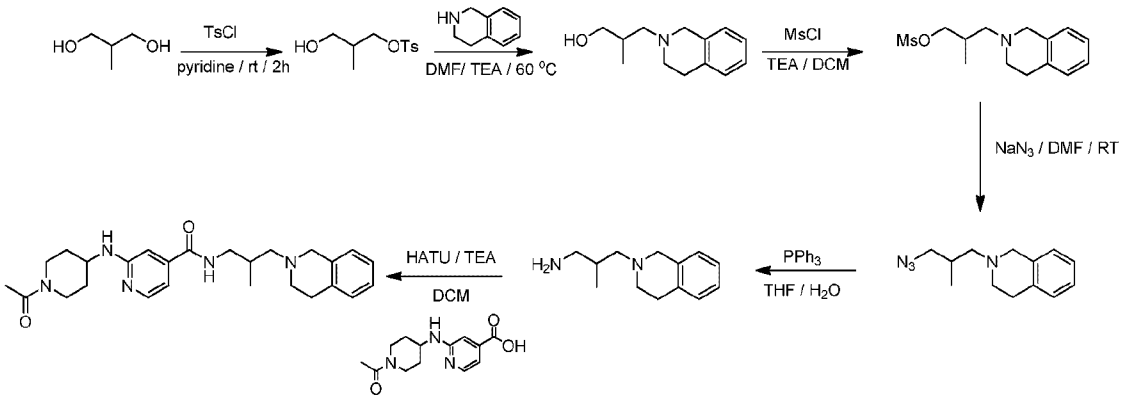
Scheme 9

[00353] A further exemplary synthetic route leading to the aforementioned amine analogs is described in Scheme 10.



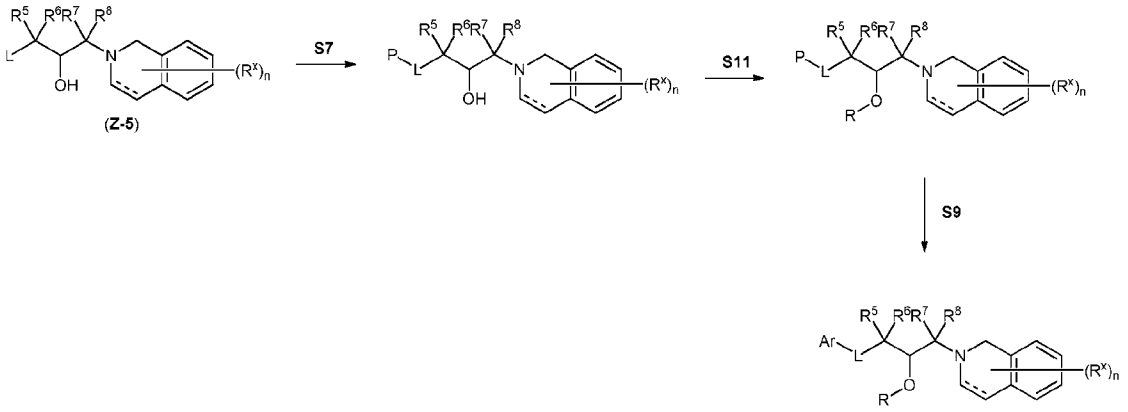
Scheme 10

[00354] A further exemplary synthetic route leading to the aforementioned amine analogs is described in Scheme 11.



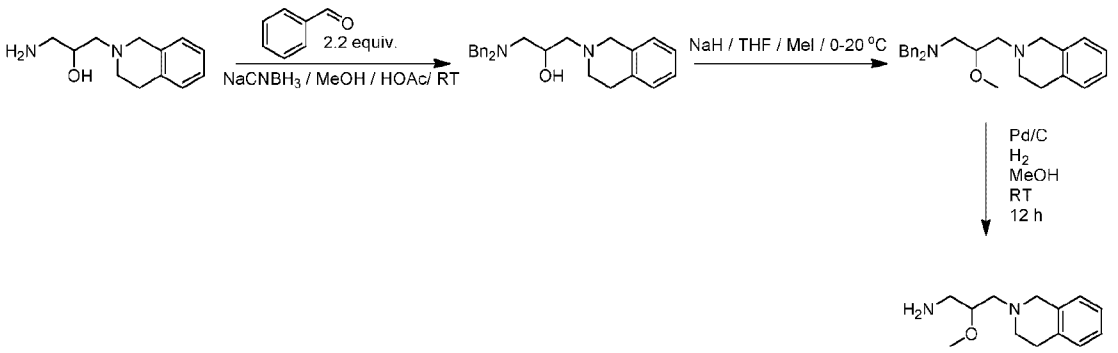
Scheme 11

[00355] A further exemplary synthetic route leading to the aforementioned amine analogs is described in Scheme 12. A tetrahydroisoquinoline or dihydroisoquinoline moiety is suitably protected on the L terminal under **S7** conditions and further alkylated under **S11** conditions (e.g. standard alkylation or Mitsunobu conditions) to provide a target amine analog.



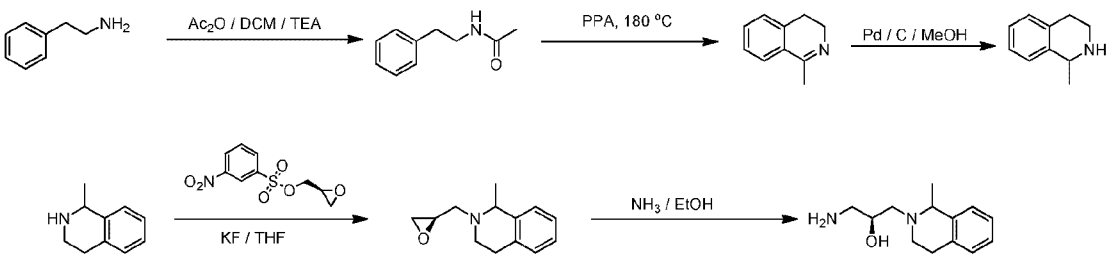
Scheme 12

[00356] A further exemplary synthetic route leading to the aforementioned amine analogs is described in Scheme 13.

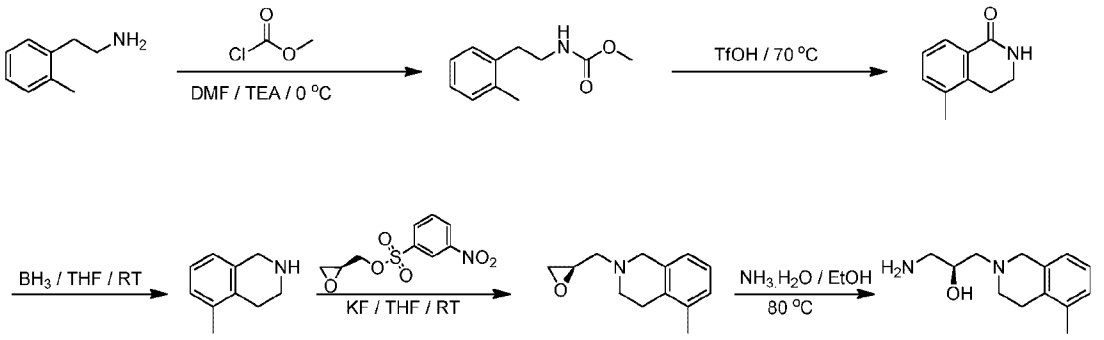


Scheme 13

[00357] A further exemplary synthetic route leading to the aforementioned amine analogs is described in Scheme 14.



Scheme 14



Scheme 15

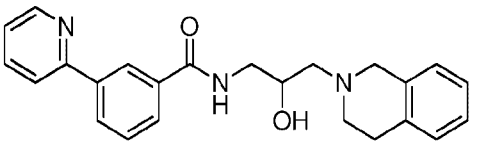
Examples

[00358] In order that the invention described herein may be more fully understood, the following examples are set forth. It should be understood that these examples are for illustrative purposes only and are not to be construed as limiting this invention in any manner.

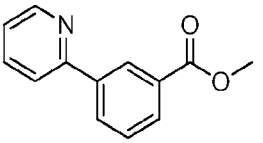
Synthetic Methods

Compound 1

N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-3-(pyridin-2-yl)benzamide

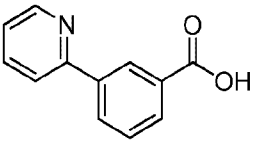


Step 1: methyl 3-(pyridin-2-yl)benzoate



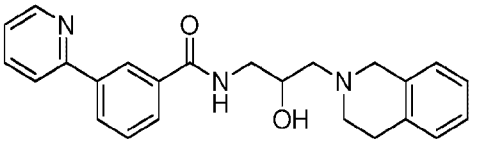
[00359] A mixture of (3-(methoxycarbonyl)phenyl)boronic acid (500 mg, 2.78 mmol), 2-bromopyridine (399 mg, 2.53 mmol), K_2CO_3 (1.0 g, 7.6 mmol) and $Pd(dppf)Cl_2$ (20 mg) in a mixture solution of dioxane (10 mL) and H_2O (2.5 mL) was stirred at 120°C for 30min under microwave heating. The catalyst was removed by filtration and the filtrate was concentrated. The residue was purified by column chromatography to give the desired product (530 mg, Yield: 90%) and this was used directly in the next step. LCMS (m/z): 214.1.

Step 2: 3-(pyridin-2-yl)benzoic acid



[00360] To a solution of methyl 3-(pyridin-2-yl)benzoate (300 mg, 1.40 mmol) in MeOH (3 mL) was added aqueous NaOH (1 mL, 0.4M). The mixture was stirred at room temperature for 3h. The reaction solution was concentrated and the residue dissolved in water and adjust pH to 5~6 with 2N of HCl. The solution was extracted with EtOAc (3x20 mL) and the combined organic layers concentrated to give the desired crude product (450 mg, Yield 90%) which was used in the next step without further purification. LCMS (m/z): 200.1(M+1).

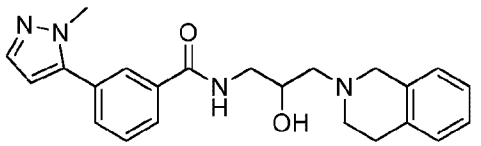
Step 3: N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-3-(pyridin-2-yl)benzamide



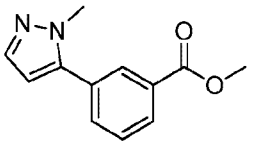
[00361] To a solution of 3-(pyridin-2-yl)benzoic acid (200 mg, 1.00 mmol) in DCM (6 mL) was added EDCI (383 mg, 2.00 mmol), HOBt (270 mg, 2 mmol), Et_3N (303 mg, 3 mmol) and 1-amino-3-(3,4-dihydroisoquinolin-2(1H)-yl)propan-2-ol (206 mg, 1.00 mmol). The mixture was stirred at room temperature for 16h. The reaction mixture was diluted with water (10 mL) and extracted with DCM (3x10 mL). The combined organic layers were then dried and concentrated. The residue was purified by Prep-HPLC to give the product as the formate salt (70 mg, Yield 18%). ^{1}H NMR (400 MHz, MeOD): 8.64 (d, *J*=4.8 Hz, 1H), 8.46 (s, 1H), 8.13 (d, *J*=8.4 Hz, 1H), 7.93-7.90 (m. 3H), 7.60 (dd, *J*=8.0 Hz, 1H), 7.40-7.37 (m, 1H), 7.26-7.14 (m, 4H), 4.44 (s, 2H), 4.38 (br.s, 1H), 3.57-3.56 (m, 4H), 3.36-3.16 (m, 4H). LCMS (m/z): 388.2 (M+1).

Compound 2

N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-3-(1-methyl-1H-pyrazol-5-yl)benzamide

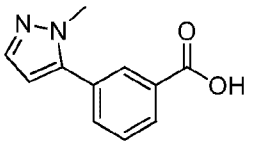


Step 1: methyl 3-(1-methyl-1H-pyrazol-5-yl)benzoate



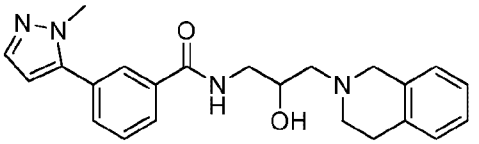
[00362] A mixture of (3-(methoxycarbonyl)phenyl)boronic acid (270 mg, 1.5 mmol), 5-bromo-1-methyl-1H-pyrazole (200 mg, 1.25 mmol), K_2CO_3 (518 mg, 3.75 mmol) and Pd(dppf)Cl_2 (10 mg) in a mixture solution of dioxane (8 mL) and H_2O (2 mL) was stirred at 120°C for 30min under microwave heating. The catalyst was filtered and the filtrate concentrated. The residue was then purified by column chromatography to give provide the desired product as a colorless oil (226 mg, Yield 60%). It was used directly in the next step. LCMS (m/z): 217.1.

Step 2: 3-(1-methyl-1H-pyrazol-5-yl)benzoic acid



[00363] To a solution of methyl 3-(1-methyl-1H-pyrazol-5-yl)benzoate (200 mg, 0.93 mmol) in MeOH (3 mL) was added aqueous NaOH (1 mL, 0.4M). The mixture was stirred at room temperature for 2h. The reaction solution was concentrated and the residue was dissolved in water and adjusted pH to 5~6 with 2N of HCl. The solution was extracted with EtOAc (2x20 mL). The combined organic layers were dried and concentrated to give the target crude product which was used directly in the next step. LCMS (m/z): 203.1(M+1).

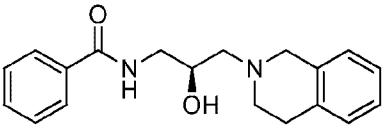
Step 3: N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-3-(1-methyl-1H-pyrazol-5-yl)benzamide



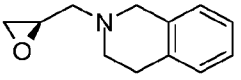
[00364] To a solution of 3-(1-methyl-1H-pyrazol-5-yl)benzoic acid (130 mg, 0.64 mmol) in DCM (6 mL) was added EDCI (245 mg, 1.28 mmol), HOBt (173 mg, 1.28 mmol), Et_3N (195 mg, 1.93 mmol) and 1-amino-3-(3,4-dihydroisoquinolin-2(1H)-yl)propan-2-ol (132 mg, 0.64 mmol). The mixture was stirred at room temperature for 16h until completion of the reaction was indicated by which TLC. The reaction solution was then diluted with water (10 mL) and extracted with DCM (2x10 mL) then the combined organic layers were concentrated. The residue was purified by prep-HPLC to give the desired product (60 mg, Yield 25%). ^1H NMR (400 MHz, MeOD): 7.55 (s, 1H), 7.52 (s, 1H), 7.24-7.15 (m, 3H), 6.85-6.73 (m, 4H), 6.03 (s, 1H), 4.22 (br.s, 1H), 4.03-3.99 (m, 1H), 3.45 (s, 3H), 3.17-2.73 (m, 7H).LCMS (m/z): 391.2 (M+1).

Compound 3

(S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)benzamide

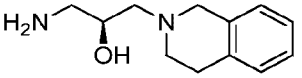


Step 1: (R)-2-(oxiran-2-ylmethyl)-1,2,3,4-tetrahydroisoquinoline



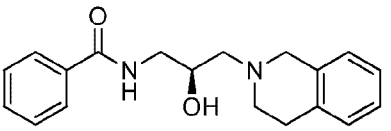
[00365] To a solution of 1,2,3,4-tetrahydroisoquinoline (1g, 7.52mmol) in MeOH (40 mL) was added K_2CO_3 (5.19 g, 37.6mmol) under 0°C. After stirring for 30 minutes, (R)-2-(chloromethyl) oxirane (0.692g, 7.52 mmol) was added the reaction. The mixture was then stirred at 0°C overnight before filtration and washing of the solid by with MeOH. The solution was concentrated and the residue purified by column separation to give the title compound as a colorless oil (70% purity). This crude was used directly in the next step. LCMS (m/z): 190.1(M+1).

Step 2: (S)-1-amino-3-(3,4-dihydroisoquinolin-2(1H)-yl)propan-2-ol



[00366] To a solution of (R)-2-(oxiran-2-ylmethyl)-1,2,3,4-tetrahydroisoquinoline (200 mg,5.2 mmol) in EtOH (20 mL) was added NH_4OH (600 mg, 35.2 mmol) at -78°C. The reaction mixture was then warmed and heated at 100°C for 3h in a seal tube. The reaction mixture was concentrated and the crude product was used in next step without further purification. LCMS (m/z): 207.1(M+1).

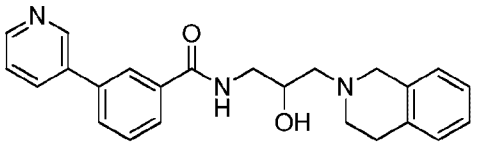
Step 3: (S)-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)benzamide



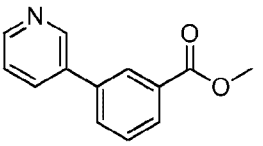
[00367] A solution of (S)-1-amino-3-(3,4-dihydroisoquinolin-2(1H)-yl)propan-2-ol (200 mg, 0.97mmol), benzoic acid (122.5 mg, 1.07 mmol), HATU (387.6mg, 1.02 mmol) and TEA (196.1 mg, 1.94 mmol) in DCM (20 mL) was stirred at room temperature for 2h until completion of the reaction. The reaction mixture was then diluted with water and extracted with DCM (20 ml x 2). The combined organic layers were dried and concentrated with the residue purified by pre-HPLC and SFC separation to give the desired compound (55 mg, Yield 18%). ^{1}H NMR (400 MHz, MeOD): 7.66 (d, *J*=8.0 Hz, 2H), 7.36-7.34 (m, 1H), 7.26 (d, *J*=7.6 Hz, 2H), 6.99-6.89 (m, 4H), 4.01-3.96 (m, 1H), 3.61 (s, 2H), 3.43-3.37 (m, 2H), 2.77-2.72 (m, 4H), 2.56-2.53 (m, 2H). LCMS (m/z): 311.1(M+1).

Compound 8

N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-3-(pyridin-3-yl)benzamide

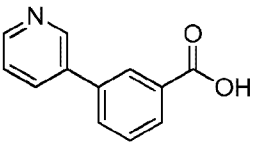


Step 1: methyl 3-(pyridin-3-yl)benzoate



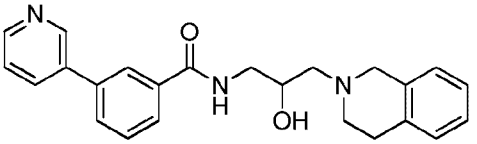
[00368] A mixture of (3-(methoxycarbonyl)phenyl)boronic acid (600 mg, 3.33 mmol), 3-bromopyridine (479 mg, 3.0 mmol), K_2CO_3 (1.2 g, 9.0 mmol) and $Pd(dppf)Cl_2$ (50 mg) in a solution of dioxane (10 mL) and H_2O (2.5 mL) was stirred at 120°C for 30 minutes with microwave heating under N_2. The catalyst was then filtered and the filtrate concentrated. The residue was then purified by column chromatography to give the desired product and used directly in the next step. (630 mg Yield 90%).

Step 2: 3-(pyridin-3-yl)benzoic acid



[00369] To a solution of methyl 3-(pyridin-3-yl)benzoate (450 mg, 2.1 mmol) in MeOH (5 mL) was added aqueous of NaOH (1.5 mL, 0.4M). The mixture was stirred at room temperature for 2h then reaction solution was concentrated and the resulting residue dissolved in water and adjusted pH to 5-6 with 2N HCl. Extracted was then performed using EtOAc with the organic layer dired and concentrated to give the target product which was used without further purification (600 mg, Yield 90%). LCMS (m/z): 200.1 (M+1).

Step 3: N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-3-(pyridin-3-yl)benzamide

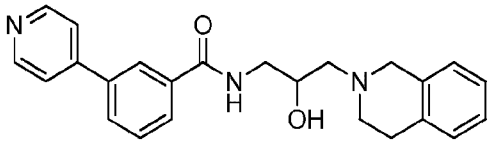


[00370] To a solution of 3-(pyridin-3-yl)benzoic acid (150 mg, 0.75 mmol) in DCM (6 mL) was added EDCI (215 mg, 1.10 mmol), HOBt (148 mg, 1.10 mmol), Et_3N (228 mg, 2.25 mmol) and 1-amino-3-(3,4-dihydroisoquinolin-2(1H)-yl)propan-2-ol (185 mg, 0.90 mmol). The mixture was stirred at room temperature for 16h. The reaction solution was then washed with water and extracted with DCM. The organic layer was concentrated, dried and the residue purified by prep-HPLC to give the desired title product (110 mg, Yield 34%). ^1H

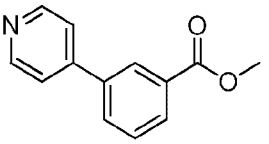
NMR (400MHz, MeOD) δ 8.80 (d, J=2.0 Hz, 1H), 8.52 (dd, J_1=4.8 Hz, J_2=3.6 Hz, 1H), 8.10 (s, 1H), 8.09 (dd, J_1=8.8 Hz, J_2=1.6 Hz, 1H), 7.83 (d, J=7.6 Hz, 1H), 7.77 (d, J=7.6 Hz, 1H), 7.51-7.46 (m, 2H), 7.06-6.95 (m, 4H), 4.15-4.10 (m, 1H), 3.69 (s, 2H), 3.60-3.47 (m, 2H), 2.85-2.79 (m, 4H), 2.69-2.59 (m, 2H). LCMS (m/z): 388.2 (M+1).

Compound 9

N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-3-(pyridin-4-yl)benzamide

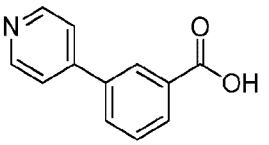


Step 1: methyl 3-(pyridin-4-yl)benzoate



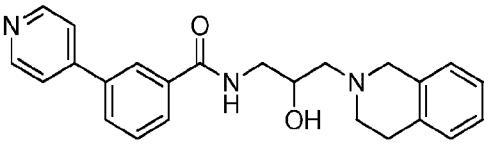
[00371] A mixture of (3-(methoxycarbonyl)phenyl)boronic acid (600 mg, 3.33 mmol), 4-bromopyridine (583.5 mg, 3.0 mmol), K_2CO_3 (1.2 g, 9.0 mmol) and Pd(dppf)Cl_2 (50 mg) in a solution of dioxane (10 mL) and H_2O (2.5 mL) was stirred at 120°C for 30min with microwave heating. The catalyst was filtered and the filtrate concentrated. The residue was then purified by column chromatography to give the title product (630 mg Yield 90%).

Step 2: 3-(pyridin-4-yl)benzoic acid



[00372] To a solution of methyl 3-(pyridin-4-yl)benzoate (450 mg, 2.1 mmol) in MeOH (5 mL) was added an aqueous solution of NaOH (1.5 mL, 0.4M). The mixture was stirred at room temperature for 2h. The reaction solution was then concentrated, the residue was next dissolved in water and adjusted pH to 5~6 with the 2N HCl. After extraction with EtOAc, the organic layers were dried and concentrated to give the product desired (600 mg, Yield 90%). LCMS (m/z): 200.1 (M+1).

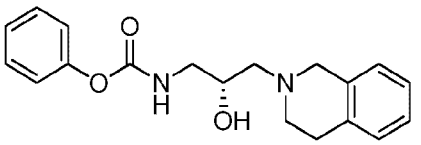
Step 3: N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-3-(pyridin-4-yl)benzamide



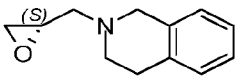
[00373] To a solution of 3-(pyridin-4-yl)benzoic acid (300 mg, 1.5 mmol) in DCM (6 mL) was added EDCI (430 mg, 2.20 mmol), HOBt (296 mg, 2.20 mmol), Et_3N (556 mg, 4.50 mmol) and 1-amino-3-(3,4-dihydroisoquinolin-2(1H)-yl)propan-2-ol (370 mg,1.80 mmol). The mixture was stirred at room temperature for 16h, then the reaction mixture was washed with water and extracted with DCM. The organic layer was then dried, concentrated and the residue purified by prep-HPLC to give the title product (230 mg, Yield 40%). ^{1}H NMR (400MHz, MeOD) δ 8.54 (d, *J*=4.0 Hz, 2H), 8.16 (s, 1H), 7.85-7.80 (m, 2H), 7.64 (dd *J*=4.0 Hz, 2H), 7.48 (dd, *J* =7.6 Hz, 1H), 7.03-6.95 (m, 4H), 4.13 (br.s, 1H), 3.66 (s, 2H), 3.60-3.48 (m, 2H), 2.80-2.77 (m, 4H), 2.63-2.59 (m, 2H). LCMS (m/z): 388.2 (M+1).

Compound 11

(R)-phenyl (3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)carbamate

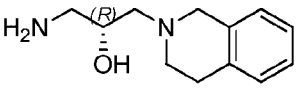


Step 1:(S)-2-(oxiran-2-ylmethyl)-1,2,3,4-tetrahydroisoquinoline



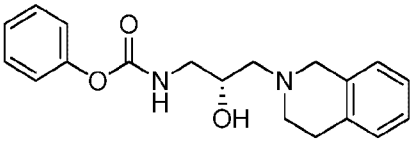
[00374] To a solution of 1,2,3,4-tetrahydroisoquinoline (5g, 7.52mmol) in THF(100 mL) was added KF (8.57 g, 150.4mmol) at 0°C. (R)-oxiran-2-ylmethyl 3-nitrobenzenesulfonate (10.7g, 41.4 mmol) was added to the reaction in 1h. The solution was stirred at room temperature overnight. The solid was removed by filtration and washed with THF. The solution was then concentrated and the residue used for next step without further purification (11.3 g Yield 80%). LCMS (m/z): 190.1 (M+1).

Step 2: (R)-1-amino-3-(3,4-dihydroisoquinolin-2(1H)-yl)propan-2-ol



[00375] To a solution of (S)-2-(oxiran-2-ylmethyl)-1,2,3,4-tetrahydroisoquinoline (2.2g,0.012 mol) in EtOH (30 mL), NH_3 was bubbled to the solution under -78°C. The reaction mixture was then sealed and heated at 80°C for 3h. After LCMS indicated completion of the reaction, the mixture was concentrated and the crude product was used in next step without further purification (2.2 g, Yield 90%). LCMS (m/z): 207.1 (M+1).

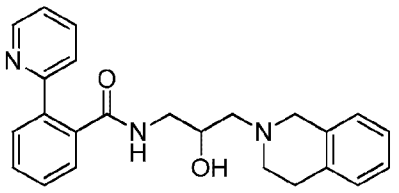
Step 3: (R)-phenyl (3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)carbamate



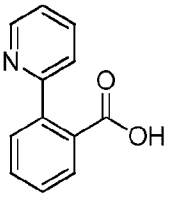
[00376] To the stirring solution of (R)-1-amino-3-(3,4-dihydroisoquinolin-2(1H)-yl)propan-2-ol (200 mg, 0.97 mmol) in 15 mL dry DCM was added TEA (1 mL) and the solution was cooled to 0°C. Phenyl carbonochloridate (151.3mg, 1.02 mmol) in DCM(10 mL) was then added drop wise to the reaction over 20 minutes and the solution was then stirred at room temperature overnight. The solution was then diluted with water, extracted with DCM, the organic layer was concentrated, purified by pre-HPLC to give the product as formate salt (125 mg, Yield 40%). ^{1}H NMR (400MHz, MeOD) δ 7.35 (dd, J=7.6 Hz, 2H), 7.31-7.18 (m, 5H), 7.08 (d, J=7.6 Hz, 2H), 4.33 (s, 2H), 4.22-4.19 (m, 1H), 3.48 (t, *J*=6.0 Hz, 2H), 3.27-3.10 (m, 6H). LCMS (m/z): 327.2 (M+1).

Compound 12

N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-2-(pyridin-2-yl)benzamide

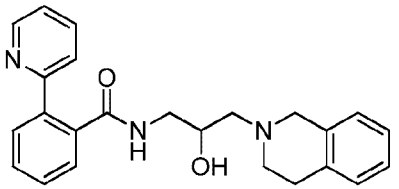


Step 1: 2-(pyridin-2-yl)benzoic acid



[00377] A mixture of 2-boronobenzoic acid (400 mg, 2.4 mmol), 2-bromopyridine (416 mg, 2.6 mmol), K_2CO_3 (994 mg, 7.2 mmol) and $Pd(dppf)Cl_2$ (20 mg) in dioxane (8 mL) and H_2O (2 mL) was stirred at 125 °C for 30 min. under microwave heating under N_2. The catalyst was filtered, and the filtrate was acidified with 2N HCl to pH 5~6. The solution was concentrated, and the residue was dissolved in MeOH and filtered. The filtrate was concentrated, and the residue was purified by prep-TLC to give the title compound (205 mg, Yield 42.9%). LCMS (m/z): 200.0 (M+1).

Step 2: N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-2-(pyridin-2-yl) benzamide



[00378] To a solution of 2-(pyridin-2-yl)benzoic acid (150 mg, 0.75 mmol) in DCM (6 mL) was added EDCI (215 mg, 1.1 mmol), HOBt (148 mg, 1.1 mmol), Et3N (228 mg, 2.25 mmol) and 1-amino-3-(3,4-dihydroisoquinolin-2(1H)-yl)propan-2-ol (185 mg, 0.9 mmol). The mixture was stirred at 25 °C for 16 h. The reaction solution was washed with water and extracted with DCM. The organic layer was then concentrated, and the residue was purified by prep-HPLC to give the title compound (80 mg, Yield 27.5%). ^1H NMR (CD_3OD, 400 MHz): δ 8.60-8.53 (m, 1H), 7.89-7.81 (m, 1H), 7.63-7.51 (m, 4H), 7.48-7.43 (m, 1H), 7.39-7.32 (m, 1H), 7.12-7.05 (m, 3H), 7.05-6.98 (m, 1H), 4.05-3.93 (m, 1H), 3.73-3.63 (s, 2H), 3.46-3.37 (m, 1H), 3.31-3.23 (m, 1H), 2.92-2.75 (m, 4H), 2.56 (s, 2H). LCMS (m/z): 388.2 (M+1).

DEMANDES OU BREVETS VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVETS COMPREND PLUS D'UN TOME.

CECI EST LE TOME __1___ DE __2___

NOTE: Pour les tomes additionels, veillez contacter le Bureau Canadien des Brevets.

JUMBO APPLICATIONS / PATENTS

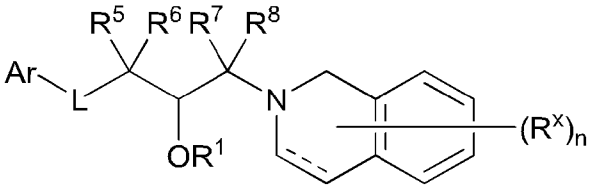
THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE THAN ONE VOLUME.

THIS IS VOLUME __1___ OF __2___

NOTE: For additional volumes please contact the Canadian Patent Office.

Claims

1. A compound of Formula (**I**):



I

or a pharmaceutically acceptable salt thereof,

wherein

$\overset{\text{------}}{=}$ represents a single or double bond;

R^1 is hydrogen, R^z, or $-C(O)R^z$, wherein R^z is optionally substituted C_{1-6} alkyl;

L is $-N(R)C(O)-$, $-C(O)N(R)-$, $-N(R)C(O)O-$, or $-OC(O)N(R)-$;

each R is independently hydrogen or optionally substituted C_{1-6} aliphatic;

Ar is a monocyclic or bicyclic aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Ar is substituted with 0, 1, 2, 3, 4, or 5 R^y groups, as valency permits;

each R^y is independently selected from the group consisting of halo, -CN, $-NO_2$, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, $-OR^A$, $-N(R^B)_2$, $-SR^A$, $-C(=O)R^A$, $-C(O)OR^A$, $-C(O)SR^A$, $-C(O)N(R^B)_2$, $-C(O)N(R^B)N(R^B)_2$, $-OC(O)R^A$, $-OC(O)N(R^B)_2$, $-NR^BC(O)R^A$, $-NR^BC(O)N(R^B)_2$, $-NR^BC(O)N(R^B)N(R^B)_2$, $-NR^BC(O)OR^A$, $-SC(O)R^A$, $-C(=NR^B)R^A$, $-C(=NNR^B)R^A$, $-C(=NOR^A)R^A$, $-C(=NR^B)N(R^B)_2$, $-NR^BC(=NR^B)R^B$, $-C(=S)R^A$, $-C(=S)N(R^B)_2$, $-NR^BC(=S)R^A$, $-S(O)R^A$, $-OS(O)_2R^A$, $-SO_2R^A$, $-NR^BSO_2R^A$, or $-SO_2N(R^B)_2$;

each R^A is independently selected from the group consisting of hydrogen, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

each R^B is independently selected from the group consisting of hydrogen, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, or two R^B groups are taken together with their intervening atoms to form an optionally substituted heterocyclic ring;

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R^5, R^6, R^7, and R^8 are independently hydrogen, halo, or optionally substituted aliphatic;

each R^x is independently selected from the group consisting of halo, -CN, optionally substituted aliphatic, -OR', and -$N(R'')_2$;

R' is hydrogen or optionally substituted aliphatic;

each R" is independently hydrogen or optionally substituted aliphatic, or two R" are taken together with their intervening atoms to form a heterocyclic ring; and

n is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, as valency permits;

wherein, and unless otherwise specified,

heterocyclyl or heterocyclic refers to a radical of a 3–10 membered non–aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur;

carbocyclyl or carbocyclic refers to a radical of a non–aromatic cyclic hydrocarbon group having from 3 to 10 ring carbon atoms and zero heteroatoms in the non–aromatic ring system;

aryl refers to a radical of a monocyclic or polycyclic aromatic ring system having 6–14 ring carbon atoms and zero heteroatoms provided in the aromatic ring system; and

heteroaryl refers to a radical of a 5–10 membered monocyclic or bicyclic 4n+2 aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen and sulfur; wherein

optional carbon atom substituents are selected from halogen, –CN, $–NO_2$, $–N_3$, $–SO_2H$, $–SO_3H$, –OH, $–OR^{aa}$, $–ON(R^{bb})_2$, $–N(R^{bb})_2$, $–N(R^{bb})_3{}^+X^-$, $–N(OR^{cc})R^{bb}$, –SH, $–SR^{aa}$, $–SSR^{cc}$, $–C(=O)R^{aa}$, $–CO_2H$, –CHO, $–C(OR^{cc})_2$, $–CO_2R^{aa}$, $–OC(=O)R^{aa}$, $–OCO_2R^{aa}$, $–C(=O)N(R^{bb})_2$, $–OC(=O)N(R^{bb})_2$, $–NR^{bb}C(=O)R^{aa}$, $–NR^{bb}CO_2R^{aa}$, $–NR^{bb}C(=O)N(R^{bb})_2$, $–C(=NR^{bb})R^{aa}$, $–C(=NR^{bb})OR^{aa}$, $–OC(=NR^{bb})R^{aa}$, $–OC(=NR^{bb})OR^{aa}$, $–C(=NR^{bb})N(R^{bb})_2$, $–OC(=NR^{bb})N(R^{bb})_2$, $–NR^{bb}C(=NR^{bb})N(R^{bb})_2$, $–C(=O)NR^{bb}SO_2R^{aa}$, $–NR^{bb}SO_2R^{aa}$, $–SO_2N(R^{bb})_2$, $–SO_2R^{aa}$, $–SO_2OR^{aa}$, $–OSO_2R^{aa}$, $–S(=O)R^{aa}$, $–OS(=O)R^{aa}$, $–Si(R^{aa})_3$, $–OSi(R^{aa})_3$ $–C(=S)N(R^{bb})_2$, $–C(=O)SR^{aa}$, $–C(=S)SR^{aa}$, $–SC(=S)SR^{aa}$, $–SC(=O)SR^{aa}$, $–OC(=O)SR^{aa}$, $–SC(=O)OR^{aa}$, $–SC(=O)R^{aa}$, $–P(=O)_2R^{aa}$, $–OP(=O)_2R^{aa}$, $–P(=O)(R^{aa})_2$, $–OP(=O)(R^{aa})_2$, $–OP(=O)(OR^{cc})_2$, $–P(=O)_2N(R^{bb})_2$, $–OP(=O)_2N(R^{bb})_2$, $–P(=O)(NR^{bb})_2$, $–OP(=O)(NR^{bb})_2$, $–NR^{bb}P(=O)(OR^{cc})_2$, $–NR^{bb}P(=O)(NR^{bb})_2$, $–P(R^{cc})_2$, $–P(R^{cc})_3$, $–OP(R^{cc})_2$, $–OP(R^{cc})_3$, $–B(R^{aa})_2$, $–B(OR^{cc})_2$, $–BR^{aa}(OR^{cc})$, $C_{1–10}$ alkyl, $C_{1–10}$ perhaloalkyl, $C_{2–10}$ alkenyl, $C_{2–10}$ alkynyl, $C_{3–10}$ carbocyclyl, 3–14 membered heterocyclyl, $C_{6–14}$ aryl, and 5–14 membered heteroaryl,

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wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups; or two geminal hydrogens on a carbon atom are replaced with the group =O, =S, $=NN(R^{bb})_2$, $=NNR^{bb}C(=O)R^{aa}$, $=NNR^{bb}C(=O)OR^{aa}$, $=NNR^{bb}S(=O)_2R^{aa}$, $=NR^{bb}$, or $=NOR^{cc}$;

optional nitrogen atom substituents are selected from hydrogen, –OH, $–OR^{aa}$, $–N(R^{cc})_2$, –CN, $–C(=O)R^{aa}$, $–C(=O)N(R^{cc})_2$, $–CO_2R^{aa}$, $–SO_2R^{aa}$, $–C(=NR^{bb})R^{aa}$, $–C(=NR^{cc})OR^{aa}$, $–C(=NR^{cc})N(R^{cc})_2$, $–SO_2N(R^{cc})_2$, $–SO_2R^{cc}$, $–SO_2OR^{cc}$, $–SOR^{aa}$, $–C(=S)N(R^{cc})_2$, $–C(=O)SR^{cc}$, $–C(=S)SR^{cc}$, $–P(=O)_2R^{aa}$, $–P(=O)(R^{aa})_2$, $–P(=O)_2N(R^{cc})_2$, $–P(=O)(NR^{cc})_2$, $C_{1–10}$ alkyl, $C_{1–10}$ perhaloalkyl, $C_{2–10}$ alkenyl, $C_{2–10}$ alkynyl, $C_{3–10}$ carbocyclyl, 3–14 membered heterocyclyl, $C_{6–14}$ aryl, and 5–14 membered heteroaryl, or two R^{cc} groups attached to a nitrogen atom are joined to form a 3–14 membered heterocyclyl or 5–14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

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

each instance of R^{bb} is, independently, selected from hydrogen, –OH, $–OR^{aa}$, $–N(R^{cc})_2$, –CN, $–C(=O)R^{aa}$, $–C(=O)N(R^{cc})_2$, $–CO_2R^{aa}$, $–SO_2R^{aa}$, $–C(=NR^{cc})OR^{aa}$, $–C(=NR^{cc})N(R^{cc})_2$, $–SO_2N(R^{cc})_2$, $–SO_2R^{cc}$, $–SO_2OR^{cc}$, $–SOR^{aa}$, $–C(=S)N(R^{cc})_2$, $–C(=O)SR^{cc}$, $–C(=S)SR^{cc}$, $–P(=O)_2R^{aa}$, $–P(=O)(R^{aa})_2$, $–P(=O)_2N(R^{cc})_2$, $–P(=O)(NR^{cc})_2$, $C_{1–10}$ alkyl, $C_{1–10}$ perhaloalkyl, $C_{2–10}$ alkenyl, $C_{2–10}$ alkynyl, $C_{3–10}$ carbocyclyl, 3–14 membered heterocyclyl, $C_{6–14}$ aryl, and 5–14 membered heteroaryl, or two R^{bb} groups are joined to form a 3–14 membered heterocyclyl or 5–14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

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

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each instance of R^{dd} is, independently, selected from halogen, –CN, $–NO_2$, $–N_3$, $–SO_2H$, $–SO_3H$, –OH, $–OR^{ee}$, $–ON(R^{ff})_2$, $–N(R^{ff})_2$, $–N(R^{ff})_3^+X^–$, $–N(OR^{ee})R^{ff}$, –SH, $–SR^{ee}$, $–SSR^{ee}$, $–C(=O)R^{ee}$, $–CO_2H$, $–CO_2R^{ee}$, $–OC(=O)R^{ee}$, $–OCO_2R^{ee}$, $–C(=O)N(R^{ff})_2$, $–OC(=O)N(R^{ff})_2$, $–NR^{ff}C(=O)R^{ee}$, $–NR^{ff}CO_2R^{ee}$, $–NR^{ff}C(=O)N(R^{ff})_2$, $–C(=NR^{ff})OR^{ee}$, $–OC(=NR^{ff})R^{ee}$, $–OC(=NR^{ff})OR^{ee}$, $–C(=NR^{ff})N(R^{ff})_2$, $–OC(=NR^{ff})N(R^{ff})_2$, $–NR^{ff}C(=NR^{ff})N(R^{ff})_2$,$–NR^{ff}SO_2R^{ee}$, $–SO_2N(R^{ff})_2$, $–SO_2R^{ee}$, $–SO_2OR^{ee}$, $–OSO_2R^{ee}$, $–S(=O)R^{ee}$, $–Si(R^{ee})_3$, $–OSi(R^{ee})_3$, $–C(=S)N(R^{ff})_2$, $–C(=O)SR^{ee}$, $–C(=S)SR^{ee}$, $–SC(=S)SR^{ee}$, $–P(=O)_2R^{ee}$, $–P(=O)(R^{ee})_2$, $–OP(=O)(R^{ee})_2$, $–OP(=O)(OR^{ee})_2$, $C_{1–6}$ alkyl, $C_{1–6}$ perhaloalkyl, $C_{2–6}$ alkenyl, $C_{2–6}$ alkynyl, $C_{3–10}$ carbocyclyl, 3–10 membered heterocyclyl, $C_{6–10}$ aryl, 5–10 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups, or two geminal R^{dd} substituents can be joined to form =O or =S;

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

each instance of R^{ff} is, independently, selected from hydrogen, $C_{1–6}$ alkyl, $C_{1–6}$ perhaloalkyl, $C_{2–6}$ alkenyl, $C_{2–6}$ alkynyl, $C_{3–10}$ carbocyclyl, 3–10 membered heterocyclyl, $C_{6–10}$ aryl and 5–10 membered heteroaryl, or two R^{ff} groups are joined to form a 3–14 membered heterocyclyl or 5–14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups; and

each instance of R^{gg} is, independently, halogen, –CN, $–NO_2$, $–N_3$, $–SO_2H$, $–SO_3H$, –OH, $–OC_{1–6}$ alkyl, $–ON(C_{1–6}$ alkyl$)_2$, $–N(C_{1–6}$ alkyl$)_2$, $–N(C_{1–6}$ alkyl$)_3^+X^–$, $–NH(C_{1–6}$ alkyl$)_2^+X^–$, $–NH_2(C_{1–6}$ alkyl$)^+X^–$, $–NH_3^+X^–$, $–N(OC_{1–6}$ alkyl$)(C_{1–6}$ alkyl), $–N(OH)(C_{1–6}$ alkyl), –NH(OH), –SH, $–SC_{1–6}$ alkyl, $–SS(C_{1–6}$ alkyl), $–C(=O)(C_{1–6}$ alkyl), $–CO_2H$, $–CO_2(C_{1–6}$ alkyl), $–OC(=O)(C_{1–6}$ alkyl), $–OCO_2(C_{1–6}$ alkyl), $–C(=O)NH_2$, $–C(=O)N(C_{1–6}$ alkyl$)_2$, $–OC(=O)NH(C_{1–6}$ alkyl), $–NHC(=O)(C_{1–6}$ alkyl), $–N(C_{1–6}$ alkyl$)C(=O)(C_{1–6}$ alkyl), $–NHCO_2(C_{1–6}$ alkyl), $–NHC(=O)N(C_{1–6}$ alkyl$)_2$, $–NHC(=O)NH(C_{1–6}$ alkyl), $–NHC(=O)NH_2$, $–C(=NH)O(C_{1–6}$ alkyl),$–OC(=NH)(C_{1–6}$ alkyl), $–OC(=NH)OC_{1–6}$ alkyl, $–C(=NH)N(C_{1–6}$ alkyl$)_2$, $–C(=NH)NH(C_{1–6}$ alkyl), $–C(=NH)NH_2$, $–OC(=NH)N(C_{1–6}$ alkyl$)_2$, $–OC(NH)NH(C_{1–6}$ alkyl), $–OC(NH)NH_2$, $–NHC(NH)N(C_{1–6}$ alkyl$)_2$, $–NHC(=NH)NH_2$, $–NHSO_2(C_{1–6}$ alkyl), $–SO_2N(C_{1–6}$ alkyl$)_2$, $–SO_2NH(C_{1–6}$ alkyl), $–SO_2NH_2$,$–SO_2C_{1–6}$ alkyl, $–SO_2OC_{1–6}$ alkyl, $–OSO_2C_{1–6}$ alkyl, $–SOC_{1–6}$ alkyl, $–Si(C_{1–6}$ alkyl$)_3$, $–OSi(C_{1–6}$ alkyl$)_3$ –

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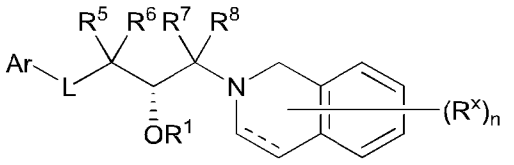
$C(=S)N(C_{1-6}\ alkyl)_2$, $C(=S)NH(C_{1-6}\ alkyl)$, $C(=S)NH_2$, $-C(=O)S(C_{1-6}\ alkyl)$, $-C(=S)SC_{1-6}$ alkyl, $-SC(=S)SC_{1-6}$ alkyl, $-P(=O)_2(C_{1-6}\ alkyl)$, $-P(=O)(C_{1-6}\ alkyl)_2$, $-OP(=O)(C_{1-6}\ alkyl)_2$, $-OP(=O)(OC_{1-6}\ alkyl)_2$, C_{1-6} alkyl, C_{1-6} perhaloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocyclyl, C_{6-10} aryl, 3–10 membered heterocyclyl, 5–10 membered heteroaryl; or two geminal R^{gg} substituents can be joined to form =O or =S; wherein X^- is a counterion.

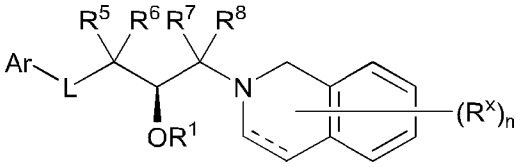
2. The compound of claim 1, wherein the compound is of Formula (**I-a**):



I-a

or a pharmaceutically acceptable salt thereof.

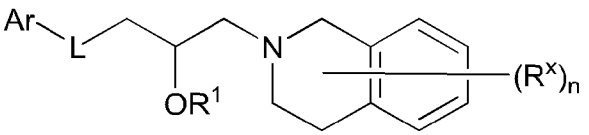
3. The compound of claim 1, wherein the compound is of Formula (**I-b**):



I-b

or a pharmaceutically acceptable salt thereof.

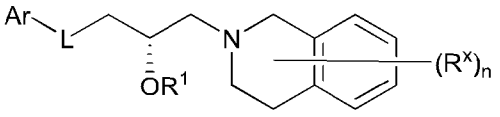
4. The compound of claim 1, wherein the compound is of Formula (**I'**):



I'

or a pharmaceutically acceptable salt thereof.

5. The compound of claim 1, wherein the compound is of Formula (**I'-a**):



I'-a

or a pharmaceutically acceptable salt thereof.

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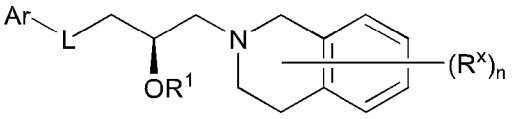
6. The compound of claim 1, wherein the compound is of Formula (**I'-b**):



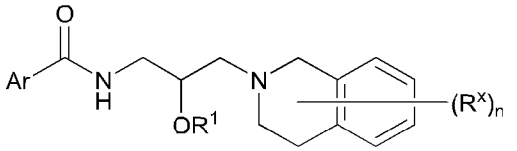
I'-b

or a pharmaceutically acceptable salt thereof.

7. The compound of any one of claims 1-6, wherein L is –C(O)N(R)–.

8. The compound of any one of claims 1-6, wherein L is –OC(O)NH-.

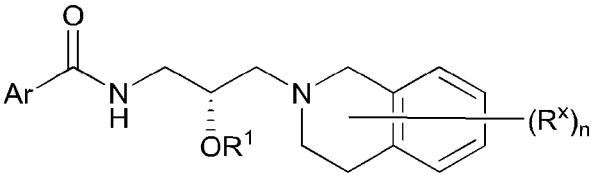
9. The compound of claim 1, wherein the compound is of Formula (**II**):



II

or a pharmaceutically acceptable salt thereof.

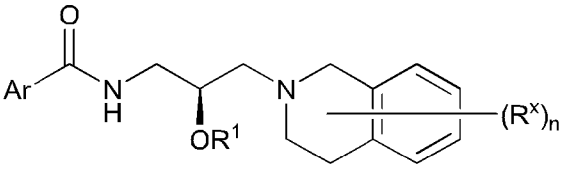
10. The compound of claim 1, wherein the compound is of Formula (**II-a**):



II-a

or a pharmaceutically acceptable salt thereof.

11. The compound of claim 1, wherein the compound is of Formula (**II-b**):



II-b

or a pharmaceutically acceptable salt thereof.

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12. The compound of any one of claims 1-11, wherein R^1 is hydrogen.

13. The compound of any one of claims 1-12, wherein n is 0.

14. The compound of any one of claims 1-12, wherein n is 1.

15. The compound of any one of claims 1-12, wherein n is 2.

16. The compound of any one of claims 1-15, wherein Ar is phenyl.

17. The compound of any one of claims 1-15, wherein Ar is heteroaryl.

18. The compound of claim 17, wherein Ar is a 5- to 6-membered heteroaryl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

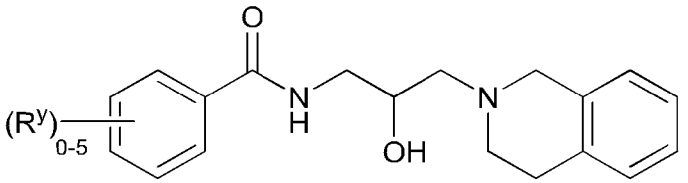
19. The compound of claim 18, wherein Ar is pyridyl.

20. The compound of any one of claims 1-19, wherein Ar is unsubstituted.

21. The compound of any one of claims 1-19, wherein Ar is substituted with 1 or 2 R^y groups.

22. The compound of claim 21, wherein Ar is substituted with one R^y group.

23. The compound of claim 1, wherein the compound is of Formula (**III**):

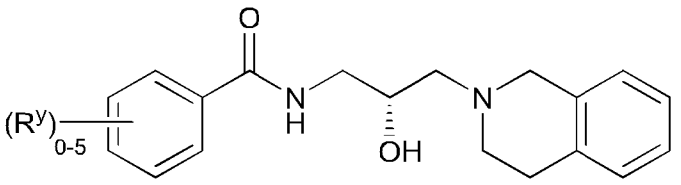


III

or a pharmaceutically acceptable salt thereof.

24. The compound of claim 1, wherein the compound is of Formula (**III-a**):

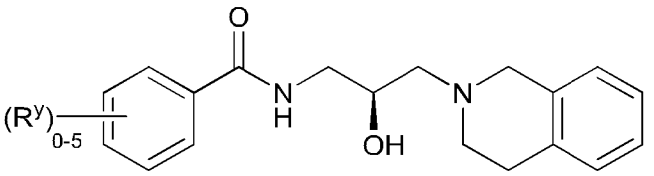
Date Reçue/Date Received 2020-11-02



III-a

or a pharmaceutically acceptable salt thereof.

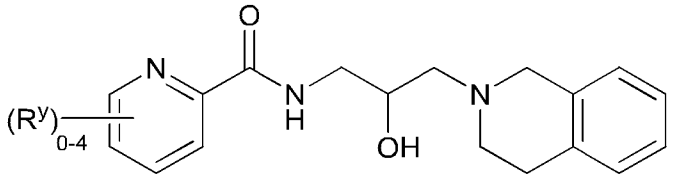
25. The compound of claim 1, wherein the compound is of Formula (**III-b**):



III-b

or a pharmaceutically acceptable salt thereof.

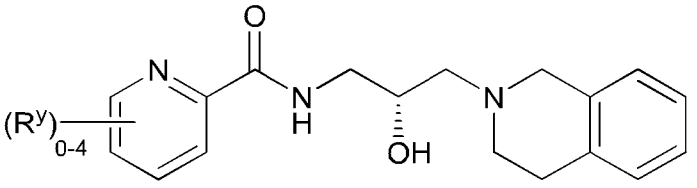
26. The compound of claim 1, wherein the compound is of Formula (**IV**):



IV

or a pharmaceutically acceptable salt thereof.

27. The compound of claim 1, wherein the compound is of Formula (**IV-a**):

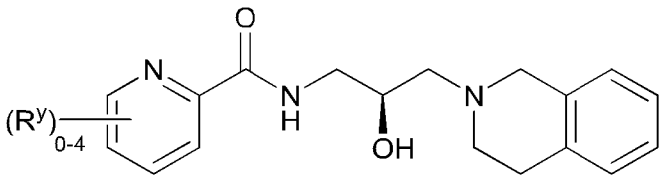


IV-a

or a pharmaceutically acceptable salt thereof.

28. The compound of claim 1, wherein the compound is of Formula (**IV-b**):

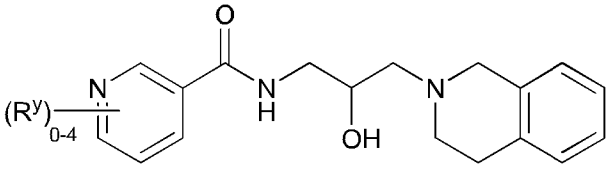
Date Reçue/Date Received 2020-11-02



IV-b

or a pharmaceutically acceptable salt thereof.

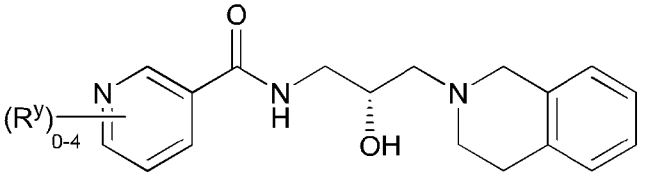
29. The compound of claim 1, wherein the compound is of Formula (**V**):



V

or a pharmaceutically acceptable salt thereof.

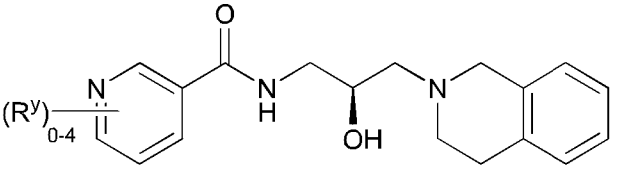
30. The compound of claim 1, wherein the compound is of Formula (**V-a**):



V-a

or a pharmaceutically acceptable salt thereof.

31. The compound of claim 1, wherein the compound is of Formula (**V-b**):

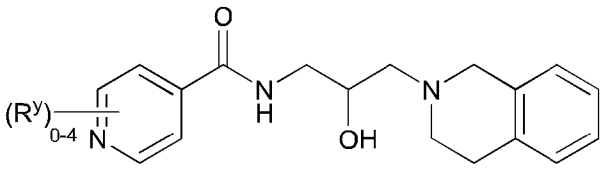


V-b

or a pharmaceutically acceptable salt thereof.

32. The compound of claim 1, wherein the compound is of Formula (**VI**):

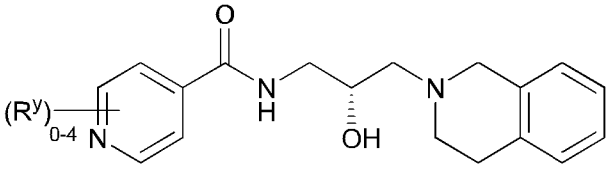
Date Reçue/Date Received 2020-11-02



VI

or a pharmaceutically acceptable salt thereof.

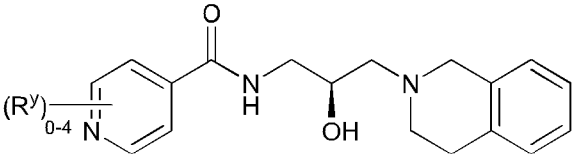
33. The compound of claim 1, wherein the compound is of Formula (**VI-a**):



VI-a

or a pharmaceutically acceptable salt thereof.

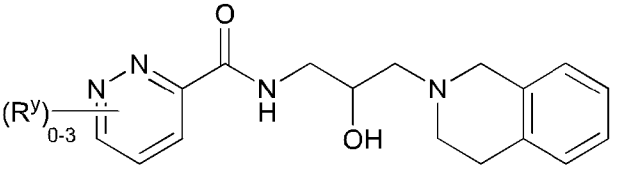
34. The compound of claim 1, wherein the compound is of Formula (**VI-b**):



VI-b

or a pharmaceutically acceptable salt thereof.

35. The compound of claim 1, wherein the compound is of Formula (**VII**):

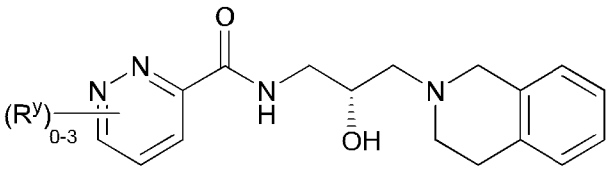


VII

or a pharmaceutically acceptable salt thereof.

36. The compound of claim 1, wherein the compound is of Formula (**VII-a**):

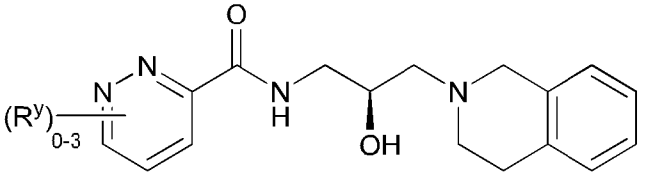
Date Reçue/Date Received 2020-11-02



VII-a

or a pharmaceutically acceptable salt thereof.

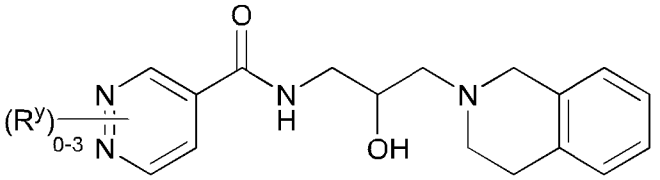
37. The compound of claim 1, wherein the compound is of Formula (**VII-b**):



VII-b

or a pharmaceutically acceptable salt thereof.

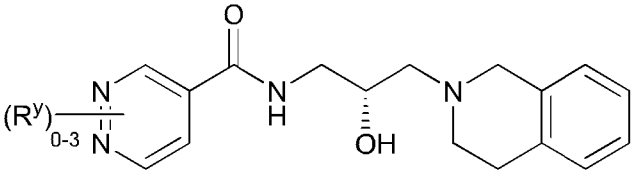
38. The compound of claim 1, wherein the compound is of Formula (**VIII**):



VIII

or a pharmaceutically acceptable salt thereof.

39. The compound of claim 1, wherein the compound is of Formula (**VIII-a**):

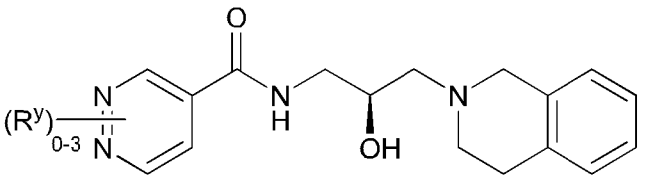


VIII-a

or a pharmaceutically acceptable salt thereof.

40. The compound of claim 1, wherein the compound is of Formula (**VIII-b**):

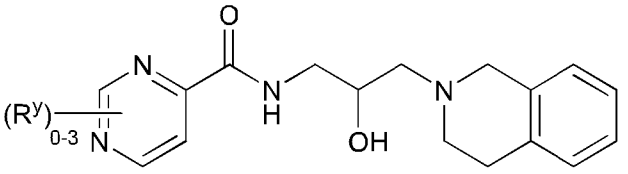
Date Reçue/Date Received 2020-11-02



VIII-b

or a pharmaceutically acceptable salt thereof.

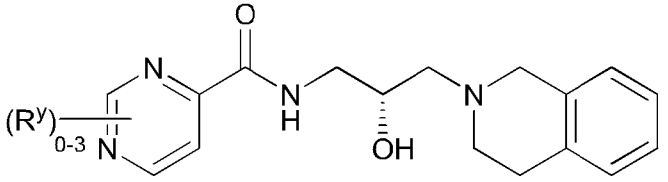
41. The compound of claim 1, wherein the compound is of Formula (**IX**):



IX

or a pharmaceutically acceptable salt thereof.

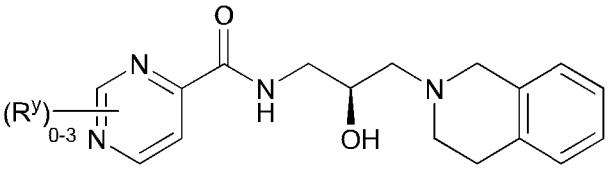
42. The compound of claim 1, wherein the compound is of Formula (**IX-a**):



IX-a

or a pharmaceutically acceptable salt thereof.

43. The compound of claim 1, wherein the compound is of Formula (**IX-b**):

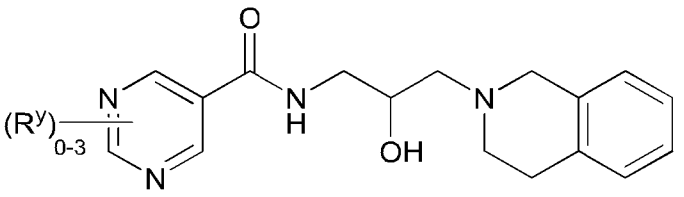


IX-b

or a pharmaceutically acceptable salt thereof.

44. The compound of claim 1, wherein the compound is of Formula (**X**):

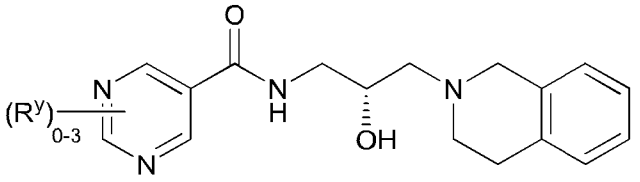
Date Reçue/Date Received 2020-11-02



X

or a pharmaceutically acceptable salt thereof.

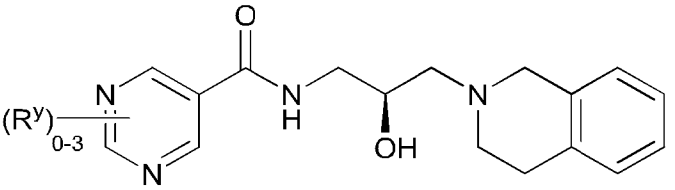
45. The compound of claim 1, wherein the compound is of Formula (**X-a**):



X-a

or a pharmaceutically acceptable salt thereof.

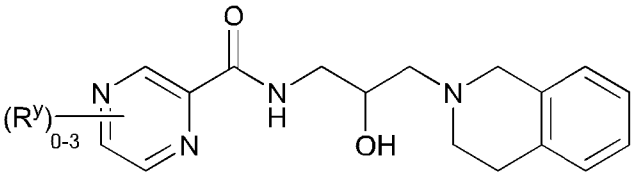
46. The compound of claim 1, wherein the compound is of Formula (**X-b**):



X-b

or a pharmaceutically acceptable salt thereof.

47. The compound of claim 1, wherein the compound is of Formula (**XI**):

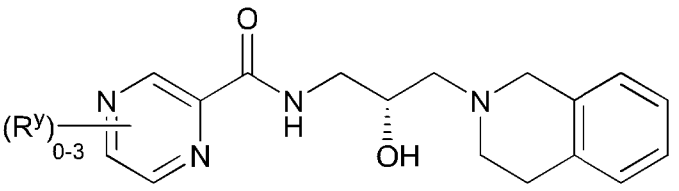


XI

or a pharmaceutically acceptable salt thereof.

48. The compound of claim 1, wherein the compound is of Formula (**XI-a**):

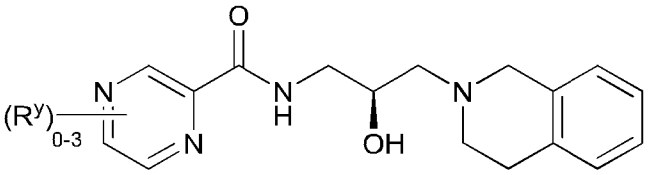
Date Reçue/Date Received 2020-11-02



XI-a

or a pharmaceutically acceptable salt thereof.

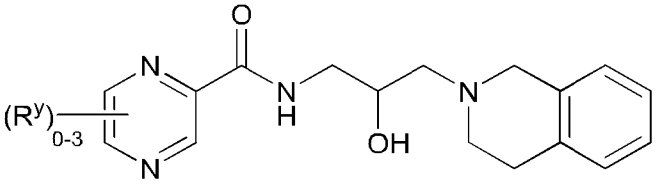
49. The compound of claim 1, wherein the compound is of Formula (**XI-b**):



XI-b

or a pharmaceutically acceptable salt thereof.

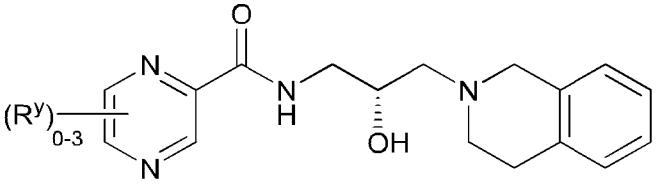
50. The compound of claim 1, wherein the compound is of Formula (**XII**):



XII

or a pharmaceutically acceptable salt thereof.

51. The compound of claim 1, wherein the compound is of Formula (**XII-a**):

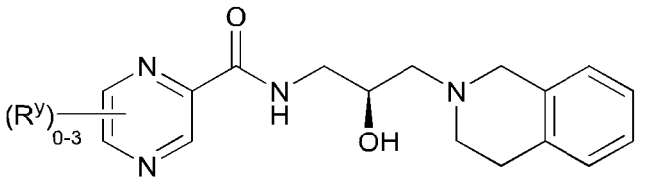


XII-a

or a pharmaceutically acceptable salt thereof.

52. The compound of claim 1, wherein the compound is of Formula (**XII-b**):

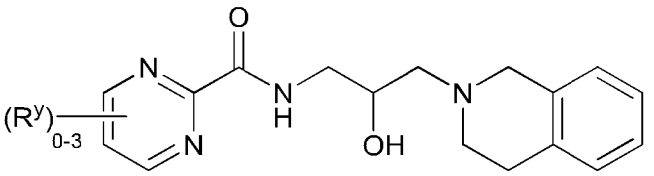
Date Reçue/Date Received 2020-11-02



XII-b

or a pharmaceutically acceptable salt thereof.

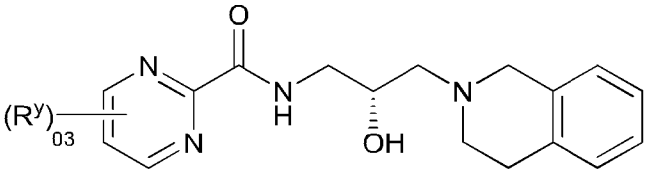
53. The compound of claim 1, wherein the compound is of Formula (**XIII**):



XIII

or a pharmaceutically acceptable salt thereof.

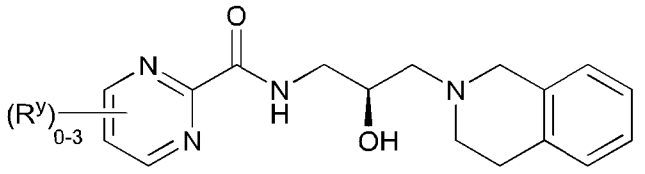
54. The compound of claim 1, wherein the compound is of Formula (**XIII-a**):



XIII-a

or a pharmaceutically acceptable salt thereof.

55. The compound of claim 1, wherein the compound is of Formula (**XIII-b**):

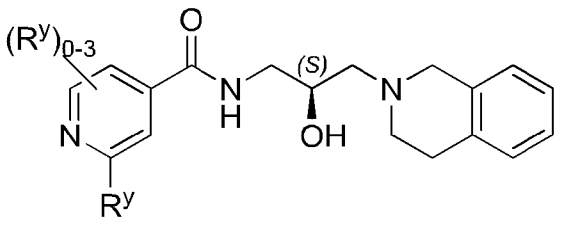


XIII-b

or a pharmaceutically acceptable salt thereof.

56. The compound of claim 1, wherein the compound is of Formula (**XV**):

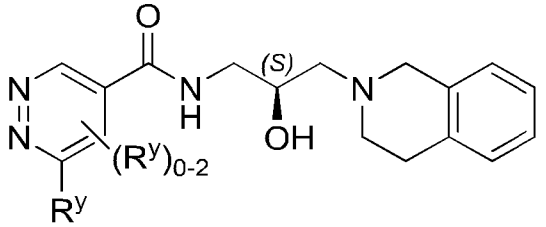
Date Reçue/Date Received 2020-11-02



XV

or a pharmaceutically acceptable salt thereof.

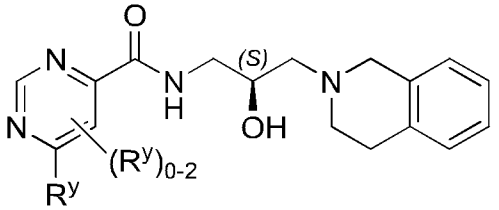
57. The compound of claim 1, wherein the compound is of Formula (**XVI**):



XVI

or a pharmaceutically acceptable salt thereof.

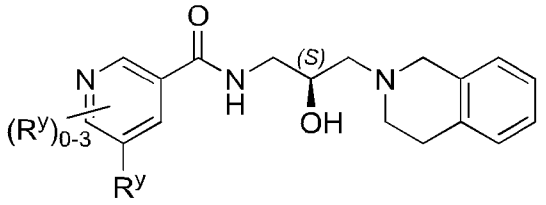
58. The compound of claim 1, wherein the compound is of Formula (**XVII**):



XVII

or a pharmaceutically acceptable salt thereof.

59. The compound of claim 1, wherein the compound is of Formula (**XVIII**):

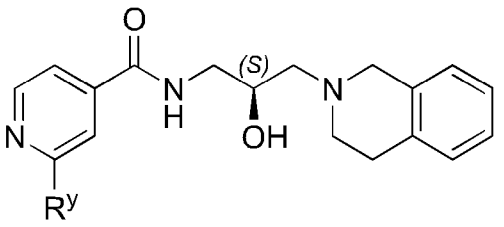


XVIII

or a pharmaceutically acceptable salt thereof.

Date Reçue/Date Received 2020-11-02

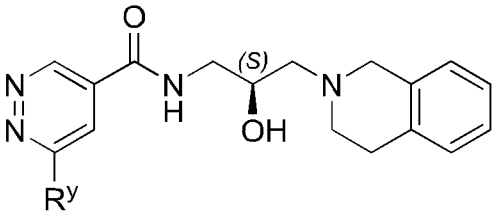
60. The compound of claim 1, wherein the compound is of Formula (**XV-a**):



XV-a

or a pharmaceutically acceptable salt thereof.

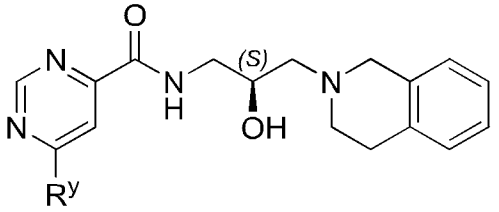
61. The compound of claim 1, wherein the compound is of Formula (**XVI-a**):



XVI-a

or a pharmaceutically acceptable salt thereof.

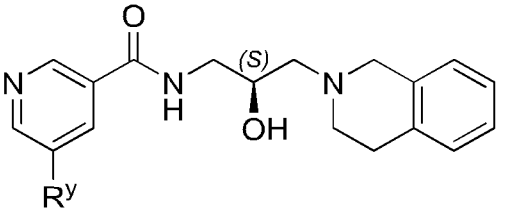
62. The compound of claim 1, wherein the compound is of Formula (**XVII-a**):



XVII-a

or a pharmaceutically acceptable salt thereof.

63. The compound of claim 1, wherein the compound is of Formula (**XVIII-a**):



XVIII-a

or a pharmaceutically acceptable salt thereof.

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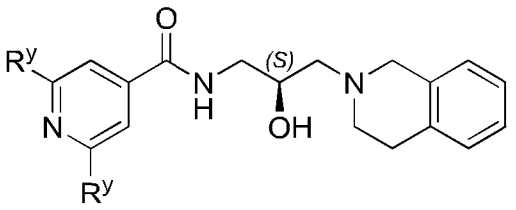
64. The compound of claim 1, wherein the compound is of Formula (**XV-b**):



XV-b

or a pharmaceutically acceptable salt thereof.

65. The compound of any one of claims 1-19 and 21-64, wherein at least one R^y is heteroaryl or heterocyclyl.

66. The compound of claim 65, wherein at least one R^y is 5- to 6-membered heteroaryl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

67. The compound of claim 66, wherein at least one R^y is a 6-membered heteroaryl having 1-3 nitrogens.

68. The compound of claim 67, wherein at least one R^y is pyridyl.

69. The compound of claim 66, wherein at least one R^y is a 5-membered heteroaryl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

70. The compound of claim 69, wherein at least one R^y is optionally substituted pyrazole.

71. The compound of claim 69, wherein at least one R^y is pyrrole.

72. The compound of claim 65, wherein at least one R^y is a 5- to 6-membered heterocyclyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

73. The compound of claim 72, wherein at least one R^y is a 5-membered heterocyclyl having one heteroatom selected from nitrogen, oxygen, and sulfur.

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74. The compound of claim 73, wherein at least one R^y is optionally substituted pyrrolidine.

75. The compound of claim 72, wherein at least one R^y is a 6-membered heterocyclyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

76. The compound of claim 75, wherein at least one R^y is optionally substituted piperazine.

77. The compound of claim 75, wherein at least one R^y is morpholine.

78. The compound of any one of claims 1-19 and 21-64, wherein at least one R^y is optionally substituted aliphatic.

79. The compound of claim 78, wherein at least one R^y is optionally substituted C_{1-6} alkyl.

80. The compound of claim 79, wherein at least one R^y is C_{1-6} alkyl substituted with an aryl, heteroaryl, or heterocyclyl.

81. The compound of claim 80, wherein at least one R^y is $-CH_2$-aryl, $-CH_2$-heteroaryl, or $-CH_2$-heterocyclyl.

82. The compound of any one of claims 1-19 and 21-64, wherein at least one R^y is $-N(R^B)_2$.

83. The compound of claim 82, wherein one R^B is optionally substituted heterocyclyl, and the other R^B is C_{1-4} alkyl.

84. The compound of claim 82, wherein one R^B is optionally substituted heteroaryl, and the other R^B is C_{1-4} alkyl.

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85. The compound of claim 82, wherein one R^B is optionally substituted cycloalkyl, and the other R^B is C_{1-4} alkyl.

86. The compound of claim 82, wherein at least one R^y is $-NHR^B$.

87. The compound of claim 86, wherein R^B is optionally substituted heterocyclyl.

88. The compound of claim 86, wherein R^B is optionally substituted heteroaryl.

89. The compound of claim 86, wherein R^B is optionally substituted cycloalkyl.

90. The compound of any one of claims 1-19 and 21-64, wherein at least one R^y is $-SO_2N(R^B)_2$.

91. The compound of claim 90, wherein at least one R^y is $-SO_2NHR^B$.

92. The compound of claim 91, wherein at least one R^y is $-SO_2NH_2$.

93. The compound of any one of claims 1-19 and 21-64, wherein at least one R^y is $-C(O)N(R^B)_2$.

94. The compound of claim 93, wherein at least one R^y is $-C(O)NHR^B$.

95. The compound of claim 94, wherein at least one R^y is $-C(O)NH_2$.

96. The compound of any one of claims 1-19 and 21-64, wherein at least one R^y is $-NR^BC(O)R^A$.

97. The compound of claim 96, wherein at least one R^y is $-NHC(O)R^A$.

98. The compound of claim 97, wherein at least one R^y is $-NHC(O)CH_3$.

99. The compound of any one of claims 1-19 and 21-64, wherein at least one R^y is $-NR^BSO_2R^A$.

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100. The compound of claim 99, wherein at least one R^y is $-NHSO_2R^A$.

101. The compound of claim 100, wherein at least one R^y is $-NHSO_2CH_3$.

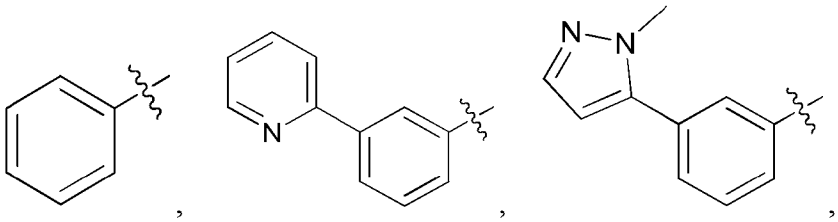
102. The compound of any one of claims 1-19 and 21-64, wherein at least one R^y is $-OR^A$.

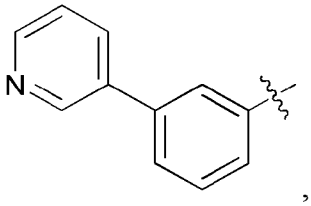
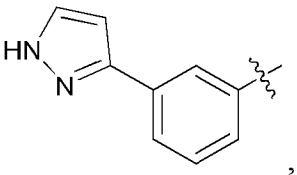
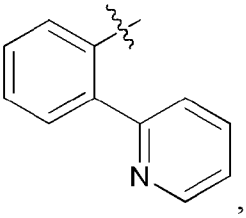
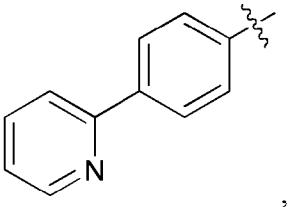
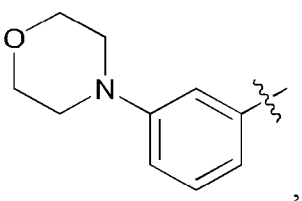
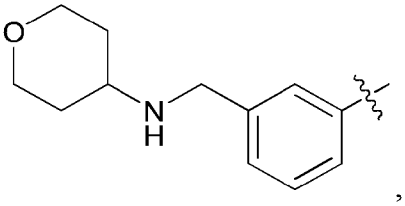
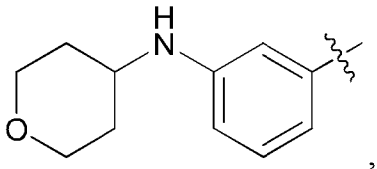
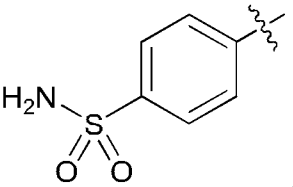
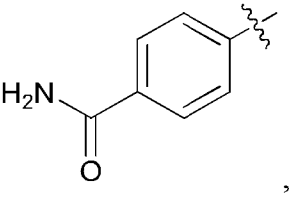
103. The compound of claim 102, wherein R^A is optionally substituted heterocyclyl.

104. The compound of claim 102, wherein R^A is optionally substituted heteroaryl.

105. The compound of claim 102, wherein R^A is optionally substituted cycloalkyl.

106. The compound of any one of claims 1-15, wherein Ar is selected from the group consisting of:



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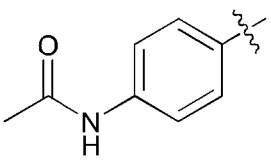
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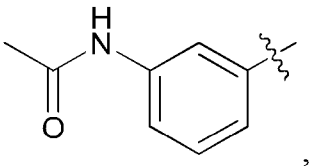
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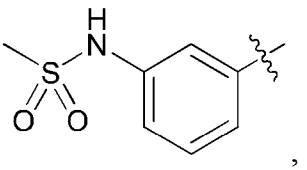
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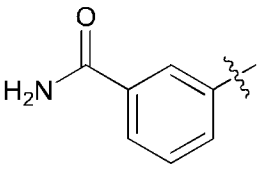
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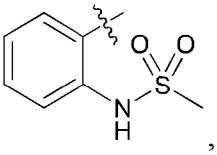
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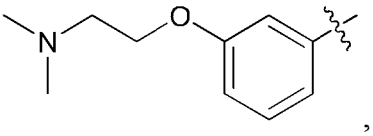
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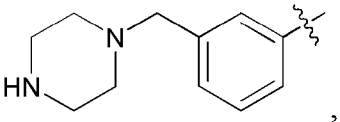
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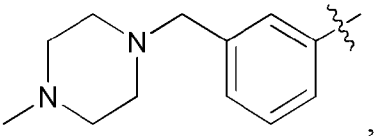
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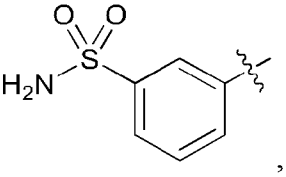
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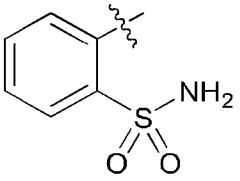
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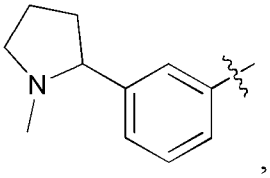
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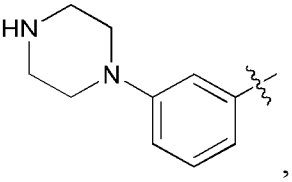
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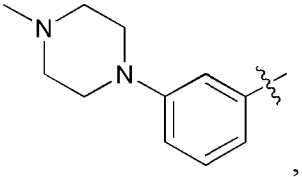
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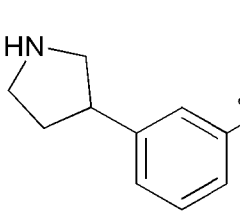
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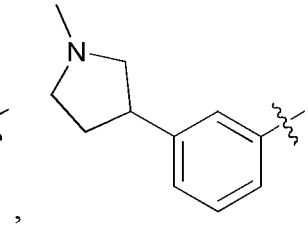
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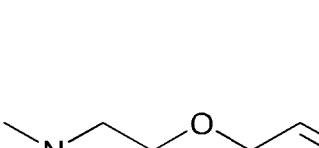
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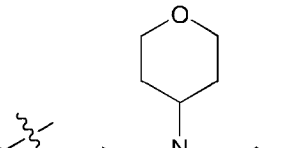
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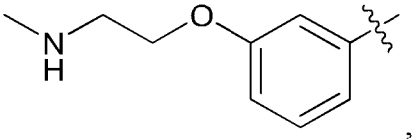
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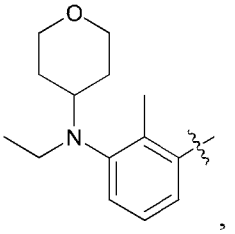
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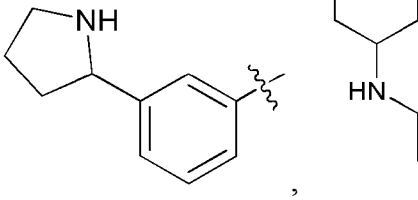
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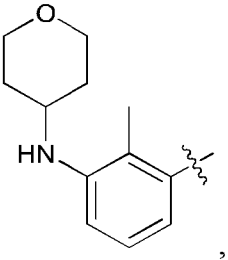
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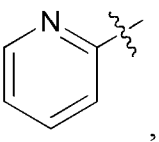
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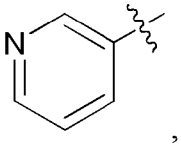
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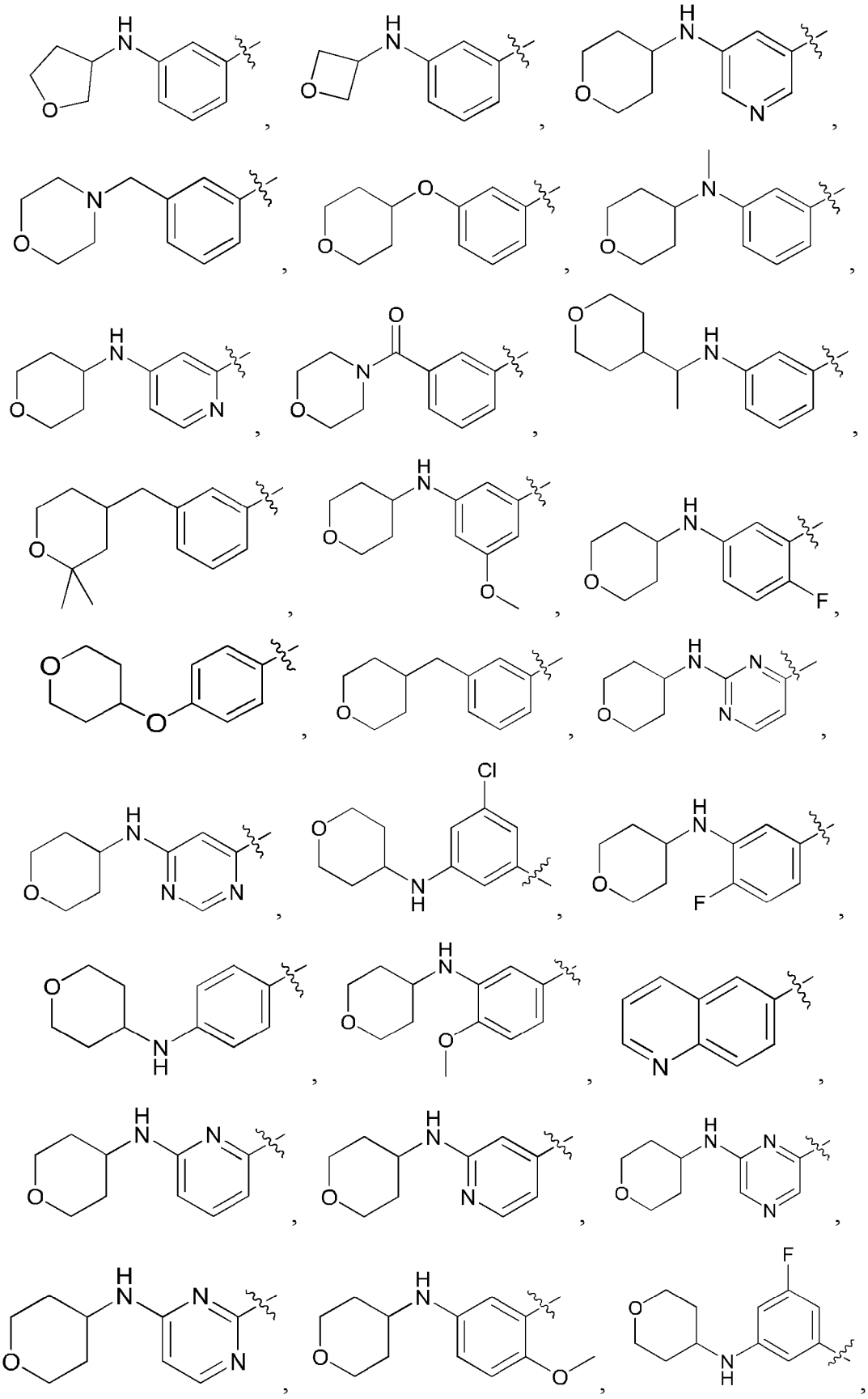

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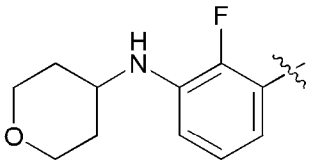
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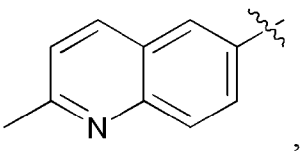
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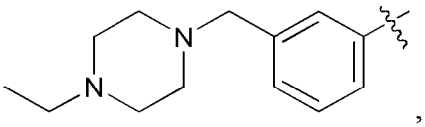
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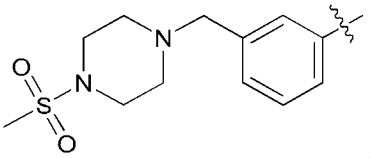
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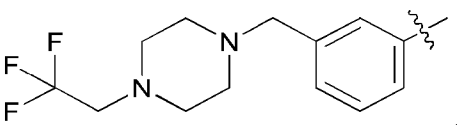
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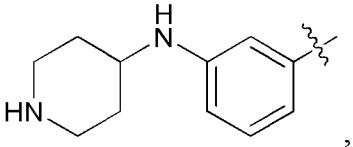
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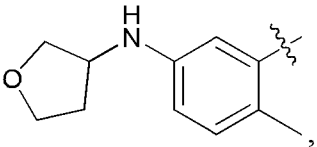
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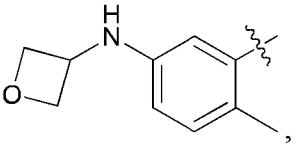
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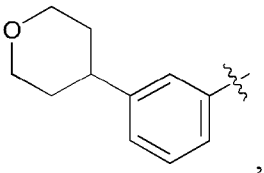
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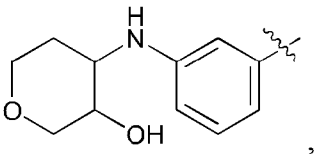
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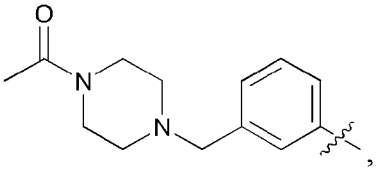
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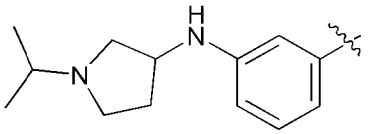
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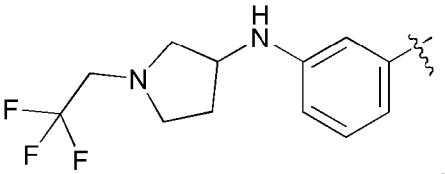
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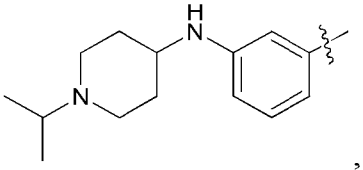
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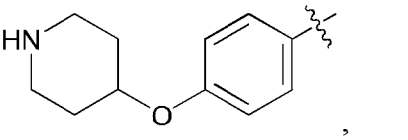
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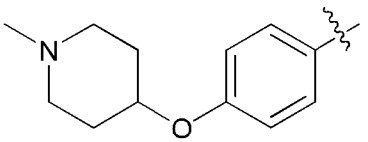
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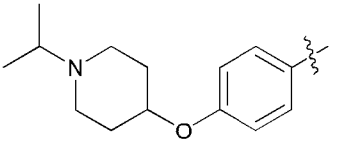
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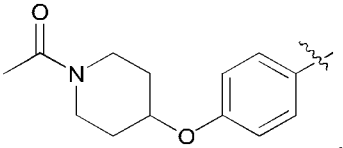
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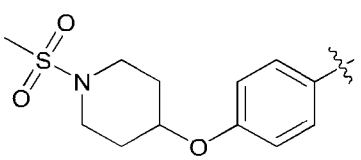
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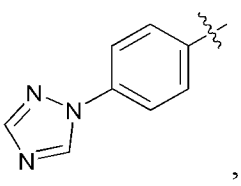
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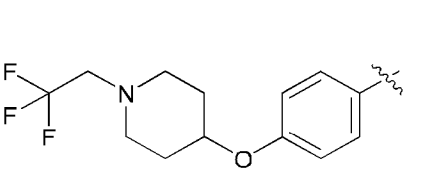
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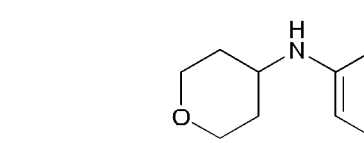
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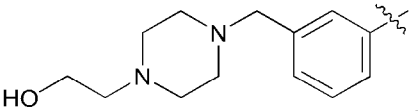
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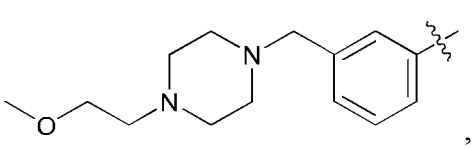
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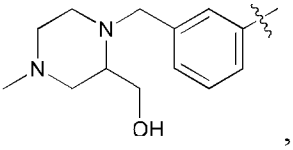
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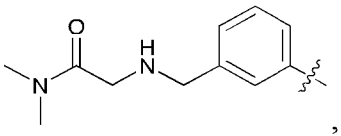
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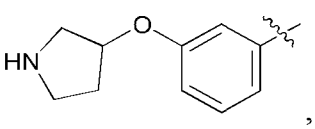
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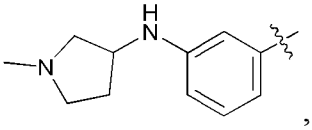
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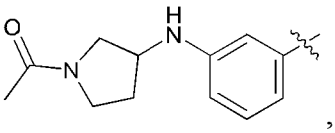
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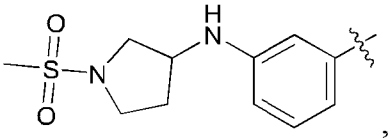
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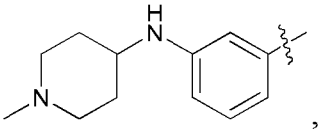
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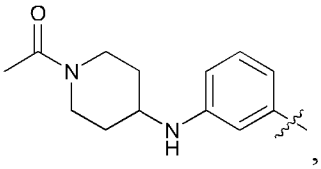
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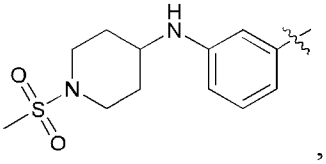
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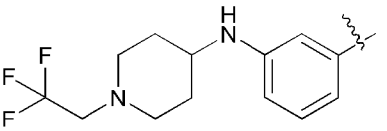
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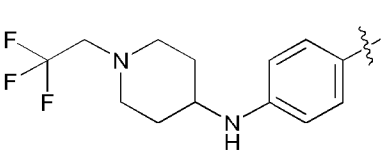
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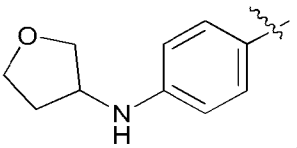
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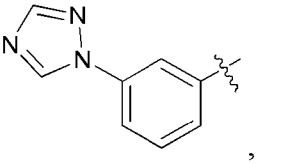
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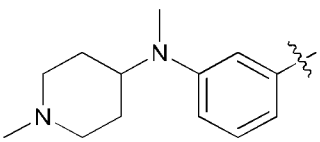
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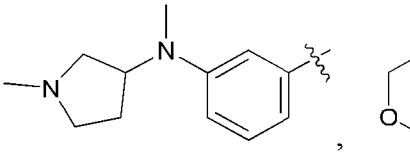
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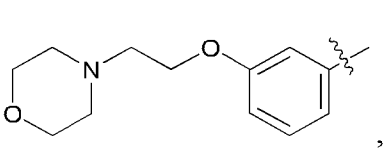
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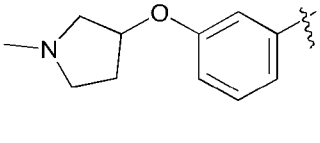
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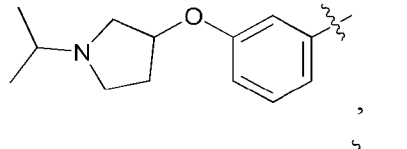
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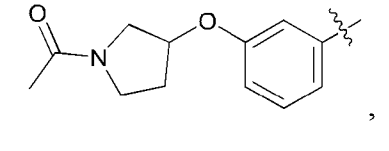
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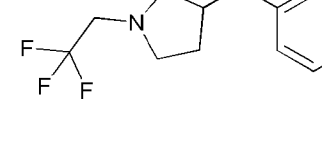
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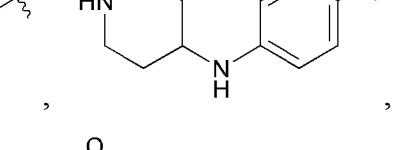
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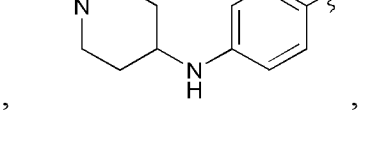
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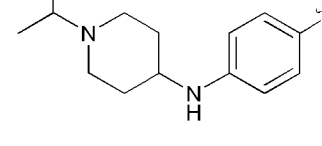
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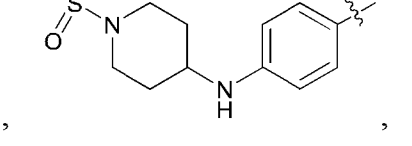
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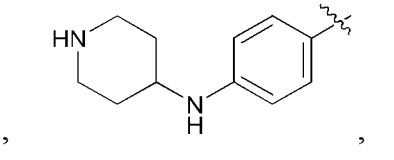
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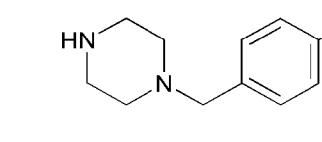
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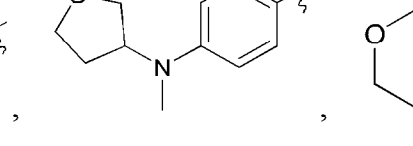
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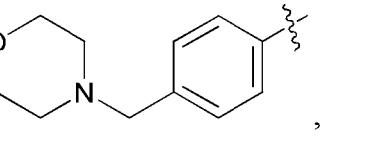
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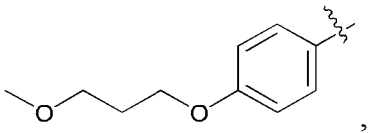
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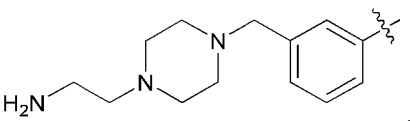
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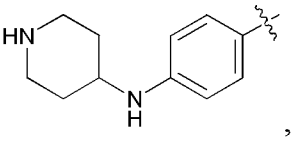
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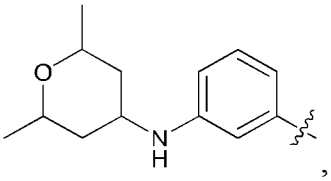
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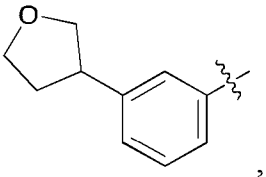
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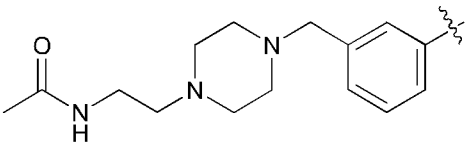
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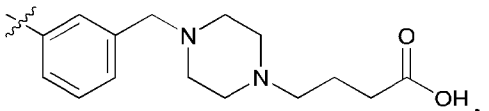
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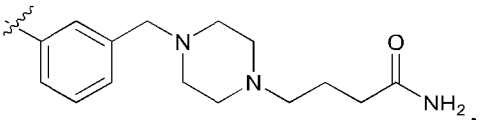
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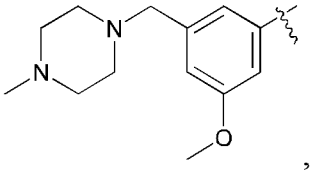
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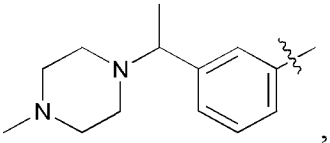
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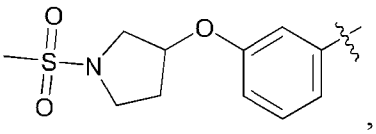
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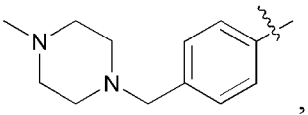
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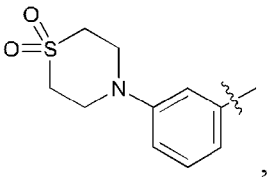
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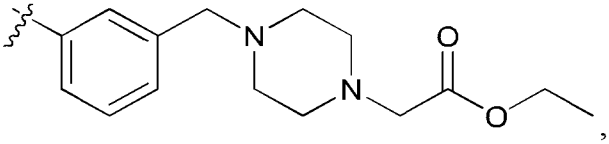
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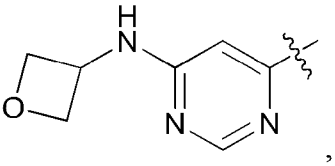
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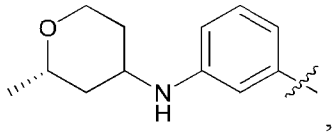
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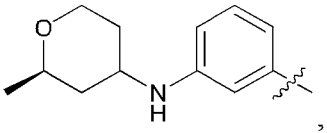
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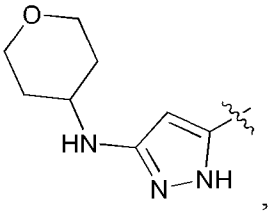
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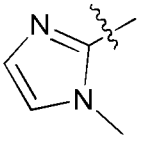
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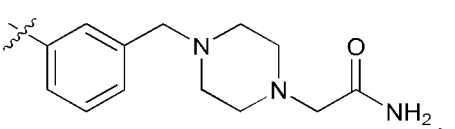
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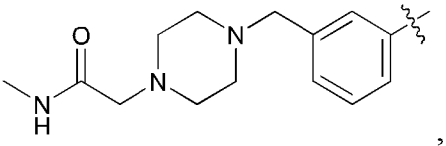
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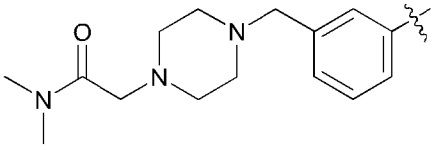
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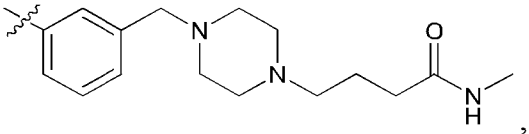
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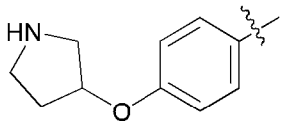
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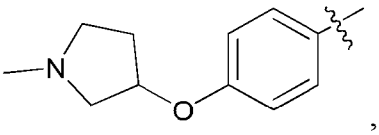
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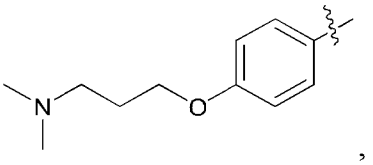
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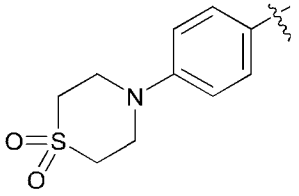
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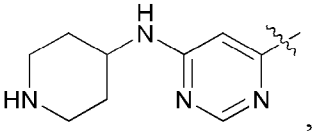
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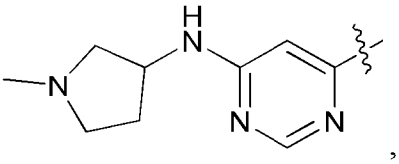
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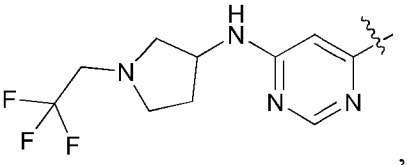
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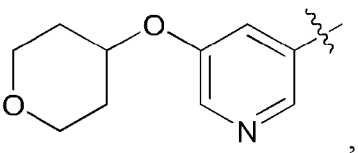
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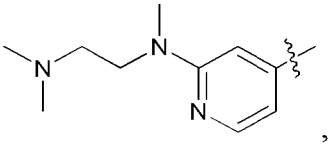
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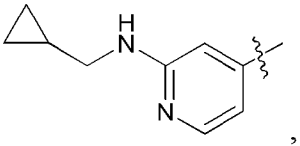
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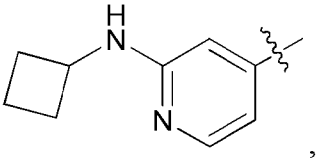
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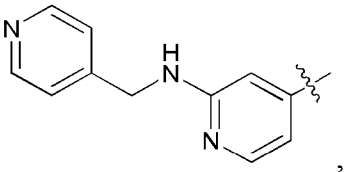
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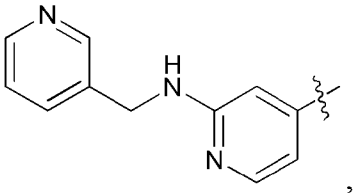
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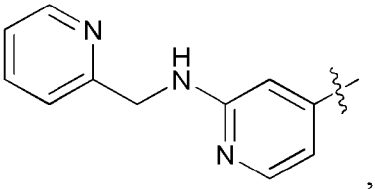
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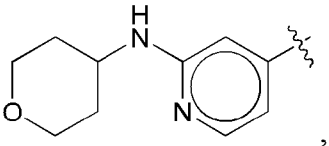
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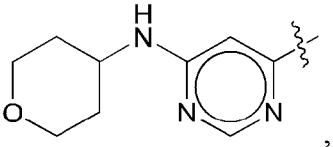
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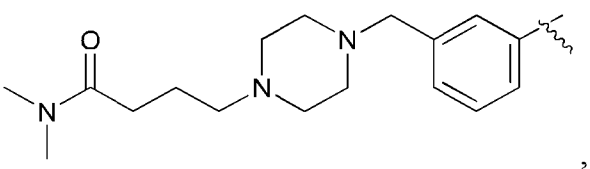
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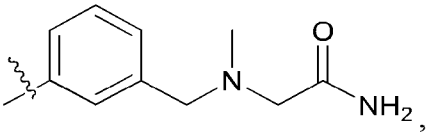
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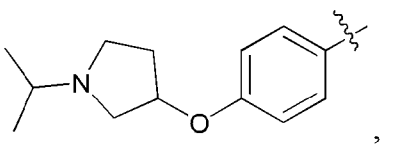
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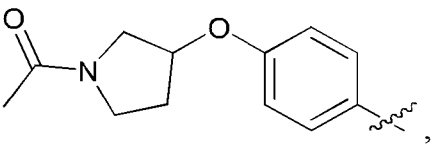
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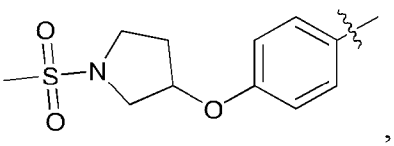
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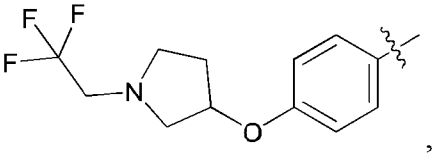
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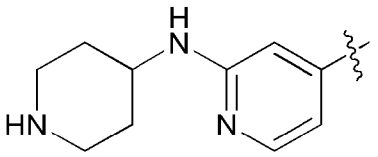
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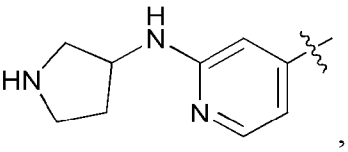
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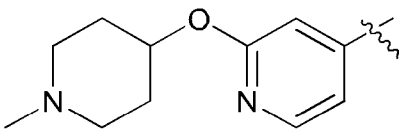
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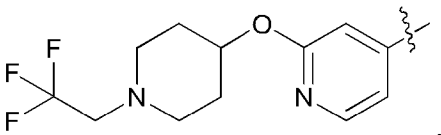
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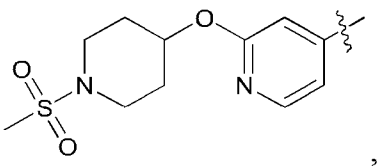
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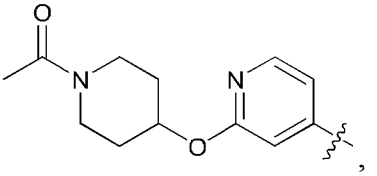
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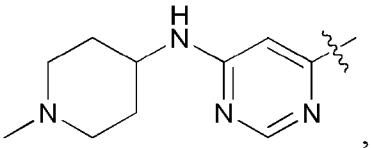
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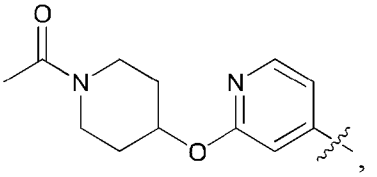
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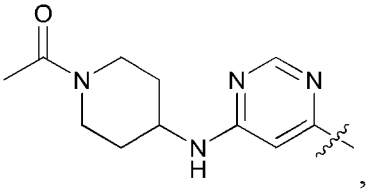
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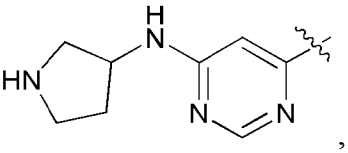
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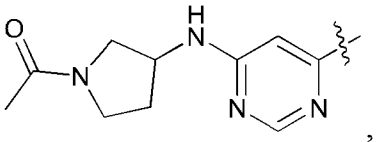
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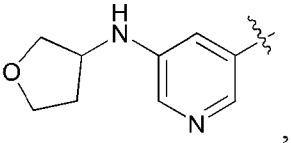
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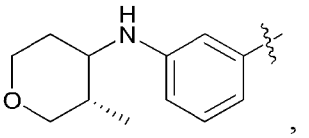
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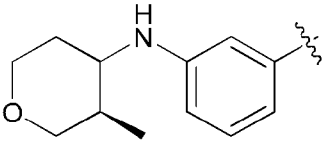
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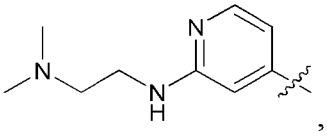
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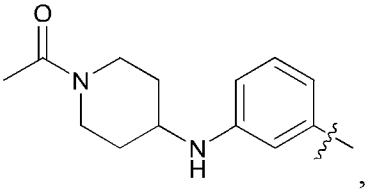
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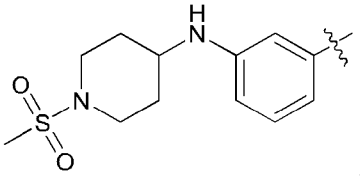
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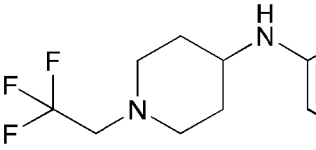
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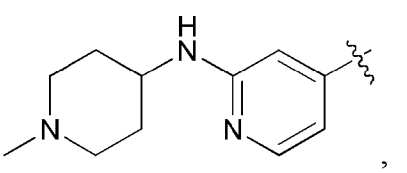
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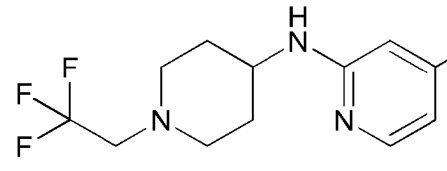
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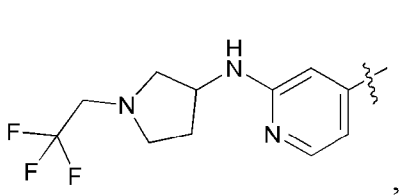
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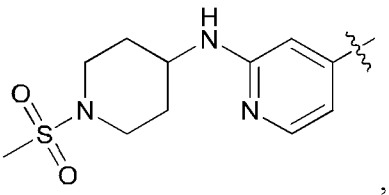
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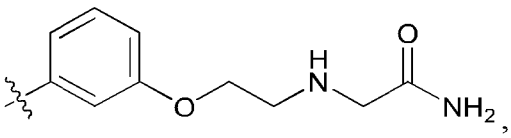
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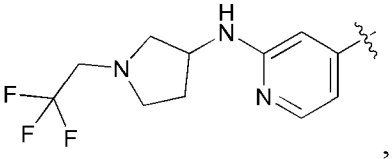
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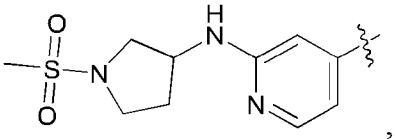
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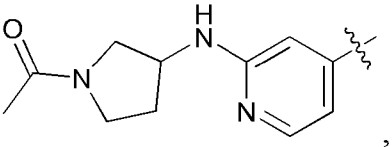
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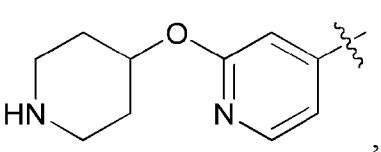
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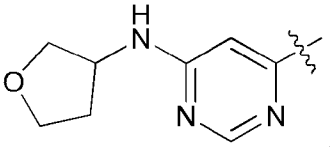
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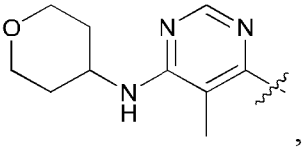
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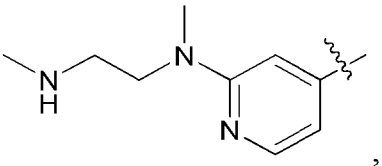
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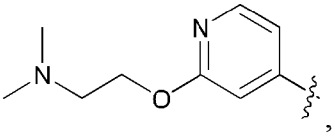
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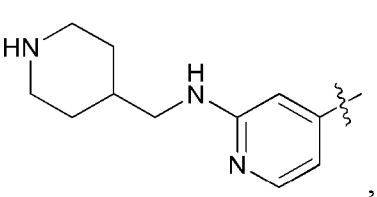
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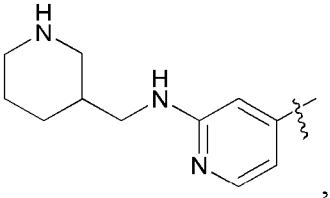
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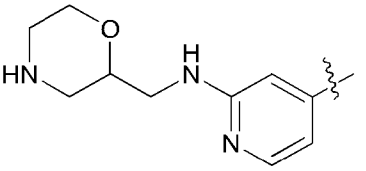
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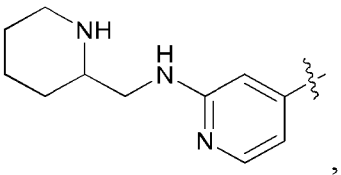
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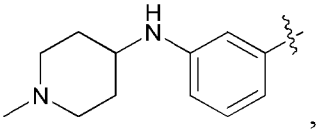
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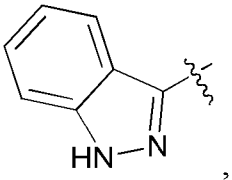
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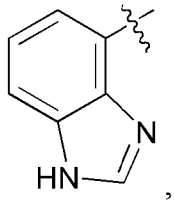
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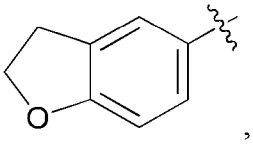
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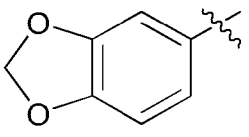
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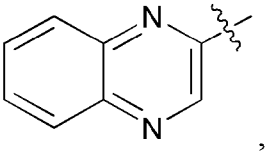
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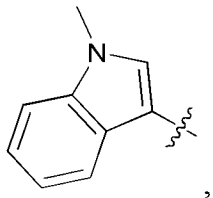
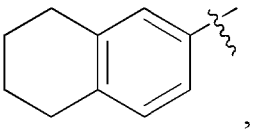
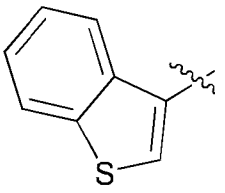
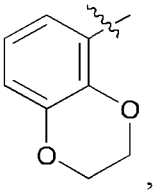
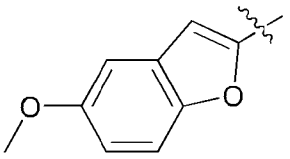
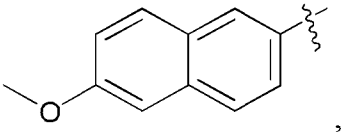
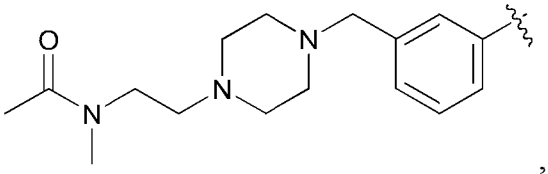
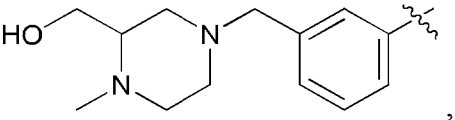
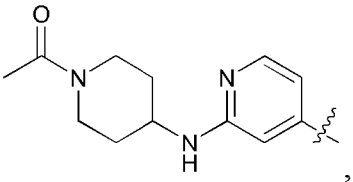
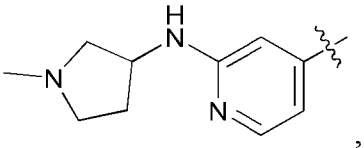
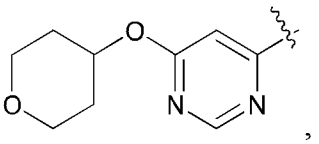
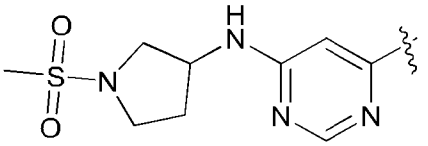
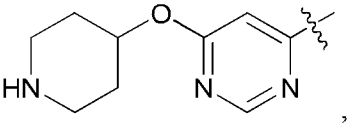
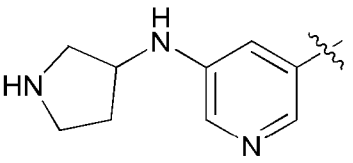
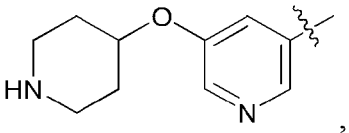
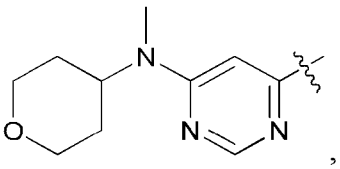
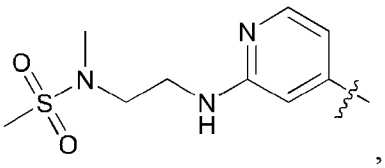
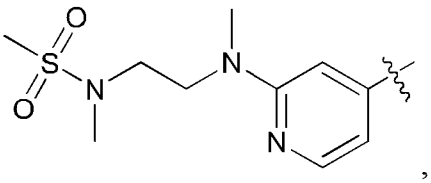
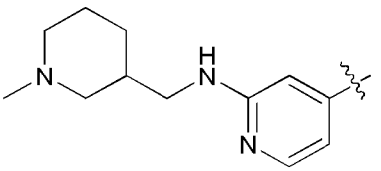
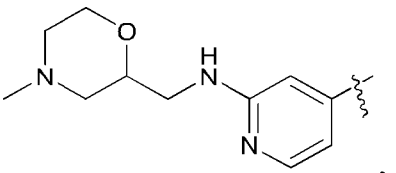
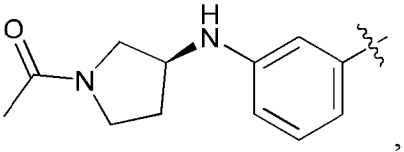
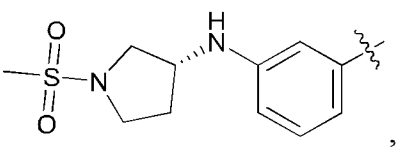

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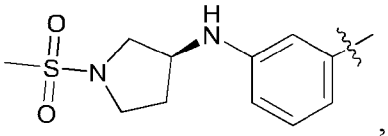
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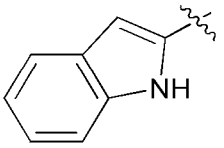
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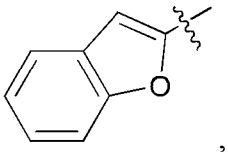
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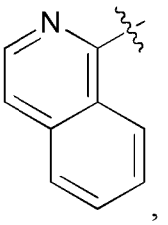
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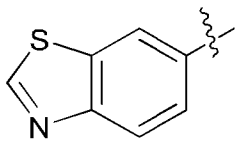
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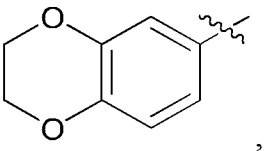
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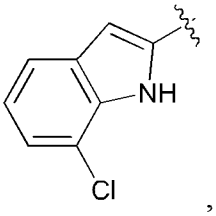
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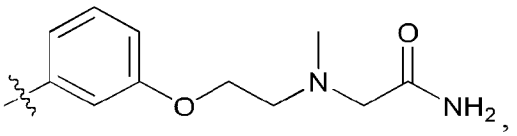
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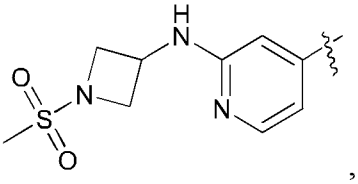
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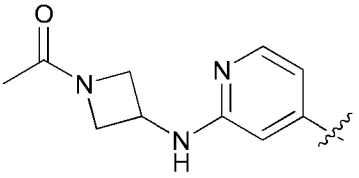
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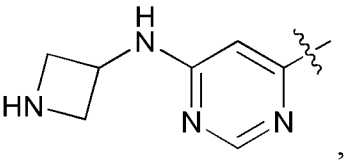
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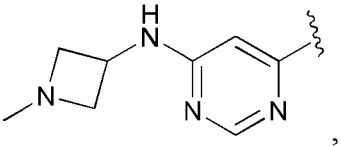
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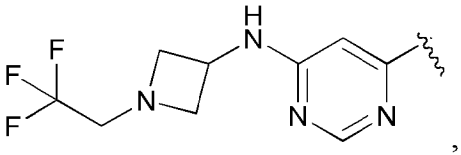
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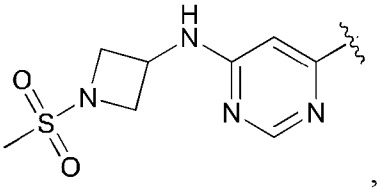
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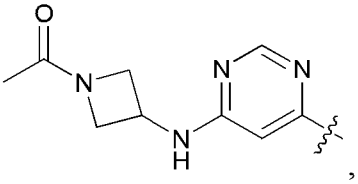
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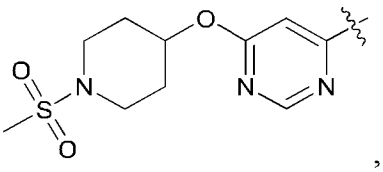
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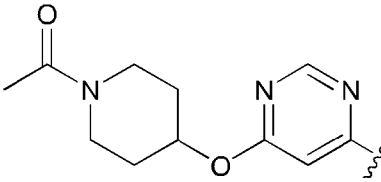
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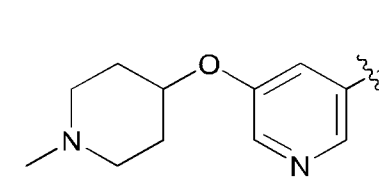
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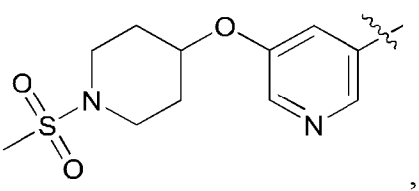
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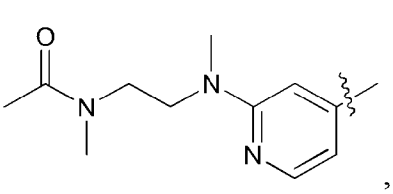
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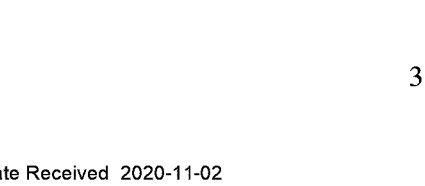
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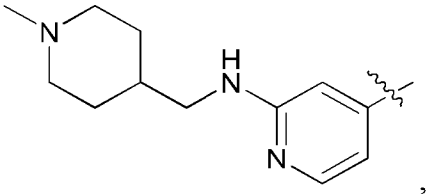
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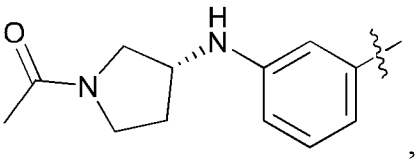
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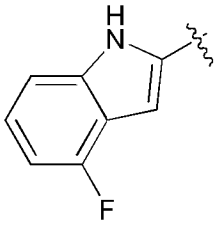
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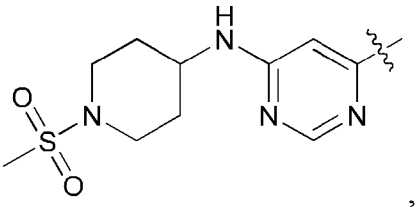
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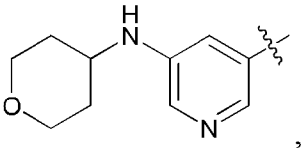
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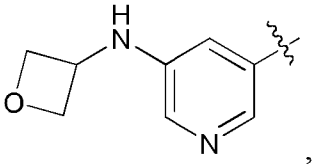
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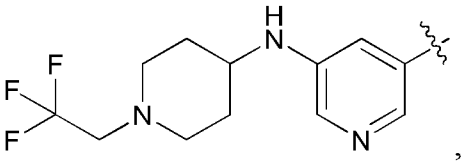
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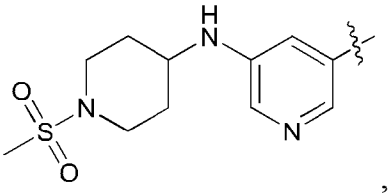
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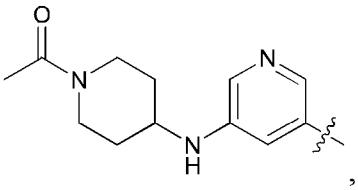
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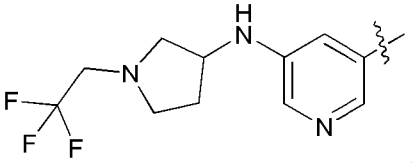
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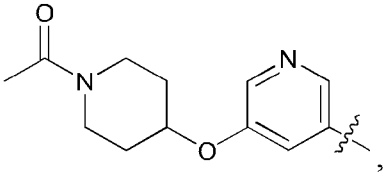
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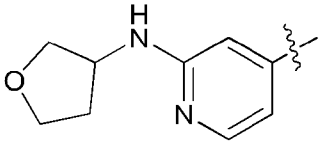
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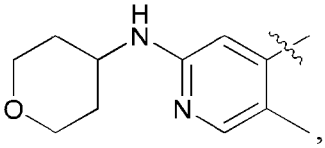
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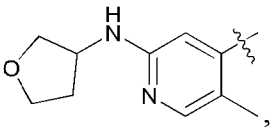
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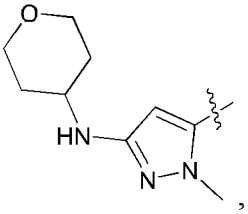
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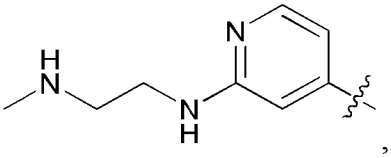
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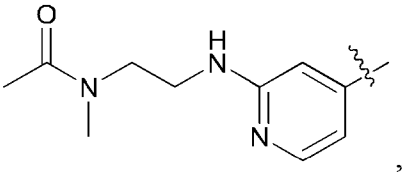
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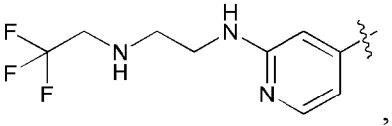
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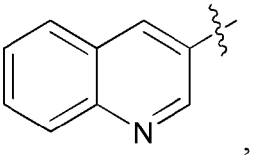
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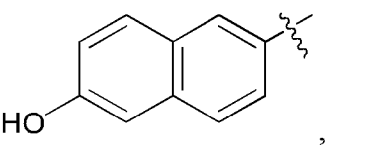
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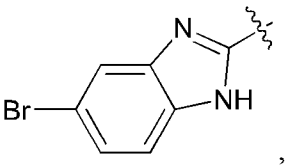
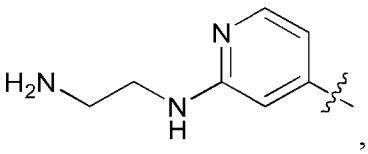
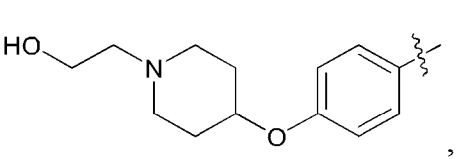
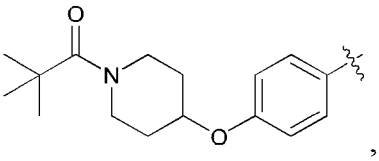
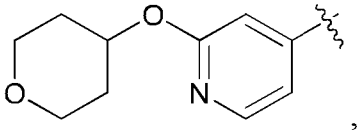
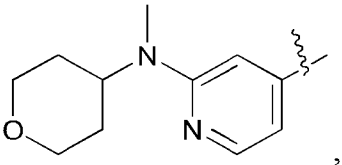
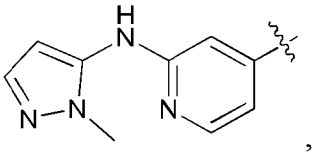
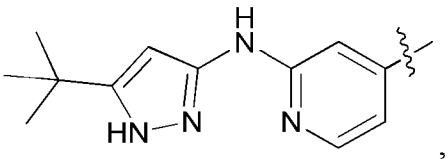
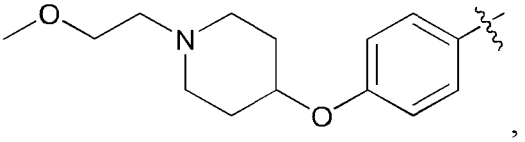
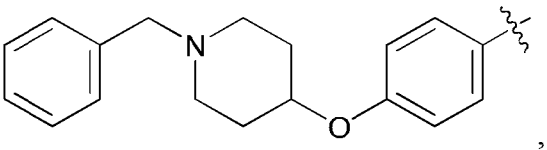
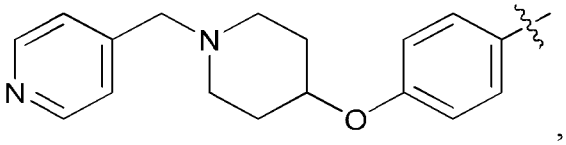
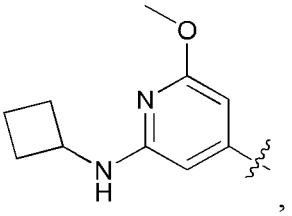
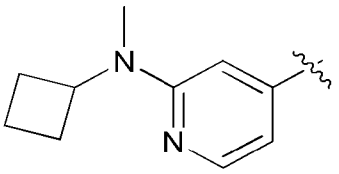
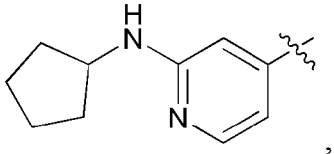
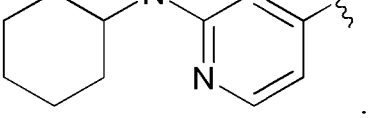

and

107. The compound of claim 1, wherein the compound is selected from the group consisting of the following compounds:

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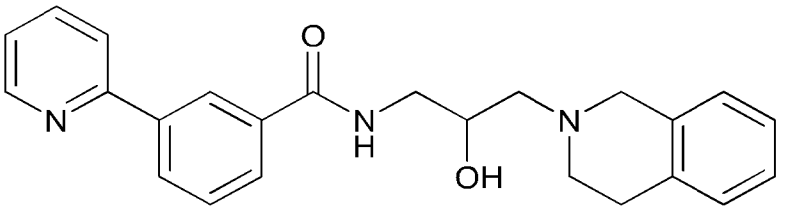
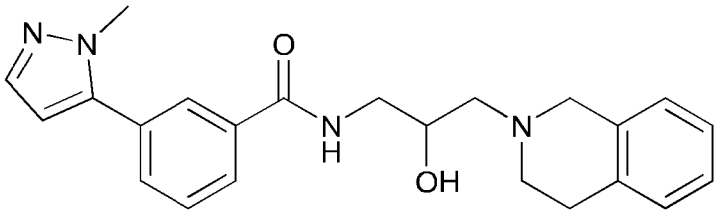
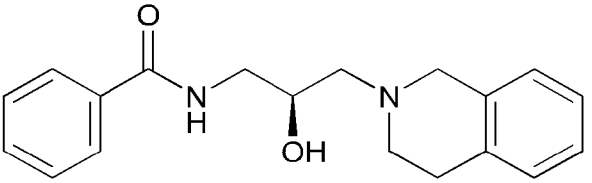
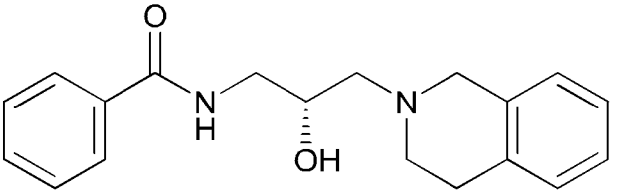
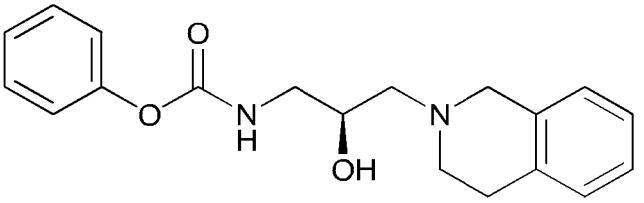
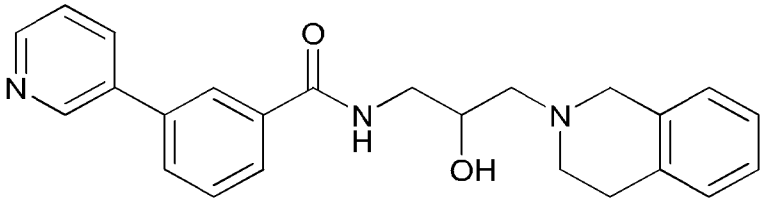
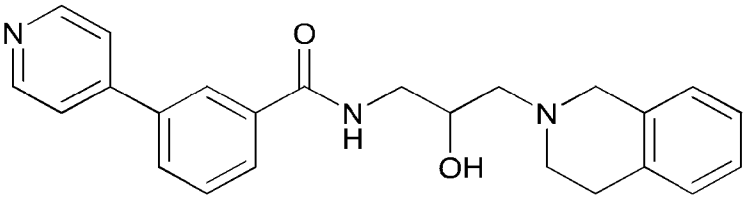
1	
2	
3	
4	
7	
8	
9	

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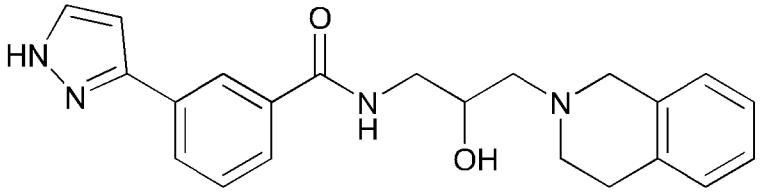
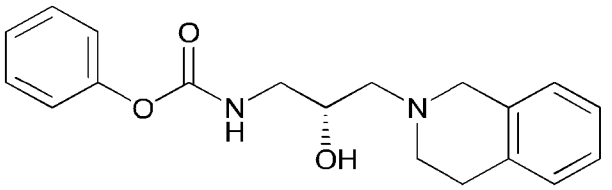
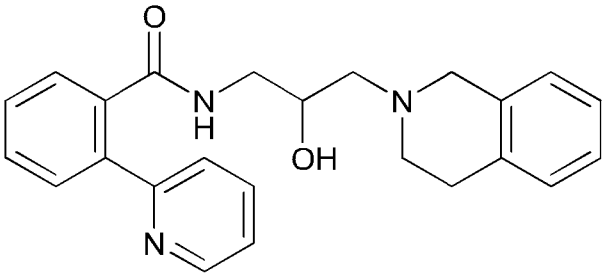
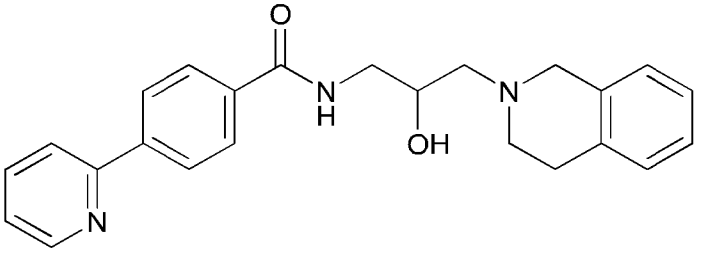
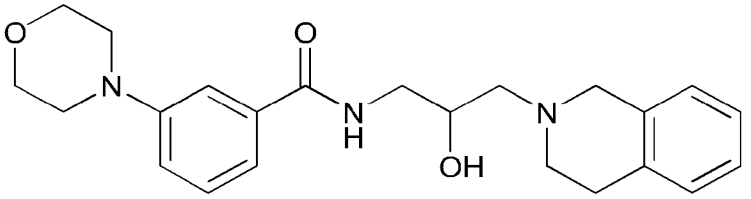
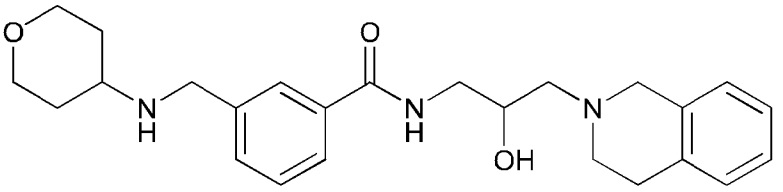
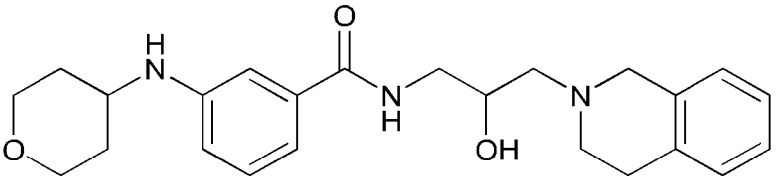
10	
11	
12	
13	
14	
15	
16	

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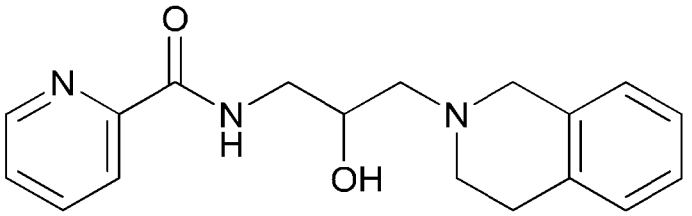
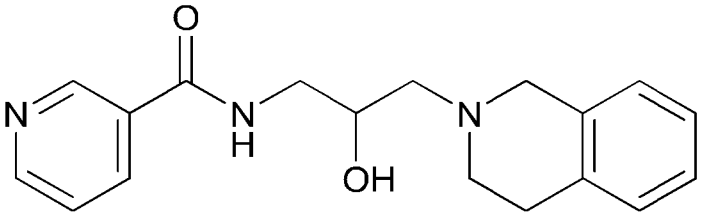
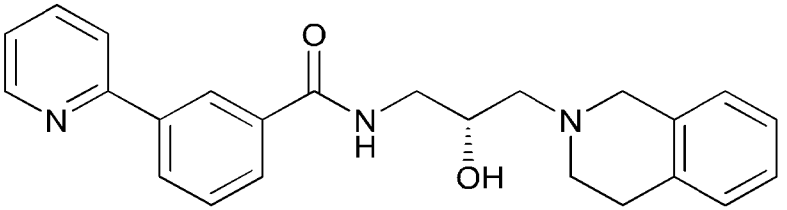
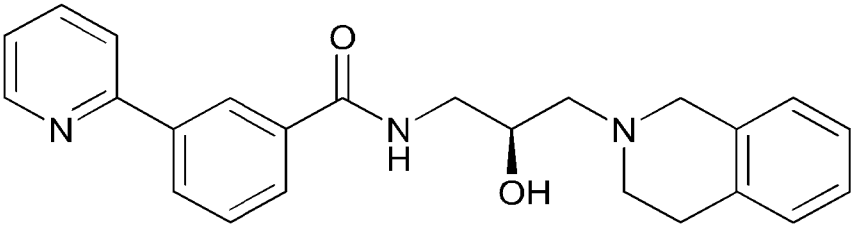
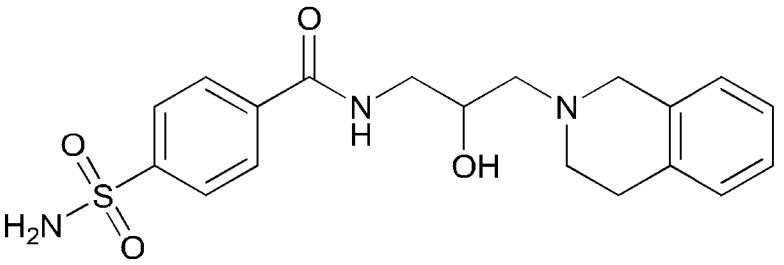
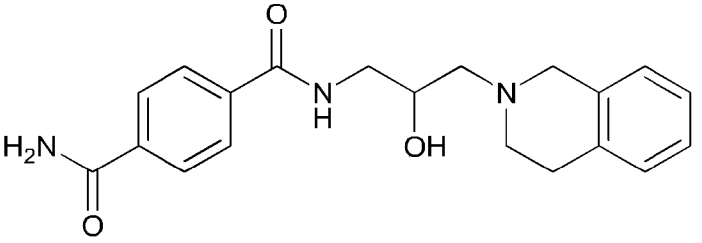
17	
18	
19	
20	
21	
22	

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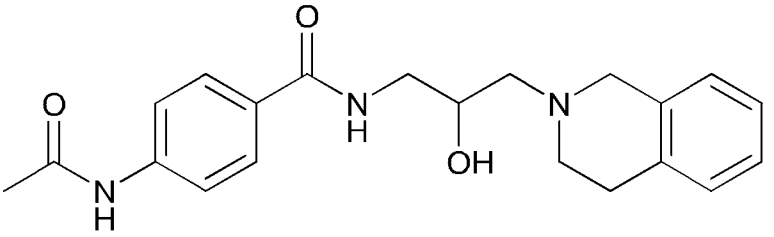
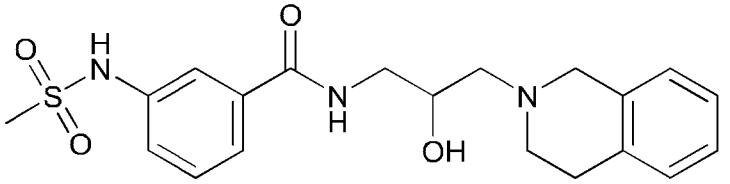
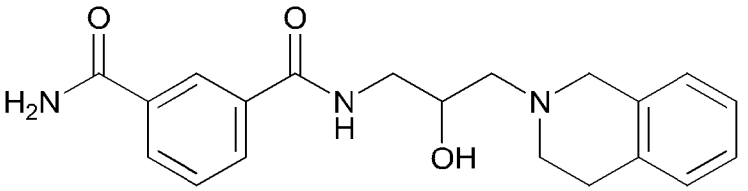
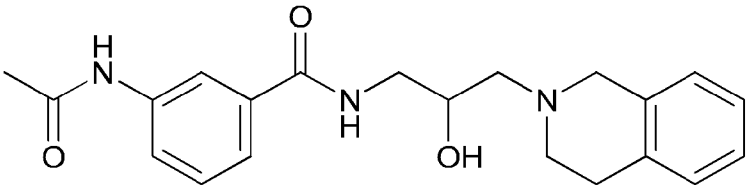
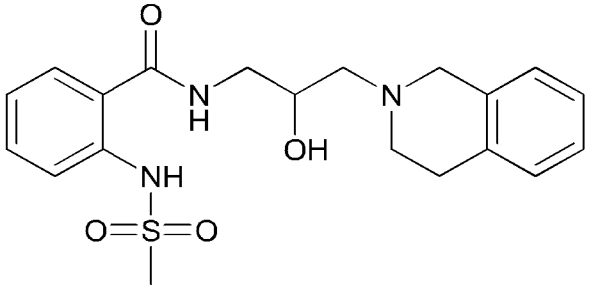
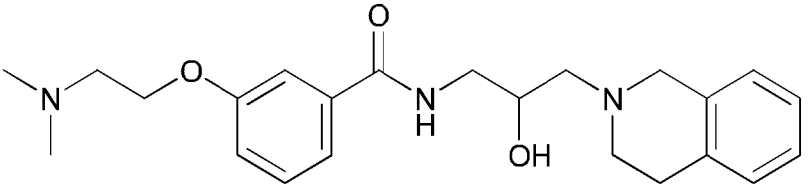
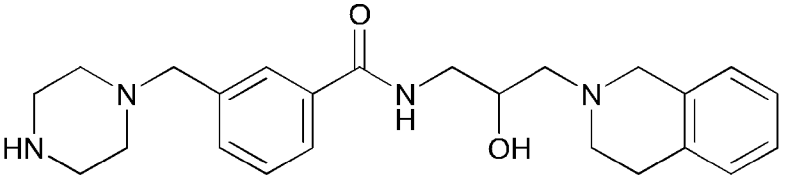
23	
24	
25	
26	
27	
28	
29	

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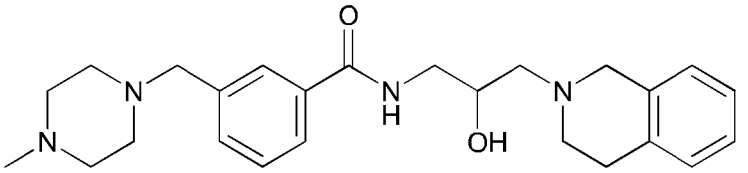
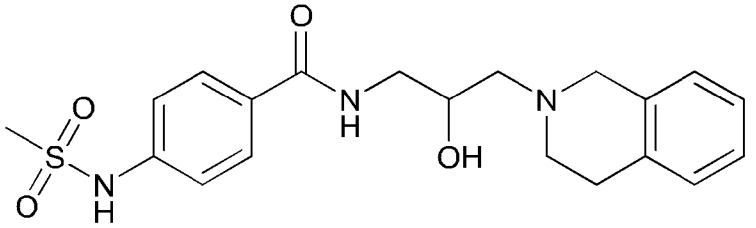
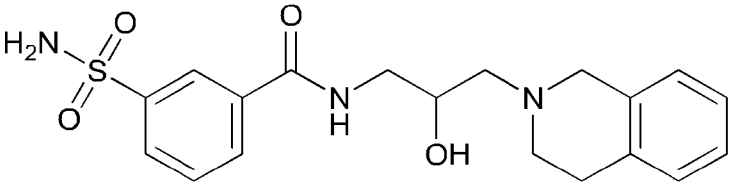
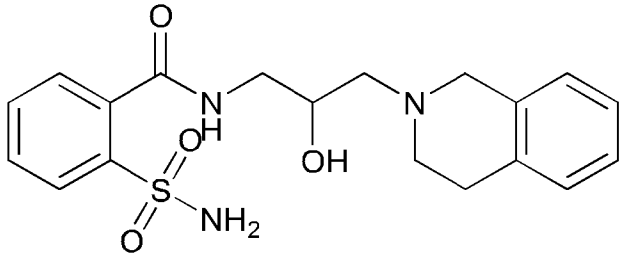
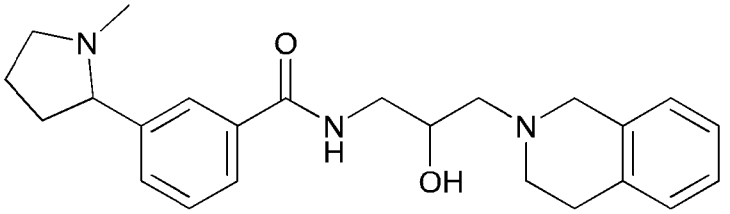
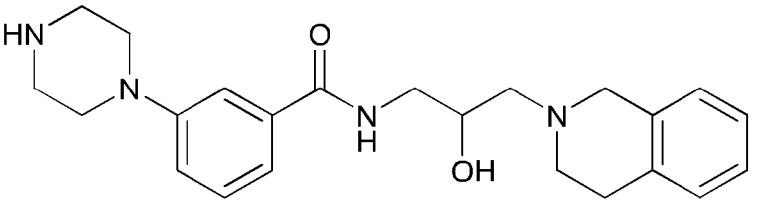
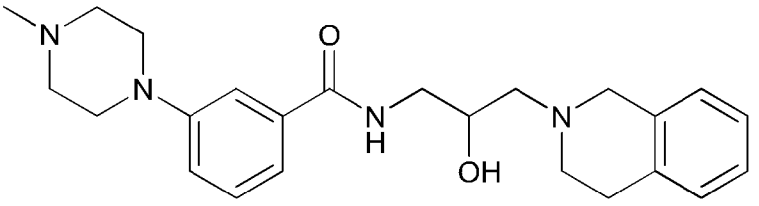
30	
31	
32	
33	
34	
35	
36	

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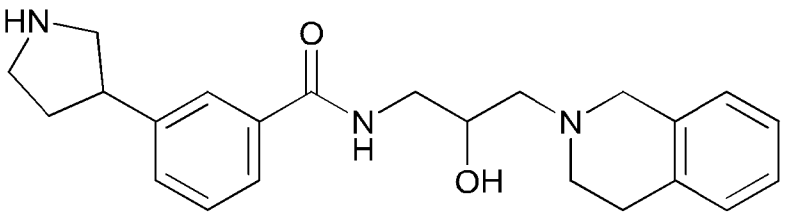
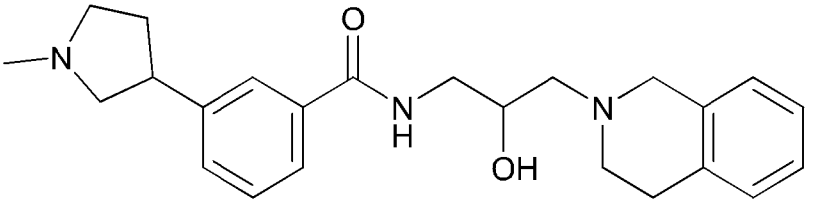
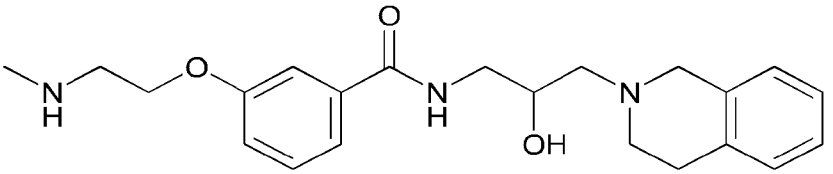
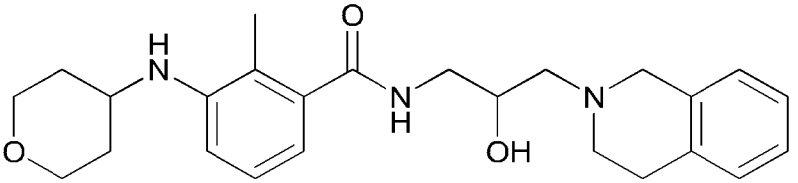
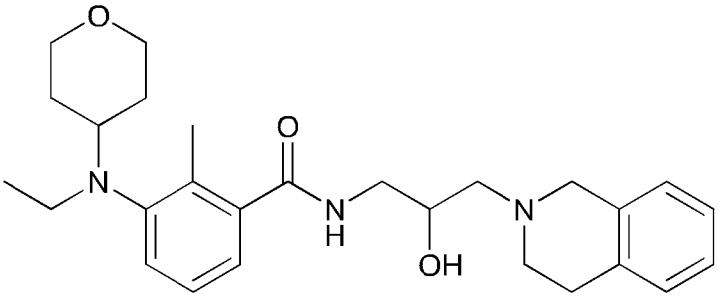
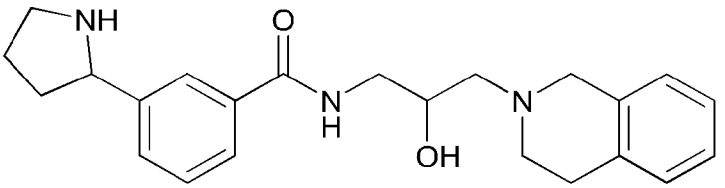
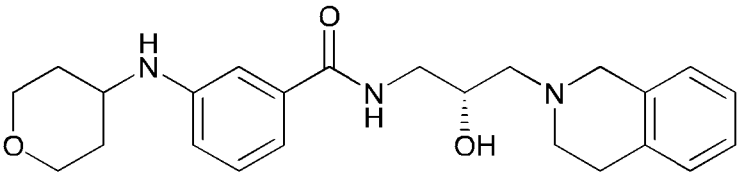
37	
38	
39	
40	
41	
42	
43	

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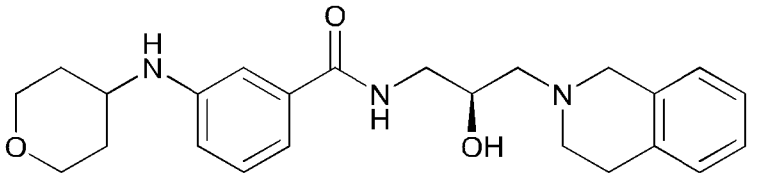
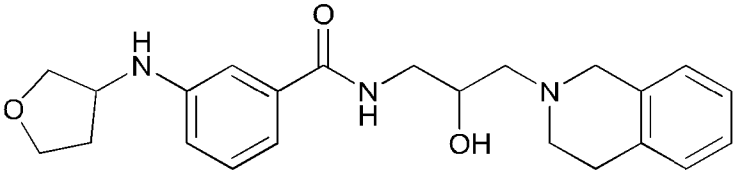
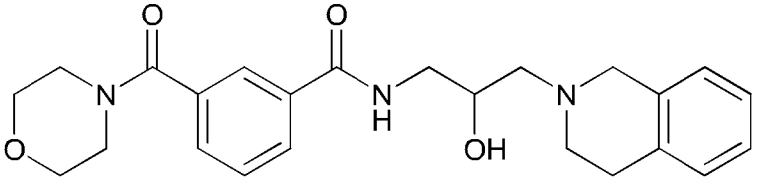
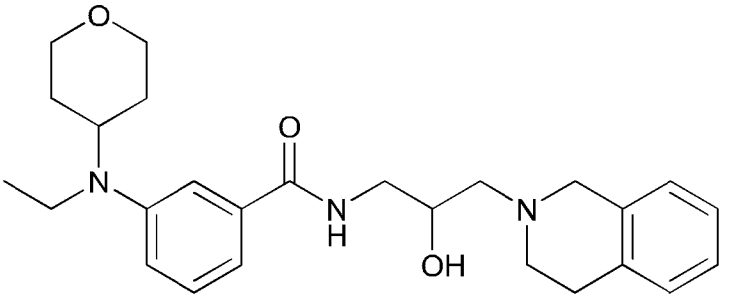
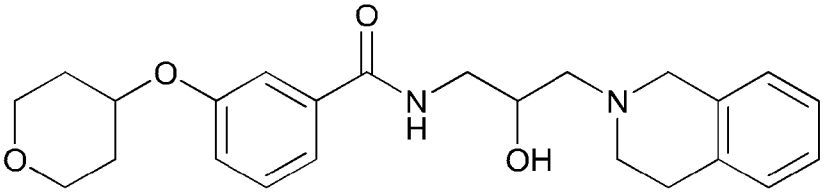
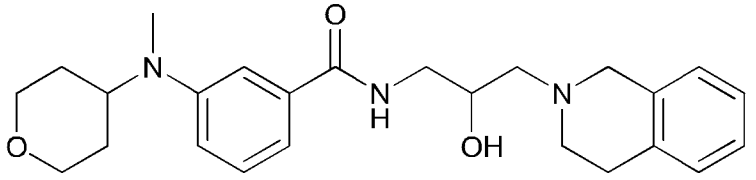
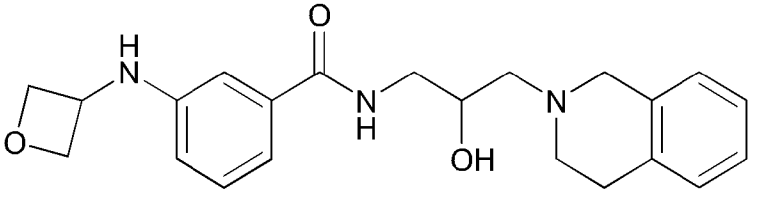
44	
45	
46	
47	
48	
49	
50	

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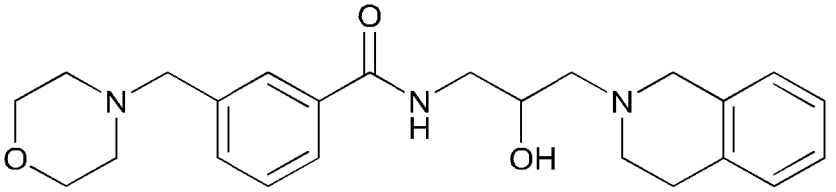
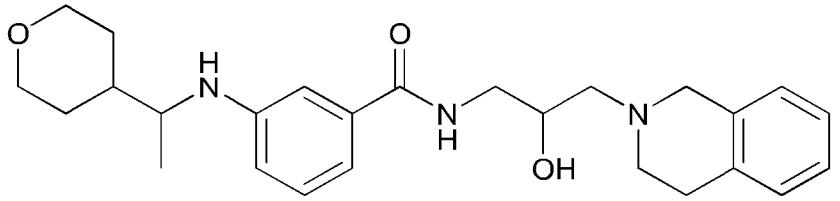
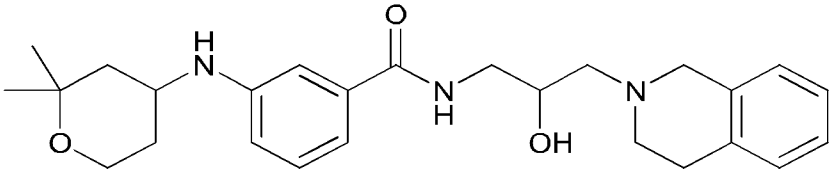
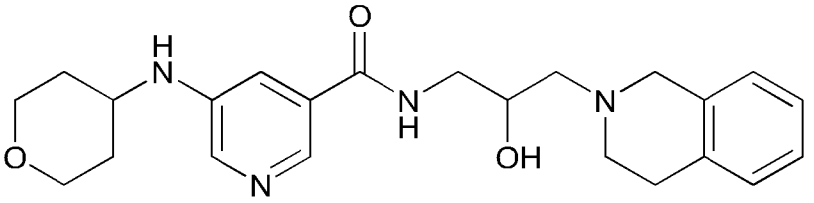
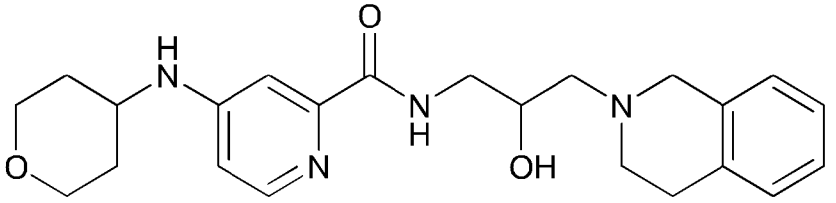
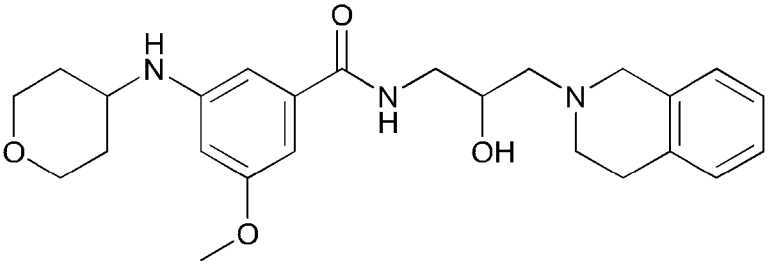
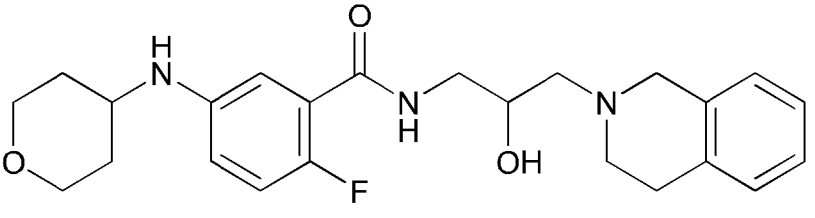
51	
52	
53	
54	
55	
56	
57	

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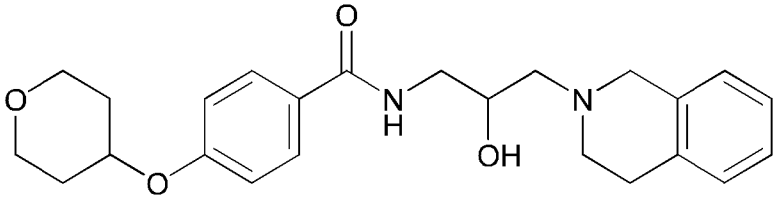
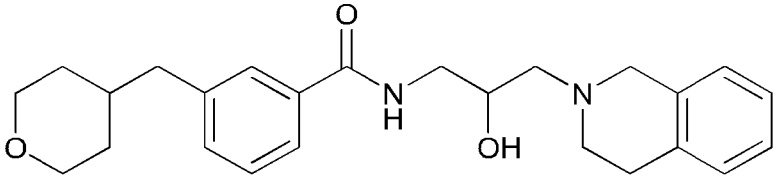
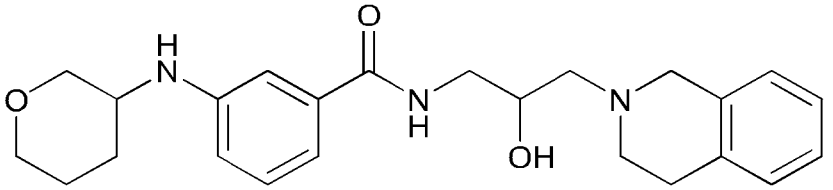
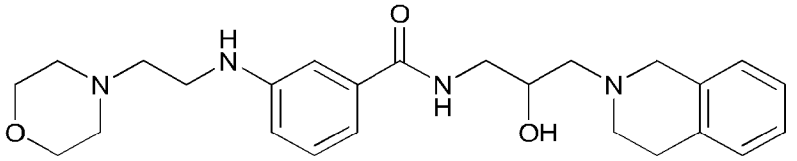
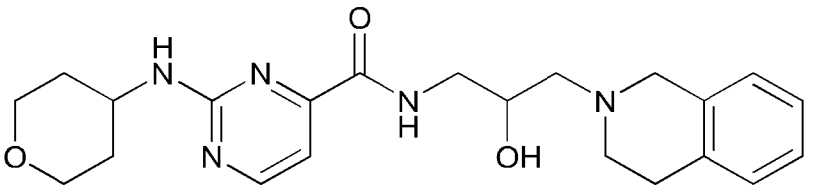
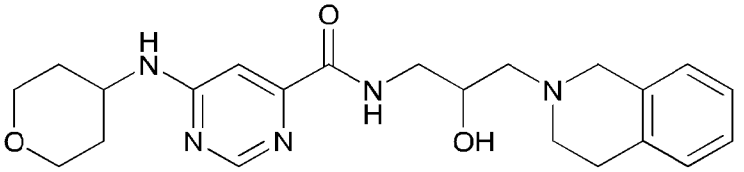
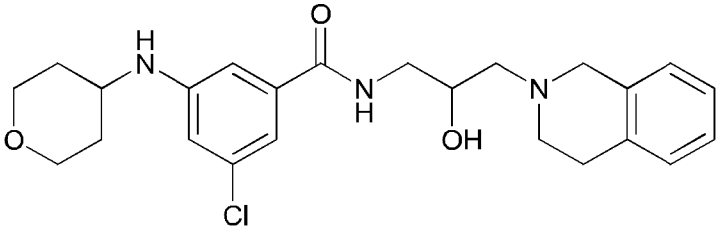
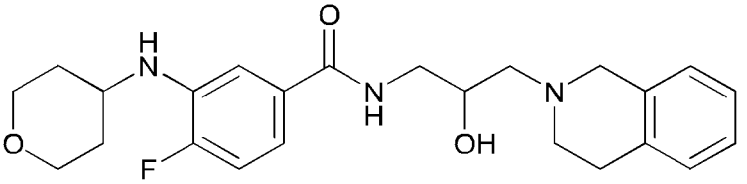
58	
59	
60	
61	
62	
63	
64	
65	

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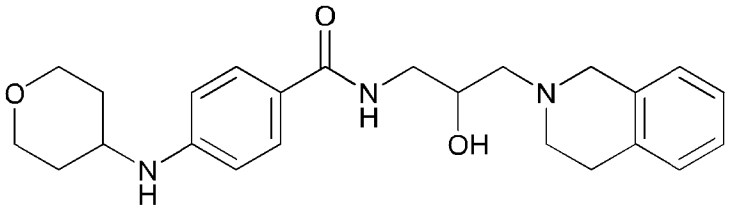
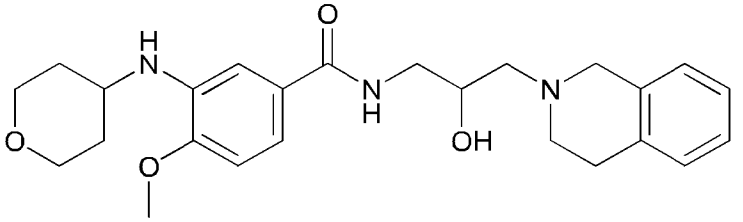
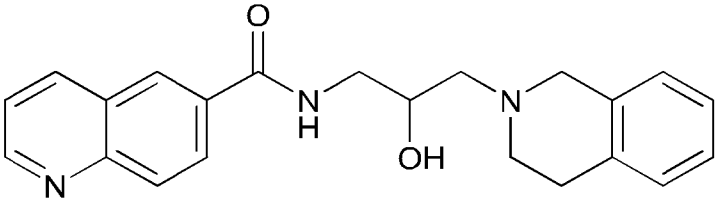
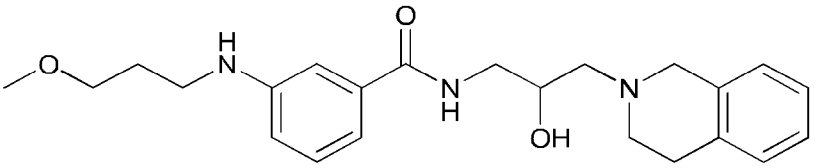
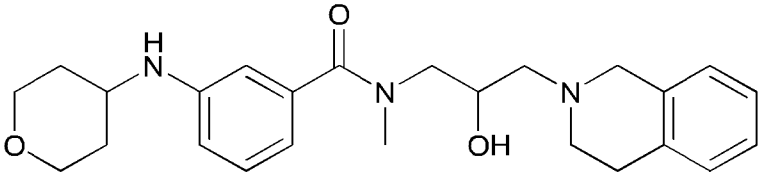
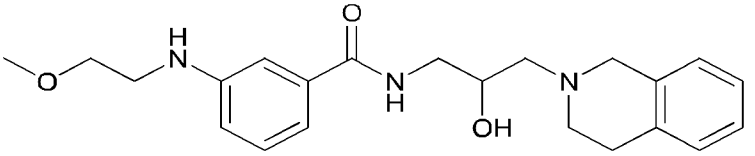
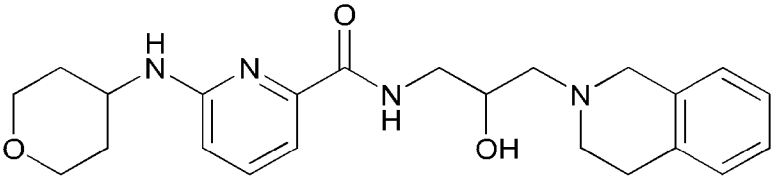
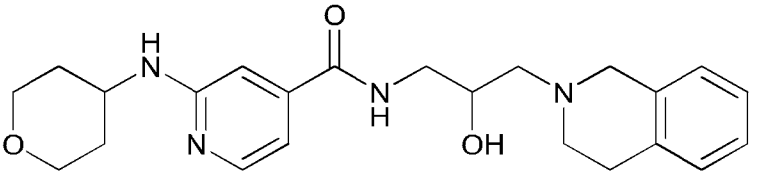
66	
67	
68	
69	
71	
72	
73	
74	

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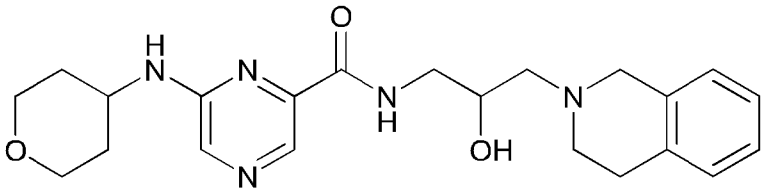
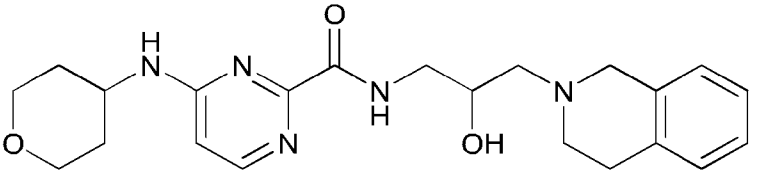
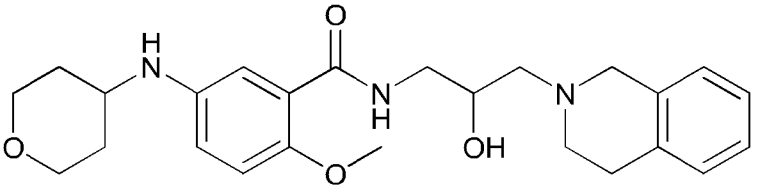
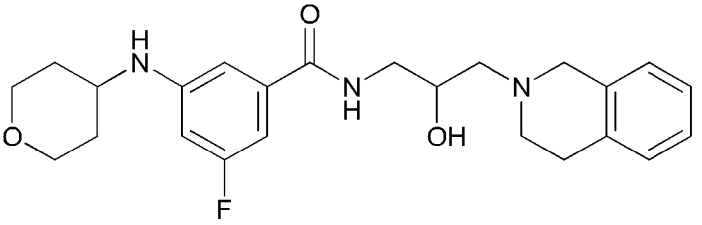
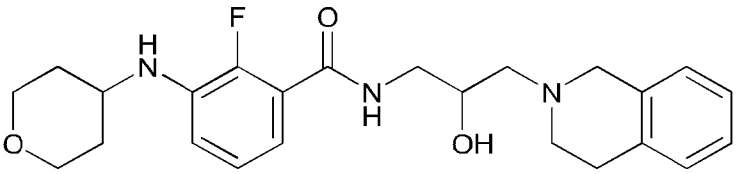
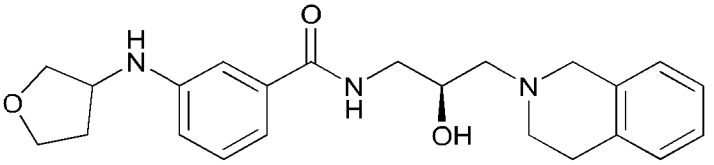
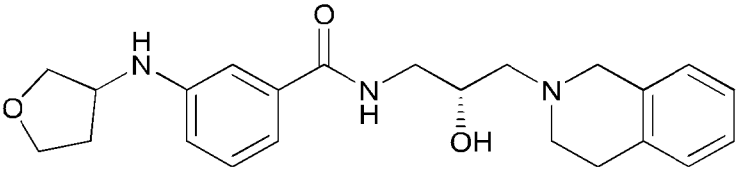
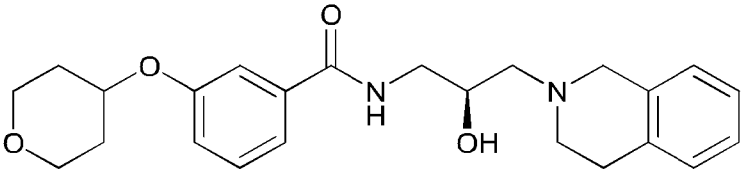
75	
76	
77	
78	
79	
80	
81	
82	

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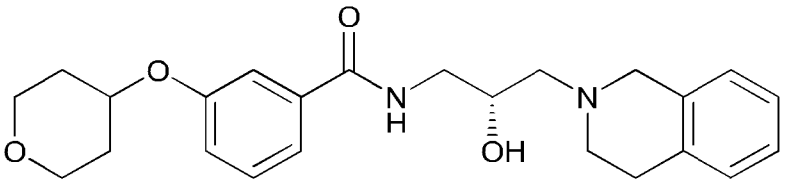
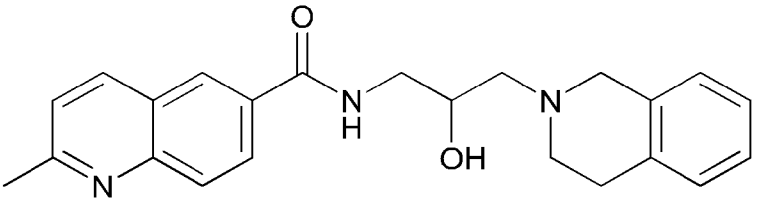
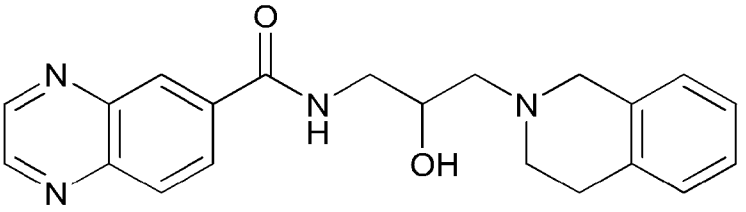
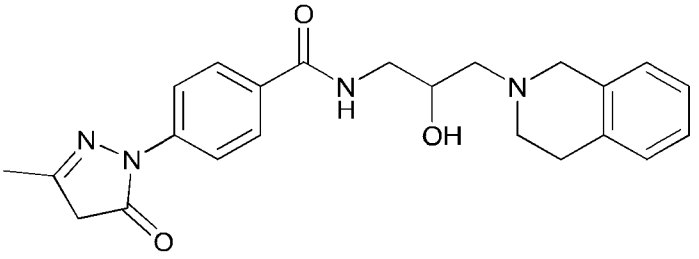
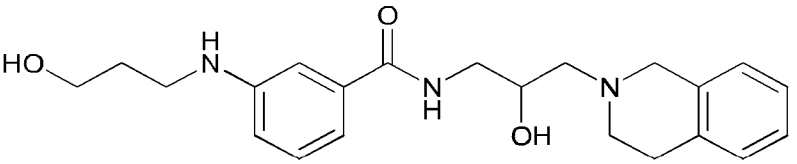
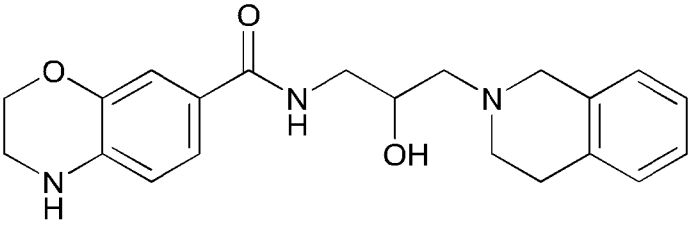
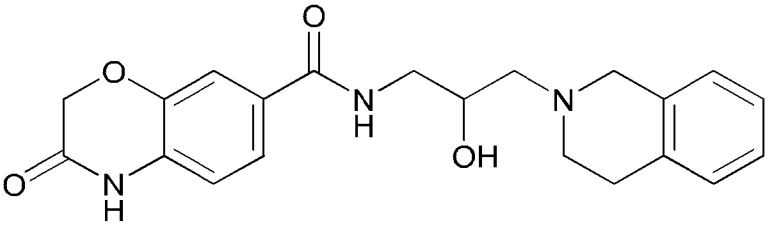
83	
84	
85	
86	
87	
88	
89	

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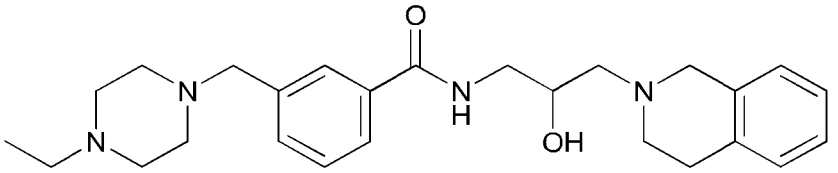
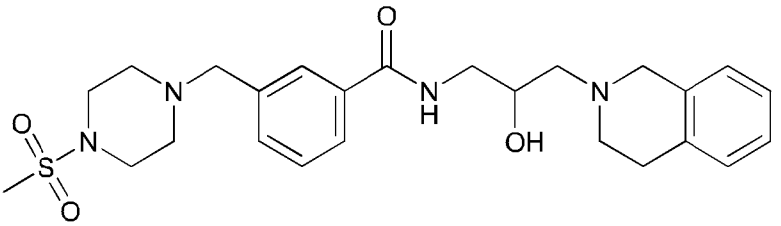
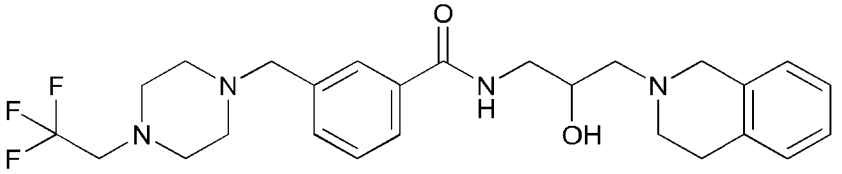
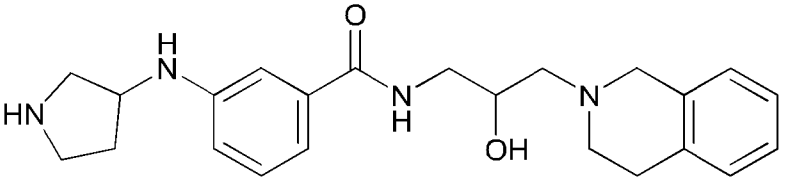
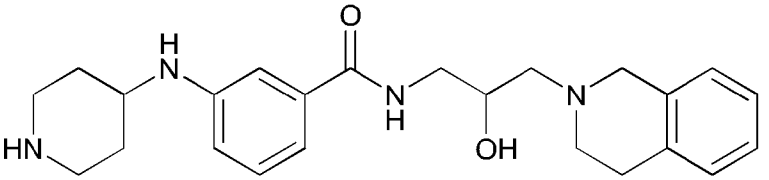
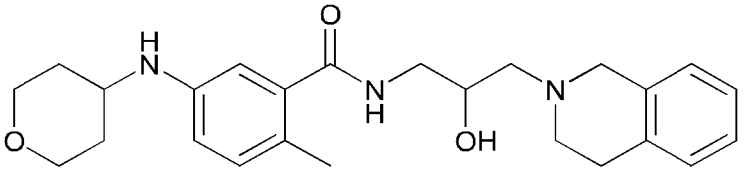
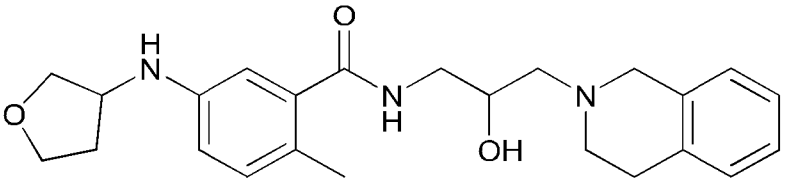
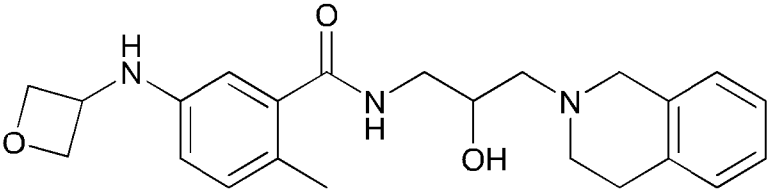
90	
91	
92	
93	
94	
95	
96	
97	

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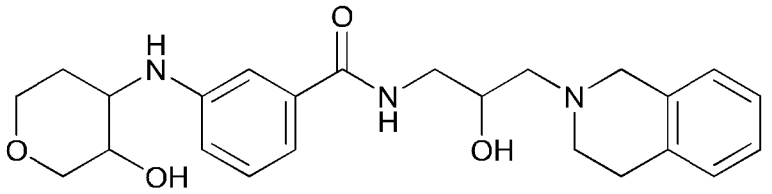
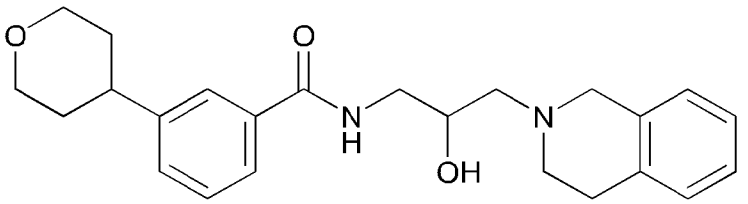
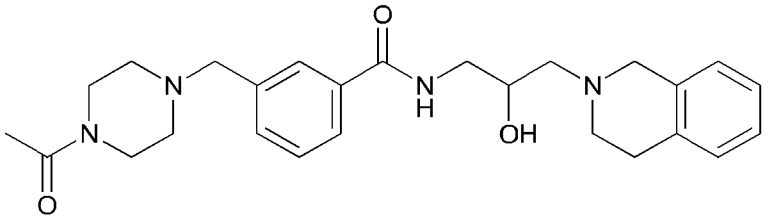
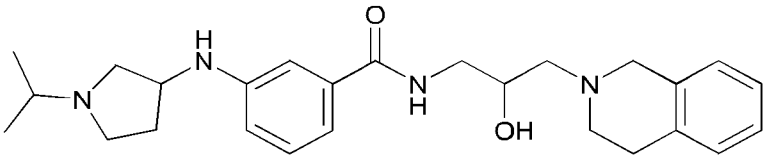
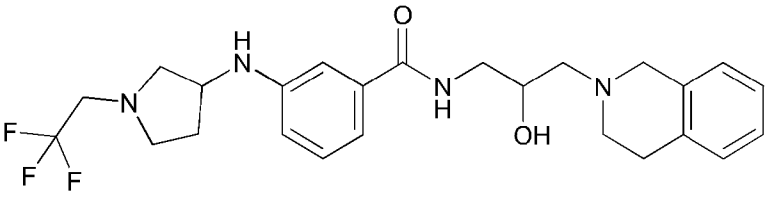
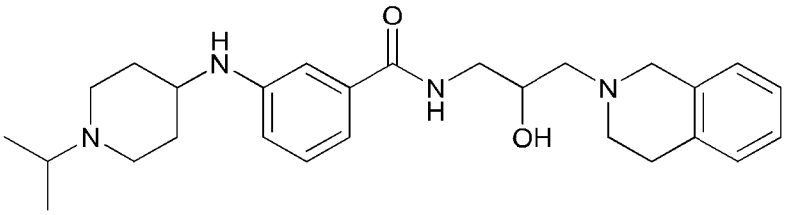
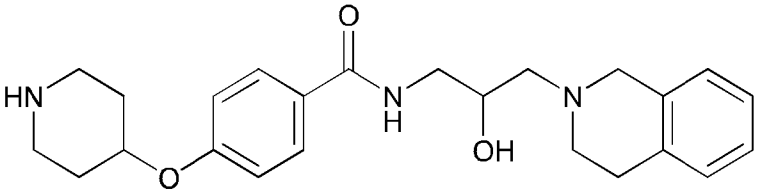
98	
99	
100	
101	
102	
103	
104	

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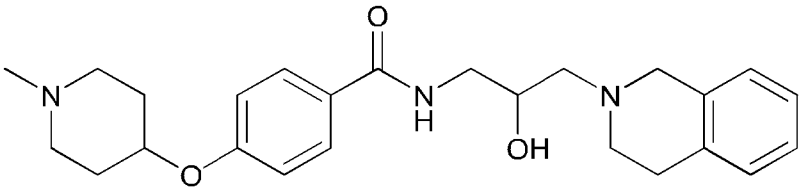
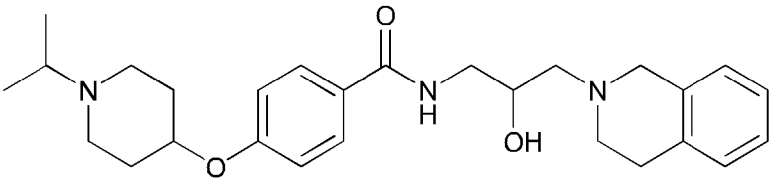
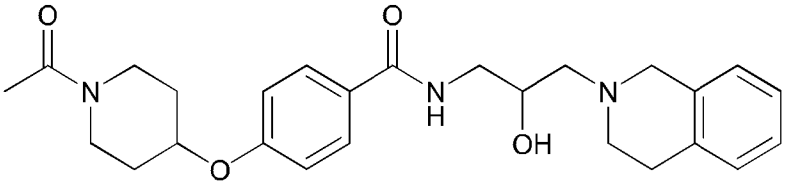
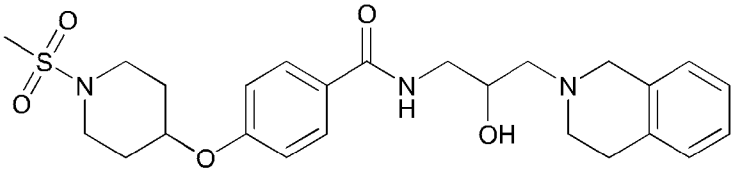
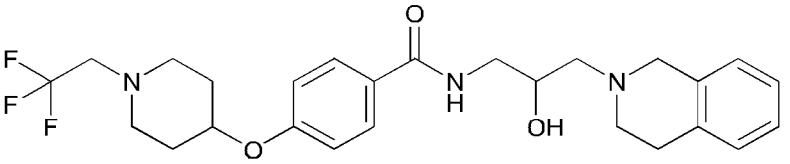
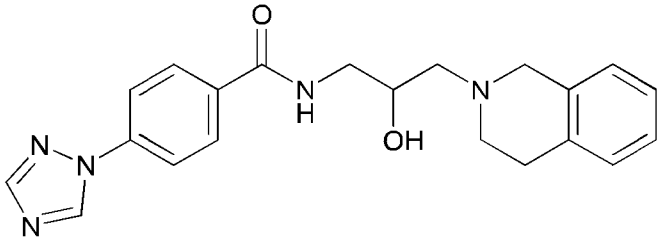
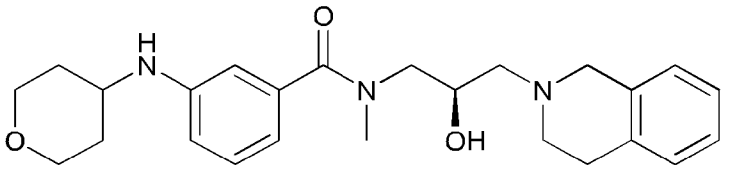
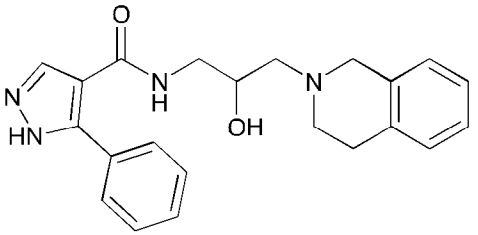
105	
106	
107	
108	
109	
110	
111	
112	

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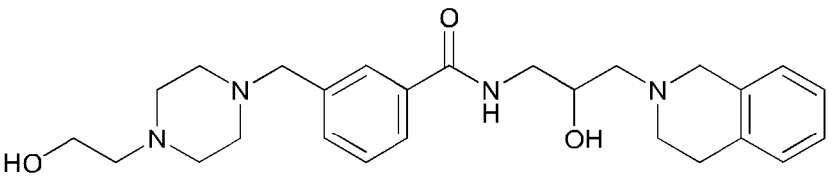
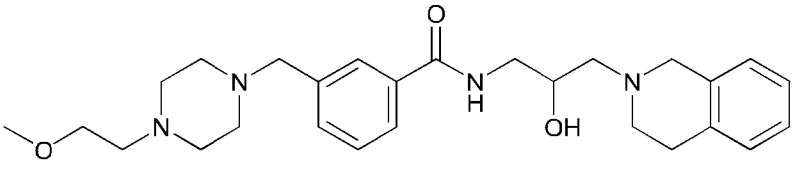
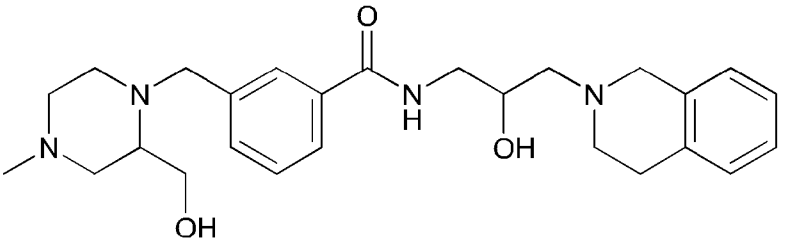
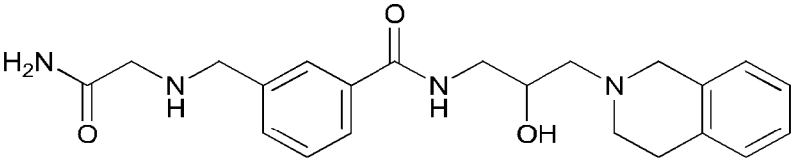
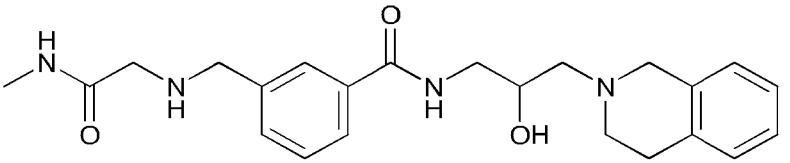
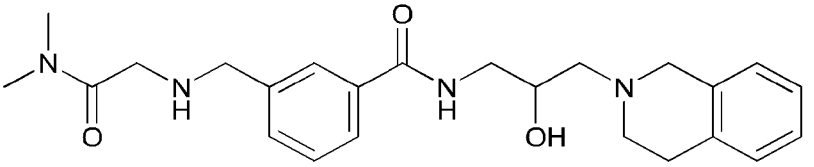
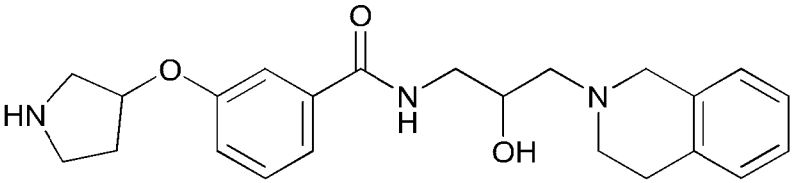
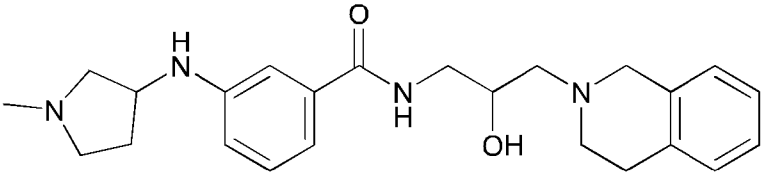
113	
114	
115	
116	
117	
118	
119	
120	

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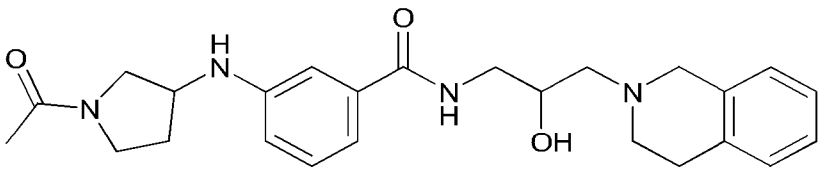
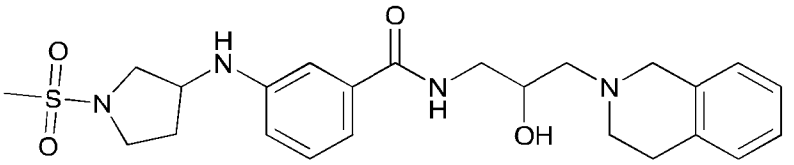
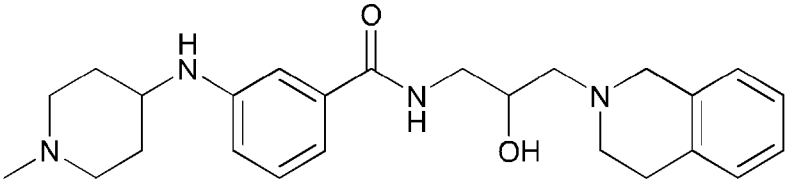
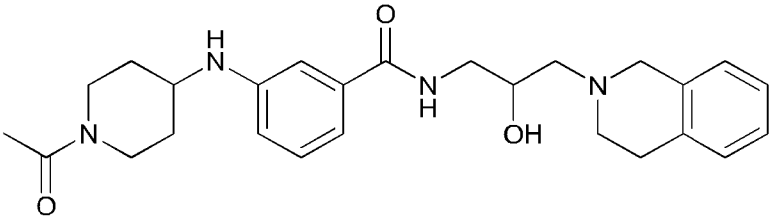
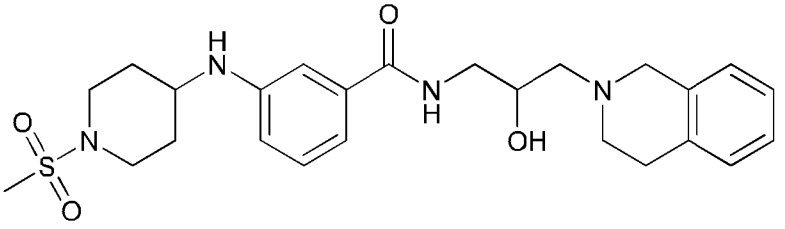
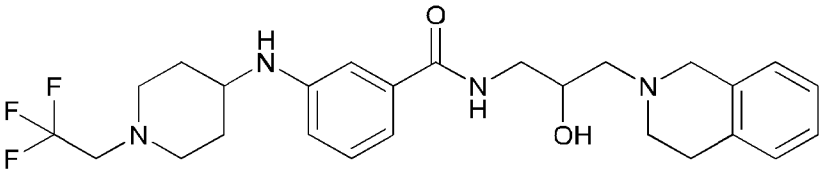
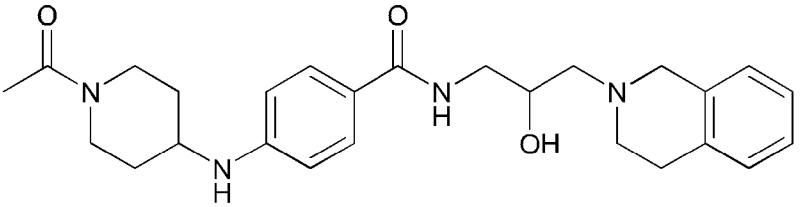
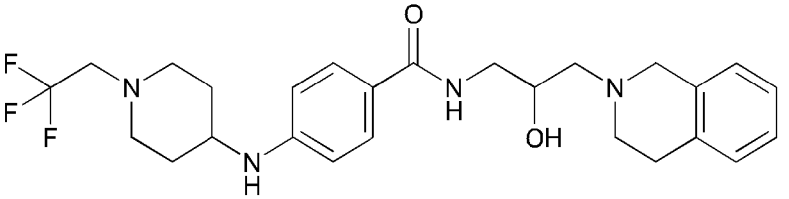
121	
122	
123	
124	
125	
126	
127	
128	

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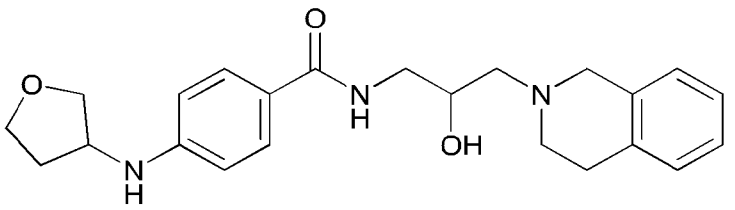
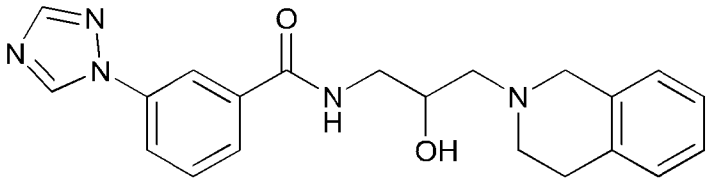
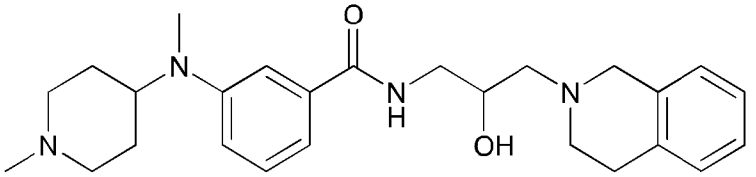
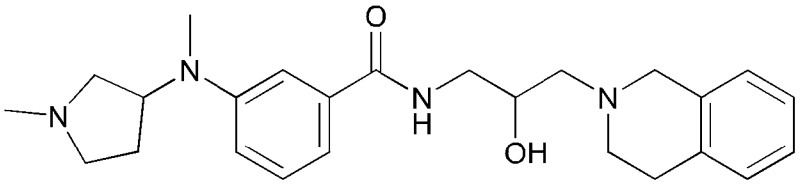
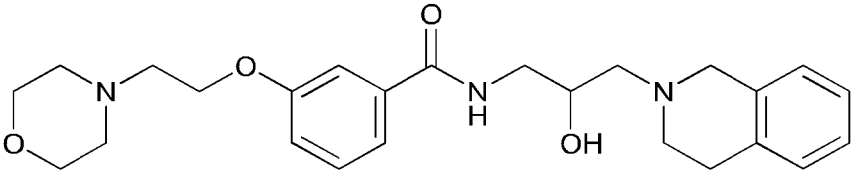
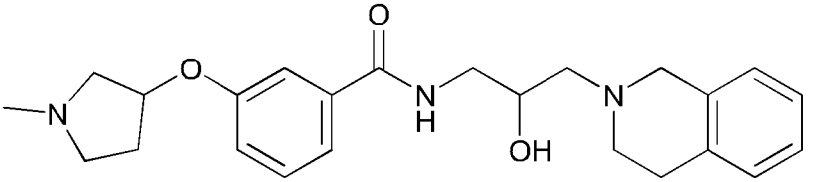
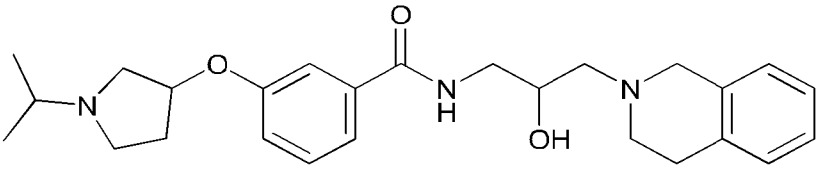
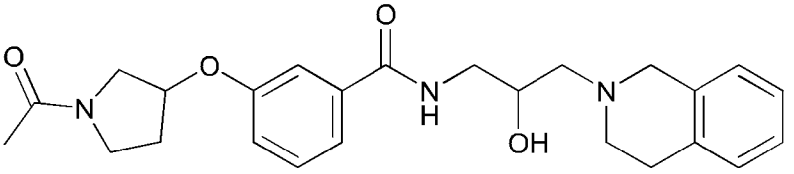
129	
130	
131	
132	
133	
134	
135	
136	

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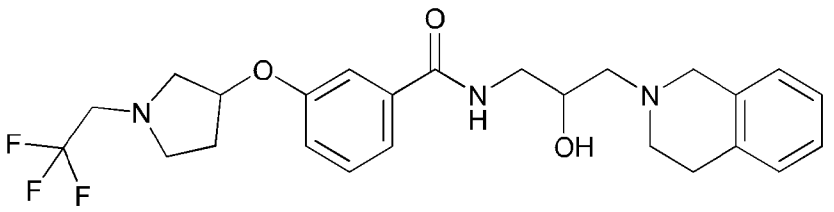
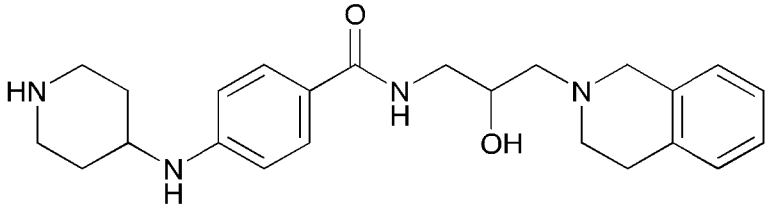
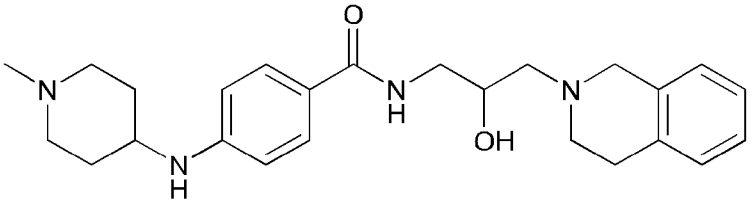
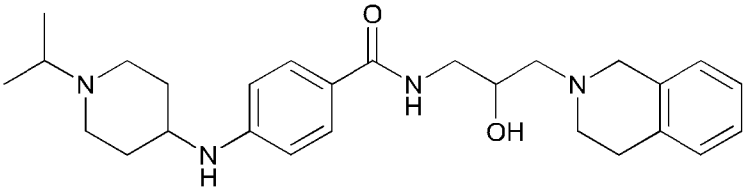
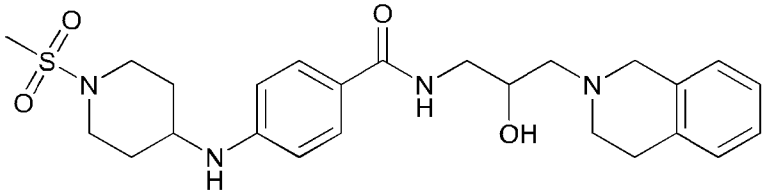
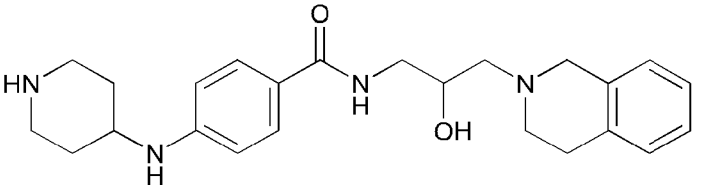
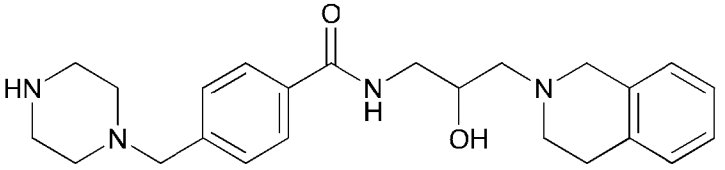
137	
138	
139	
140	
141	
142	
143	

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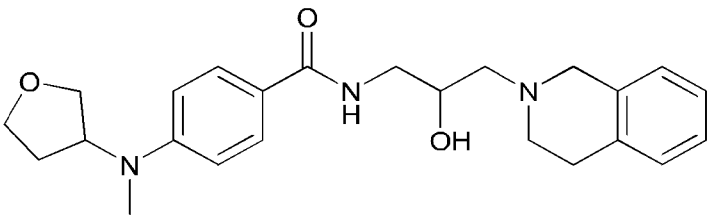
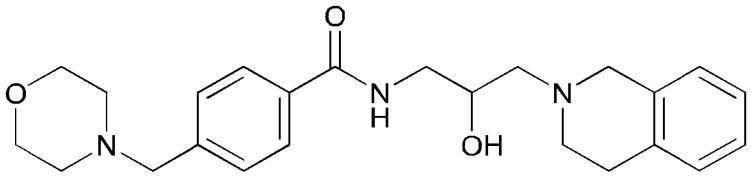
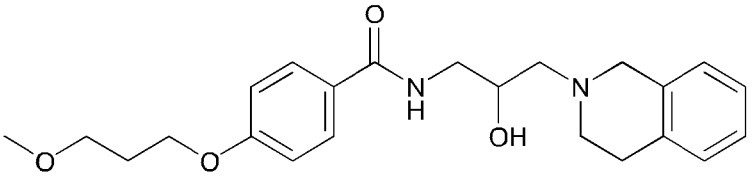
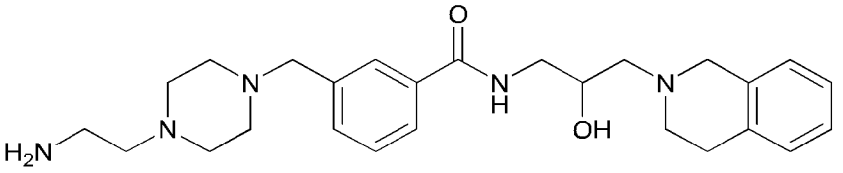
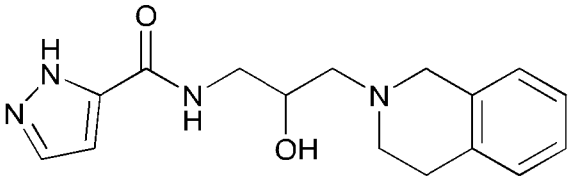
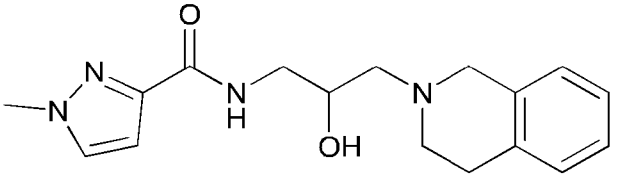
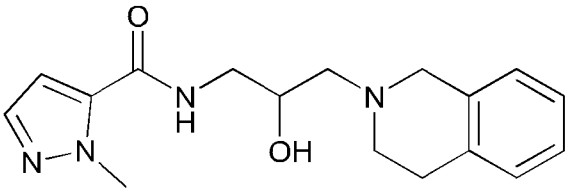
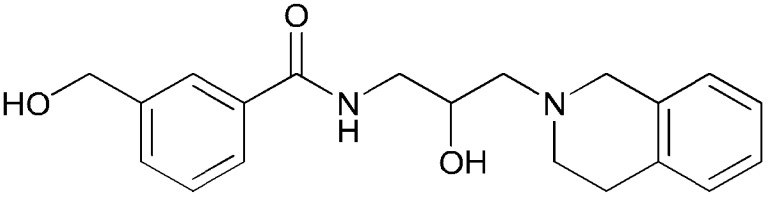
144	
145	
146	
147	
148	
149	
150	
151	

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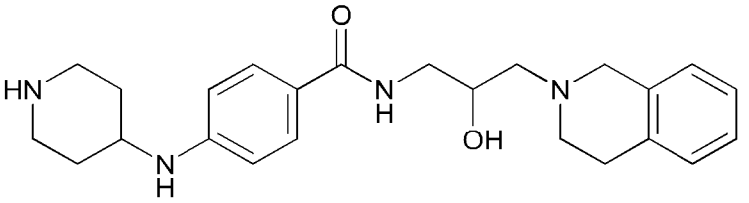
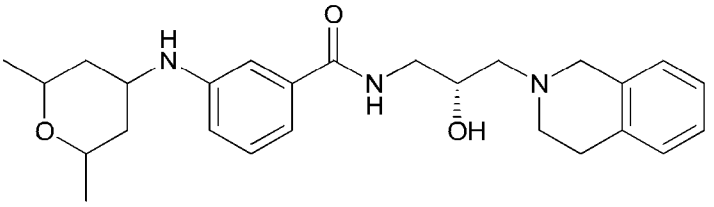
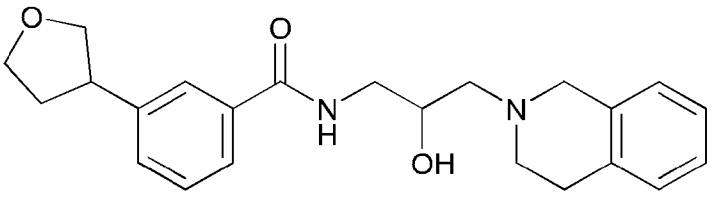
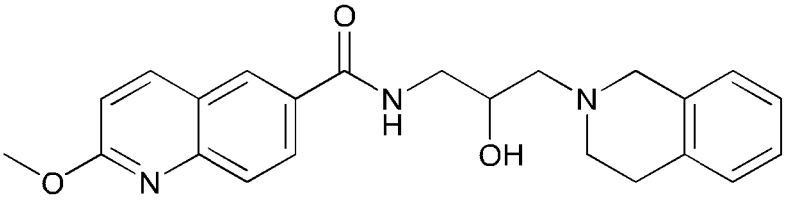
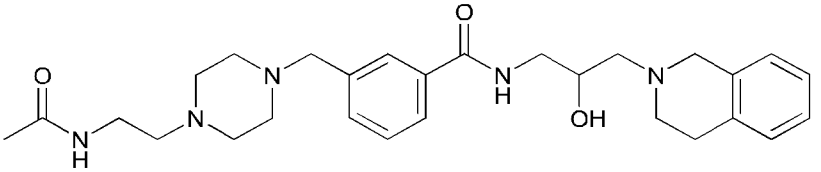
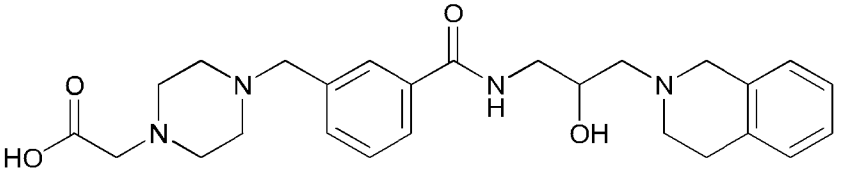
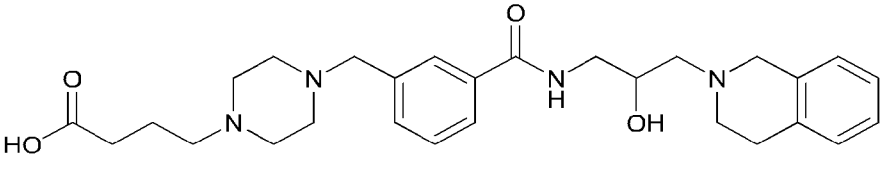
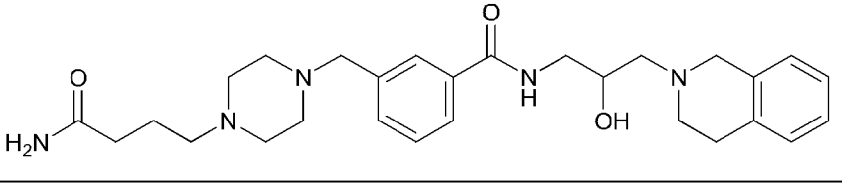
152	
153	
154	
155	
156	
157	
158	
159	

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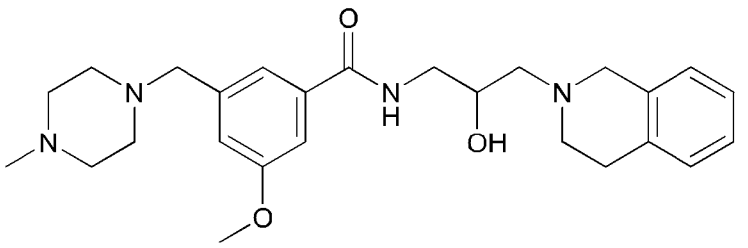
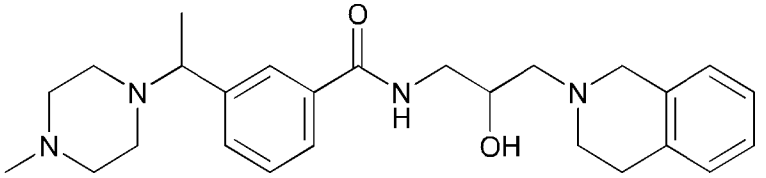
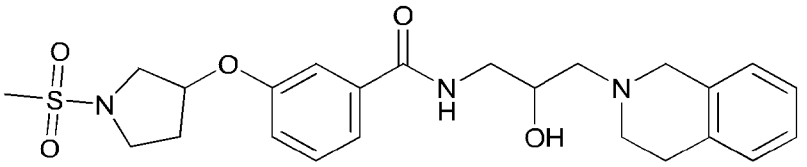
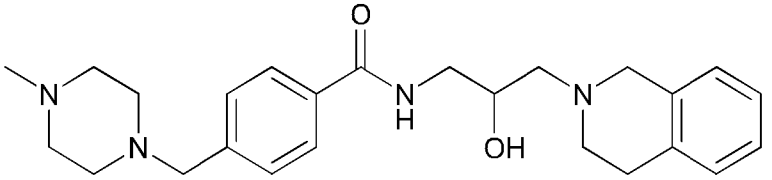
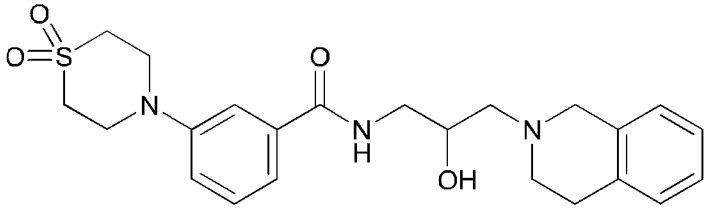
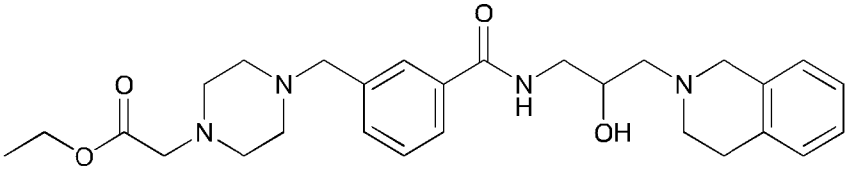
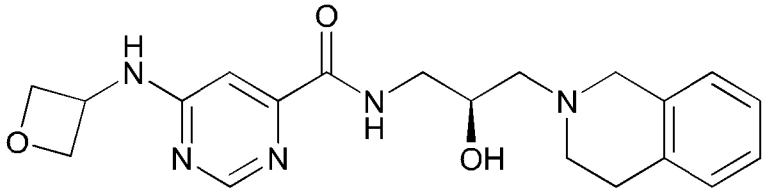
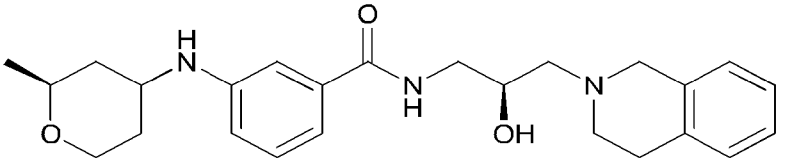
160	
161	
162	
163	
164	
165	
166	
167	

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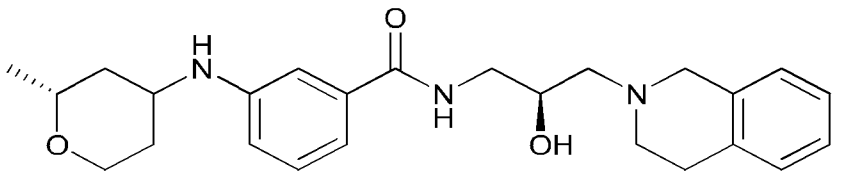
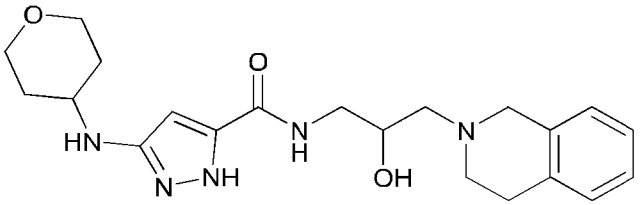
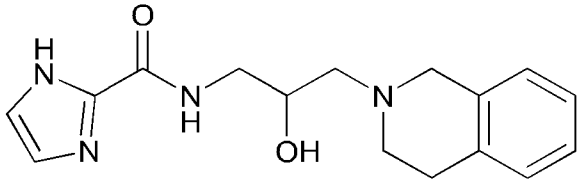
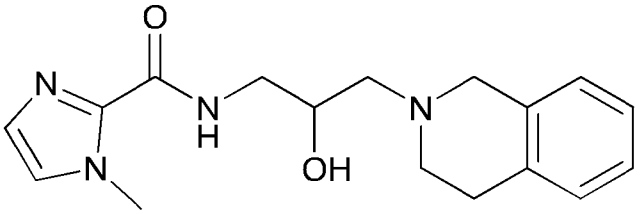
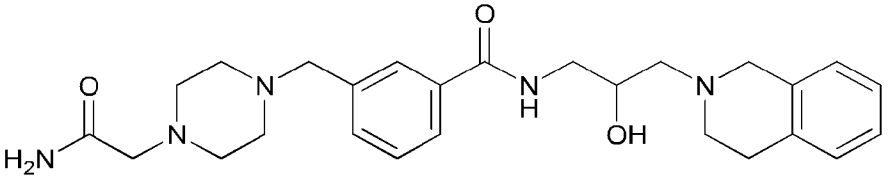
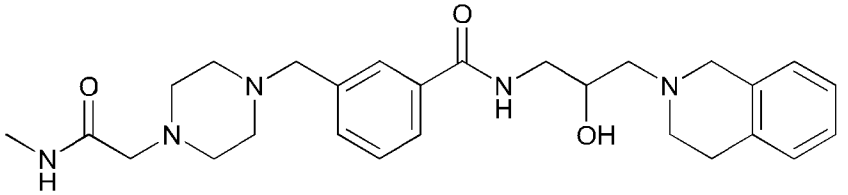
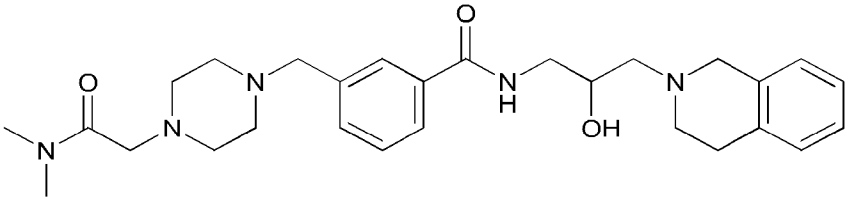
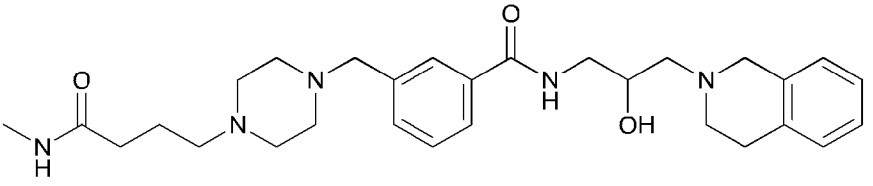
168	
169	
170	
171	
172	
173	
174	
175	

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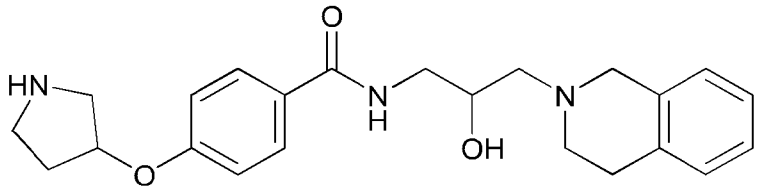
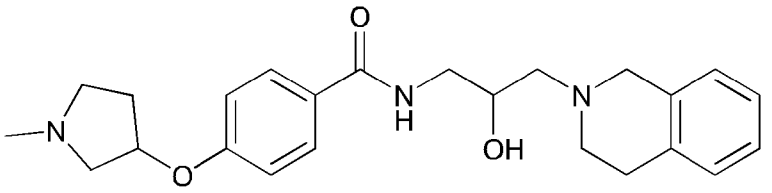
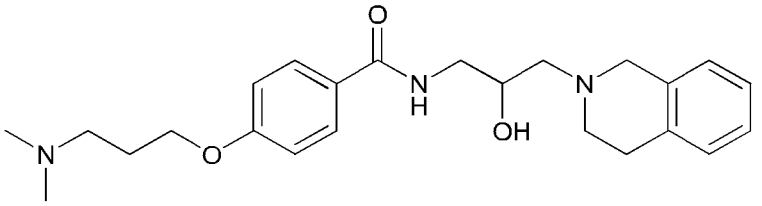
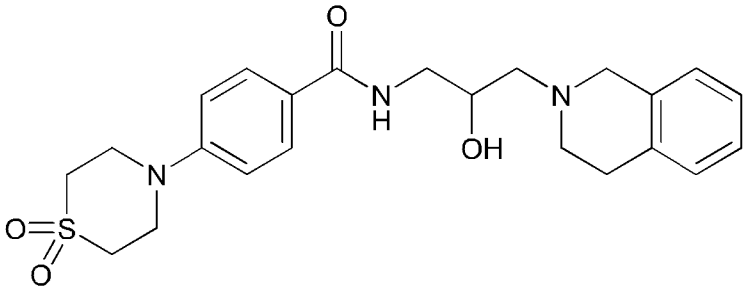
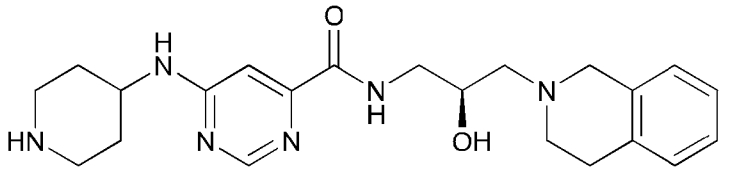
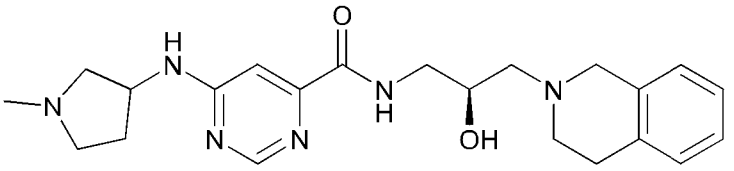
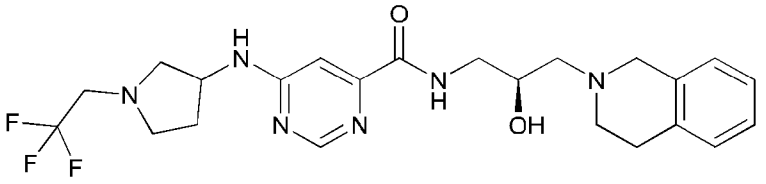
176	
177	
178	
179	
180	
181	
182	

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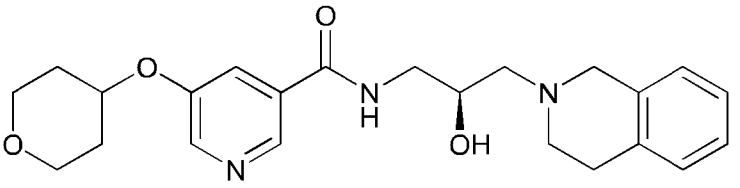
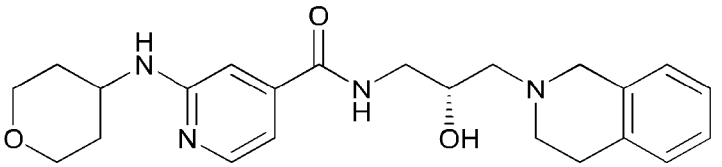
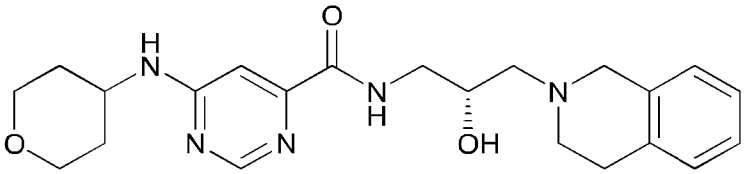
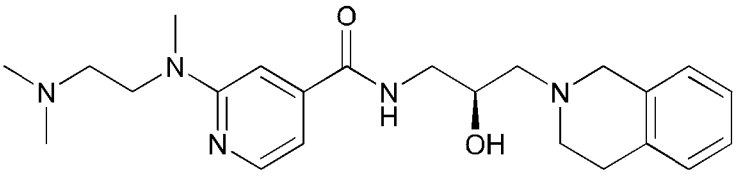
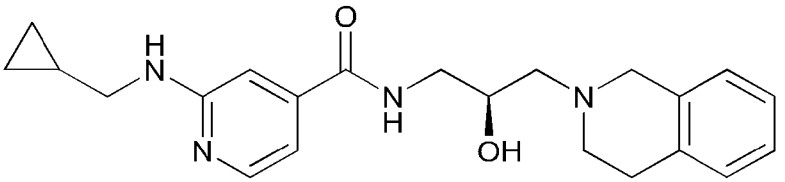
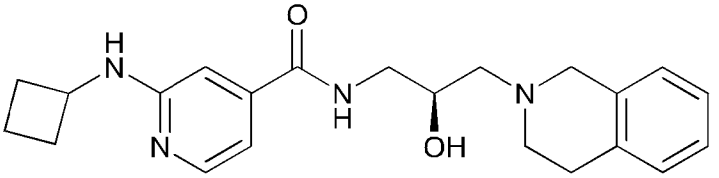
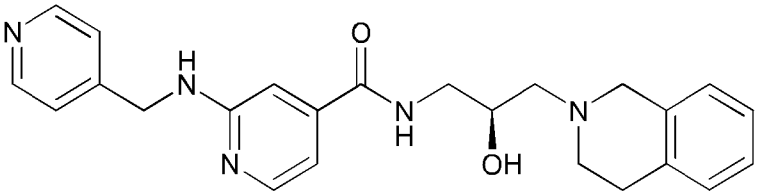
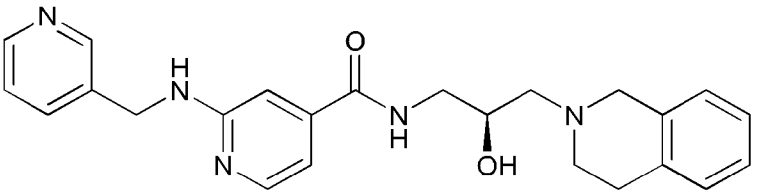
183	
184	
185	
186	
187	
188	
189	
190	

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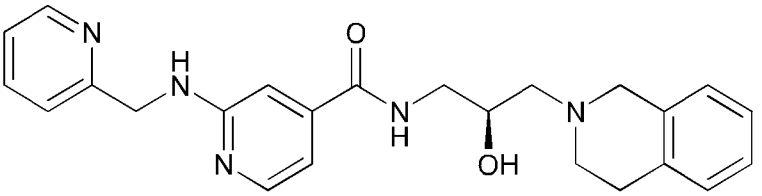
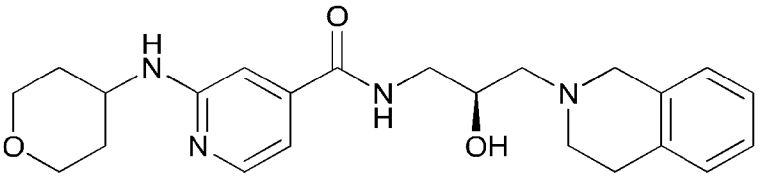
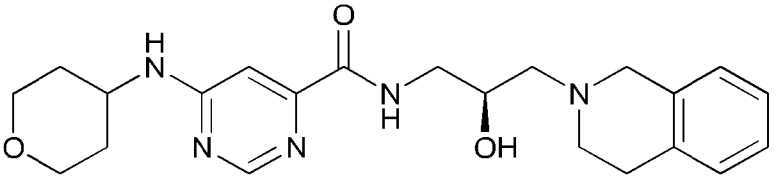
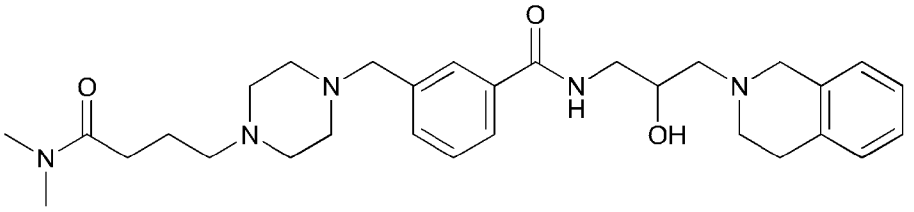
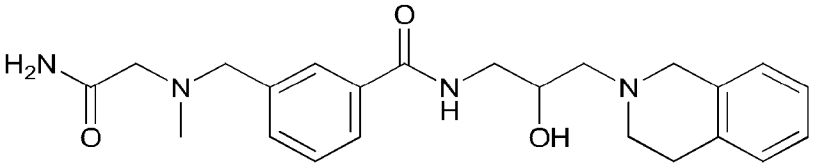
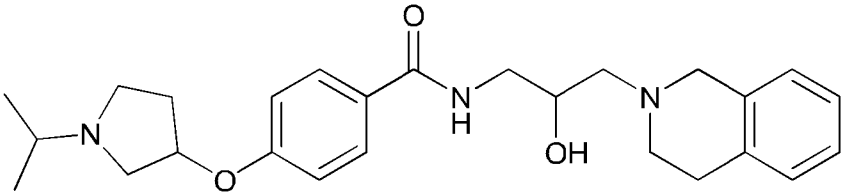
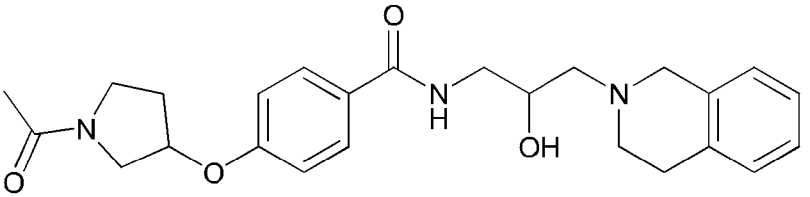
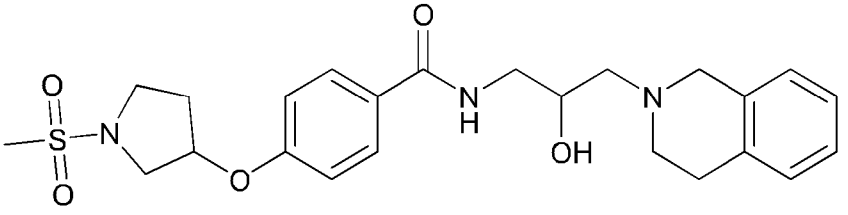
191	
192	
193	
194	
195	
196	
197	
198	

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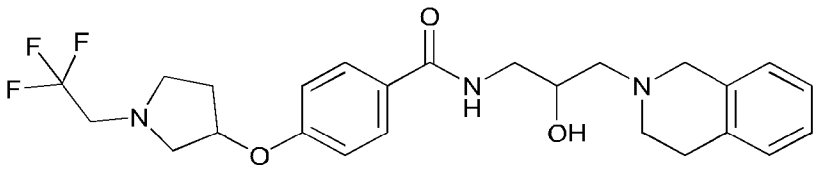
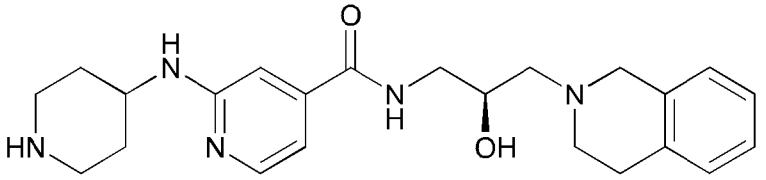
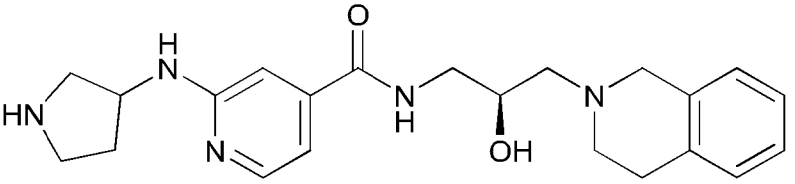
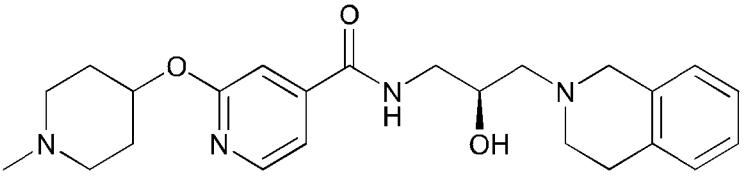
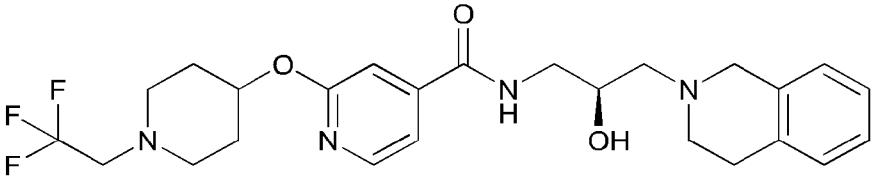
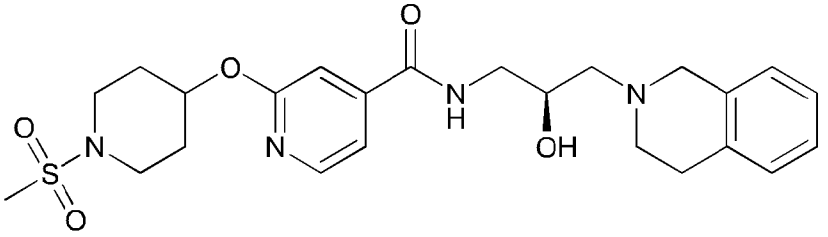
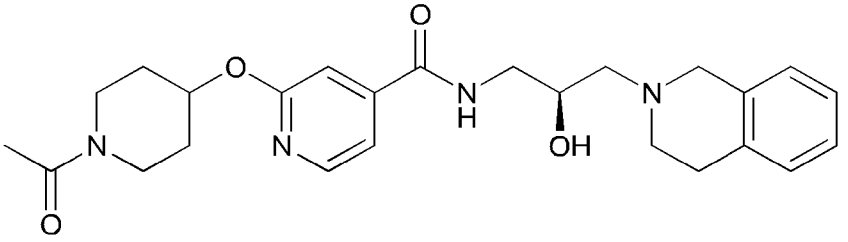
199	
200	
201	
202	
203	
204	
205	

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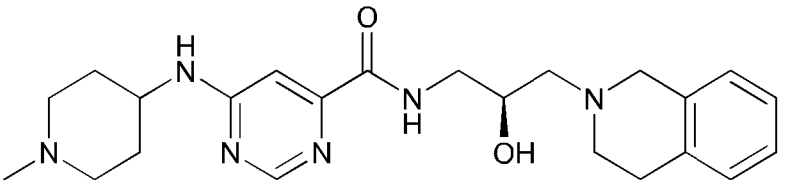
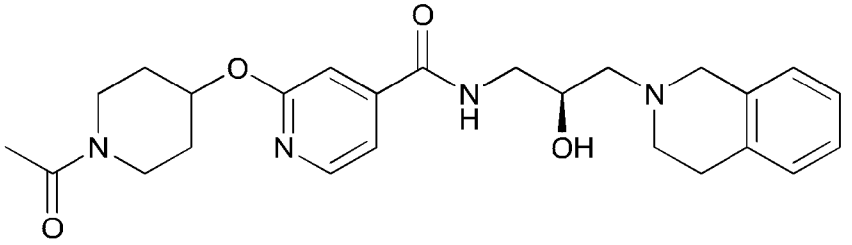
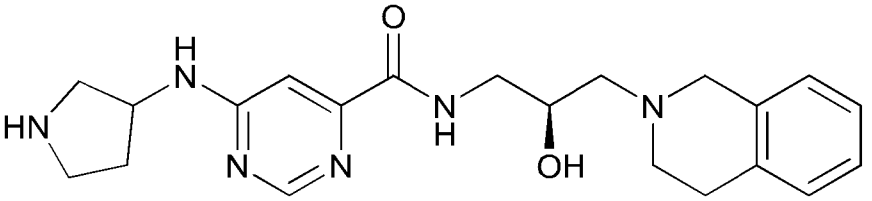
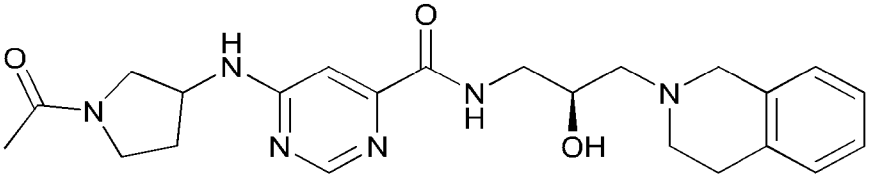
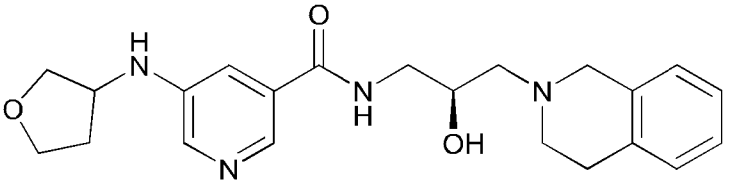
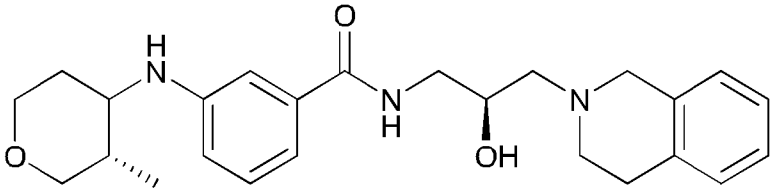
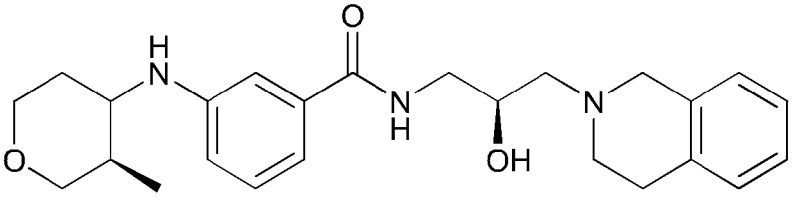
206	
207	
209	
210	
211	
212	
213	

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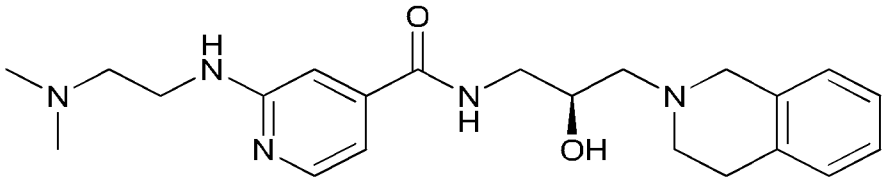
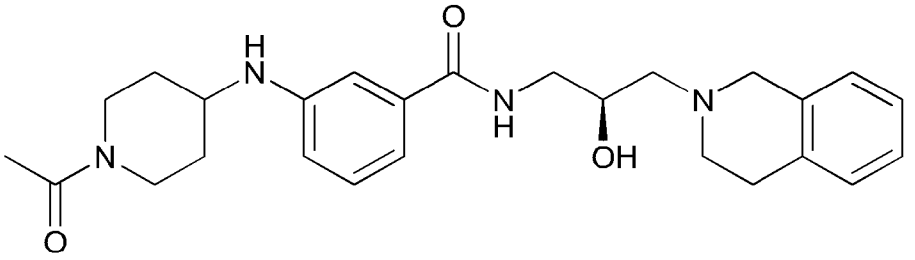
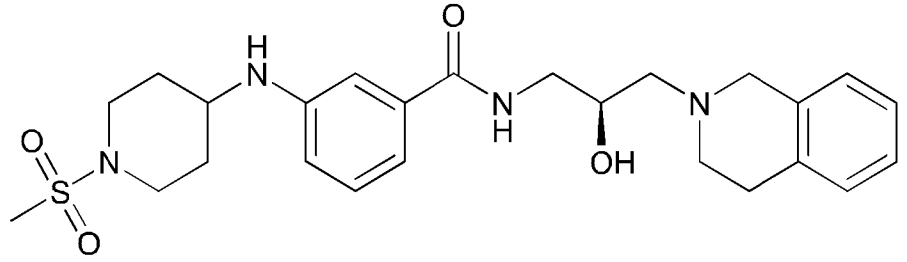
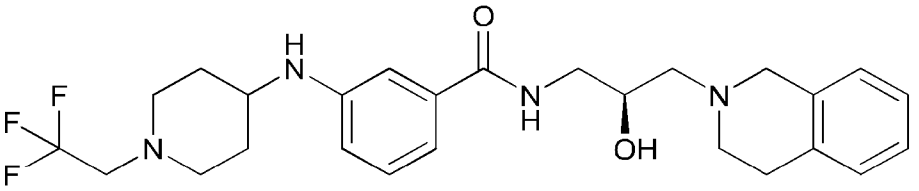
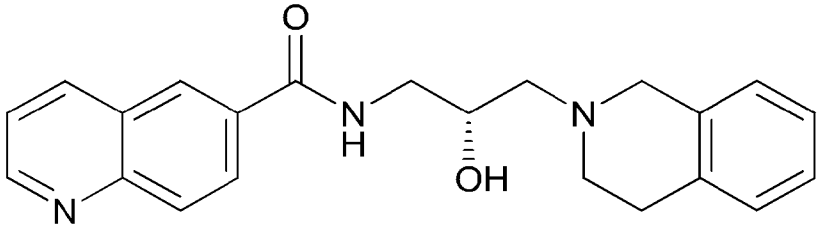
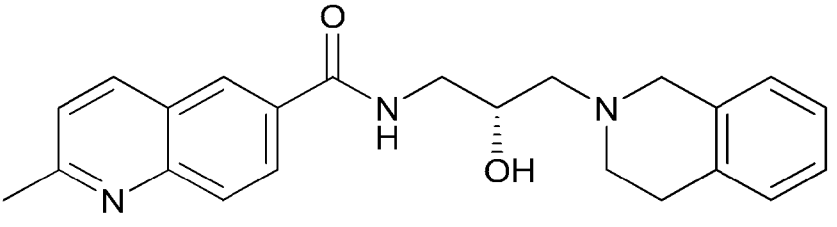
214	
215	
216	
217	
218	
219	

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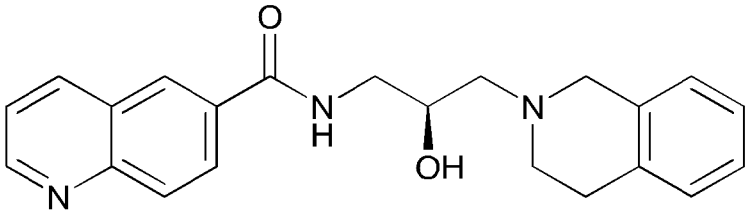
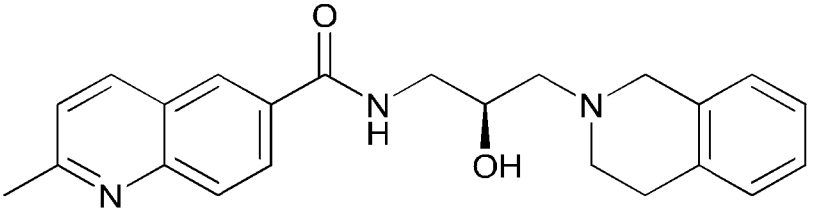
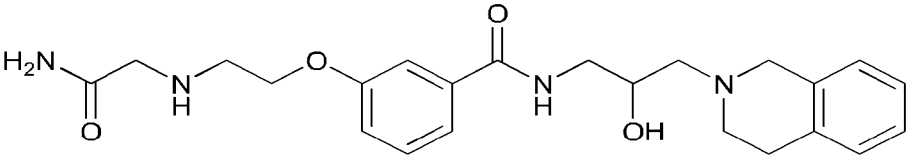
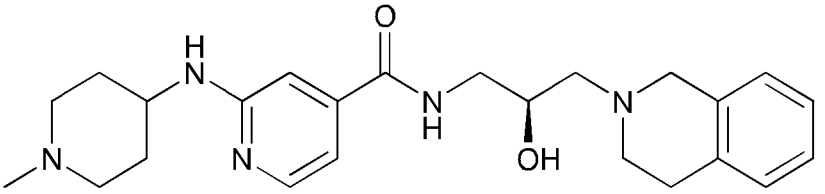
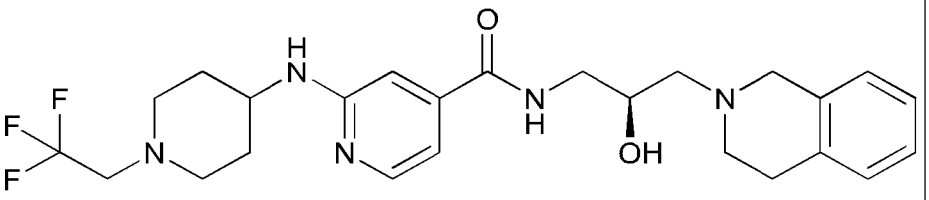
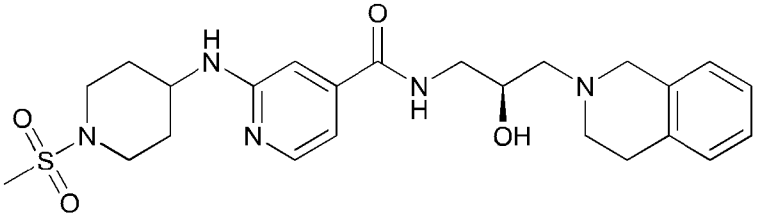
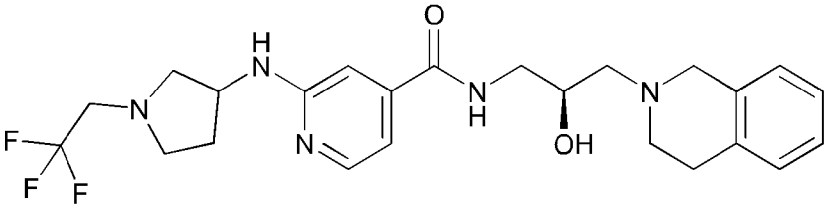
220	
221	
222	
223	
224	
225	
226	

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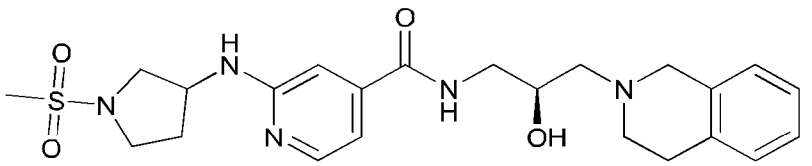
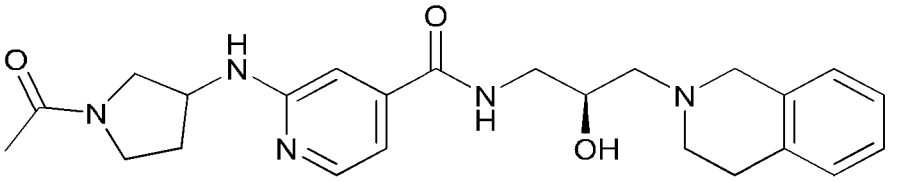
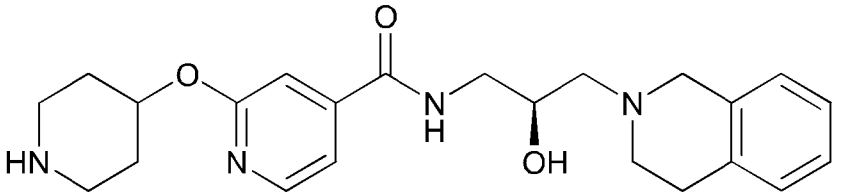
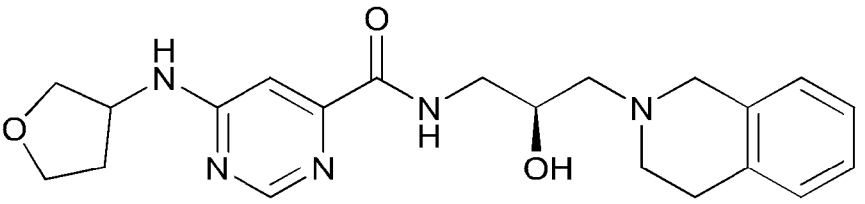
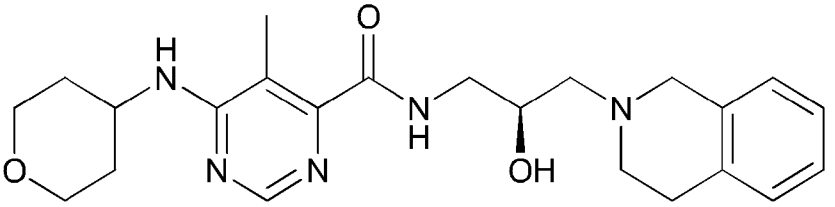
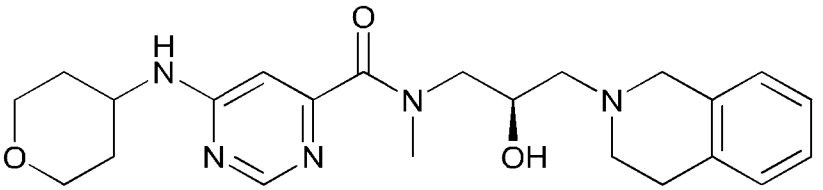
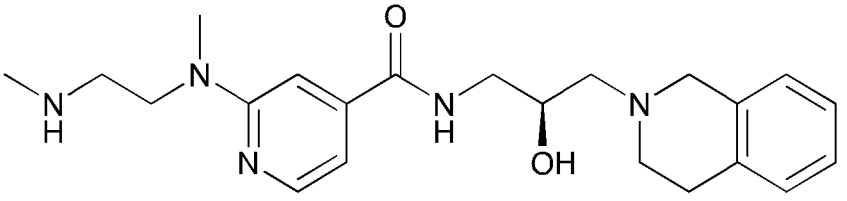
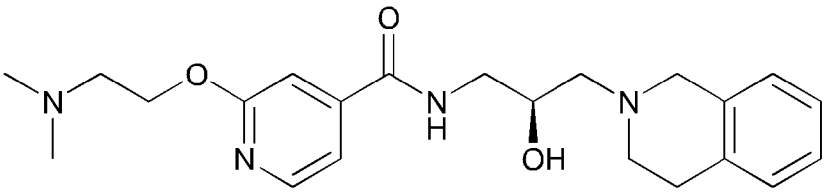
227	
228	
229	
230	
231	
232	
233	
234	

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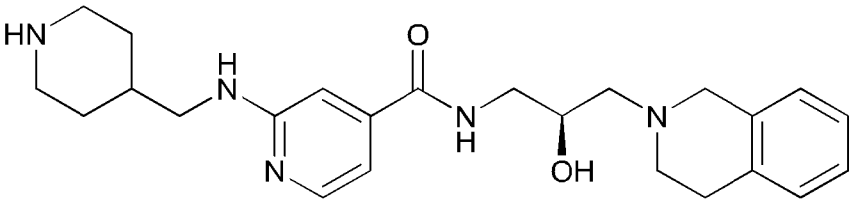
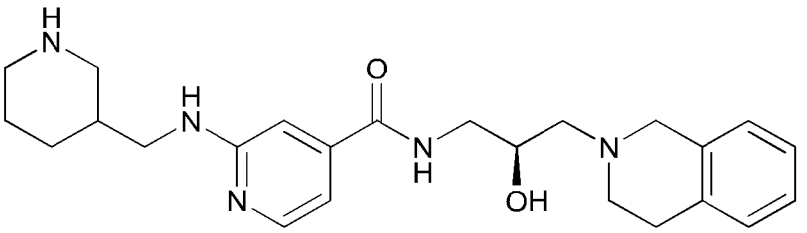
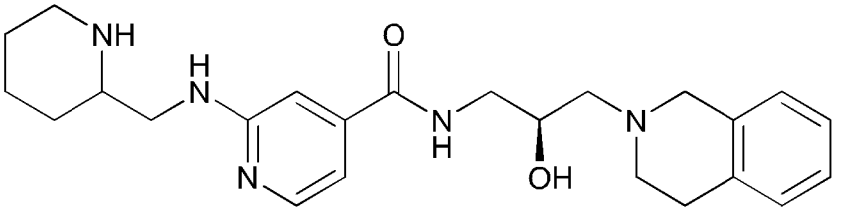
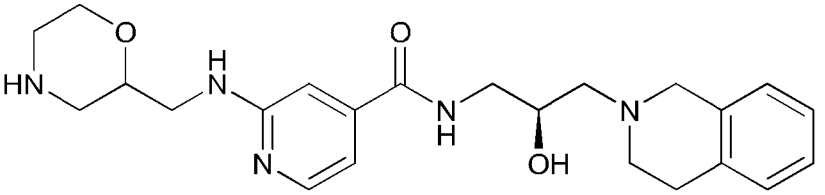
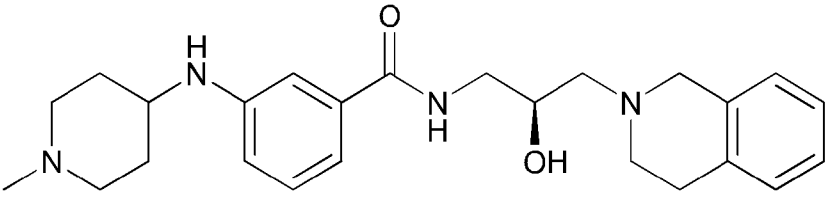
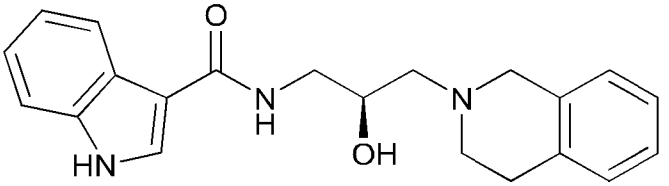
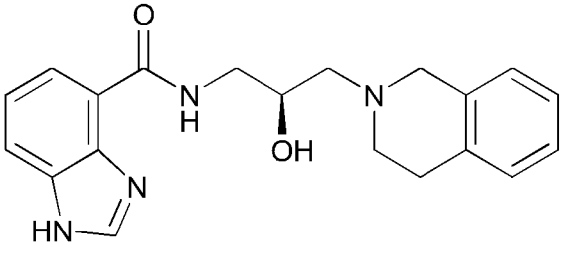
235	
236	
237	
238	
239	
240	
241	

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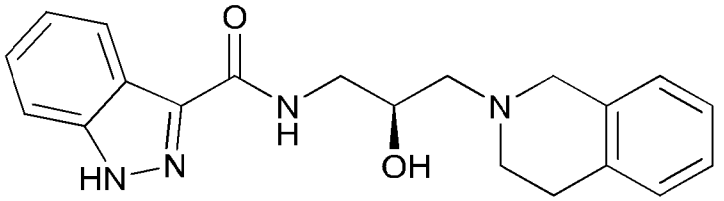
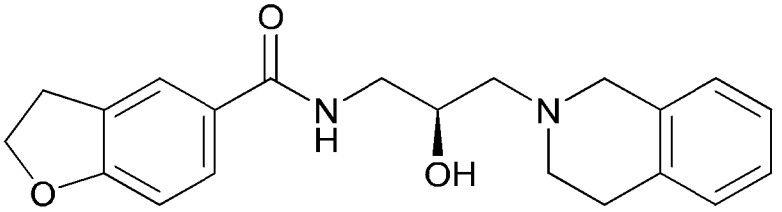
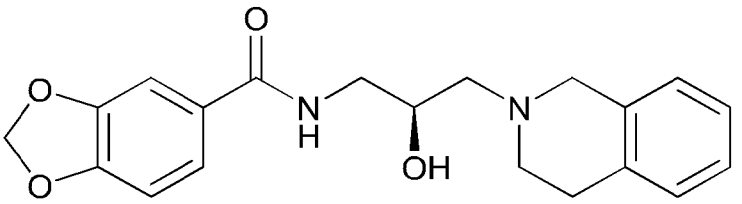
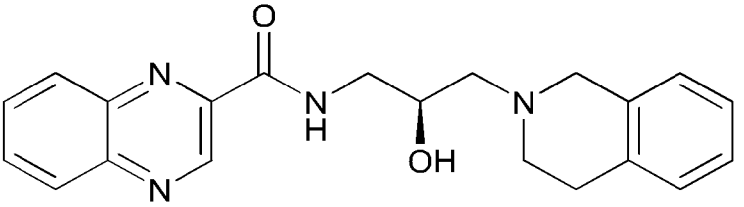
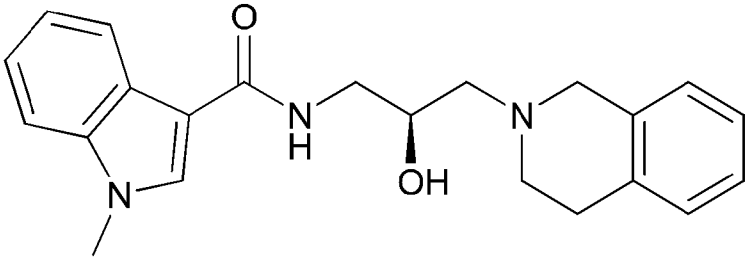
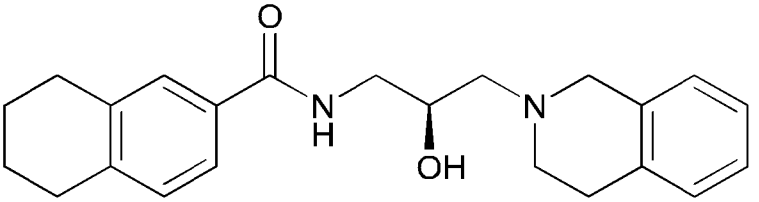
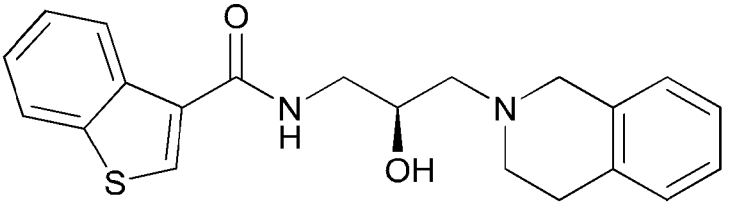
242	
243	
244	
245	
246	
247	
248	

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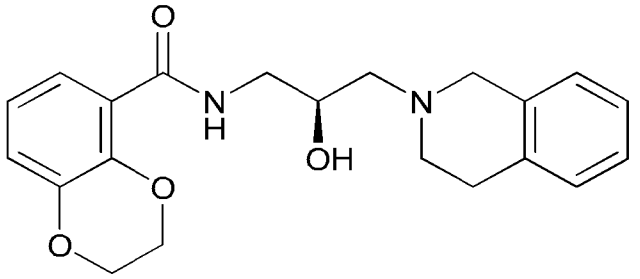
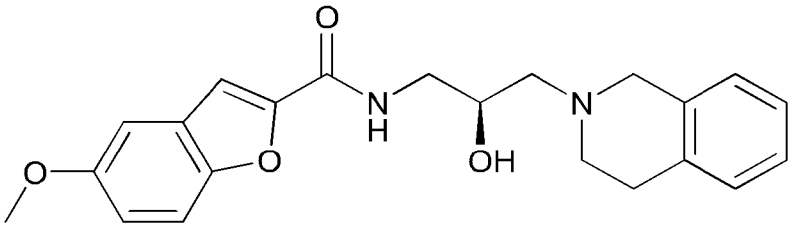
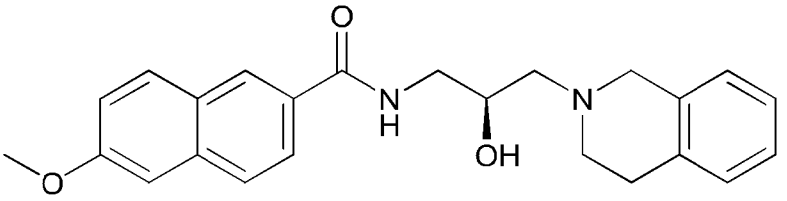
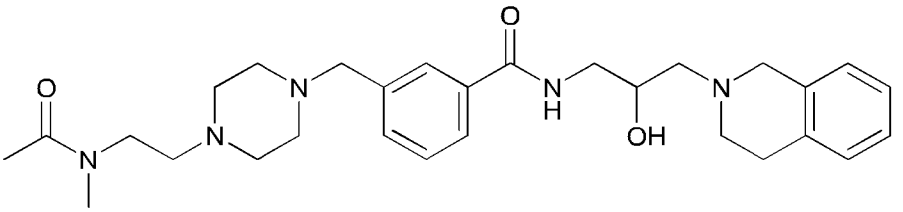
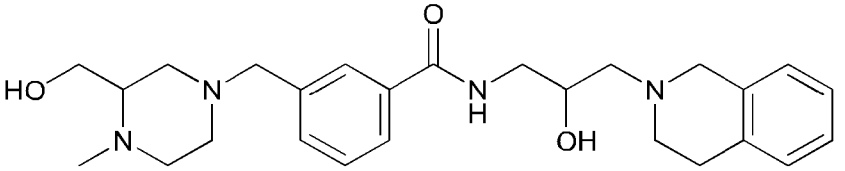
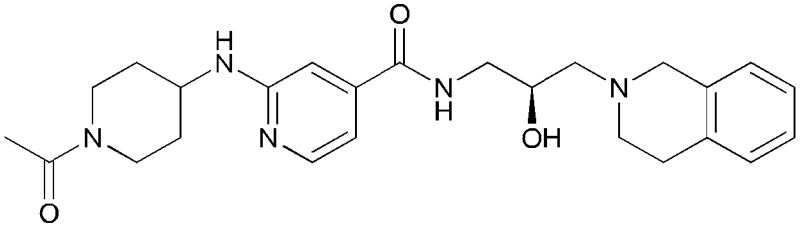
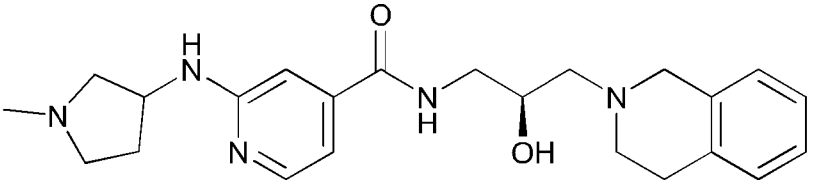
249	
250	
251	
252	
253	
254	
255	

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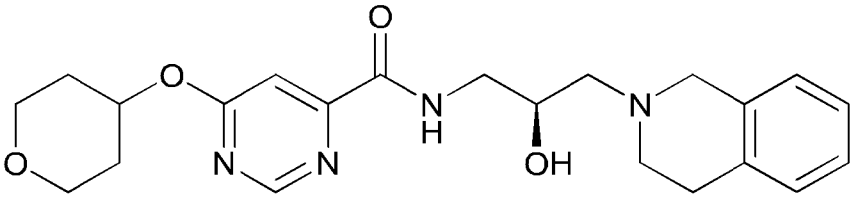
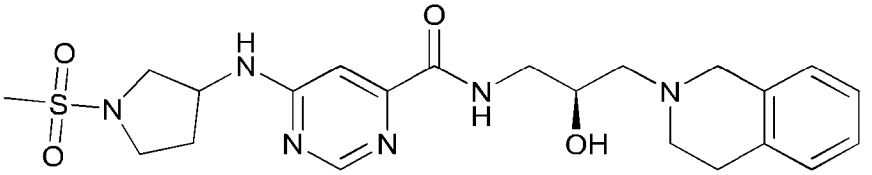
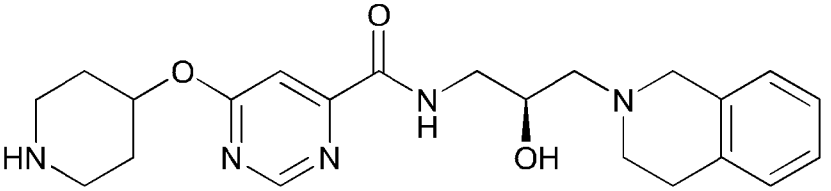
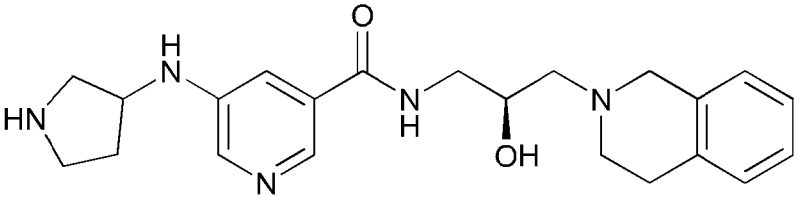
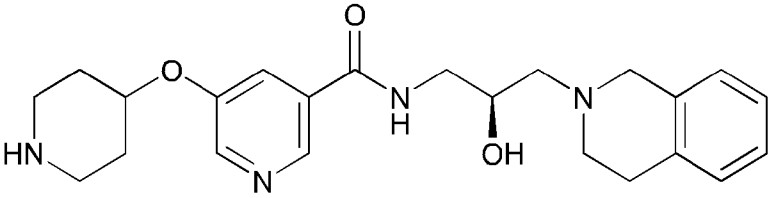
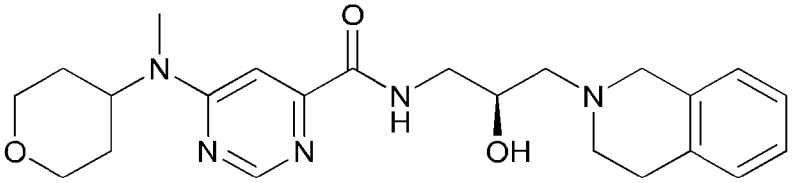
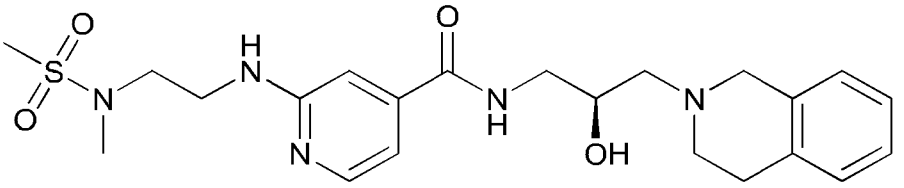
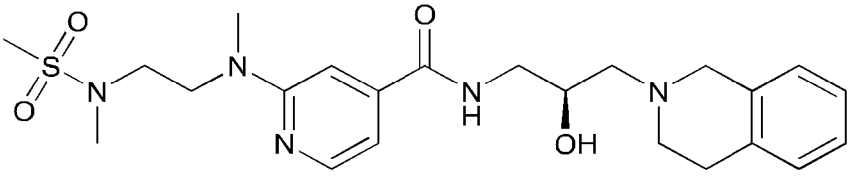
256	
257	
258	
259	
260	
261	
262	
263	

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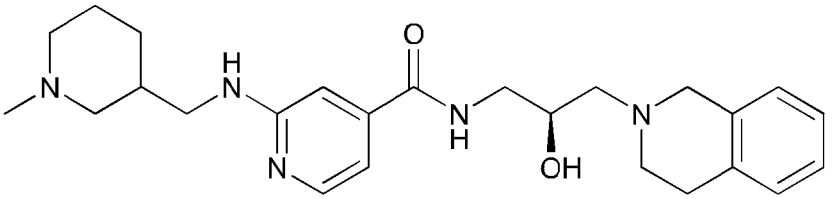
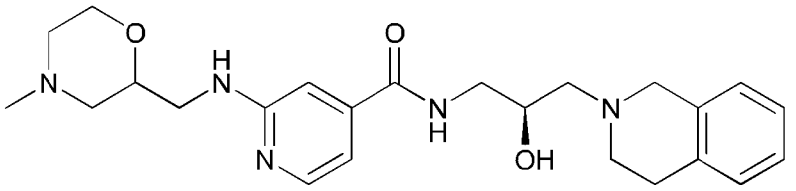
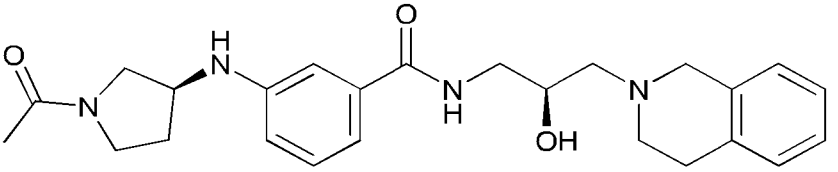
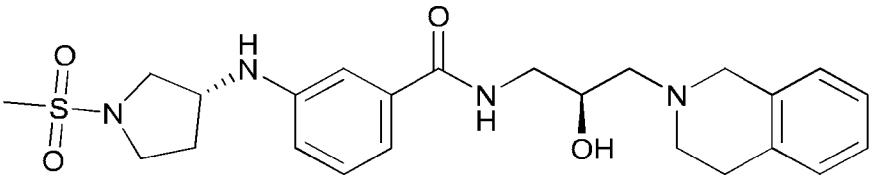
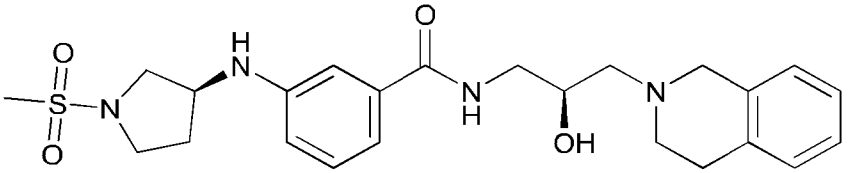
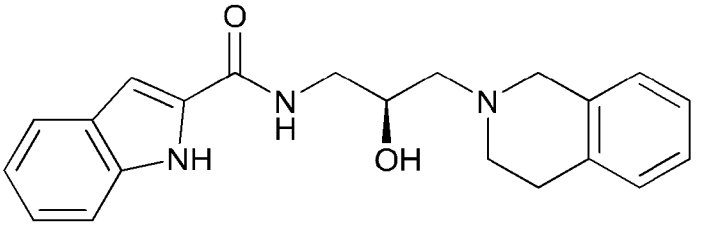
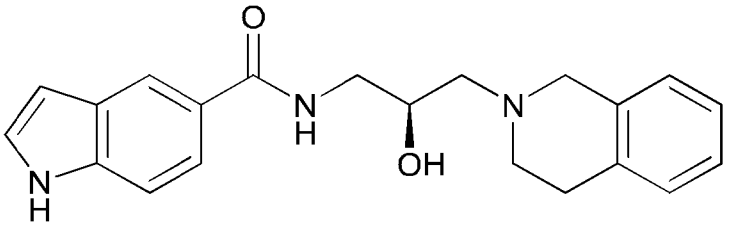
264	
265	
266	
267	
268	
269	
270	

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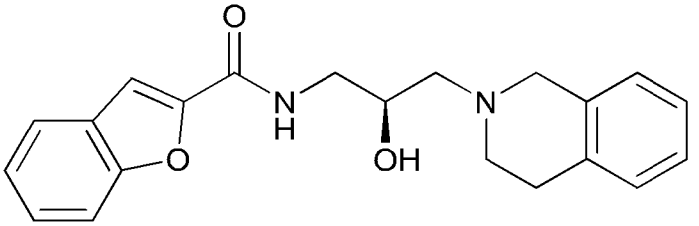
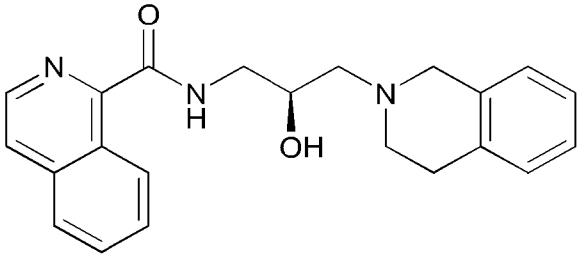
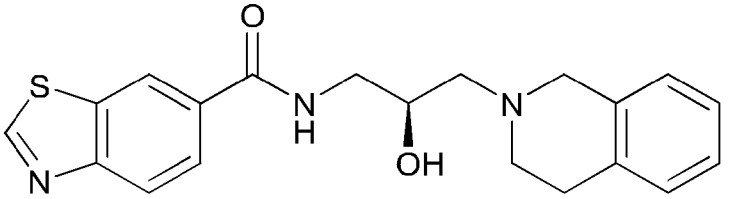
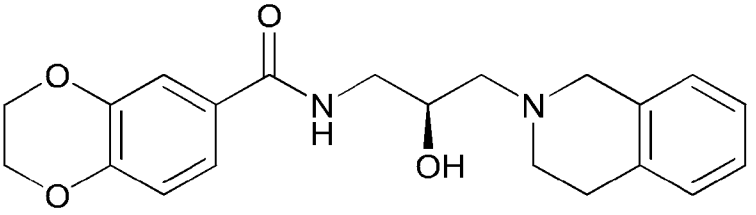
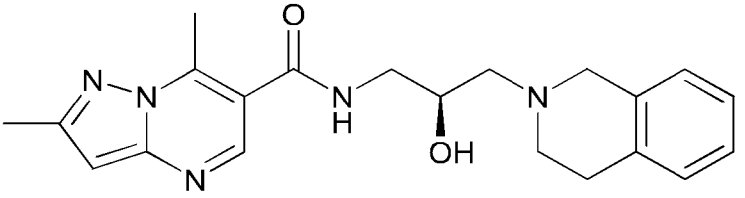
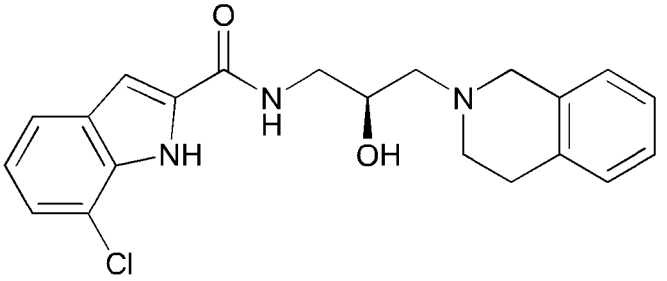
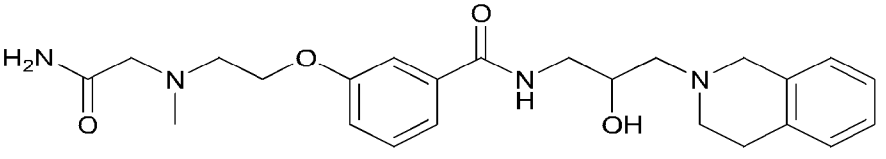
271	
272	
273	
274	
275	
276	
277	

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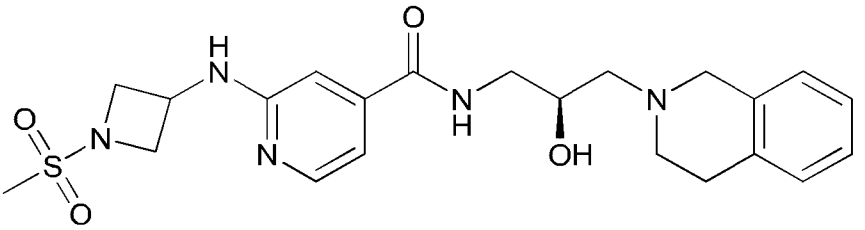
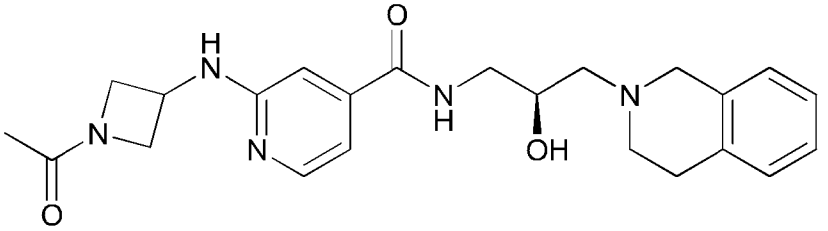
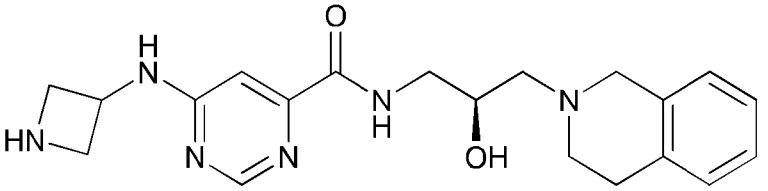
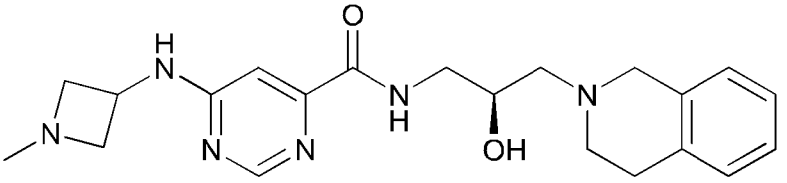
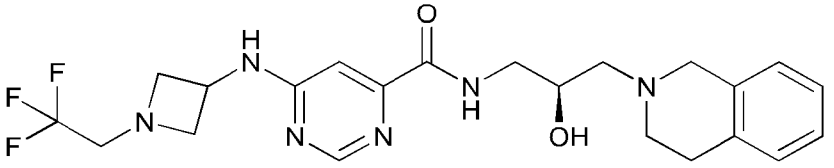
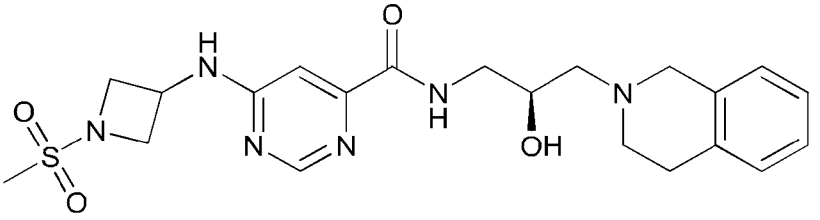
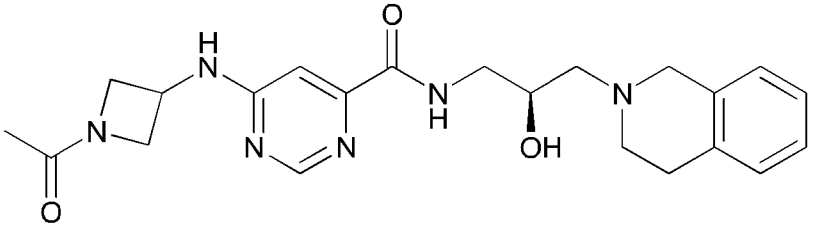
278	
279	
280	
281	
282	
283	
284	

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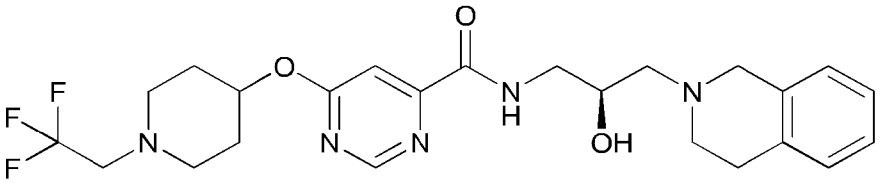
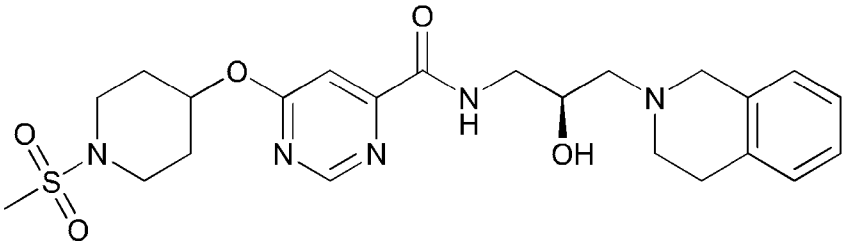
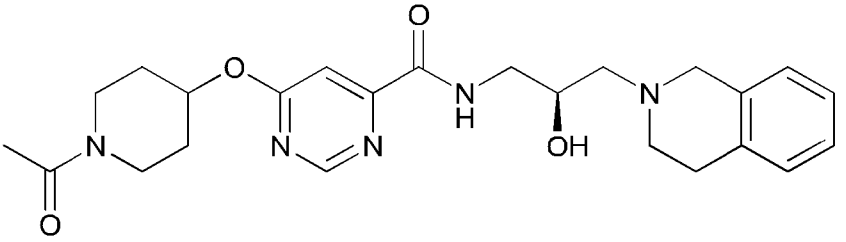
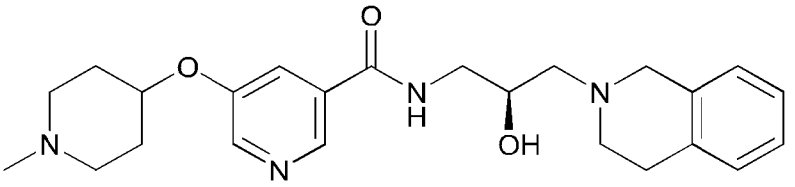
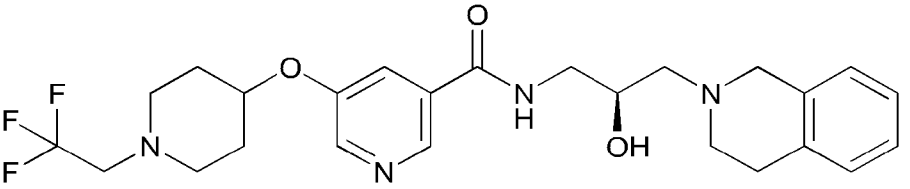
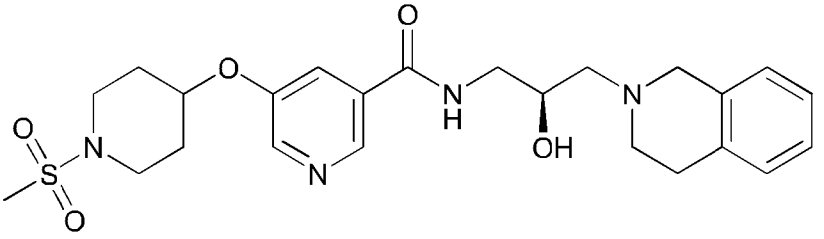
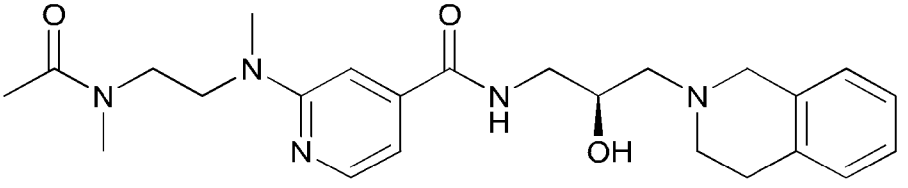
285	
286	
287	
288	
289	
290	
291	

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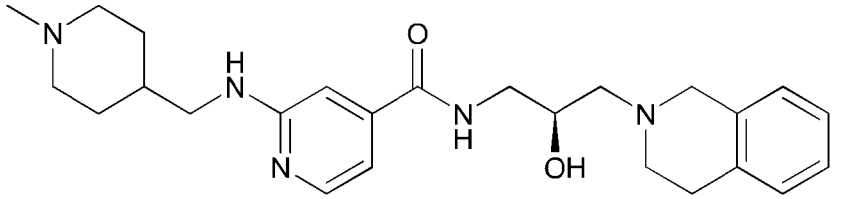
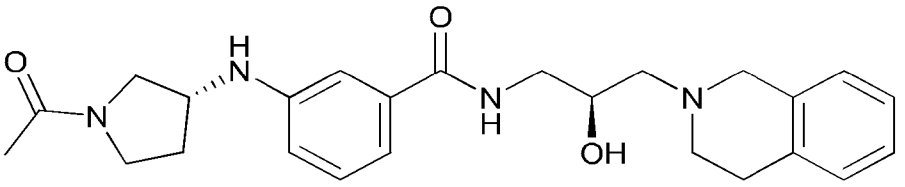
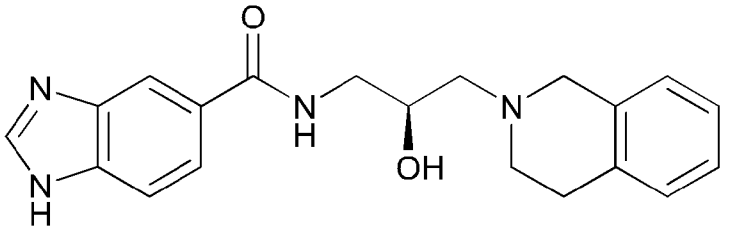
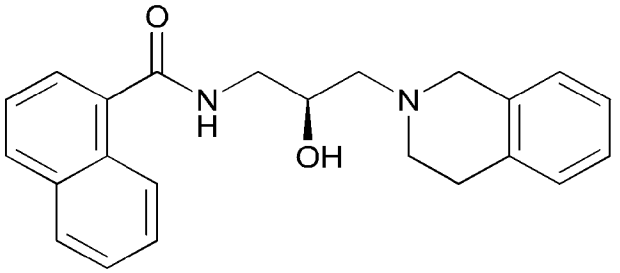
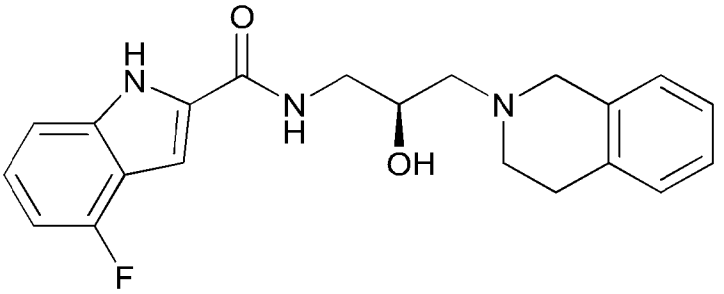
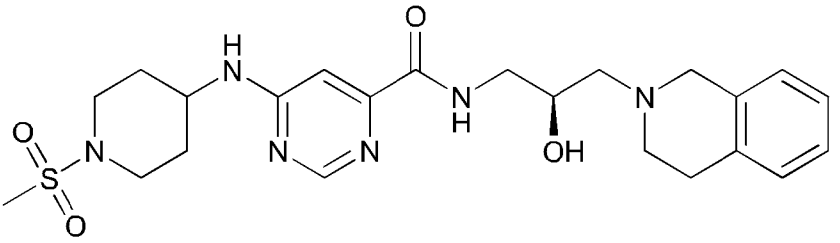
292	
293	
294	
295	
296	
297	

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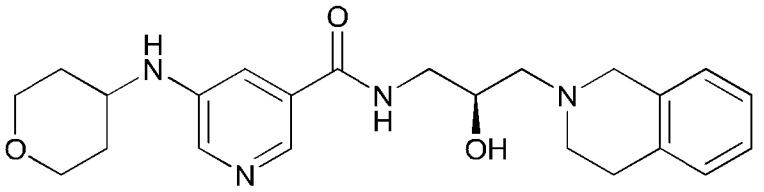
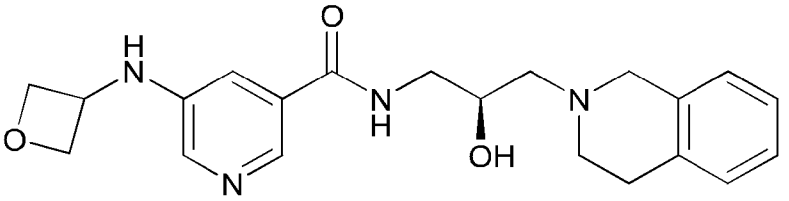
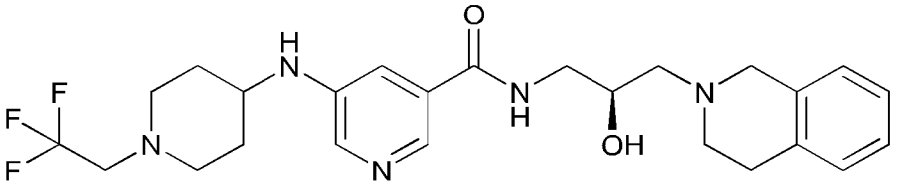
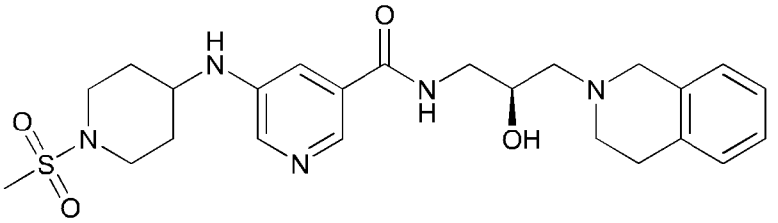
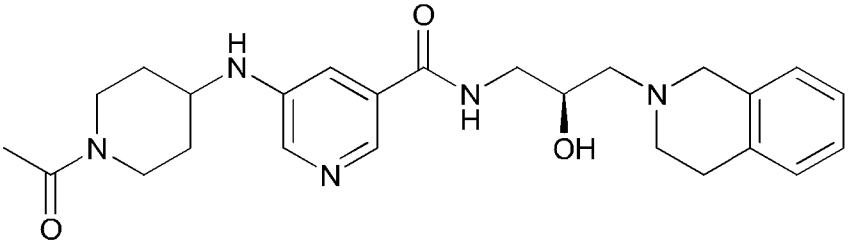
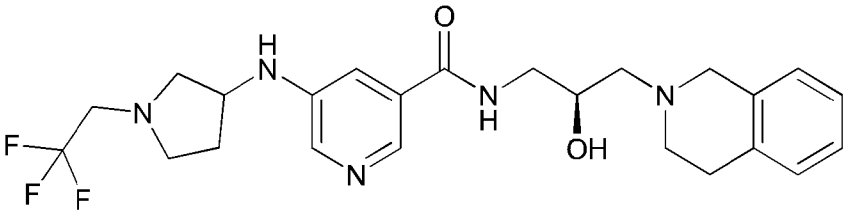
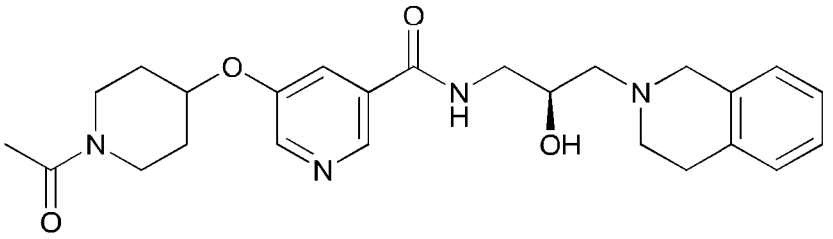
298	
299	
300	
301	
302	
303	
304	

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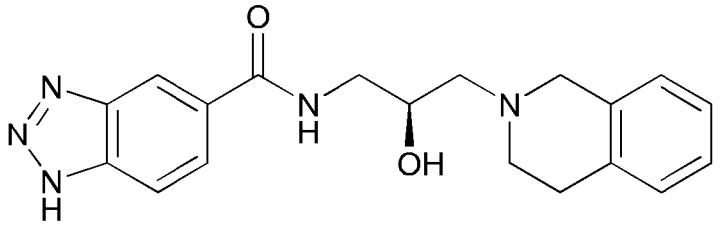
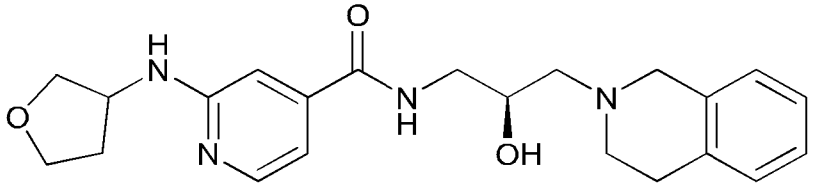
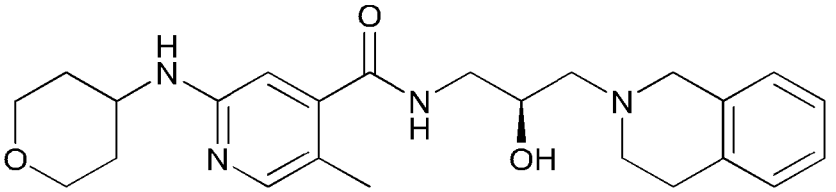
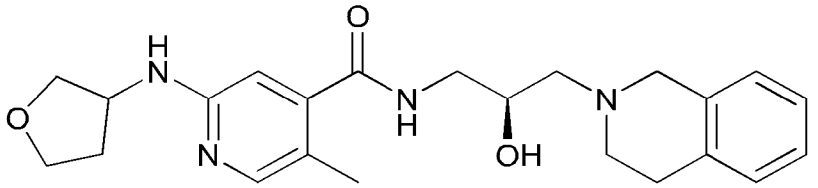
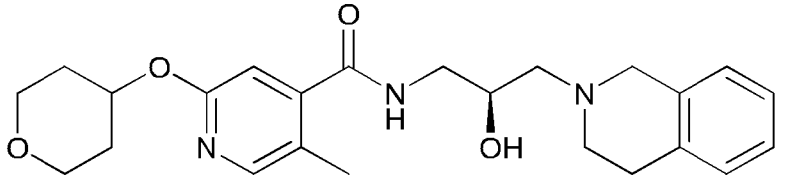
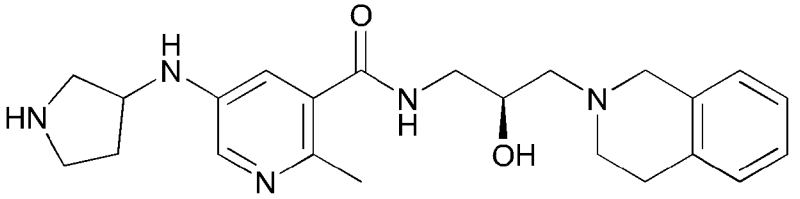
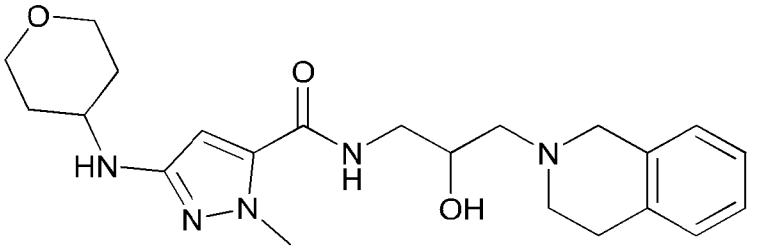
305	
306	
307	
308	
309	
310	
311	

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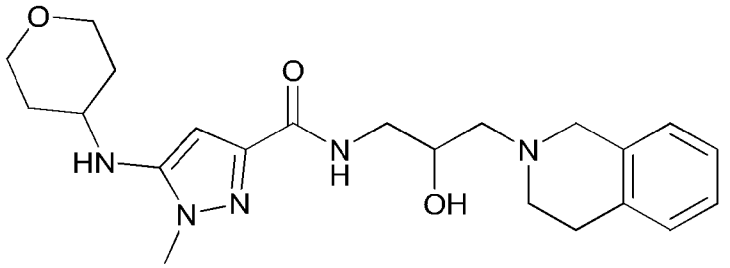
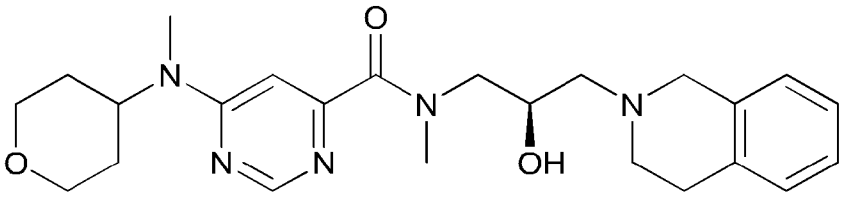
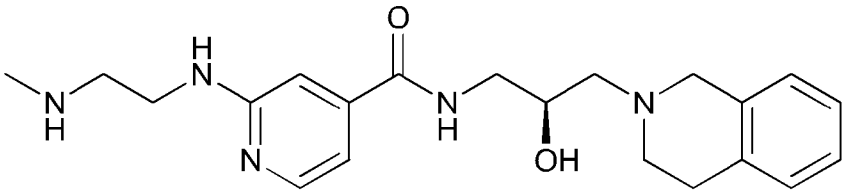
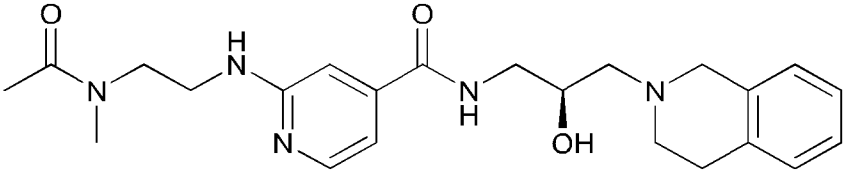
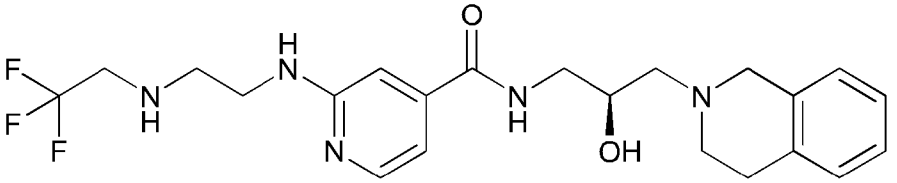
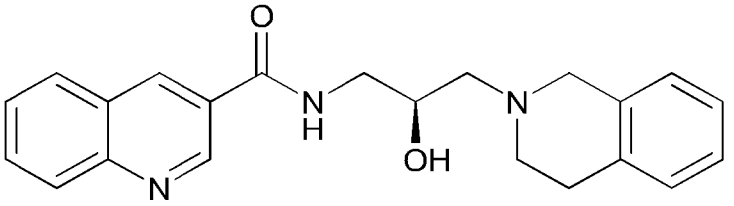
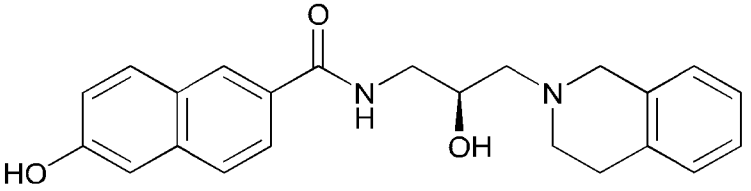
312	
313	
314	
315	
316	
317	
318	

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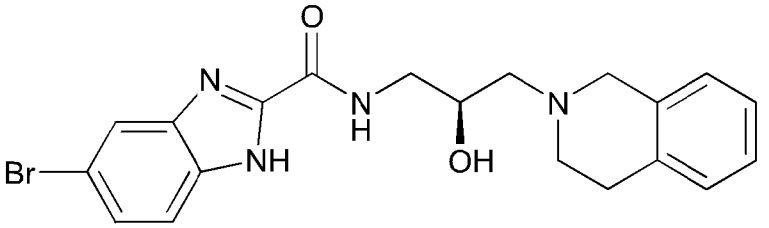
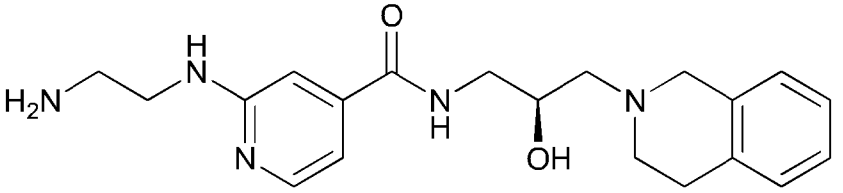
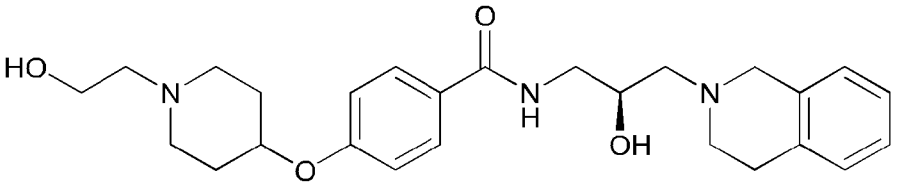
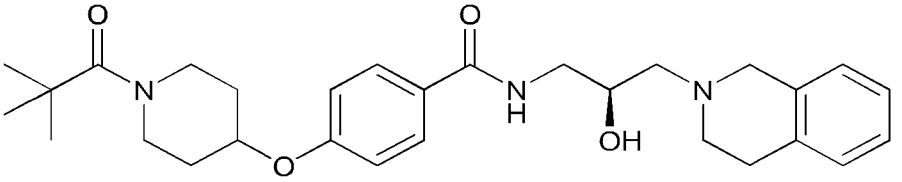
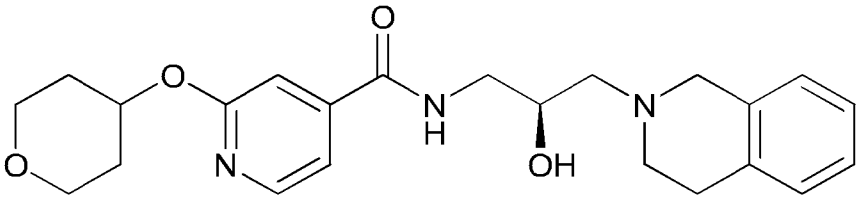
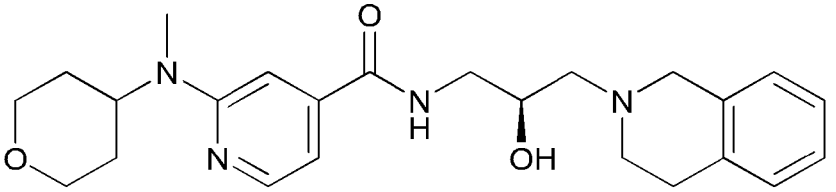
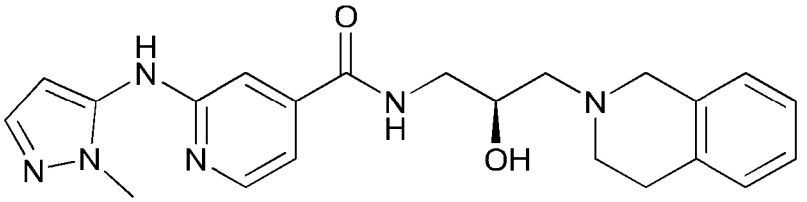
319	
320	
321	
322	
323	
324	
325	

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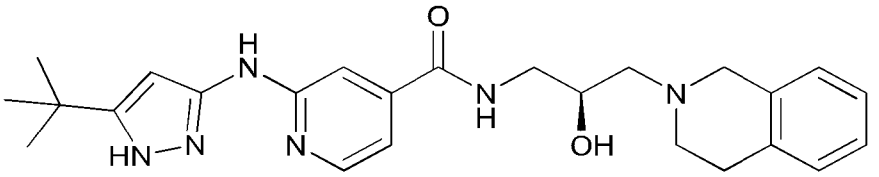
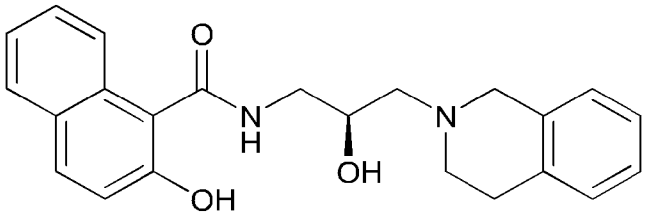
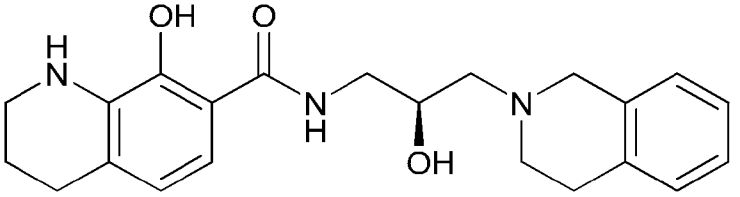
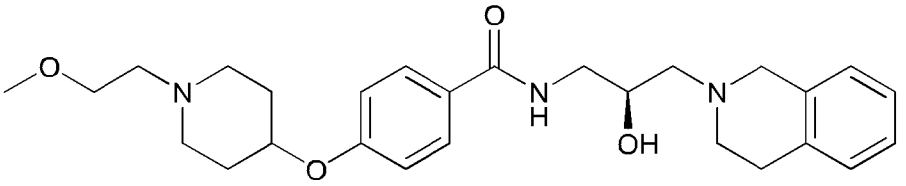
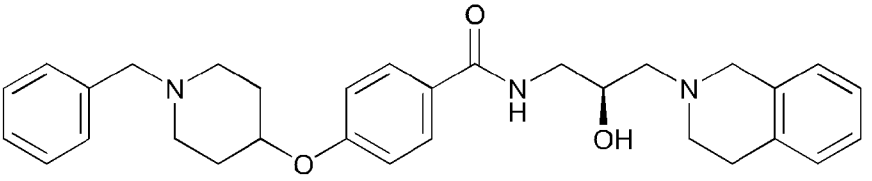
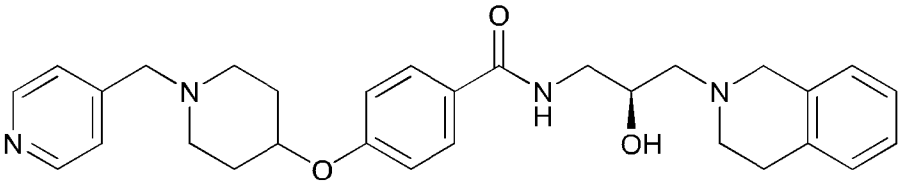
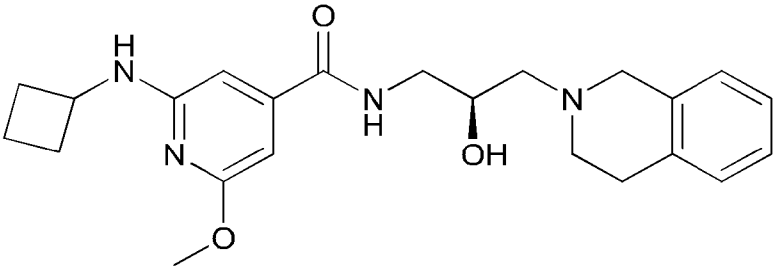
326	
327	
328	
329	
330	
331	
332	

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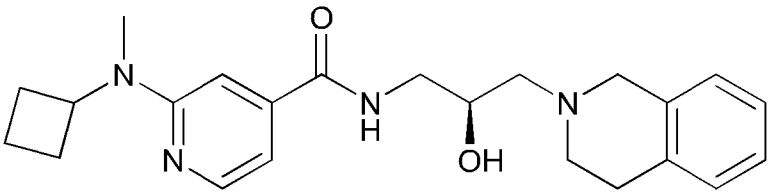
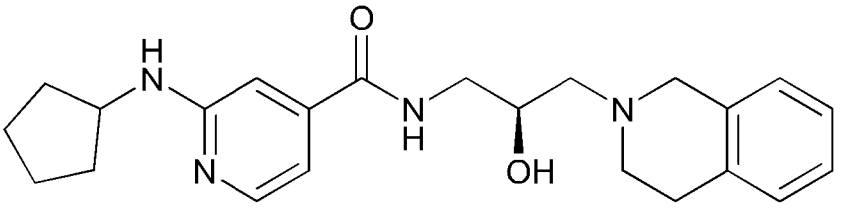
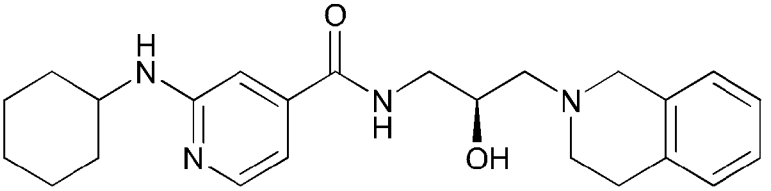
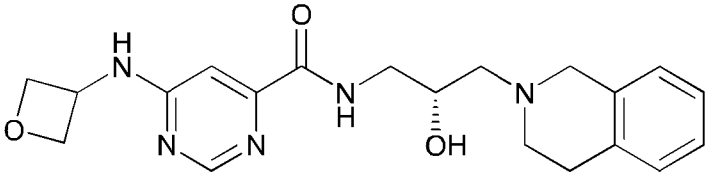
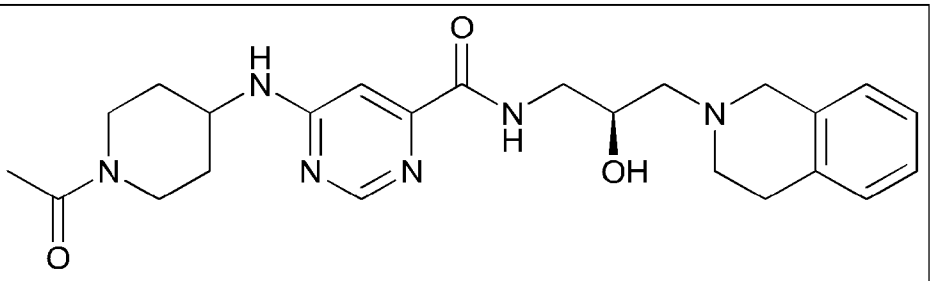
333	
334	
335	 , and
336	

or a pharmaceutically acceptable salt thereof.

108. The compound of claim 1, wherein the compound is

208	

or a pharmaceutically acceptable salt thereof.

109. A pharmaceutical composition comprising a compound of any one of claims 1-108, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

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110. A pharmaceutical composition comprising the compound of claim 108, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

111. A compound of any one of claims 1-108 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 109 or 110 for use in treating or preventing a PRMT5-mediated disorder.

112. The compound of any one of claims 1-108 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 109 or 110 for the use as defined in claim 111, wherein the disorder is a proliferative disorder.

113. The compound of any one of claims 1-108 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 109 or 110 for the use as defined in claim 111, wherein the disorder is cancer.

114. The compound of any one of claims 1-108 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 109 or 110 for the use as defined in claim 111, wherein the disorder is a metabolic disorder.

115. The compound of any one of claims 1-108 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 109 or 110 for the use as defined in claim 114, wherein the metabolic disorder is diabetes or obesity.

116. The compound of any one of claims 1-108 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 109 or 110 for the use as defined in claim 111, wherein the disorder is a blood disorder.

117. The compound of any one of claims 1-108 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 109 or 110 for the use as defined in claim 116, wherein the blood disorder is a hemoglobinopathy, sickle cell anemia, or β-thalessemia.

118. The compound of any one of claims 1-108 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 109 or 110 for the use as defined in claim

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113, wherein the cancer is selected from hematopoietic cancer, lung cancer, prostate cancer, melanoma, or pancreatic cancer.

119. A kit or packaged pharmaceutical comprising a compound of any one of claims 1-108, or a pharmaceutical composition of claim 109 or 110, and instructions for use thereof.

120. A method of inhibiting PRMT5 comprising contacting a cell with an effective amount of a compound of any one of claims 1-108 or a pharmaceutically acceptable salt thereof or a pharmaceutical composition of claim 109 or 110, wherein the cell is *in vitro*.

121. A method of altering gene expression comprising contacting a cell with an effective amount of a compound of any one of claims 1-108 or a pharmaceutically acceptable salt thereof or a pharmaceutical composition of claim 109 or 110, wherein the cell is *in vitro*.

122. A method of altering transcription comprising contacting a cell with an effective amount of a compound of any one of claims 1-108 or a pharmaceutically acceptable salt thereof or a pharmaceutical composition of claim 109 or 110, wherein the cell is *in vitro*.

123. A use of a compound of any one of claims 1-108 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 109 or claim 110 for inhibiting PRMT5 in a cell.

124. A use of a compound of any one of claims 1-108 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 109 or 110 for altering gene expression influenced by or involving PRMT5 in a cell.

125. A use of a compound of any one of claims 1-108 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 109 or 110 for altering transcription influenced by or involving PRMT5 in a cell.

126. The use of any one of claims 123-125, wherein the cell is *in vitro*.

127. The use of any one of claims 123-125, wherein the cell is in a subject.

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128. A use of a compound of any one of claims 1-108, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 109 or claim 110 for treating or preventing a PRMT5-mediated disorder.

129. The use of claim 128, wherein the disorder is a proliferative disorder.

130. The use of claim 129, wherein the proliferative disorder is cancer.

131. The use of claim 130, wherein the cancer is hematopoietic cancer, lung cancer, prostate cancer, melanoma, or pancreatic cancer.

132. The use of claim 128, wherein the disorder is a metabolic disorder.

133. The use of claim 132, wherein the metabolic disorder is diabetes.

134. The use of claim 132, wherein the metabolic disorder is obesity.

135. The use of claim 128, wherein the disorder is a blood disorder.

136. The use of claim 135, wherein the blood disorder is a hemoglobinopathy.

137. The use of claim 136, wherein the blood disorder is sickle cell anemia.

138. The use of claim 136, wherein the blood disorder is β-thalessemia.

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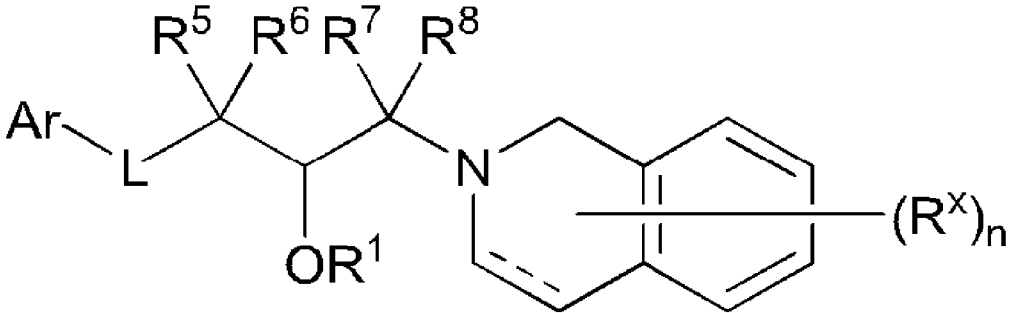

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